



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Alemtuzumab

Proprietary Product Name: Lemtrada, Remniq

Sponsor: Sanofi-Aventis Australia Pty Ltd

February 2014

TGA Health Safety
Regulation

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New dosage strength, new patient group, new dosage regime
<i>Decision:</i>	Approved
<i>Date of decision:</i>	11 December 2013
<i>Active ingredient:</i>	Alemtuzumab (rch)
<i>Product names:</i>	Lemtrada, Remniq
<i>Sponsor's name and address:</i>	Sanofi-Aventis Australia Pty Ltd 12-24 Talavera Road Macquarie Park NSW 2113
<i>Dose form:</i>	Concentrated solution for infusion
<i>Strength:</i>	10 mg/mL
<i>Container:</i>	Vial
<i>Pack size:</i>	1
<i>Approved therapeutic use:</i>	Lemtrada/Remniq is indicated for the treatment of relapsing forms of multiple sclerosis (MS) for patients with active disease defined by clinical or imaging features to slow the accumulation of physical disability and reduce the frequency of clinical relapses.
<i>Route of administration:</i>	Intravenous (IV) infusion
<i>Dosage (abbreviated):</i>	The recommended dose is 12 mg/day administered by IV infusion for 2 treatment courses. <ul style="list-style-type: none">• Initial treatment course: 12 mg/day for 5 consecutive days (60 mg total dose)• Second treatment course: 12 mg/day for 3 consecutive days (36 mg total dose) administered 12 months after the initial treatment course.
<i>ARTG numbers:</i>	200941 and 200948

Product background

Alemtuzumab is a humanised monoclonal antibody directed against the cell surface antigen CD52. CD52 is present at high levels on the surface of T and B lymphocytes and at lower levels on natural killer (NK) cells, monocytes and macrophages. CD52 is rarely

present on the surfaces of neutrophils, plasma cells or bone marrow stem cells. Binding of alemtuzumab to the surface of lymphocytes initiates antibody-dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) of these cells.

Multiple sclerosis (MS) is an autoimmune disease in which lymphocyte-mediated inflammation in the central nervous system (CNS) has a fundamental role in the pathogenesis of the disease. In MS, the objective is to achieve immunomodulation via depletion of autoreactive lymphocytes followed by repopulation of T and B lymphocytes potentially leading to a rebalancing of the immune system.

The role of the immune system in MS is not understood but it has been established that reducing immune-mediated inflammation can reduce the symptoms of the disease. Reducing immune-mediated inflammation and hence the symptoms of MS by depleting lymphocytes is the basis of alemtuzumab's use in this disease.

This AusPAR describes the application by Sanofi-Aventis Australia Pty Ltd (the sponsor) to register alemtuzumab 10 mg/mL injection concentrated vial (trade names Lemtrada and Remniq) for the following indication:

Lemtrada/Remniq is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to slow the accumulation of physical disability and reduce the frequency of clinical relapses.

The active ingredient alemtuzumab (as a 30 mg/mL injection solution) has been approved since 2006 under the tradename MabCampath. It was initially approved for treatment of patients with B-cell chronic lymphocytic leukaemia (B-CLL) who have relapsed after failure of two prior therapies. This was extended in 2009 to allow first-line treatment of patients with B-CLL.

Lemtrada/Remniq presents alemtuzumab as a different dosage strength (10 mg/mL) for a different patient population and dosing regimen.

Regulatory status

Lemtrada and Remniq received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 18 December 2013.

At the time TGA considered this application, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) had issued (on 27 June 2013) a positive opinion for Lemtrada (alemtuzumab 10 mg/mL) in the indication: *for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features*, and a similar application was under review in 8 additional countries including the USA, Switzerland and Canada.

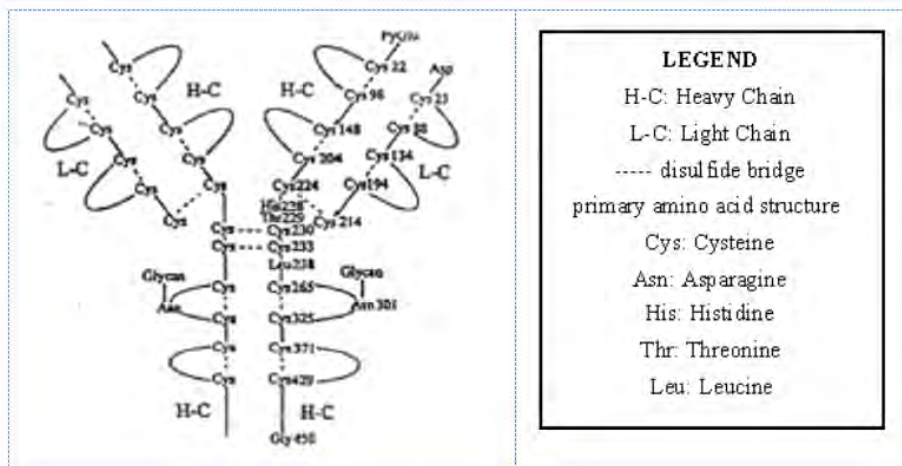
Product Information

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

II. Quality findings

Drug substance (active ingredient)

The drug substance has the following structure:

Figure 1. Structure of alemtuzumab

Manufacture

The active substance is manufactured by recombinant deoxyribonucleic acid (DNA)-technology. This is followed by purification and modification reactions. Size exclusion chromatography is then performed to remove product and process related impurities. The product is formulated by addition of excipients and diluted to the drug substance product concentration. The product is then transferred for aseptic filling.

Cell banking processes are satisfactory. All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Physical and chemical properties

Alemtuzumab (rch) is a Y-shaped molecule consisting of two 24-kilodalton (kD) light polypeptide chains (L-C) and two 49-kD heavy polypeptide chains (H-C) linked together by 2 interdisulfide (L-C)-(H-C) bridges and two interdisulfide (H-C)-(H-C) bridges. Each molecule also contains a total of 12 intra-chain disulfide bridges and an asparagine residue in each heavy chain that is amenable to glycosylation. The antibody has an approximate molecular weight of 150 kD.

The characterisation of alemtuzumab was performed by assessing the primary, secondary and tertiary structures of the protein and other physicochemical properties.

A number of potential impurities have been identified which fall into two main groups: process-related and product related.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use, are satisfactory. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time/stressed conditions to characterise the stability/degradation profile of the substance and to establish a shelf life.

The real time data submitted support a shelf life of 6 months at 2-8°C.

Drug product

Formulation

The composition of the drug product is the same as drug substance. The drug product is a sterile, clear, and colourless to yellowish isotonic solution for intravenous infusion. Each vial has a nominal fill volume of 1.2 mL with an overage of approximately 0.18 mL. Each vial is intended for single use administration only.

Manufacture

The manufacture of alemtuzumab drug product consists of three major steps:

- filtration and filling;
- stoppering/capping;
- labelling and packaging.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product, are satisfactory. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product.

Based upon the long term data currently available, an expiration dating period of 36 months is proposed for alemtuzumab drug product when stored at 2-8°C.

In-use stability data have also been submitted. The proposed shelf life and storage condition for the diluted product is 24 hours when stored at 2-8°C or room temperature and then infused at room temperature over an 8 hour period.

Biopharmaceutics

Biopharmaceutic data are not required for this product because it is a monoclonal antibody and is given by IV infusion

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The Module 3 evaluators recommended that Lemtrada (alemtuzumab (rch)) solution for infusion 12 mg vial and Remniq (alemtuzumab (rch)) solution for infusion 12 mg vial should be approved with respect to Module 3 data.

Should the product be approved, the conditions of registration should include conditions relating to batch release testing by the TGA Office of Laboratories and Scientific Services.¹

III. Nonclinical findings

Introduction

General comments

The submitted nonclinical data were in general accordance with the International Conference on Harmonisation (ICH) guideline (ICH S9) on the nonclinical evaluation of anticancer pharmaceuticals. All pivotal repeat-dose toxicity and reproductive toxicity studies were compliant with Good Laboratory Practice (GLP). The sponsor used two animal models to investigate the kinetics and toxicity of alemtuzumab: cynomolgus monkeys and huCD52 transgenic (huCD52Tg) mice. Immune responses in the monkeys were consistent with CD52 expression on lymphocytes. One study examined alemtuzumab tissue cross-reactivity in this species using biotin-alemtuzumab but due to technical issues the pattern of binding has not been elucidated. Alemtuzumab binds about 10 times less strongly to monkey target antigens than human; there is no information about binding to other peripheral tissues. This may limit the usefulness of the cynomolgus monkey as a model in toxicology studies. Tissue cross reactivity studies in the transgenic mice indicated similar distribution of CD52 to that in humans.

Some of the submitted studies were evaluated in a previous submission to the TGA regarding alemtuzumab.

Pharmacology

Primary pharmacology

Alemtuzumab depletes B and T lymphocytes by binding to the CD52 antigen present on the surface of various subsets of lymphocytes. Treatment with alemtuzumab leads to a massive depletion of lymphocytes which then recover. Recovery is possible because bone marrow progenitor cells are not depleted by alemtuzumab. B lymphocytes recover in approximately 6 months whereas T lymphocytes remain depleted for longer periods, probably because T cells regenerating in a lymphopaenic environment die rapidly as a result of apoptosis. This prolonged depletion of T lymphocytes leads to an amelioration of the symptoms of MS.

In humans CD52 is expressed principally on lymphoid tissues. It is also expressed in parts of the male and female reproductive systems, although evidence for expression in the central nervous system (glia) and peripheral nervous system (Schwann cells) is equivocal. Alemtuzumab has been shown to cross-react with all these tissues *in vitro*. There is no cross-reactivity of alemtuzumab with tissues from non-primate species. Cynomolgus monkeys do express a variant of human CD52 on lymphocytes and in some animals also on erythrocytes. Only the former group was used in the nonclinical studies.

In vitro primary pharmacology studies examined the expression of CD52 on peripheral blood mononuclear cells (PBMCs) from human normal subjects and MS patients and the consequences of this expression for cytotoxicity. Absolute levels of CD52 expression on individual PBMC subsets were highly variable between different donors. The trend in the

¹ Details of these conditions are beyond the scope of the AusPAR.

hierarchy of differential CD52 expression levels, however, was similar in healthy donors and the MS patients examined. Complement mediated cytotoxicity studies in 4 healthy donors showed that, amongst lymphocytes, 10.0 µg/mL alemtuzumab mediated marked cytotoxic effects on B and T cells with minimal effect on NK cells, correlating with the density of CD52 on these cells. Other studies demonstrated that alemtuzumab (0.25-10.0 µg/mL) was cytotoxic to T cells via CDC mechanisms and via ADCC mechanisms at concentrations from 0.01 to 10.0 µg/mL *in vitro*. These concentrations compare to the expected clinical maximum plasma concentration (C_{max}) of about 3 µg/mL. Following depletion of T cells with alemtuzumab 10.0 µg/mL there was an increase in the percentage of T cells with a regulatory phenotype (CD4⁺ FOXP3⁺) in the surviving population.

In vivo studies were conducted in transgenic mice derived from CD-1 embryonic stem cells which had a bacmid construct containing 145 kilobases of genomic DNA from human chromosome 1 integrated into their genome (huCD52Tg mice), and in cynomolgus monkeys. These studies established the comparability of the pattern of expression of CD52 in the transgenic mice and the similar pattern of susceptibility of lymphocytes to depletion by alemtuzumab (0.1-1.0 mg/kg single intravenous (IV) dose; 0.5-1.0 mg/kg single subcutaneous (SC) dose; 0.5 mg/kg IV repeat dose) in this model. Depletion of lymphocytes following alemtuzumab (3.0 mg/kg) with partial recovery (to within normal physiological range) after 28 days was demonstrated in cynomolgus monkeys.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacology studies examined the time course of immune cell repopulation following depletion with a five day cycle of alemtuzumab in huCD52Tg mice and cynomolgus monkeys. The results of these studies are limited by the small numbers of animals and, in the case of mice, a short follow-up period. The general pattern of depletion and re-population of B and T cells in these animal models does however seem to follow a similar pattern to that seen in human subjects. This is rapid depletion of both B and T lymphocytes with relatively rapid recovery of B cells and much slower, or no, recovery of T lymphocytes. In the monkey there is a suggestion that T lymphocytes in females do not recover as completely (or possibly as fast) as in males but the extremely small numbers studied preclude any firm conclusions. No effect of gender on alemtuzumab pharmacodynamics (PDs) has been observed in clinical studies.

Other secondary pharmacology studies examined cytokine release in huCD52Tg mice following single IV or SC injections of alemtuzumab. Observations noted elevated levels (relative to phosphate buffered saline (PBS) controls) of interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1) and tumour necrosis factor alpha (TNF-α) following single IV doses of 0.5 and 3.0 mg/kg, of IL-10 following 3.0 mg/kg IV, of IL-6 and MCP-1 following single SC doses of 0.5 and 3.0 mg/kg, and of TNF-α following 3.0 mg/kg SC, occurring 1-4 h after dosing. Similar increases in cytokine release have been reported in humans following administration of alemtuzumab and are thought to contribute to the transient symptomatic deterioration seen in MS patients following alemtuzumab administration. The effect in huCD52Tg mice may be of some significance in relation to the effects seen on implantation.

Dedicated safety pharmacology studies were not conducted but observations of cardiovascular and respiratory effects were made in a single-dose study and a repeat-dose study in cynomolgus monkeys. In conscious animals there were no effects on heart rate, blood pressure or electrocardiogram (ECG) at doses up to 30 mg/kg IV (infused over 3 h), while in anaesthetised animals alemtuzumab (10 and 30 mg/kg IV, infused over 40 min) caused dose-dependent hypotension and tachycardia but no notable effects on the ECG. ECGs were recorded from conscious animals in another study but much of the data was lost. Based on the available data no abnormalities in ECG parameters were observed with the exception of one high dose (HD) animal that displayed premature ventricular

complexes following the first dose of alemtuzumab. Evaluation of central nervous system (CNS) effects was not undertaken as alemtuzumab is unlikely to cross the blood brain barrier due to its molecular size.

Pharmacokinetics

The plasma kinetics of alemtuzumab were examined following IV or SC dosing in huCD52Tg mice, wild type CD-1 mice or cynomolgus monkeys in this submission. Some references were made to studies previously evaluated by the TGA for another submission concerning alemtuzumab; however, significant improvements were made to the detection method and the animal model used in the present submission and so the pharmacokinetic (PK) characterisation in the present studies is likely to be more reliable. Both single and repeat-dose studies were performed using mice and monkeys. Approximately dose-proportional increases in exposure were seen in both huCD52Tg mice and cynomolgus monkeys in single dose, but not repeat dose, studies where non-linear PK profiles were seen in both species although not exclusively and this is presumably due to saturable clearance dependant on the drug target concentration. The SC bioavailability of alemtuzumab in huCD52Tg mice was 75% and 54% at doses of 0.5 and 1 mg/kg respectively. In monkeys the SC bioavailability of alemtuzumab was 60% and 63% at doses of 0.3 and 3 mg/kg respectively. The half-life of alemtuzumab in huCD52Tg mice was very similar for 0.5 and 1.0 mg/kg single doses administered SC and IV. Values ranged from 34.5 (SC 1 mg/kg) to 45.3 (SC 0.5 mg/kg) h. In monkeys the half-life was about 4 days and 6 days following single IV doses of 0.3 and 3 mg/kg respectively. In monkeys a modest increase in half-life was seen in the second cycle of dosing which occurred 28 days after the initial cycle. In humans the half-life ($t_{1/2\alpha}$) was estimated at around 2 days and was demonstrated to be independent of cycle, anti-alemtuzumab status and dose level in these patients at doses of 12 or 24 mg.

No studies were performed to investigate the tissue distribution of alemtuzumab in non-pregnant animals. *In vitro* cross reactivity studies revealed alemtuzumab binding in mononuclear cells in multiple tissues, granulocytes in select tissues, and hematopoietic cells in the bone marrow in both humans and transgenic mice. Mononuclear cell staining was present in all lymphoid organs (spleen, lymph node, bone marrow, thymus, and tonsil [human only]), mucosal associated lymphoid tissue (colon, gastrointestinal tract, and lung [transgenic mouse only]) and mononuclear cell infiltrates (interstitial, lamina propria/submucosal/muscularis, intravascular, dermal and/or intraepithelial) in various tissues (adrenal gland, bladder, brain [2.0 µg/mL in transgenic mouse only], breast, endothelium [transgenic mouse only], epididymis [transgenic mouse only], eyes [transgenic mouse only], fallopian tube, heart [transgenic mouse only], kidney, liver, lung, ovary, pancreas, placenta [human only], prostate, skin [human only], parathyroid [transgenic mouse only], pituitary [10.0 µg/mL only in human, 2.0 µg/mL and 10.0 µg/mL in transgenic mouse], prostate, spinal cord, striated muscle [transgenic mouse only], testes, thyroid, ureter [human only] and uterus).

The influence of the drug target was well demonstrated by comparison of PK parameters of alemtuzumab in huCD52Tg mice and wild type CD-1 mice. Alemtuzumab was removed from the blood more readily resulting in shorter half-life and increased clearance and the apparent volume of distribution was greater in mice expressing the human CD52 cell surface antigen. These differences align with those seen in the huCD52Tg mouse repeat-dose study. An increase in area under the plasma concentration-time curve (AUC) and decrease in both clearance and volume of distribution was noted following 5 daily doses at 1 mg/kg (SC and IV) suggesting that low levels of target availability (as would be the case in the wild type CD-1 mouse or following repeat dosing) was the cause of the differences

in drug disposition. In humans (B-CLL patients) it has been noted that clearance of alemtuzumab decreases with decreasing target availability (Mould *et al.*, 2007²).

No metabolism studies were performed since alemtuzumab is a member of a therapeutic class that is understood to be degraded into smaller peptides and individual amino acids.

Although antibodies were detected in huCD52Tg mice the titres were low and there was no evidence of a significant effect on alemtuzumab PK in these studies. One of six monkeys in the repeat-dose study developed anti-alemtuzumab antibodies, increasing during cycle 1, and this correlated with undetectable serum alemtuzumab concentrations as well as attenuated PD effects on lymphocytes during cycle 2. Data from this animal were omitted from PK parameter calculations. Overall the presence of anti-alemtuzumab antibodies did not hinder the characterisation of alemtuzumab PK in this submission. The development of anti-alemtuzumab antibodies in humans has been noted in human patients.

The PK profiles in huCd52Tg mice and cynomolgus monkeys were sufficiently similar to provide prospective information about the disposition of the drug to inform its use in humans. The reduction in clearance and concomitant increase in AUC with repeat-dosing in huCD52tg mice was consistent across species and is most likely to be due to reduction in target availability.

Pharmacokinetic drug interactions

No studies of PK drug interactions were performed. Alemtuzumab is a recombinant humanised monoclonal antibody and is expected to be metabolically degraded through peptide hydrolysis and is therefore unlikely to interact with cytochrome P450 (CYP450) enzymes.

Toxicology

Acute toxicity

No dedicated single-dose toxicity studies were conducted. Although some studies examined only single doses, were not designed to establish lethality or a maximum tolerated dose (MTD). All investigated haematological changes following single doses and one investigated cardiovascular and respiratory effects under anaesthesia. Alemtuzumab did not produce acute toxicity (other than the desired outcome of depleting lymphocytes) in doses up to 10 mg/kg IV in monkeys. A single fatality was recorded in one of 4 animals given 30 mg/kg under ketamine anaesthesia but the cause of death was unclear. These studies were evaluated in a previous submission to the TGA.

Repeat-dose toxicity

One repeat-dose toxicity study (Study TTDR/90/0036-4) was evaluated by the TGA for the previous submission concerning alemtuzumab. This report noted that the small numbers used in the study limited the conclusions and indicated that the toxicity of alemtuzumab had not been adequately investigated. The difficulties of finding adequate animal models in which to test alemtuzumab and the availability of extensive human data mean that the limitations in the nonclinical toxicity data do not necessarily present a risk.

The only deaths recorded in the monkey studies were secondary to infection. Major infections at the infusion points developed in several cynomolgus monkeys receiving

² Mould DR, Baumann A, Kuhlmann J, Keating MJ, Weitman S, Hillmen P *et al.* Population pharmacokinetics-pharmacodynamics of alemtuzumab (Campath) in patients with chronic lymphocytic leukaemia and its link to treatment response. *Br J Clin Pharmacol* 2007;64(3);278-291.

3 mg/kg/day and 30 mg/kg/day but not in animals receiving 10 mg/kg/day. These animals were euthanised due to the uncontrollable nature of the infections. Because there was no clear dose dependence the relationship between these deaths and treatment with alemtuzumab was not clear.

Relative exposure

Human PK values were obtained in 216 patients with relapsing remitting MS given 12 or 24 mg/day for 5 consecutive days, followed by 3 days treatment 12 months after the initial treatment cycle (Studies CAMMS223, CAMMS323, CAMMS324). Serum concentrations increased with each daily dose of the cycle, with the first cycle C_{max} of 3014 ng/mL (occurring on Day 5) and the second cycle C_{max} of 2276 ng/mL (Day 3). Serum concentrations became low or undetectable within 30 days following each treatment cycle.

Relative exposure comparisons were based on animal:human plasma exposure ratios. Human serum AUC values were estimated based on simulated serum concentration-time profiles for individual patients using the population PK model. A clinical AUC mean value of 1290 $\mu\text{g}\cdot\text{h}/\text{mL}$ (12 mg dose) was initially used³ for exposure comparisons, derived from the AUC post the 5th dose of cycle 1 (AUC over day 4 to 102, $\text{AUC}_{\text{Day 4-102}}$) in MS patients from the PK sub-studies in the clinical development program. In a response to a TGA request for further information on clinical AUC values, the sponsor indicated that the 1290 $\mu\text{g}\cdot\text{h}/\text{mL}$ value was derived from a preliminary simulation dataset using an earlier version of the population PK model. A re-calculation with the final simulated $\text{AUC}_{\text{Day 4-102}}$ values using the final population PK model, which was used in the current nonclinical evaluation report, gave a mean $\text{AUC}_{\text{Day 4-102}}$ of 774 $\mu\text{g}\cdot\text{h}/\text{mL}$.

The relative exposure (AUC) achieved was adequate compared to anticipated clinical values (up to 10 in mice and 54 in monkeys) (Table 1). The PK study in monkeys (FFA00109) used a similar dose regimen to that proposed clinically with daily dosing for 5 consecutive days in cycle 1 and 3 days in cycle 2 but with only 28 days between cycles. The maximum serum concentration following cycle 1 was 249 $\mu\text{g}/\text{mL}$ (83 times the clinical C_{max}) and following cycle 2 this was 190 $\mu\text{g}/\text{mL}$ (63 times the clinical C_{max}). The maximum plasma concentration measured during the repeat-dose infusion toxicity study (FFA00142) was in one of the two 30 mg/kg dose groups which averaged 2196 $\mu\text{g}/\text{mL}$ (730 times the clinical C_{max}). No PK analysis was performed for this study; hence it is not represented in Table 1. However, given the known plasma kinetics in this species, it is likely that AUC values in this study would have been up to about 10 fold those tabulated below for the 3 mg/kg dose, with corresponding 10 fold greater exposure margins (>300, based on AUC).

Table 1. Relative exposure in repeat-dose studies

Species	Study Number	Study duration	Dose (mg/kg/d ay)	$\text{AUC}_{0-\infty}$ ($\mu\text{g}\cdot\text{h}/\text{mL}$)	AUC exposure ratio [#]	C_{max} ($\mu\text{g}/\text{mL}$)	C_{max} exposure ratio [^]
Mouse (huCD52tr g CD-1)	06-0755	9 days	1 [qDx5]	251	0.3	16	5
	11-01228	19 days	3 [qDx5]	2590	3.3	104	35
			10 [qDx5]	7622	9.8	318	105

³ The 1290 $\mu\text{g}\cdot\text{h}/\text{mL}$ value was used for safety margin calculations in the sponsor's nonclinical overview, toxicology written summary and draft PI document.

Species	Study Number	Study duration	Dose (mg/kg/day)	AUC _{0-∞} (µg·h/mL)	AUC exposure ratio [#]	C _{max} (µg/mL)	C _{max} exposure ratio [^]
Monkey (Cynomolgus)	FFA00109	9 weeks, 2 cycle	3 [Cycle 1]	42120**	54	249	83
			3 [Cycle 2]	22656**	29	190	63
Human (RRMS patients)	CAMMS223, CAMMS323, CAMMS324	1 year	[12 mg (qDx5)]	774*	-	3	-

= animal:human plasma AUC. ^ = animal:human plasma C_{max}. * see text. qDx5 = once daily for 5 consecutive days. ** Cycle 1 AUC derived from AUC₀₋₃₂; Cycle 2 AUC derived from AUC₃₂₋₆₂ values

It should be borne in mind that binding affinity of alemtuzumab to CD52 expressed in cells from cynomolgus monkeys is 10 to 16 times lower than the binding to human CD52 (a limitation of the animal model) and therefore monkeys may require much higher levels in order to exhibit toxicity than humans. However, the estimated exposure margins are sufficiently high to offset concerns arising from this consideration.

It is also noted that the maximal total clinical dose of alemtuzumab from treatment with Lemtrada (60 mg in 12 months) is much smaller than from treatment with MabCampath (1123 mg in 3 months).

Major toxicities

The actions of alemtuzumab are confined to cells or tissues where the CD52 antigen is expressed. The FDA suggests that monoclonal antibodies, such as alemtuzumab, should be assessed for binding to target and possible binding to non-target human tissues and tissues of animal species used for their preclinical safety evaluation (*Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use*, U.S. FDA [CBER], 28 Feb 1997). A positive result will identify potential tissue sites or organ systems and allow these to be investigated more thoroughly in subsequent preclinical studies. Cross-reactivity studies in huCD52Tg mice established that alemtuzumab binding had similar target specificity, character, and intensity to that observed in human tissues. Cross-reactivity studies in cynomolgus monkeys were unsuccessful and the pattern of binding to tissues in this species has not been established. Toxicity studies show clearly that alemtuzumab binds to lymphocytes in cynomolgus monkeys but binding to other tissues in this species remains uncertain.

The major toxicity of alemtuzumab in the studies in monkeys (doses up to 30 mg/kg once daily for 5 days) and the huCD52Tg mouse (doses up to 10 mg/kg once daily for 5 days in the reproductive toxicity studies) is the same as the desired clinical effect, viz., depletion of lymphocytes. At the doses tested there was no evidence of any other major organ toxicity. There were sporadic observations of the development of antibodies to alemtuzumab in both monkeys and huCD52Tg mice. The antibody titre was generally low and in these instances the development of these antibodies did not appear to cause any pharmacological effect. In the one monkey that developed a high antibody titre the PD response to alemtuzumab was attenuated.

Genotoxicity

No genotoxicity studies were conducted. This was considered acceptable and in accordance with the relevant EMA/ICH guideline (CHMP/ICH/299/95; ICH S6 (R1)).

Carcinogenicity

No carcinogenicity studies were conducted. This is considered acceptable given the nature of the drug (CHMP/ICH/299/95; ICH S6 (R1)).

Reproductive toxicity

All reproductive toxicity studies were conducted in huCD52Tg mice. The studies covered fertility, early embryonic, embryofetal and post-natal development. Group sizes and study designs were adequate. The use of only this species is appropriate as none of the usual species used in reproductive toxicity testing could be employed because of their lack of CD52 receptors. The sponsor justifies the decision not to use cynomolgus monkeys in the reproductive toxicity studies on the basis that “a portion of monkeys develop anti-alemtuzumab antibodies following repeated alemtuzumab exposure”. This does not seem entirely plausible as huCD52Tg mice used in some of the reproductive toxicity studies also developed anti-alemtuzumab antibodies. That said, the results from the studies in mice give a clear picture of the reproductive toxicity of alemtuzumab and the use of primates is probably not justified.

Relative exposure

Proper comparison of alemtuzumab concentrations between dams and fetuses could not be performed. Alemtuzumab was measured in fetal homogenates at a single time point (gestation day (GD) 18) regardless of the exposure schedule of the dams. This time point was 168 h after the last dose in animals exposed on GD 6/7–GD 10/11 and 72 h after the last dose in animals exposed on GD 11/12–GD 15/16. Alemtuzumab serum concentrations in dams exposed on GD 6/7–GD 10/11 were below the limit of quantitation (BLQ) at the 168 h time point although alemtuzumab was detected in the 10 mg/kg exposed fetuses. Alemtuzumab concentrations in the dams exposed on GD 11/12–GD 15/16 were low. Alemtuzumab was detected in the fetuses in this later dosing group. The results of the PK study in pregnant mice were consistent with significant movement of alemtuzumab into the fetus especially in the GD 11/12–GD 15/16 dosing group.

Table 2. Relative exposure in reproductive toxicity studies

Species	Study	Dose (mg/kg/day IV) [Schedule]	AUC _{0-∞} (µg·h/m L)	AUC exposu re ratio [#]	C _{max} (µg/mL)	C _{max} expos ure ratio [^]
Mouse (huCD52) Male	Fertility 002000081 5/6 (11-01228 PK)	3 [qDx5]	2866	3.7	89.1	30
		10 [qDx5]	9125	12	323	107
Mouse (huCD52) Female	[5 days]	3 [qDx5]	2234	2.9	124	41
		10 [qDx5]	6118	7.9	313	104
Mouse	Embryofetal	3 [GD 6/7–	1275	1.6	61.9	21

Species	Study	Dose (mg/kg/day IV) [Schedule]	AUC _{0-∞} (µg·h/mL)	AUC exposure ratio [#]	C _{max} (µg/mL)	C _{max} exposure ratio [^]
(huCD52tr g)	development 002000227 7 (11-01187 PK)	GD 10/11]				
		10 [GD 6/7- GD 10/11]	5726	7.4	276	92
		3 [GD 11/12 - GD 15/16]	747	1.0	60.2	20
		10 [GD 11/12 - GD 15/16]	3131	4.0	265	88
Mouse (huCD52tr g)	Pre/postnatal development 002000287 1, 20010591	10 [LD 8-12]	-	-	208 ^{&}	69 ^{\$}
Human (RRMS patients)	CAMMS223, CAMMS323, CAMMS324	[12 mg (qDx5)]	774 [*]	-	3	-

[#] = animal:human plasma AUC; human AUC value of 774 µg.h/mL used for comparison, as in Table 1 (see text).

[^] = animal:human plasma C_{max}; human C_{max} value of 3 µg/mL used for comparison, as in Table 1 (see text).

[&] = plasma concentration Day 5 post-dose (15 min).

^{\$} = animal:human exposure ratio based on animal plasma concentration and human C_{max}.

GD, gestation day. LD, lactation day. * see text. qDx5 = once daily for 5 consecutive days

Animal exposure values for the embryofetal development studies were obtained from the separate toxicokinetic study (11-01187) in pregnant mice, with animal/human relative exposure based on AUC values (C_{max} values are also tabulated for completeness). For the fertility studies in non-pregnant/male mice, kinetic data were sourced from the repeat dose study (11-01228). Plasma concentrations measured at 15 min post-dose on Day 5 in these fertility studies were similar to the C_{max} values in Studies 11-01187 and 11-01228. For the pre-/post-natal studies, plasma concentration at 15 min (the approximate T_{max}) on day 5 (208 µg/mL) is somewhat lower than the C_{max} values in non-pregnant or pregnant females at the 10 mg/kg dose (Table 2). Although AUC data were not available for the pre-/post-natal studies, the AUC relative exposure is likely to have been in the range 4-8, based on the other female data.

The relative exposure (AUC) achieved in the reproductive toxicity studies was modest and the results suggest that fetal and neonatal exposure could reasonably be expected at the anticipated clinical level; placental transfer and excretion in milk were both demonstrated in the reproductive toxicity studies in huCD52Tg mice. (As in the repeat dose toxicity studies, peak plasma (C_{max}) relative exposures were larger than those based on AUC, although the latter are considered to have greater validity and are recommended for use in relevant PI statements).

In humans the CD52 antigen has been reported to be present in the epididymis, seminal vesicle, seminal plasma and on the surface of mature (but not testicular) spermatozoa

(Hale *et al.*, 1993⁴). It is possible that sperm may be protected by the high concentrations of soluble antigen in seminal plasma, which may inhibit binding of antibodies such as alemtuzumab (Hale *et al.*, 1993). In male huCD52Tg mice alemtuzumab (3 and 10 mg/kg for 5 days; AUCs of 3.7 and 12 times the human exposure at the recommended daily dose) caused a significant decrease in the numbers of normal sperm and a significant increase in the percentage of abnormal sperm; a no-effect dose was not established. The number of detached heads/no heads was significantly increased at the 10 mg/kg dose only. There were, however, no measurable effects on mating or fertility and the significance of the effects on sperm morphology is unclear. This finding should nevertheless be mentioned in the PI.

Exposure of female huCD52Tg mice to 10 mg/kg alemtuzumab (AUC 7.9 times the human exposure at the recommended daily dose) for 5 days prior to mating significantly reduced the numbers of corpora lutea and implantation sites (although pre- and post-implantation losses were not significantly affected). Pharmacokinetic analysis demonstrated that alemtuzumab was detectable in the serum of huCD52Tg mice for at least 5 days following the last dose of the 5 day cycle. Murine CD52 has been shown to be expressed in the mouse uterus during pregnancy with peak expression at the initiation of embryo implantation (Kumamoto, 2009⁵) and in human and mouse cumulus cells (Hasegawa *et al.*, 2008⁶) where expression increases after ovulation.

Embryofetal development studies did not show any clear pattern of effects of alemtuzumab on fetal development. There were some puzzling observations: fetal weights were significantly higher in fetuses from dams dosed at 3 and 10 mg/kg on GDs 6-10 (AUCs of 1.6 and 7.4 times the human exposure at the recommended daily dose) and there was a significant increase in pre-implantation loss in dams dosed at 10 mg/kg on GDs 11-15 (AUC 4.0 times the human exposure at the recommended daily dose). As implantation is complete well before GD 11 in this species, this seems unlikely to be treatment-related. Although the numbers did not reach statistical significance post-implantation loss was greater in both the 3 and 10 mg/kg GDs 11-15 groups with some evidence of dose-dependence (AUCs 1.0 and 4.0 times the human exposure at the recommended daily dose). In the GD 11-15, 10 mg/kg dose group, there were more dams with all conceptuses dead or resorbed and fewer dams with viable fetuses. This should be investigated further if alemtuzumab is to be used in pregnant humans.

There was evidence that exposure of dams to alemtuzumab during gestation (3, 10 mg/kg IV; GD 6-10 or GD 11-15) or preweaning (10 mg/kg IV; lactation day (LD) 8-12) affected peripheral blood total lymphocyte numbers and lymphocyte subpopulations in both male and female offspring. Interpretation of study results was confounded by differences in statistical significance in absolute versus percent values, sex differences, and inconsistent dose-dependency. Overall, however, the available data (and significance of trend analysis) support the conclusion of the study authors of an effect of alemtuzumab during gestation and lactation. In a further study of postnatal effects, exposure of nursing mice to alemtuzumab during LD 8-12 resulted in measurable concentrations of alemtuzumab in the milk and higher serum concentrations in the pups than in the dams.

Immunophenotyping (flow cytometry) did not show evidence of changes to the lymphocyte population. The functional immunity of these pups was examined by assessing their ability to mount an immunoglobulin G (IgG) and IgM T lymphocyte dependent antibody responses (TDARs) to keyhole limpet haemocyanin (KLH). IgG TDARs appeared

⁴ Hale G, Rye PD, Warford A, Lauder I, Brito-Babapulle A. The glycosylphosphatidylinositol-anchored lymphocyte antigen CDw52 is associated with the epididymal maturation of human spermatozoa. *J reproductive immunology* 1993;23(2):189-205.

⁵ Kumamoto K, Yang XZ, Hasegawa A, Komori S, Koyama K. CD52 expression is induced in the mouse uterus at the time of embryo implantation. *J reproductive immunology* 2009;82(1):32-39.

⁶ Hasegawa A, Takenobu T, Kasumi H, Komori S, Koyama K. CD52 is synthesized in cumulus cells and secreted into the cumulus matrix during ovulation. *Am J reproductive immunology* 2008;60(3):187-191.

intact but IgM TDARs were reduced in females. The individual results were, however, variable so this observation should be interpreted with caution and subjected to further investigation.

The effects on lymphocyte numbers in animals whose mothers were exposed during gestation may be a matter of concern. While alterations in lymphocyte numbers and function are the expected effects of alemtuzumab, and form the basis of its therapeutic use, alterations in immune function during development may have unforeseen consequences. The maturing immune system represents a vulnerable target for toxicants as it progresses through a series of novel prenatal and perinatal events that are critical for later-life host defence against a wide array of diseases. Critical maturational windows in the immune system are sensitive to disruption with the outcome usually taking the form of persistent immune dysfunction. The effects seen in the studies on huCD52Tg mice were not great and there were interpretative problems with the data, but there has been no long-term follow-up of these animals and the possibility of sustained alterations to immune function has not been eliminated.

Pregnancy classification

The sponsor has proposed pregnancy Category B2.^{7,8} Based on the studies in mice this is not appropriate. There is clear evidence that alemtuzumab elicited post-implantation loss when given on GD 11-16. The possible effects on lymphocyte parameters in the offspring of mothers exposed during gestation may also be a cause for concern. Category B3⁹ is recommended based on the nonclinical data.

Local tolerance

No specific local tolerance studies were performed. In nonclinical toxicity studies, there were no serious adverse findings related to the injection/infusion of alemtuzumab some of which used the proposed clinical formulation. The excipients in the clinical formulation are commonly used in injection products.

Paediatric use

Alemtuzumab is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Comments on the Safety Specification of the Risk Management Plan

Results and conclusions drawn from the nonclinical program for alemtuzumab detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of

⁷ Use in Pregnancy Category B2 is defined as *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.*

⁸ MabCampath has a B2 category, reflecting the lack of reproductive toxicity information at the time of its registration.

⁹ Use in Pregnancy Category B3 is defined as *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.*

Revised nonclinical recommendation: The nonclinical evaluator initially considered that the nonclinical data justified a pregnancy Category of **C**. Following the sponsor's response to the nonclinical evaluation report and a re-examination of the submitted data, it was considered that Category **B3** was warranted. The sponsor originally proposed and wished to maintain pregnancy Category **B2**, but this was not considered appropriate in view of the new reproductive (embryofetal toxicity) data for alemtuzumab.

the nonclinical evaluator. The RMP highlights the increase in antibiotic resistant infections in monkeys. The relevance to humans is interpreted but this remains for the clinical evaluator to assess.

Nonclinical summary and conclusions

- Alemtuzumab is a humanised monoclonal antibody which binds to the cell surface antigen CD52 present on the surface of lymphocytes, monocytes, NK cells, macrophages, sperm and male reproductive tissues in humans. Binding of alemtuzumab initiates CDC and ADCC of B and T lymphocytes leading to a profound reduction in the numbers in the circulation. The role of the immune system in MS is not understood but it has been established that reducing immune-mediated inflammation can reduce the symptoms. Reducing immune-mediated inflammation and hence the symptoms of MS by depleting lymphocytes is the basis of the use of alemtuzumab in this disease.
- The submitted Module 4 data were in general accordance with the EU/ICH guidelines (ICH S6 and S9) on the nonclinical evaluation of anticancer and biotechnology-derived pharmaceuticals. All pivotal repeat-dose toxicity and reproductive toxicity studies were GLP-compliant.
- Primary pharmacology *in vitro* studies were conducted on lymphocytes from healthy and MS human subjects. These studies confirmed the presence of CD52 on various subsets of lymphocytes and demonstrated that depletion of these by alemtuzumab was related to the pattern of CD52 expression and mediated via both CDC and ADCC. Nonclinical studies *in vivo* are hampered by the absence of the CD52 antigen (to which alemtuzumab binds) in most common laboratory species; these studies were thus confined to cynomolgus monkeys which express a slightly modified form of CD52 and transgenic mice which had the CD52 gene inserted into their DNA (huCD52Tg mice). *In vivo* studies established the comparability of the pattern of expression of CD52 in the transgenic mice and the similar pattern of susceptibility of lymphocytes to depletion by alemtuzumab. Lymphocyte depletion by alemtuzumab was also demonstrated in cynomolgus monkeys.
- Secondary pharmacology studies establish a similar pattern of lymphocyte re-population following depletion in the animal models. Elevated levels of cytokines IL-6, IL-10, MCP-1 and TNF- α were seen in huCD52Tg mice following administration of alemtuzumab (3 mg/kg IV). Similar increases in cytokine release have been reported in humans following administration of alemtuzumab.
- Dedicated safety pharmacology studies were not conducted but observations of cardiovascular and respiratory effects were made in cynomolgus monkey studies. ECG data from conscious animals did not reveal any effects of alemtuzumab. Evaluation of CNS effects was not conducted as alemtuzumab is unlikely to cross the blood brain barrier due to its molecular size.
- Non-linear PK profiles were seen in both test species (although not exclusively) which are similar to those in humans. The PK profile in mice and monkeys was dependent on the presence of the drug target CD52. In wild type CD-1 mice lacking the CD52 cell surface antigen, exposures were higher and clearance was reduced. Similarly, in repeat-dose studies in mice and monkeys, an increase in exposure and concomitant decrease in clearance and volume of distribution was seen, most likely due to target depletion. In monkeys the half-life was about 4 and 6 days following single IV doses of 0.3 and 3 mg/kg respectively, with a modest increase in the second cycle of dosing (28 days after the initial cycle). Shorter half-lives were seen in mice. One of six monkeys in the repeat-dose study developed anti-alemtuzumab antibodies, increasing during cycle

1, and this correlated with undetectable serum alemtuzumab concentrations as well as attenuated PD effects on lymphocytes during cycle 2.

- No dedicated acute toxicity studies were conducted and an MTD was not established.
- No deaths were recorded in repeat-dose studies on huCD52Tg mice; deaths in monkeys were all secondary to infection. The major toxicity of alemtuzumab identified in the repeat-dose studies in monkeys and huCD52Tg mice is the same as the desired clinical effect, viz., depletion of lymphocytes. At the doses tested there was no evidence of any other major organ toxicity.
- In huCD52Tg mice, alemtuzumab (up to 10 mg/kg once daily for 5 consecutive days IV) had no effect on male fertility (although adverse effects on sperm were reported), while females had fewer corpora lutea and implantations. Alemtuzumab crosses the placenta and was detected in milk in mice. Exposure of females during organogenesis was associated with increased post-implantation losses, but no teratogenicity. Lymphocyte numbers were reduced in pups exposed *in utero* and, in one of two studies, a reduction in lymphocytes and a reduced IgM response were observed in pups whose dams were treated prior to weaning (10 mg/kg/day IV, postpartum days 8-12).

Conclusions and recommendation

- The toxicity of alemtuzumab in animals has not been comprehensively investigated but the active ingredient has been registered for some years with a much higher approved dosage regimen. No clinically relevant hazards other than immunosuppression were identified in the limited toxicity studies submitted.
- The pharmacological activity of alemtuzumab was demonstrated in nonclinical studies. A reduction in lymphocyte numbers and alterations in the peripheral blood phenotypes was observed during repopulation.
- In transgenic mice, there was evidence that alemtuzumab caused post-implantation loss when given during late organogenesis. The alterations in lymphocyte numbers and reduced antibody response in the offspring of dams exposed during gestation or lactation may be a cause for concern. The sponsor has proposed pregnancy Category B2, but Category B3 is recommended on the basis of the nonclinical findings.
- There are no nonclinical objections to proposed extension of indications for alemtuzumab.

Recommended revisions to nonclinical statements in the proposed PI are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Alemtuzumab is a recombinant, DNA-derived humanised monoclonal antibody. The proposed indication is:

for the treatment of patients with relapsing forms of multiple sclerosis (MS) to slow or reverse the accumulation of physical disability and reduce the frequency of clinical relapses.

According to the *Guideline on clinical investigation of Medicinal Products for the Treatment of Multiple Sclerosis* (CPMP/EWP/561/98 Rev 1, 16 November 2006) the term relapsing MS (RMS) applies to those patients either with a relapsing remitting form of MS (RRMS) or a secondary progressive MS (SPMS) form that are suffering relapses. The term relapsing MS includes 1) patients with RRMS, 2) patients with SPMS and superimposed relapses and 3) patients with a single demyelinating clinical event who show lesion dissemination on subsequent magnetic resonance imaging (MRI) scans according to McDonald's criteria.

The Guideline also states:

2.1 Different goals of treatments

- a. Treatment of acute relapses to shorten their duration and/or severity of symptoms and/or preventing their sequelae.
- b. Modification of the natural history of the disease. This includes:
 - Preventing or delaying the accumulation of disability. This may refer to the sustained accumulation of disability related with relapses or to the progression of disability either in the progressive phase of the disease (SPMS) or in PPMS. Those three situations demand a separate approach.
 - Preventing or modifying relapses. It is not clear to what extent the effect on relapses is related to the prevention or delay in the long-term accumulation of disability, which is considered a more clinically relevant effect.
- c. Improvement of an apparently stable residual disability

Clinical rationale

Alemtuzumab depletes circulating B and T lymphocytes. The mechanism by which alemtuzumab exerts its therapeutic effects in MS is not fully elucidated but may involve immunomodulation through the depletion and repopulation of lymphocytes. MS is an autoimmune disease in which lymphocyte-mediated inflammation in the CNS has a fundamental role in the pathogenesis of the disease (in MS, the objective is to achieve immunomodulation via depletion of autoreactive lymphocytes followed by repopulation of T and B lymphocytes potentially leading to a rebalancing of the immune system).

Multiple sclerosis is characterised by demyelinated plaques in the brain and spinal cord combined with inflammatory infiltrates consisting of lymphocytes (T cells and B cells) and activated macrophages/microglia; axonal loss and gliosis with astrocyte proliferation and glial fibre production are also noted. The clinical course of MS typically manifests as initial episodes of transient neurological compromise (relapses, clinical exacerbations or attacks) with variable recovery (remissions), eventually leading to cumulative deficits that may increase acutely with each new relapse episode (RRMS). It is estimated that as many as 80% of all MS patients present with RRMS.

Over time, approximately 70% of patients with relapsing forms of MS develop SPMS, characterised by deterioration that steadily worsens with or without superimposed relapses.

Subclinical disease activities detected by MRI, where new inflammatory lesions develop in the CNS without affecting eloquent areas and thus remain clinically silent, comprise the majority of inflammatory events in MS with approximately only 1 in 5 actually leading to clinical symptoms. Early in the disease course inflammation is the most prominent factor behind the pathogenesis and clinical manifestations of RRMS. The pronounced T- and B-cell inflammatory infiltrates in the brains of acute and relapsing MS patients correlate with the activity of demyelinating lesions with a highly significant association with axonal injury. Further, acute axonal damage is most extensive early in MS and correlates with the

degree of inflammation and cortical neuronal loss is directly associated with inflammatory demyelination in patients with early stage MS.

Guidance

A pre-submission meeting between the sponsor and TGA staff to discuss the application was held on 12 June 2012.

Contents of the clinical dossier

The submission contained the following clinical information:

- A clinical pharmacology study: CARE-MS semen substudy analysis of sperm count, motility, morphology, agglutination, and antisperm antibodies in a subgroup of male patients participating in Study CAMMS323 or CAMMS324
- A population PK/PD report using pooled data from clinical Studies CAMMS 223, 323 and 324
- Efficacy/safety studies
 - Study 223 [CAMMS223]: A 3 year, Phase II, randomised, open-label, three-arm study comparing low- and high-dose alemtuzumab and high-dose SC interferon beta-1a (Rebif) in patients with early, active RRMS.
 - Study 323 [CAMMS323 (CARE-MS I)]: A 2 year, Phase III randomised, rater-blinded study comparing 2 annual cycles of IV alemtuzumab to 3 times weekly SC interferon beta-1a (Rebif) in treatment-naïve patients with RRMS.
 - Study 324 [CAMMS324 (CARE-MS II)]: A 2 year, Phase III randomised, rater- and dose-blinded study comparing 2 annual cycles of IV low- and high-dose alemtuzumab to 3 times weekly SC interferon beta-1a (Rebif) in patients with RRMS who have relapsed on therapy.
- Sponsor's clinical overview, summary of clinical efficacy and summary of clinical safety, and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The studies were carried out in accordance with Good Clinical Practice.

Pharmacokinetics

Studies providing pharmacokinetic data

The submission included only a population PK/PD report using pooled data from clinical efficacy Studies CAMMS 223, 323 and 324. The primary objectives for the population PK analysis in patients with MS were:

- To develop a population PK model for alemtuzumab
- To identify and characterise patient factors that influence variability in the PKs of alemtuzumab
- To estimate the magnitude of unexplained variability in alemtuzumab PKs

- To evaluate the performance of the PK model developed for alemtuzumab.

The objectives for the exploratory graphical PK/PD analyses were:

- To conduct graphical evaluation of concentration or dose response relationships for alemtuzumab using selected PD measures of activity (for example, blood cell counts of CD8⁺, CD4⁺, CD16⁺ and CD56⁺ lymphocytes).

The objectives for the population PK/PD analyses were:

- To develop a population PK/PD model to describe the concentration effect of alemtuzumab for three selected PD markers (blood cell counts of CD3⁺ lymphocytes, CD19⁺ lymphocytes and total lymphocytes)
- To estimate the magnitude of unexplained variability in alemtuzumab PDs
- To evaluate the performance of the PD model developed for alemtuzumab.

In the studies providing data (223, 323 and 324), alemtuzumab was administered at doses of 12 or 24 mg/day IV given as multiple cycles (3-5 day annual cycles) for up to 3 years.

Details and discussion of the PK findings are provided in the Delegates' overview (see *Overall conclusion and risk/benefit assessment*, below).

Pharmacodynamics

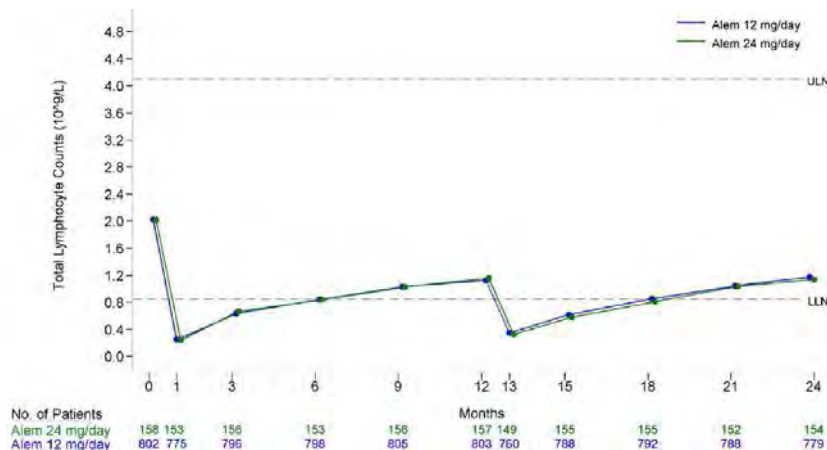
Studies providing pharmacodynamic data

The submission included only a population PK/PD report using pooled data from clinical efficacy Studies CAMMS 223, 323 and 324 and the CARE-MS semen substudy analysis of sperm count, motility, morphology, agglutination, and antisperm antibodies in a subgroup of male patients participating in CAMMS323 or CAMMS324.

Evaluator's overall conclusions on pharmacodynamics

Figure 2 shows total lymphocyte counts over time in patients treated with alemtuzumab 12 and 24 mg/day. The mode of action of alemtuzumab relates to lymphocyte depletion. The higher dose did not result in an observed lower total lymphocyte count when compared with the 12 mg/day dose.

Figure 2. Mean (\pm Standard Error) Total Lymphocyte Counts over Time (Studies CAMMS 323 and 324)



Details and discussion of the PD findings are provided in the Delegates' overview (see *Overall conclusion and risk/benefit assessment*, below).

Dosage selection for the pivotal studies

The selection of the alemtuzumab dose level and administration timing was based on safety and efficacy data from the CAMMS223 Phase II study's Year 2 interim analysis¹⁰ and previously conducted pilot studies with alemtuzumab in RRMS.

- **Study223:**

The 2 alemtuzumab dose levels (12 mg/day and 24 mg/day) used in the initial 3 year treatment period of this study were selected to identify dose-dependent relationships in terms of efficacy or safety variables. Pilot studies of alemtuzumab treatment for MS used dosages in the same range (for example, Moreau *et al*, 1996¹¹, Coles *et al*, 2006¹²). In pilot studies with RRMS patients, a dosage of 20 mg/day for 5 days appeared efficacious but with associated toxicities. The 2 alemtuzumab dose levels selected for study CAMMS223 were, respectively, higher or lower than the pilot study regimen. The alemtuzumab retreatment dose was calculated as 60% of the initial dose, that is, a 3-day cycle instead of 5 days, to account for the reduction in lymphocyte levels at Month 12 and 24 compared with baseline. These regimens were selected following discussions with clinical experts and regulatory authorities.

For ease of prescription and administration, a fixed dose for all patients was selected regardless of the patient's body weight, as had been the practice in treating MS patients with alemtuzumab in prior investigator sponsored studies. The initial administration period of 5 consecutive days to deliver the desired total cumulative dose was specified to reduce the amount of alemtuzumab administered in a single day or by a single infusion to minimise infusion reactions (the "first dose" phenomenon) that were reported in pilot studies (Moreau, 1996¹³) and other potential issues with tolerability.

In addition, the alemtuzumab retreatment dose of 36 mg (12 mg/day over 3 consecutive days) in the retreatment period was selected based on interim safety and efficacy data from this study suggesting that the 12 mg/day regimen was comparably safe and effective as the higher dose.

Efficacy

Studies providing efficacy data

Efficacy studies submitted for this application are summarised in Table 3.

¹⁰ Also used for re-treatment period in Study 223.

¹¹ Moreau T *et al*. CAMPATH-IH in multiple sclerosis. *Mult Scler* 1996;1(6):357-65.

¹² Coles AJ *et al*. The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. *J Neurol*. 2006;253(1):98-108.

¹³ Moreau T, Coles A, Wing M, Isaacs J, Hale G, Waldmann H, et al. Transient increase in symptoms associated with cytokine release in patients with multiple sclerosis. *Brain* 1996;119 (Pt 1):225-37.

Table 3. Summary of efficacy studies

Protocol Number	First / Last Patient Randomized	Study Design, Control Type, and Key Objectives	Study & Control Drugs	Number of Patients Entered/ Completed by Arm	Duration	Gender ^a Median Age (Range)	Diagnosis	Co-Primary Efficacy Endpoints
Number of Study Centers (Locations)	Enrollment status # Treated		Dose, Route & Regimen					
CAMMS223 49 (US, EU, Croatia, Russia)	04 Dec 2002/ 21 Jul 2004 Completed 323 treated	Randomized, rater-blinded, 3-arm, active-controlled study to evaluate efficacy and safety	IFNB-1a SC 44 µg tiw Alem IV 12 mg/day in annual cycles ^b Alem IV 24 mg/day in annual cycles ^b	111/66 113/92 110/92	3 years ^c	119 M, 214 F 31 years (18.0–60.0 years)	RRMS	Time to 6-month SAD Relapse rate
CAMMS323 97 (US, EU, Argentina, Brazil, Mexico, Canada, Australia, Serbia, Croatia, Russia, Ukraine)	07 Sep 2007/ 17 Apr 2009 Completed 563 treated	Randomized, rater-blinded, 2-arm, active-controlled study to evaluate efficacy and safety	IFNB-1a SC 44 µg tiw Alem IV 12 mg/day, for 2 cycles ^b	195/173 386/367	2 years	198 M, 365 F 33 years (18.0–53.0 years)	RRMS and MRI scan showing MS lesions	Time to 6-month SAD Relapse rate
CAMMS324 181 (US, EU, Argentina, Brazil, Mexico, Canada, Australia, Serbia, Croatia, Russia,	20 Oct 2007/ 18 Sep 2009 Completed 798 treated	Randomized, rater- and dose-blinded, 3-arm, active-controlled study to evaluate efficacy and safety	IFNB-1a SC 44 µg tiw Alem IV 12 mg/day for 2 cycles Alem IV 24 mg/day for 2 cycles ^{b,d}	231/175 436/416 173/164	2 years	266 M, 532 F 35.1 years (18.0–55.0 years)	RRMS and MRI scan showing MS lesions exceeding a specified minimum	Time to 6-month SAD Relapse rate

Table 3 continued. Summary of efficacy studies

Protocol Number	First / Last Patient Randomized	Study Design, Control Type, and Key Objectives	Study & Control Drugs	Number of Patients Entered/ Completed by Arm	Duration	Gender ^a	Diagnosis	Co-Primary Efficacy Endpoints
Number of Study Centers (Locations)	Enrollment status # Treated		Dose, Route & Regimen			Median Age (Range)		
Ukraine, Israel)								
CAMMS03409	05 Aug 2009/ (first patient enrolled)/ NA Ongoing 496 ^e	Open-label, rater-blinded, uncontrolled study to evaluate long-term safety and efficacy	<u>Patients previously treated with IFNB-1a:</u> Alem IV 12 mg/day for 2 cycles ^f <u>Patients previously treated with alem:</u> cycles of alem IV 12 mg/day as needed (i.e., upon documented evidence of resumed disease activity)	1320 total entered/ 0 completed Patients with Data as of 31Dec2011 ^{e, f} Previous SC IFNB-1a: 289; Previous Alem 12 mg/day: 735	3 years	459 M, 861 F 36 years (20–61 years)	Eligible patients with MS from CAMMS223, CAMMS323, and CAMMS324	Exploratory evaluation of relapse, disability and MRI endpoints

Number of study centres that randomised patients. **a** Demographic characteristics are for all patients in the full analysis set. In CAMMS223, 1 randomised patient was excluded from the full analysis set because after randomisation the patient was found to have cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy rather than MS. **b** Alemtuzumab cycles = At Month 0 alemtuzumab was administered IV over 5 consecutive days at a dose of 12 mg/day (total dose of 60 mg) or 24 mg/day (total dose 120 mg). At Month 12, alemtuzumab was administered IV over 3 consecutive days at a dose of 12 mg/day (total dose 36 mg) or 24 mg/day (total dose of 72 mg). In CAMMS223 only, an optional 3-day cycle could be administered at Month 24 and with Amendment 10 additional cycles were allowed beyond Cycle 3. **c** The primary efficacy analyses in CAMMS223 were based on the originally-planned 3-year follow-up. Follow-up in the study was extended by 2 or more years to support long-term monitoring of safety and efficacy outcomes. **d** The alemtuzumab 24 mg/day arm was closed to enrolment following protocol amendment 2 in CAMMS324, details are provided in Section 2.1. **e** CAMMS03409 patient information as of 31 Dec 2011. **f** In CAMMS03409, patients previously treated with interferon beta-1a received alemtuzumab IV 12 mg/day for 5 consecutive days (60 mg total dose) at study entry and for 3 consecutive days (36 mg total dose) 12 months later and for any subsequent as-needed treatment. Patients previously treated with alemtuzumab received alemtuzumab IV 12 mg/day for 3 consecutive days (36 mg total dose) as needed (i.e., only in the setting of resumed disease activity per protocol specified criteria). Alem = alemtuzumab; EU = European Union; F = female; IV = intravenous; M = male; MRI = magnetic resonance imaging; MS = multiple sclerosis; NA = not applicable; SC = subcutaneous; tiw = 3 times weekly; US = United States.

Evaluator's conclusions on clinical efficacy

There were 2 similar pivotal studies (323 and 324) each with 2 primary variables and 4 secondary variables. There were in addition 20 efficacy tertiary endpoints.

The study was to be considered to have met its primary efficacy objective if the p-values corresponding to the analysis of the primary endpoints satisfied at least 1 of the following conditions: (1) The maximum of the two p-values was ≤ 0.05 , (2) the minimum of the two p-values was ≤ 0.025 . Therefore, the study would be considered to have met its efficacy objective if a statistically significant treatment effect of alemtuzumab over SC interferon beta-1a was demonstrated in either or both of the co-primary efficacy endpoints: time to sustained accumulation of disability (SAD¹⁴) and relapse rate.¹⁵

Hypothesis testing for the secondary efficacy analyses was to be performed using a closed testing procedure with the following rank order:

2. The proportion of patients who are relapse free at Year 2.
3. Change from baseline in Expanded Disability Status Scale (EDSS¹⁶).
4. Percent change from baseline in MRI-T2 hyper-intense lesion volume at Year 2.¹⁷
5. Acquisition of disability as measured by the Multiple Sclerosis Functional Composite (MSFC¹⁸).

The above is the order that the analysis was changed to in the final statistical analysis plan (SAP) with acquisition of disability moved to last in the order.

To slow or reverse the accumulation of physical disability

Primary variable: 'Time to Sustained Accumulation of Disability' showed no statistical difference between treatments in Study 323 and while it did in Study 324 the 95% confidence intervals (CIs) for the Kaplan Meier (KM) estimate of event overlapped (15.95, 27.68 versus 9.89, 16.27).

Secondary variables:

In all studies EDSS change from baseline was a secondary endpoint. For change from baseline in EDSS score, with treatment naïve patients in Study 323 (mean baseline EDSS 2.0), at Year 2, the difference between the alemtuzumab and interferon beta-1a groups was not statistically significant (with the step down procedure no further secondary variables were analysed for Study 323).

¹⁴ Sustained accumulation of disability (SAD) was based on a patient's score on the Expanded Disability Status Scale (EDSS), a neurological examination-based scoring system that quantifies the level of disability a patient exhibits that is attributable to MS.

¹⁵ A relapse was any new neurological symptom or worsening of previous neurological symptoms with an objective change on neurological examination.

¹⁶ The EDSS used the standardised "Neurostatus" training and scoring system developed by Ludwig Kappos. The scale as defined by Kurtzke (Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;33(11):1444-52) ranged from 0.0 (normal neurological examination) to 10.0 (death due to MS). In addition, each score was based on specific functional systems grade(s) from the Neurostatus scheme (each of which ranged from 0 to 5 or 6; 0 was normal): Pyramidal Functions; Cerebellar Functions; Brain Stem Functions; Sensory Functions; Bowel and Bladder Functions; Visual or Optic Functions; Cerebral or Mental Functions. "Other" is also measured but does not contribute to the score.

¹⁷ The total volume of T2-hyperintense lesions reflect the inflammatory demyelination and oedema of active MS lesions, as well as the sclerotic gliosis of end-stage MS plaques, and is indicative of cumulative disease activity.

¹⁸ The MSFC is a composite (3-part) measure of disability in MS patients with component tests of ambulation, arm coordination and dexterity, and cognitive function. Increases from baseline in MSFC represent improvement.

In Study 223 (also treatment naïve patients, mean baseline EDSS 2.0, but a study that had an interrupted and different from the proposed treatment history): at Year 2 there was a statistically significant difference in change from baseline in EDSS between the groups, favouring alemtuzumab, which also showed a statistically significant difference in improvement from baseline.

In Study 324 (previously treated patients who relapsed, mean baseline EDSS 2.7), alemtuzumab-treated patients had significantly lower mean changes in EDSS scores after treatment compared with interferon beta-1a treated patients ($p < 0.0001$).

The *Integrated Summary of Effectiveness* (Studies 323, 324 and 223) showed there was no significant difference between treatment groups with respect to change from baseline in EDSS for the subgroup of patients with baseline EDSS < 2 . The report included tabulation of subgroup analyses but not of the total combined effect on change from baseline in EDSS either in the combined analysis or the combined primary Studies 323 and 324.

For percent change in T2-hyperintense lesion volume from baseline to Year 2 there was no significant difference between alemtuzumab and interferon beta-1a ($p = 0.1371$) in Study 324 (with the step down procedure no further secondary variables were analysed).

While the changes from baseline in EDSS were statistically significant for alemtuzumab, in the absence of a placebo group the clinical significance is unclear.

Subgroup analyses across studies of the endpoints 'change from baseline in EDSS score at 2 years' and 'time to SAD' up to 2 year show no statistical difference from interferon beta-1a in those patients with less than the median EDSS score of 2 (less severe disability).

To reduce the frequency of clinical relapses

Primary Variable: Relapse rate at 2 years was significantly reduced in alemtuzumab patients compared with those on interferon beta-1a in both studies.

Secondary Variables:

In both studies (323 and 324) it was claimed there was a significant increase in the proportion of alemtuzumab treated patients who were relapse free through 2 years compared with patients treated with interferon beta-1a.

Study 223 was a Phase II study with considerable changes to primary objective and primary and efficacy endpoints after the study commenced. The study was interrupted for 2 years by safety concerns. The numbers of patients dwindled and the numbers of courses in many patients exceeded the proposed alemtuzumab regime as did the dose for some. Thus the study has limited relevance of its results to efficacy in the proposed usage.

Safety

Studies providing evaluable safety data

The following studies (summarised details in Table 4) provided evaluable safety data:

- CAMMS223
- CAMMS323 (CARE-MS I)
- CAMMS324 (CARE-MS II)
- CAMMS03409

Table 4. Safety Analysis populations

Study	All Active-Controll ed Studies, 2-Year Follow up (Pool A) (N=1684)	All Active-Controll ed Studies, 3-Year Follow up (Pool E) (N=1684)	Phase 3 Studies, 2-Year Follow up (Pool B) (N=136)	Treatme nt -Naïve Patients, 2-Year Follow up (Pool D) (N=886)	Treatme nt -Naïve Patients, 3-Year Follow up (Pool F) (N=886)	Alemtuzum ab All Treated Patients, All Available Follow up (Pool C) (N=1485)
CAMMS223	X	X		X		X
CAMMS323	X	X	X	X	X	X
CAMMS324	X	X	X			X
CAMMS034 09						X

Patient exposure

The extent of exposure to alemtuzumab and duration of patient follow-up is summarised in Tables 5 and 6, respectively.

In Study 323, 2 patients at a single study site inadvertently received an infusion of alemtuzumab > 12 mg (48 mg for one patient and 60 mg for the other patient) and both patients subsequently experienced serious infusion associated reactions.

Table 5. Exposure to alemtuzumab in All Alemtuzumab-Treated Patients (All Available Follow Up, Pool C)

	Alemtuzumab 12 mg/day (N=1194)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1463)
Total Dose Taken (mg), n (%)			
<60	5 (0.4)	1 (0.4)	6 (0.4)
60-<96	237 (19.5)	0	237 (16.0)
96-<120	779 (64.1)	0	779 (52.5)
120-<192	194 (16.0)	20 (7.4)	214 (14.4)
≥192	1 (0.1)	248 (92.2)	249 (16.8)
n	1216	269	1485
Mean (SD)	95.8 (22.78)	203.4 (33.69)	115.3 (48.45)
Median	96.0	192.0	96.0
Total Number of Cycles Received, n (%)			
1 cycle	214 (17.6)	9 (3.3)	223 (15.0)
2 cycles	808 (66.4)	179 (66.5)	987 (66.5)
3 cycles	172 (14.1)	68 (25.3)	240 (16.2)
4 cycles	21 (1.7)	10 (3.7)	31 (2.1)
5 cycles	1 (0.1)	3 (1.1)	4 (0.3)

Percentages in the rows under each cycle are based on the number of alemtuzumab-treated patients who received that specific cycle in the corresponding treatment group.

Table 6. Duration of follow Up in All Alemtuzumab-Treated Patients (All Available Follow Up, Pool C)

	Alemtuzumab Pooled					
	Total Number of Alemtuzumab Treatment Cycles Received					
	Any	1	2	3	4	5
Patients treated	1485	223	987	240	31	4
Months of follow-up						
Mean (SD)	34.4 (19.65)	11.1 (10.82)	35.1 (13.98)	48.3 (22.06)	67.7 (26.60)	94.0 (5.94)
Median	33.1	8.8	33.2	37.9	72.1	93.7
Min, Max	0.8, 106.8	0.8, 81.2	12.1, 96.8	26.4, 106.8	36.5, 105.0	87.6, 101.0
Q1, Q3	24.6, 39.2	5.8, 10.8	28.7, 38.5	33.5, 54.5	40.9, 94.9	89.2, 98.7
Total Person-years	4262.14	206.08	2883.84	965.93	174.96	31.33

Percentages are based on the total number of alemtuzumab-treated patients in the corresponding treatment group and column. Follow-up duration computed from start of first alemtuzumab treatment cycle to completion/discontinuation or data cut-off. Q = quartile.

Summary of treatment-emergent adverse events

Table 7 shows a summary of treatment-emergent adverse events (AEs) by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC). See Attachment 2 for details of treatment-related and other AEs.

Table 7. Incidence of Treatment-Emergent Adverse Events by MedDRA SOC (Pool A)

System Organ Class	SC IFNB-1a (N=496) n (%)	Alemtuzumab 12 mg/day (N=919) n (%)	Alemtuzumab 24 mg/day (N=269) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Any Event	469 (94.6)	896 (97.5)	266 (98.9)	1162 (97.8)
Skin and subcutaneous tissue disorders	126 (25.4)	714 (77.7)	251 (93.3)	965 (81.2)
Nervous system disorders	342 (69.0)	668 (72.7)	221 (82.2)	889 (74.8)
Infections and infestations	262 (52.8)	650 (70.7)	198 (73.6)	848 (71.4)
General disorders and administration site conditions	317 (63.9)	598 (65.1)	200 (74.3)	798 (67.2)
Gastrointestinal disorders	163 (32.9)	450 (49.0)	176 (65.4)	626 (52.7)
Musculoskeletal and connective tissue disorders	194 (39.1)	432 (47.0)	147 (54.6)	579 (48.7)
Respiratory, thoracic and mediastinal disorders	91 (18.3)	351 (38.2)	127 (47.2)	478 (40.2)
Psychiatric disorders	152 (30.6)	281 (30.6)	107 (39.8)	388 (32.7)
Investigations	132 (26.6)	259 (28.2)	90 (33.5)	349 (29.4)
Injury, poisoning and procedural complications	96 (19.4)	238 (25.9)	93 (34.6)	331 (27.9)
Vascular disorders	50 (10.1)	186 (20.2)	52 (19.3)	238 (20.0)
Eye disorders	73 (14.7)	153 (16.6)	52 (19.3)	205 (17.3)
Renal and urinary disorders	65 (13.1)	149 (16.2)	48 (17.8)	197 (16.6)
Cardiac disorders	22 (4.4)	148 (16.1)	41 (15.2)	189 (15.9)
Reproductive system and breast disorders	45 (9.1)	144 (15.7)	45 (16.7)	189 (15.9)
Blood and lymphatic system disorders	68 (13.7)	132 (14.4)	40 (14.9)	172 (14.5)
Endocrine disorders	13 (2.6)	122 (13.3)	26 (9.7)	148 (12.5)
Ear and labyrinth disorders	30 (6.0)	86 (9.4)	32 (11.9)	118 (9.9)
Metabolism and nutrition disorders	16 (3.2)	61 (6.6)	24 (8.9)	85 (7.2)
Immune system disorders	16 (3.2)	53 (5.8)	15 (5.6)	68 (5.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (2.4)	36 (3.9)	9 (3.3)	45 (3.8)
Hepatobiliary disorders	16 (3.2)	17 (1.8)	3 (1.1)	20 (1.7)
Congenital, familial and genetic disorders	6 (1.2)	3 (0.3)	0 (0.0)	3 (0.3)
Social circumstances	1 (0.2)	3 (0.3)	0 (0.0)	3 (0.3)
Surgical and medical procedures	1 (0.2)	3 (0.3)	2 (0.7)	5 (0.4)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	1 (0.1)	1 (0.4)	2 (0.2)

Percentages are based on the number of treated patients in the corresponding treatment group. A patient is counted only once within each SOC. SOCs are presented by decreasing incidence in the alemtuzumab 12 mg/day group.

Evaluator's overall summary and conclusions on clinical safety

The incidence of treatment related AEs was much higher (by 29%) with alemtuzumab than with interferon beta-1a. This was reflected in most SOCs except 'Investigations', where they were higher (by 14%) for interferon beta-1a (reflecting primarily a much higher incidence of elevated liver enzymes), and 'General Disorders and Administration Site Conditions', which showed an overall similar incidence (but with considerable differences in individual preferred terms and number of injections/infusions the patient was exposed to).

There were however considerably more (85%) study discontinuations (defined as permanent discontinuation from study participation) due to AEs in those patients on interferon beta-1a. Much of the difference was due to 'Injection/Infusion Reactions' and 'Elevated Liver Function Tests'.

There were no deaths related to interferon beta-1a, but for alemtuzumab there were 3 deaths that were considered treatment related. The death from idiopathic thrombocytopenic purpura was of concern.

Overall 5 (0.4%) patients all in the 12 mg/day alemtuzumab dose group had nephropathies, 4 of which were considered treatment related.

While mean platelet levels remained normal and post-baseline shifts to below normal were reported in a larger percentage of interferon beta-1a patients, during all available follow up in all alemtuzumab patients, very severe (Grade 4) low platelet counts were reported for 3 patients during Year 1, 8 patients during Year 2, 7 patients during Year 3, and 1 patient during Year 4. All patients were confirmed Immune Thrombocytopenic Purpura (ITP¹⁹) cases, with the exception of an isolated value in 1 patient which was within normal limits on repeat measurement 3 days later.

The mean neutrophil counts in all treatment groups in Pool A decreased at Month 1, but the mean neutrophil count for alemtuzumab patients had increased by Month 2, while that for interferon beta-1a remained low. Shifts from baseline Common Terminology Criteria (CTC) Grade 0 to Grade 3 and 4²⁰ were greater for alemtuzumab 24 mg than 12 mg suggesting a dose related effect.

While mean monocyte counts remained within the normal range without notable fluctuations over time in both the alemtuzumab and the interferon beta-1a dose groups, those for alemtuzumab were consistently lower.

The incidence in patients on interferon beta-1a of 1.6% for hypothyroidism and 0.8% for hyperthyroidism was not unexpected. However the corresponding figures for alemtuzumab 12 mg/day (3.5% and 4.6%) suggested a higher incidence than expected in MS patients by year. This was supported by the overall incidence in Pool C of 6.7% for hypothyroidism and 7.1% for hyperthyroidism. Of the 5 patients on alemtuzumab who had thyroid cancer (0.33%), 2 had a history of thyroid neoplasm and 3 were felt to be related to treatment, while there was no thyroid cancer among 496 patients on interferon beta-1a.

¹⁹ ITP was defined as platelet count < 100 x 10⁹/L in the absence of other causes or disorders that may be associated with thrombocytopenia.

²⁰ For AEs not included in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), investigators assessed the intensity of the AE using the following categories and associated guidelines: Grade 1: Mild disease, possibly asymptomatic. No treatment necessary; Grade 2: Moderate disease. Symptomatic therapy or low-risk disease-specific treatment (e.g., a short course of oral antibiotics); Grade 3: Severe disease. Disease-modifying treatment with higher risk (e.g., IV antibiotics, insulin-requiring diabetes); Grade 4: Very severe disease. Potentially life-threatening or disabling. High-risk medical interventions; Grade 5: Fatal outcome.

A medical review of all ITP cases found that no consistent cases in interferon beta-1a treated patients, while in alemtuzumab treated patients 18 cases were confirmed as ITP, but 2 of these had a confirmed cause, leaving 16 cases with no confirmed alternative aetiology for ITP and likely related to alemtuzumab treatment.

First round benefit-risk assessment

First round assessment of benefits

The benefits of alemtuzumab in the proposed usage are:

- Relapse rate at 2 years was significantly reduced in alemtuzumab patients compared with those on interferon beta-1a in both pivotal studies, both in patients with RRMS who were treatment-naïve and in patients with active RRMS who relapsed during prior treatment.
- A lower incidence of elevated liver enzymes compared with interferon beta-1a.
- A lower incidence of discontinuations due to AEs compared with interferon beta-1a (the difference was mostly from elevated liver enzymes and 'Injection/Infusion Reactions').
- A less intense treatment programme: two annual cycles (5 consecutive days and 3 consecutive days) of IV alemtuzumab versus 3 times weekly SC interferon beta-1a.

First round assessment of risks

The risks of alemtuzumab in the proposed usage are:

- 3 deaths that were considered treatment related with alemtuzumab.
- An incidence of ITP (1.3% medically confirmed) with one death.
- An incidence of treatment related AEs much higher than with interferon beta-1a.
- A similar incidence of 'Infusion Associated Reactions' compared with Interferon beta-1a despite the latter requiring more injections/infusions.
- An increased incidence of hypothyroidism and hyperthyroidism (overall incidence in Pool C of 6.7% for hypothyroidism and 7.1% for hyperthyroidism). Of the 5 patients on alemtuzumab who had thyroid cancer (0.33%), 2 had a history of thyroid neoplasm and 3 were felt to be related to treatment while there was no thyroid cancer among 496 patients on interferon beta-1a.
- An incidence of nephropathies, 4 of which were considered treatment related.

First round assessment of benefit-risk balance

The benefit-risk balance of alemtuzumab, given the proposed usage, is unfavourable.

While alemtuzumab has been shown to have benefit in treatment naïve patients (Study 323) by reducing relapse rate it does so with an increased risk of treatment related deaths and AEs.

The evaluator therefore recommended use for the more restricted population of:

in whom treatment with Interferon beta or glatiramer is not possible or contraindicated

The qualifier "not possible" allows for patients in whom there is the advantage of a less intense treatment programme.

The qualifier “contraindicated” allows an alternative to interferon beta or glatiramer for such patients. Study 324 in patients with active RRMS who relapsed during prior treatment with interferon beta or glatiramer acetate in whom alemtuzumab showed benefit by reducing relapse rate (54.5% had interferon beta-1a previously, 36.2% had interferon beta-1b and 34.3% had glatiramer acetate).

List of questions

None.

Recommendation regarding authorisation

The evaluator recommended that the proposed extension of indications, as proposed by the sponsor, not be approved. The evaluator recommended that the following extension of indications be approved (evaluator’s modification from that proposed by the sponsor is in bold text):

*Alemtuzumab (Lemtrada/Remniq) is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) **in whom treatment with interferon beta-1a or glatiramer is not possible or contraindicated** to reduce the frequency of clinical relapses*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version: 1.0, dated June 2012, with an Australian Specific Annex (ASA), Version: 1.0, dated September 2012] which was reviewed by the TGA’s Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE and the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows:

Table 8. Summary of the Ongoing Safety Concerns

Important Identified Risks	<ul style="list-style-type: none"> • Infusion-associated reactions • Autoimmune disorders: <ul style="list-style-type: none"> ○ Thyroid disorders ○ Immune thrombocytopenic purpura (ITP) ○ Nephropathies including anti-GBM disease • Serious infections
Important Potential Risks	<ul style="list-style-type: none"> • Other autoimmune disorders including cytopenias (autoimmune haemolytic anaemia, pancytopenia) • Malignancy
Important Missing Information	<ul style="list-style-type: none"> • Pregnancy, lactation and reproductive toxicity • Impact on response to vaccination and value of pre-treatment vaccination • Paediatric use • Geriatric population (age ≥ 65 years) • Renal and hepatic impairment • Use in HIV • Use in HCV/HBV

GBM = Glomerular basement membrane; ITP = Immune thrombocytopenic purpura

Pursuant to the evaluation of the nonclinical and clinical aspects of the SS, it was considered that the specified ongoing safety concerns are acceptable.

Pharmacovigilance plan

The ASA states that a comprehensive pharmacovigilance system is in place in the Australian Sanofi affiliate to ensure collection, verification, evaluation, and reporting of AE reports in accordance with the *Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines* (Version 1.1, dated 15 January 2013) in order to monitor all the specified ongoing safety concerns.

Furthermore, an additional pharmacovigilance activity in the form of an ongoing extension study (CAMMS03409): *Open-label, rater-blinded extension study for patients who participated in CAMMS223, CAMMS323, or CAMMS324* is being conducted to examine:

- the long-term safety and efficacy of alemtuzumab as given in the previous studies;
- the safety and efficacy of as needed re-treatment in patients previously treated with alemtuzumab;
- the safety and efficacy of 2 fixed annual cycles of alemtuzumab treatment 12 mg/day (followed by optional as needed re-treatment) in patients previously treated with SC interferon beta-1a.

In addition the sponsor plans to conduct an international, non-interventional long term post-authorisation safety study to assess long term safety in routine clinical practice and determine the incidence of identified AEs of special interest (AESI). The specific AESIs to be monitored are: serious infection, malignancy, and auto-immune mediated conditions including ITP, cytopenias, thyroid disorders, and nephropathies including anti-glomerular basement membrane (GBM) disease.

For the important missing information 'Pregnancy, lactation and reproductive toxicity', a Pregnancy Registry prospectively designed to collect data on pregnancy outcomes, including potential effects on infants in the event of exposure to alemtuzumab during pregnancy, is planned.

Risk minimisation activities

The sponsor proposes to apply routine risk minimisation activities for all the specified ongoing safety concerns, except for the important potential risk: 'Malignancy' for which no risk minimisation activities (routine and additional) are included. Furthermore additional risk minimisation activities are proposed for all the specified ongoing safety concerns, except for the important missing information: 'Paediatric use', 'Geriatric population (age \geq 65 years)', 'Renal and hepatic impairment', 'Use in human immunodeficiency virus (HIV)' and 'Use in Hepatitis C virus/Hepatitis B virus (HCV/HBV) infection'.

Routine risk minimisation activities will comprise labelling, including contraindications, special warning and precaution statements and/or notification of undesirable effects for all the specified ongoing safety concerns, except for the important potential risk: 'Malignancy' for which no risk minimisation activities (routine and additional) are included.

Additional risk minimisation activities are proposed for all the specified ongoing safety concerns, except for the important missing information: 'Paediatric use', 'Geriatric population (age \geq 65 years)', 'Renal and hepatic impairment', 'Use in HIV' and 'Use in HCV/HBV'. The ASA provides a summary of the planned communication tools and their objectives.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified; and the draft product information and consumer medicine information documents should not be revised until the Delegate's overview has been received:

1. Safety considerations may be raised by the nonclinical and clinical evaluators through the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.
2. The ASA states: "A summary of the proposed Australian RMP is presented in Table 1. The plan includes all of the routine and additional pharmacovigilance and risk minimization activities described in the EU RMP." The second statement is not entirely consistent as Table 1 of the ASA does not include the planned efficacy, safety and tolerability study proposed for patients aged \geq 10 years to $<$ 18 years (Paediatric Study CAMMS11910) for the important missing information: 'Paediatric use' found in the EU-RMP. A brief study synopsis, which does not lend itself to assessment, has been provided and the planned date for submission of final data is September 2019. The sponsor's correspondence of 7 May 2013 states that a protocol for this study will be available in December 2013. Consequently the sponsor should provide compelling justification as to why this paediatric study has not been included in Table 1 of the ASA. Alternatively, if the sponsor decides to include this study within the PP for Australia, the relevant sections of the ASA will need to be updated accordingly and the anticipated protocol should be submitted to the TGA for review when it becomes available.
3. In addition Table 1 of the ASA should be corrected as follows:

- a. The proposed pharmacovigilance activities (routine and additional) for the important identified risk: 'Nephropathies including anti-GBM disease' appears to have been inadvertently omitted.
 - b. The proposed additional pharmacovigilance activity: 'Non-interventional long-term safety study' for the important potential risk: 'Malignancy' appears to have been inadvertently omitted.
4. The sponsor should provide milestones and timelines for the submission of final data relating to the ongoing extension study (CAMMS03409). Nevertheless this ongoing study is not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols have not been reviewed. Nevertheless an update on the progress/results/analysis of this study, to be outlined in the ASA, will be expected in future periodic safety update reports (PSURs).
 5. The sponsor's justification and conclusion that routine risk minimisation activities are required for all the specified ongoing safety concerns, except for the important potential risk: 'Malignancy' for which no risk minimisation activities (routine and additional) are included appears reasonable and therefore acceptable. There is also no objection to additional risk minimisation activities being proposed for all the specified ongoing safety concerns, except for the important missing information: 'Paediatric use', 'Geriatric population (age \geq 65 years)', 'Renal and hepatic impairment', 'Use in HIV' and 'Use in HCV/HBV'.
 6. The sponsor's proposed application of routine and additional risk minimisation activities would appear to be reasonable and therefore acceptable. However, the sponsor should provide an assurance that if for any reason the local Australian risk minimisation tools are not aligned with the USA and/or EU risk minimisation tools the TGA will be immediately notified and alternative measures to assess the effectiveness of the Australian additional risk minimisation activities must be proposed and implemented as agreed to by the TGA.
 7. In regard to the proposed routine risk minimisation activities, the draft PI document is considered satisfactory.
 8. In regard to the proposed routine risk minimisation activities, the draft Consumer Medicine Information (CMI) is considered satisfactory.

Matters raised above were resolved to the satisfaction of the OPR prior to a final decision on this application.

VI. Overall conclusion and risk/benefit assessment

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

Introduction

This application proposes an extension of indications for alemtuzumab 10 mg/mL injection concentrated vial (Lemtrada/Remniq) to include the following:

Lemtrada/Remniq is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to slow the accumulation of physical disability and reduce the frequency of clinical relapses.

The recommended dose of Lemtrada/Remniq is 12 mg/day administered by IV infusion for 2 treatment courses.

- Initial treatment course: 12 mg/day for 5 consecutive days (60 mg total dose)
- Second treatment course: 12 mg/day for 3 consecutive days (36 mg total dose) administered 12 months after the initial treatment course.

Recommended concomitant medication: Patients should be premedicated with corticosteroids immediately prior to Lemtrada/Remniq administration for the first 3 days of any treatment course. Oral prophylaxis for herpes infection should be administered to all patients starting on the first day of each treatment course and continuing for a minimum of 1 month following treatment with Lemtrada/Remniq.

Alemtuzumab is currently registered under the tradename MabCampath (alemtuzumab 30 mg/mL) for treatment in patients with B-CLL. This application is to register Lemtrada and additional tradename [Remniq] for a different indication, patient population, dosage strength (10 mg/mL) and dosing regimen of alemtuzumab.

Alemtuzumab is not approved for the treatment of MS in any jurisdiction but submissions have been made in the EU and USA.

Background

Alemtuzumab is a genetically engineered humanised IgG1 kappa monoclonal antibody specific for a 21–28 kD lymphocyte cell surface glycoprotein (CD52). Alemtuzumab causes the lysis of lymphocytes by binding to CD52 antigen, which is expressed on the surface of essentially all B and T lymphocytes (benign and malignant) as well as monocytes, thymocytes and macrophages, sperm and epithelial cells of epididymis and seminal vesicle.

Binding of alemtuzumab initiates complement dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity of B and T lymphocytes leading to a profound reduction in the numbers in the circulation. The role of the immune system in MS is not understood but it has been established that reducing immune-mediated inflammation can reduce the symptoms. Reducing immune-mediated inflammation and hence the symptoms of MS by depleting lymphocytes is the basis of the use of alemtuzumab in this disease.

Alemtuzumab as MabCampath is contraindicated during pregnancy and human IgG is known to cross the placental barrier. It had been concluded that MabCampath is likely to cross the placental barrier as well and thus potentially cause fetal B and T cell lymphocyte depletion. The sponsor is not proposing to contraindicate use of alemtuzumab as Lemtrada/Remniq in pregnancy.

Quality

There are no chemistry objections to approval of this product.

The evaluator noted the general properties of alemtuzumab have not changed since the original submission with the exception of the Lemtrada/Remniq specific statement on mechanism of action in MS: *The mechanism by which alemtuzumab may suppress multiple sclerosis disease activity is not fully elucidated, but may involve immunomodulation through the depletion and repopulation of lymphocytes.*

Nonclinical

There are no nonclinical objections to proposed extension of indications for alemtuzumab.

The nonclinical evaluator noted that the toxicity of alemtuzumab in animals has not been comprehensively investigated but the medicine has been registered for some years with a

much higher approved dosage regimen. No clinically relevant hazards other than immunosuppression were identified in the limited toxicity studies submitted.

The pharmacological activity of alemtuzumab was demonstrated in nonclinical studies. A reduction in lymphocyte numbers and alterations in the peripheral blood phenotypes was observed during repopulation.

In transgenic mice, there was evidence that alemtuzumab caused post-implantation loss when given during late organogenesis. The alterations in lymphocyte numbers and reduced antibody response in the offspring of dams exposed during gestation or lactation may be a cause for concern. The sponsor has proposed pregnancy Category B2, but Category C²¹ was initially recommended on the basis of the nonclinical findings.

Clinical

Pharmacology

Current PK information for alemtuzumab was determined in patients with CLL who received higher doses for up to 12 weeks, compared with the proposed 5 day dose regimen to be repeated after 12 months for an additional 3 days. The PK of alemtuzumab in patients with MS was examined using a population PK analysis of data obtained from 3 clinical efficacy and safety studies (Studies 223, 323 and 324).

Alemtuzumab is a recombinant, humanised protein for which the expected metabolic pathway is proteolysis therefore biotransformation studies were not performed. No drug-drug interaction studies were performed due to the short duration of drug administration and because no direct CYP450-mediated drug-drug interactions were anticipated with alemtuzumab.

The central volume of distribution for alemtuzumab was directly proportional to weight and comparable to extracellular fluid volume (14.1 L (coefficient of variation (CV) 25.9%). Alemtuzumab accumulates during the treatment periods with a mean accumulation ratio of 3.1 on Day 5 of Cycle 1 and 2.1 on Day 3 of Cycle 2. Concentrations of alemtuzumab were low or undetectable within approximately 30 days following each treatment cycle for the 12 mg/day dose and within 90 days for the 24 mg/day dose. Clearance increased with increasing lymphocyte counts, and anti-alemtuzumab antibody positive status resulted in a lower clearance.

The effect of lymphocyte counts on clearance was examined by comparing values reported for patients who were anti-alemtuzumab negative between the two cycles. For a decrease in mean lymphocyte count from 2.01 to 1.09 from Cycle 1 to Cycle 2, the mean clearance decreased from 0.062 L/h to 0.051 L/h, a decrease of < 20%. For the 12 mg/day dose group mean elimination half-life was 13.8 days for the first Cycle and 15.1 days for the second Cycle. For subjects who became anti-alemtuzumab antibody positive the elimination half-life during the second Cycle was 32.1 days.

The effects of alemtuzumab on T and B lymphocyte subsets, NK cells (TBNK panel: CD3⁺, CD4⁺, CD8⁺, CD19⁺, CD16⁺, CD56⁺) and absolute lymphocyte count were assessed from pooled study data. Alemtuzumab depleted circulating T and B cells after each treatment

²¹ Use in Pregnancy Category C is defined as: *Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.*

Revised nonclinical recommendation: The nonclinical evaluator initially considered that the nonclinical data justified a pregnancy Category of **C**. Following the sponsor's response to the nonclinical evaluation report and a re-examination of the submitted data it was considered that Category **B3** was warranted. The sponsor originally proposed and wished to maintain pregnancy Category **B2**, but this was not considered appropriate in view of the new reproductive (embryofetal toxicity) data for alemtuzumab.

cycle with the lowest values typically occurring at the first post-treatment assessment which was after 1 month in the Phase III studies and as early as 2 days after the end of the first treatment cycle in the Phase II study. Lymphocyte depletion occurred to a similar extent with each of the two treatment cycles. The extent of lymphocyte depletion was similar for the 24 mg/day and 12 mg/day groups. Approximately 40% and 80% of patients receiving the 12 mg/day dose had total lymphocyte counts reaching the lower limit of normal (LLN) by 6 and 12 months respectively after each treatment cycle.

Sperm count, motility, morphology, agglutination and antisperm antibodies were examined in a subgroup of 16 men (13 given alemtuzumab and 3 given interferon beta-1a). Samples were collected to 18 months (6 months after the second cycle). None of the subjects given alemtuzumab developed aspermia, azoospermia, or consistently depressed sperm count. There was no evidence of motility disorders or an increase in sperm morphological abnormalities between treatment arms or within a treatment arm over time.

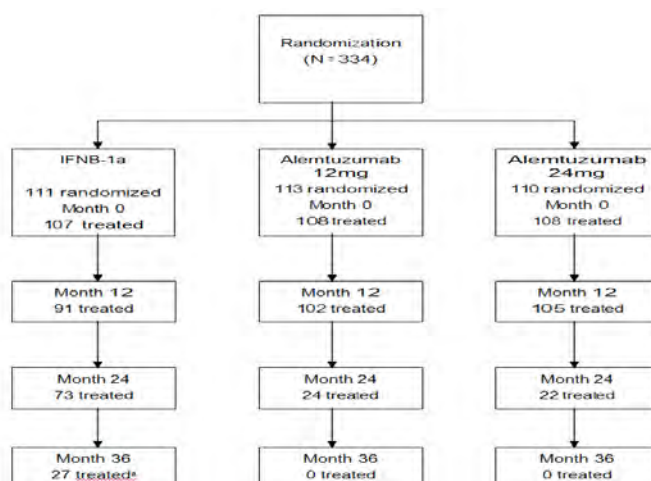
There was no correlation between the development of auto-antibodies and the degree of lymphocyte depletion. For lymphocytes and for each of the major lymphocyte subsets (that is, CD3⁺, CD4⁺, CD8⁺, CD19⁺ cells) the degree of depletion did not differ between patients who did or did not have a reported autoimmune adverse event.

Efficacy

There were 3 completed clinical studies: an open Phase II study and 2 randomised, rated-blinded studies that were considered pivotal. No formal dose-finding studies were conducted. In the sponsor's clinical overview it was stated that dosing in the pilot investigator-sponsored MS studies was guided by historical data from oncology use and by published pilot studies in patients with rheumatologic disorders. The published MS pilot studies suggested that just 1 or 2 pulsed cycles of 20 mg/day alemtuzumab (total dose of 100 mg in Cycle 1 and 60 mg in Cycle 2) significantly suppressed relapses and cerebral inflammation (measured by MRI) for at least 6 years. The subsequent selection of the dose and dosing regimen used in the later Genzyme MS program was based on these empirical observations.

The open Phase II study compared alemtuzumab 12 mg/day and 24 mg/day and interferon beta-1a. The initial study plan was for a 3 year treatment period but this study was interrupted due to safety concerns and was modified prior to completion. 24 subjects received 12 mg/day alemtuzumab for 2 treatment cycles and 22 subjects received alemtuzumab 24 mg/day for 2 treatment cycles (Figure 3).

Figure 3. Flow chart disposition to month 36



Both pivotal studies had the co-primary efficacy endpoints of MS relapse rate and time to SAD (6 month criteria). A patient was considered to have reached 6 month SAD when the following conditions were met:

- If the baseline EDSS was 0, and EDSS score increased by at least 1.5 points and remained at least 1.5 points above baseline during the next 2 scheduled assessments (that is, 6 consecutive months);
- If the baseline EDSS score was greater than or equal to 1, and EDSS score increased by at least 1 point and remained at least 1 point above baseline during the next 2 scheduled assessments (that is, 6 consecutive months).

Secondary endpoints included imaging findings along with additional relapse and disability endpoints. These were to be assessed if statistical significance was demonstrated for both co-primary endpoints.

Study 323 was a randomised, rater-blinded study comparing 2 annual cycles of IV alemtuzumab with 3 times weekly SC interferon beta-1a (Rebif) in treatment-naïve subjects with RRMS. Subjects received either the proposed dose regimen for alemtuzumab, that is, 12 mg/day for 5 days then after 12 months a further 12 mg/day for 3 days, or interferon beta-1a titrated over 4 weeks to a final dose of 44 µg via SC injection 3 times each week. Treatment was to continue over 2 years.

The major inclusion criteria were: onset of MS within 5 years and an EDSS score of from 0 to 3.0 at screening (0 = normal neurological exam; 3 = moderate disability in one functional system (FS) or mild disability in three or four functional systems. However, the person is still fully ambulatory). The major exclusion criteria were: any progressive form of MS, prior therapy for MS other than corticosteroids; previous exposure to monoclonal antibody for any reason; significant autoimmune disease; and CD4⁺, CD8⁺, B cell count or absolute neutrophil count below the LLN at screening. A total of 581 subjects were randomised to treatment in a 2:1 ratio with 386 to alemtuzumab and 195 to interferon beta-1a. Mean age was 33.1 years and 64.8% were female. Mean EDSS score at baseline was 2.0 (that is, minimal disability in one FS is present) and the mean time since the initial episode was 2.1 years.

Statistical significance was not demonstrated for 6 month SAD, the KM estimate for the proportion of patients with 6 month SAD was 8.00% for alemtuzumab and 11.12% for interferon beta-1a ($p = 0.2173$), hazard ratio (HR) 0.70 (95% CI 0.40, 1.23). Differences in relapse rates were statistically significant, 75/187 (40.1%) subjects given interferon beta-1a experienced 122 relapses compared with 82/376 (21.8%) subjects given alemtuzumab who experienced 119 relapses. Compared with interferon beta-1a, alemtuzumab reduced the relapse rate by 53% in Year 1 ($p < 0.0001$) and 57% in Year 2 (that is, from Month 12 to Month 24) ($p = 0.0002$).

Study 324 was a randomised, rater- and dose-blinded study comparing 2 annual cycles of IV low and high dose alemtuzumab to 3 times weekly SC interferon beta-1a (Rebif) in subjects with RRMS who had relapsed on prior therapy. The two groups receiving alemtuzumab received either the 12 mg/day dose regimen used in Study 323 or twice that dose (that is, 24 mg/day) for 5 days in Cycle 1 and 24 mg/day for 3 days in Cycle 2. Recruitment to the 24 mg/day dose ceased part way during the study and the major comparison was between the 12 mg/day alemtuzumab dose and interferon beta-1a. The interferon beta-1a dose was the same as in Study 323, that is, titration to 44 µg via SC injection 3 times weekly. Treatment was to continue over 2 years.

The major inclusion criteria were: onset of MS symptoms within 10 years of study and EDSS score from 0.0 to 5.0 (5.0 = able to walk 200 meters without aid or rest. Disability impairs full daily activities, such as working a full day without special provisions) and at least one relapse during treatment with a beta interferon therapy or glatiramer acetate

after having been on that therapy for at least 6 months within the last 10 years. Exclusion criteria were similar to those of Study 323. A total of 840 subjects were randomised, 436 to receive alemtuzumab 12 mg/day, 173 to receive alemtuzumab 24 mg/day and 231 to receive interferon beta-1a. Mean age was 35.1 years and 66.7% were female. The mean EDSS score at baseline was 2.7 and the mean time since initial episode was 4.5 years.

A statistically significant differences in 6 month SAD was demonstrated with SAD reported in 54/426 (12.7%) of subjects given alemtuzumab 12 mg/day and in 40/202 (19.8%) of subjects given interferon beta-1a, an absolute difference of approximately 8% over the 2 years of the study. The KM estimate for SAD was 12.71 for alemtuzumab and 21.13 for interferon beta-1a ($p = 0.0084$) and the HR was 0.58 (95% CI 0.38, 0.87). A total of 147/426 (34.5%) subjects given alemtuzumab experienced 236 relapses and 104/202 (51.5%) given interferon beta-1a experienced 201 relapses. Compared with interferon beta-1a, alemtuzumab reduced the relapse rate by 54% in Year 1 ($p < 0.0001$) and 41% in Year 2 ($p = 0.0017$). Statistical results for secondary endpoints in this study are shown in the CER (Attachment 2 of this AusPAR).

The 24 mg/day dosing regimen given in Study 324 was also evaluated in the Phase II study (Study 223). Overall there were few statistically significant differences between the 12 mg/day and the 24 mg/day dose regimens of alemtuzumab for clinical efficacy endpoints and the 24 mg/day regimen has not been proposed for registration.

Safety

A total of 1684 patients received study treatment: alemtuzumab ($n = 1188$) or interferon beta-1a ($n = 496$) in the 3 active-controlled studies in MS. Of these, 808 subjects received the proposed 2 cycles of treatment with 12 mg/day alemtuzumab and 240 subjects have received 3 cycles of either the 12 mg/day or 24 mg/day dose regimen. There were also 31 subjects who received 4 cycles of either dose regimen of alemtuzumab. A further 297 patients who received interferon beta-1a in a prior study subsequently received alemtuzumab in an ongoing extension study (Study 3409), giving an overall total of 1485 individual patients (Pool C) with RRMS who received treatment with alemtuzumab.

Nearly all subjects reported at least one AE but events considered related to study treatment were reported in 73.4% of subjects given interferon beta-1a and in 97.8% of subjects given alemtuzumab. Adverse events leading to either study withdrawal were more frequent in subjects given interferon beta-1a (7.9% for interferon beta-1a versus 2.4% for alemtuzumab) however serious treatment related AEs were more frequent with alemtuzumab than with interferon beta-1a (1.6% versus 7.3% for alemtuzumab; Table 9).

Table 9. Overview of AEs in All Active-Controlled Studies (2-Year Follow Up, Pool A)

	SC IFNB-1a (N=496)		Alemtuzumab 12 mg/day (N=919)		Alemtuzumab Pooled (N=1188)	
	Events	n (%)	Events	n (%)	Events	n (%)
Adverse Events						
Any Event	5051	469 (94.6)	15153	896 (97.5)	20682	1162 (97.8)
Related	1555	364 (73.4)	7510	865 (94.1)	10398	1128 (94.9)
Unrelated	3496	431 (86.9)	7641	803 (87.4)	10282	1053 (88.6)
Grade 1	2661	400 (80.6)	8117	815 (88.7)	11210	1066 (89.7)
Grade 2	2193	402 (81.0)	6573	831 (90.4)	8825	1084 (91.2)
Grade 3	187	106 (21.4)	419	227 (24.7)	585	318 (26.8)
Grade 4	10	10 (2.0)	39	27 (2.9)	55	41 (3.5)
Grade 5	0	0 (0.0)	3	3 (0.3)	5	4 (0.3)
AEs Leading to Treatment Withdrawal	63	39 (7.9)	29	21 (2.3)	37	28 (2.4)
AEs Leading to Study Discontinuation	22	22 (4.4)	4	4 (0.4)	6	6 (0.5)
Serious Adverse Events						
Any Serious Event	160	91 (18.3)	256	168 (18.3)	332	213 (17.9)
Related	9	8 (1.6)	92	65 (7.1)	127	87 (7.3)
Unrelated	151	85 (17.1)	164	114 (12.4)	205	141 (11.9)
Grade 1	10	6 (1.2)	19	15 (1.6)	24	19 (1.6)
Grade 2	92	56 (11.3)	97	77 (8.4)	118	92 (7.7)
Grade 3	53	38 (7.7)	114	88 (9.6)	152	114 (9.6)
Grade 4	5	5 (1.0)	23	20 (2.2)	33	29 (2.4)
Grade 5	0	0 (0.0)	3	3 (0.3)	5	4 (0.3)
SAEs Leading to Treatment Withdrawal	10	10 (2.0)	9	7 (0.8)	12	10 (0.8)
SAEs Leading to Study Discontinuation	3	3 (0.6)	0	0 (0.0)	0	0 (0.0)

Percentages are based on the number of treated patients in the corresponding treatment group. Data not available from study CAMMS223 for SAEs leading to study discontinuation due to the design of the CRFs.

There were 8 deaths in clinical studies; 7 (0.5%) subjects given alemtuzumab and 1 (0.2%) given interferon beta-1a. Three deaths in alemtuzumab-treated patients were considered at least possibly related to treatment: cardiovascular disorder in a subject with cardiac risk factors 2 months after they received their third annual cycle of alemtuzumab 12 mg/day; sepsis in a subject 19 months after the second annual cycle of alemtuzumab 12 mg/day (subject had developed autoimmune pancytopenia); and idiopathic thrombocytopenic purpura with a cerebral haemorrhage 7 months after the second annual cycle of alemtuzumab 24 mg/day. The idiopathic thrombocytopenic purpura death occurred in a subject enrolled in the Phase II study (Study 223) and prompted implementation of the risk management program currently employed in the alemtuzumab studies.

The other 4 deaths, each in the alemtuzumab 12 mg/day group, were assessed as not related to study drug. These were: road accident; auto-pedestrian accident; aspiration pneumonia; and severe bleeding after incised wound. The death in a subject given interferon beta-1a was due to a train accident. An additional death from Burkett's lymphoma was reported after an alemtuzumab-treated patient had completed Study 223. Forty months after the third annual cycle of alemtuzumab, the patient died from sepsis following chemotherapy.

The major safety concerns associated with alemtuzumab are infusion-associated reactions (IARs), autoimmune disorders and infections. The potential for malignancy may also be an issue but insufficient data are available to characterise the extent of risk. Data to date suggests an increased incidence of malignancies in subjects given alemtuzumab. The most frequent IARs are listed in Table 10, below.

These were:

- skin-related (rash, 42.8%; urticaria, 14.7%; pruritus, 12.7%; generalized rash, 6.4%),
- general disorders (pyrexia, 25.0%; chills, 9.4%; fatigue, 8.4%; chest discomfort, 6.6%; pain, 5.1%),
- nervous system (headache, 43.4%; dysgeusia, 6.9%; dizziness, 5.7%),
- gastrointestinal (nausea, 15.9%; dyspepsia, 6.1%),
- respiratory (dyspnoea, 7.2%),
- vascular (flushing, 9.4%),
- psychiatric (insomnia, 11.0%), and
- cardiac (tachycardia, 6.4%)

The majority of these events were of Grade 1 or 2 severity. Premedication with prophylactic corticosteroids, antihistamines and antipyretics was permitted at the investigator's discretion in Studies 323 and 324. Two subjects erroneously received 4 times (48 mg) and 5 times (60 mg) the prescribed daily 12 mg dose of alemtuzumab in a single infusion. These subjects had more serious IARs which resolved on the same day as the infusion either spontaneously or after standard treatment, suggesting these reactions are dose-related. These reactions also occur in patients given alemtuzumab for treatment of B-CLL.

Table 10. Infusion-Associated Reactions Reported in ≥5% of Patients in Any Treatment Group for All Alemtuzumab-Treated Patients, All Available Follow Up (Pool C)

	Alemtuzumab 12 mg/day (N=1216)	Alemtuzumab Pooled (N=1485)
System Organ Class Preferred Term	n (%)	n (%)
Any Event	1095 (90.0)	1360 (91.6)
Cardiac disorders	149 (12.3)	186 (12.5)
Tachycardia	80 (6.6)	100 (6.7)
Eye disorders	42 (3.5)	58 (3.9)
Vision blurred ^a	23 (1.9)	37 (2.5)
Gastrointestinal disorders	344 (28.3)	468 (31.5)
Nausea	195 (16.0)	267 (18.0)
Dyspepsia	72 (5.9)	98 (6.6)
Vomiting	63 (5.2)	91 (6.1)
General disorders and administration site conditions	617 (50.7)	794 (53.5)
Pyrexia	318 (26.2)	392 (26.4)
Chills	122 (10.0)	163 (11.0)
Fatigue	96 (7.9)	142 (9.6)
Chest discomfort	77 (6.3)	118 (7.9)
Pain	66 (5.4)	88 (5.9)
Musculoskeletal and connective tissue disorders	201 (16.5)	257 (17.3)
Myalgia ^a	49 (4.0)	73 (4.9)
Back pain ^a	45 (3.7)	63 (4.2)
Nervous system disorders	580 (47.7)	762 (51.3)
Headache	507 (41.7)	674 (45.4)
Dysgeusia	75 (6.2)	100 (6.7)
Dizziness	63 (5.2)	89 (6.0)
Psychiatric disorders	170 (14.0)	222 (14.9)
Insomnia	136 (11.2)	171 (11.5)
Respiratory, thoracic and mediastinal disorders	204 (16.8)	280 (18.9)
Dyspnoea	81 (6.7)	113 (7.6)
Skin and subcutaneous tissue disorders	826 (67.9)	1072 (72.2)
Rash	516 (42.4)	682 (45.9)
Urticaria	168 (13.8)	242 (16.3)
Pruritus	144 (11.8)	199 (13.4)
Rash generalized	81 (6.7)	101 (6.8)
Erythema ^a	50 (4.1)	68 (4.6)
Vascular disorders	192 (15.8)	233 (15.7)
Flushing	117 (9.6)	143 (9.6)

Percentages are based on the number of treated patients in the corresponding treatment group. A patient is counted only once within each SOC/PT. SOCs are presented alphabetically, and within SOC the PTs are presented by decreasing incidence in the Alemtuzumab 12mg/day group. IARs refer to AEs that occur between the start and stop of any Alemtuzumab infusion + 24 hours. ^aThese events occurred at an incidence of ≥ 5% in the alemtuzumab 24 mg/day group only.

Autoimmune disorders included thyroid disorders, ITP, and nephropathies (for example, anti-GBM disease). Subjects were monitored for autoimmune thyroid abnormalities in the pivotal studies because published studies conducted prior to the sponsor's clinical development program had suggested this was a concern. The incidence of thyroid AEs was

higher in the alemtuzumab 12 mg/day group (16.6%) than in the interferon beta-1a group (5.2%). The most frequently reported thyroid AEs (reported for > 2% of alemtuzumab 12 mg/day group were hypothyroidism, hyperthyroidism, Basedow's disease, and decreased blood thyroid stimulating hormone (TSH). No thyroid AEs were reported for > 2% of interferon beta-1a treated patients.

Table 11 below lists the incidence of thyroid AEs in all active controlled studies. Based on data from all clinical trials thyroid AEs were seen in an estimated 36.2% of patients in the alemtuzumab 12 mg/day group through 4 years after treatment initiation (0.138 per person-year). The sponsor's clinical expert reporter has stated that no consistent pattern was observed with regards to time of onset after treatment initiation, although the highest incidence of thyroid AEs was observed between 24 and 42 months after the first treatment cycle. Anti-thyroid peroxidase antibody (anti-TPO antibodies) were measured at baseline in the pivotal studies. Although patients with anti-TPO antibodies at baseline were more likely to develop thyroid disease approximately 80% of subjects who developed a thyroid disorder were antibody negative prior to treatment.

Table 11. Incidence of Thyroid AEs in All Active-Controlled Studies (2-Year Follow Up, Pool A)

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab Pooled (N=1188)
System Organ Class Preferred Term	n (%)	n (%)	n (%)
Any Event	26 (5.2)	153 (16.6)	191 (16.1)
Endocrine disorders	13 (2.6)	121 (13.2)	147 (12.4)
Hypothyroidism	8 (1.6)	42 (4.6)	49 (4.1)
Hyperthyroidism	4 (0.8)	32 (3.5)	41 (3.5)
Basedow's disease	0 (0.0)	22 (2.4)	31 (2.6)
Autoimmune thyroiditis	2 (0.4)	16 (1.7)	21 (1.8)
Goitre	2 (0.4)	13 (1.4)	18 (1.5)
Thyroiditis	1 (0.2)	5 (0.5)	7 (0.6)
Thyroiditis subacute	0 (0.0)	2 (0.2)	2 (0.2)
Primary hypothyroidism	0 (0.0)	1 (0.1)	1 (0.1)
Thyroid cyst	0 (0.0)	1 (0.1)	1 (0.1)
Thyroid mass	0 (0.0)	1 (0.1)	1 (0.1)
Thyrotoxic crisis	0 (0.0)	1 (0.1)	1 (0.1)
Investigations	13 (2.6)	45 (4.9)	60 (5.1)
Blood thyroid stimulating hormone decreased	5 (1.0)	21 (2.3)	29 (2.4)
Blood thyroid stimulating hormone increased	4 (0.8)	11 (1.2)	14 (1.2)
Anti-thyroid antibody positive	0 (0.0)	9 (1.0)	11 (0.9)
Thyroxine free decreased	0 (0.0)	6 (0.7)	8 (0.7)
Tri-iodothyronine free increased	1 (0.2)	4 (0.4)	7 (0.6)
Thyroid function test abnormal	0 (0.0)	3 (0.3)	3 (0.3)
Tri-iodothyronine free decreased	0 (0.0)	3 (0.3)	4 (0.3)
Thyroxine free increased	0 (0.0)	2 (0.2)	2 (0.2)
Thyroxine decreased	1 (0.2)	1 (0.1)	3 (0.3)
Thyroxine increased	1 (0.2)	1 (0.1)	2 (0.2)
Tri-iodothyronine increased	0 (0.0)	1 (0.1)	1 (0.1)
Blood thyroid stimulating hormone abnormal	1 (0.2)	0 (0.0)	0 (0.0)
Thyroxin binding globulin increased	0 (0.0)	0 (0.0)	1 (0.1)
Tri-iodothyronine decreased	0 (0.0)	0 (0.0)	2 (0.2)

Thyroid disorders refers to AEs where HLGT = Thyroid gland disorders or HLT=Thyroid analyses or PT=Blood thyroid stimulating hormone abnormal, Blood thyroid stimulating hormone increased, or Blood thyroid stimulating hormone decreased. HLGT = high level group term; HLT = high level term; PT = preferred term.

There were 18 cases of confirmed ITP in subjects given alemtuzumab compared with none given interferon beta-1a. Two of the 18 cases had a possible alternative explanation (*Coxsackie b* infection and *Helicobacter pylori* infection respectively). One of these subjects died with ITP leading to cerebral haemorrhage 7 months after receiving the second cycle (the index case). One other subject required a splenectomy after first and second line treatment for ITP were unsuccessful. The time to event data indicated that ITP was more likely to occur between 14 and 36 months after commencement of treatment.

Nephropathy including anti-GBM had been reported in 2 patients with MS who received alemtuzumab outside of Genzyme sponsored studies. The condition was not recognised initially and both patients went on to require dialysis. In the Genzyme study program one subject developed anti-GBM disease, presenting 39 months after the subject received their last alemtuzumab dose. That case was successfully treated and safety monitoring included monthly urinalysis and creatinine assessment. In total there were 5 cases of nephropathy in subjects given alemtuzumab, 2 due to anti-GMB disease.

There were 4 autoimmune cytopenias: 2 cases of haemolytic anaemia and 2 cases of pancytopenia in alemtuzumab-treated MS patients in sponsored clinical studies.

Infections occurred more frequently in subjects given alemtuzumab compared with interferon beta-1a (70.9% for alemtuzumab 12 mg/day versus 53.2% for interferon beta-1a over 2 years in the Pool A safety population). Infections reported in $\geq 5\%$ of subjects given either treatment were: nasopharyngitis, urinary tract infection (UTI), upper respiratory tract infection (URTI), sinusitis, and influenza. For the alemtuzumab 12 mg/day group, oral herpes (8.6%) and bronchitis (7.0%) were on this list of frequent infections. One patient given alemtuzumab 24 mg/day developed tuberculosis (TB). That subject was withdrawn from treatment. Serious infections were reported for 25 (2.7%) subjects given alemtuzumab 12 mg/day versus 5 (1.0%) given interferon beta-1a group over 2 years of follow up (Table 12). No subjects given 12mg/day were withdrawn due to infection.

Table 12. Incidence of Serious Infections in All Active-Controlled Studies (≥ 2 cases in 2-Year Follow Up, Pool A)

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab Pooled (N=1188)
Preferred Term	n (%)	n (%)	n (%)
Any Event	5 (1.0)	25 (2.7)	35 (2.9)
Appendicitis	1 (0.2)	4 (0.4)	4 (0.3)
Gastroenteritis	0 (0.0)	4 (0.4)	6 (0.5)
Pneumonia	0 (0.0)	4 (0.4)	5 (0.4)
Herpes zoster	0 (0.0)	2 (0.2)	4 (0.3)
Tooth infection	0 (0.0)	2 (0.2)	2 (0.2)

Percentages are based on the number of treated patients in the corresponding treatment group. Infections refers to AEs with MedDRA SOC 'Infections and infestations'. A patient is counted only once within each PT. PTs are presented by decreasing incidence in the alemtuzumab 12mg/day group.

Overall, 13/1485 (0.88%) patients reported a total of 15 malignancies in the alemtuzumab pooled dose group over all available follow-up (6 patients in the 12 mg/day group, 7 patients in the 24 mg/day group). The most common malignancies reported in more than 1 alemtuzumab-treated patient were thyroid (7 cases), breast cancer (2), and basal cell carcinoma (4), these are Table 13 and 14. Three subjects given interferon beta-1a developed malignancies (acute myeloid leukaemia, colon cancer and one subject with 2 x basal cell carcinomas). Of particular note the rate of development of malignancies was substantially higher in subjects given 24 mg/day alemtuzumab than in those given 12

mg/day, though this is based on small numbers of subjects. Malignancies became apparent within 18 months of commencement of treatment.

Table 13. Listing of Malignancies in Alemtuzumab 12mg Patients Over All Available Follow Up

Sex, age at diagnosis of malignancy	Prior Medical History / Risk Factors	Number of Cycles (or weeks) at Time of Diagnosis (Cumulative Dose)	Preferred Term (Severity Grade, seriousness, relation to study drug)	Time from First Dose to Diagnosis of Malignancy	Days from Last Dose to Diagnosis of Malignancy
Female, 24	None / None	2 Cycles (96 mg)	Thyroid cancer (Grade 3, serious, related)	688 days (23 months)	315 days (10 months)
Female, 46	Dysplastic naevus syndrome, thyroid neoplasm, thyroidectomy / former tobacco use	2 Cycles (90 mg)	Basal cell carcinoma (Grade 3, serious, related)	(~19 months)	(~5 months)
Female, 44	Basal cell carcinoma / None	2 Cycles (96 mg)	Malignant melanoma in situ (Grade 3, serious, related)	759 days (25 months)	385 days
Female, 50	Hypothyroidism, thyroid neoplasm / None	1 Cycle (60 mg)	Thyroid cancer (Grade 3, serious, not related)	325 days (11 months)	321 days (11 months)
Female, 33	Submandibular node / None	2 Cycles (96 mg)	Thyroid cancer (Grade 3, serious, not related)	697 days (23 months)	328 days (11 months)
Female, 33	None / None	2 Cycles (96 mg)	Thyroid cancer (Grade 1, not serious, not related)	789 days (26 months)	425 days (14 months)

Table 14. Listing of Malignancies in Alemtuzumab 24mg Patients Over All Available Follow Up

Sex, age at diagnosis of malignancy	Prior Medical History / Risk Factors	Number of Cycles (or weeks) at Time of Diagnosis (Cumulative Dose)	Preferred Term (Severity Grade, seriousness, relation to study drug)	Time from First Dose to Diagnosis of Malignancy	Days from Last Dose to Diagnosis of Malignancy
Female, 34 ^a	None / None	3 Cycles (264 mg)	Basal cell carcinoma (Grade 2, serious, not related)	775 days (25 months)	928 days (~31 months)
		3 Cycles (264 mg)	Basal cell carcinoma (Grade 3, serious, related)	1946 days (~63 months)	1172 days (~39 months)
		3 Cycles (264 mg)	Thyroid cancer (Grade 3, serious, related)	2021 days (70 months)	1247 (41 months)
Female, 32	None / None	2 cycles (194 mg)	Vulvar cancer stage 0 (Grade 3, serious, related)	637 days (21 months)	265 days (9 months)
Female, 46	None / None	1 cycle (120 mg)	Basal cell carcinoma (Grade 3, serious, related)	155 days (5 months)	155 days (5 months)
Female, 29	None / None	2 cycles (192 mg)	Breast cancer (Grade 2, serious, related)	816 days (27 months)	434 days (14 months)
Female, 44	None / family history of breast cancer	2 Cycles (192 mg)	Breast cancer (Grade 3, serious, not related)	943 days (31 months)	527 days (17 months)
Female, 28	None / None	2 Cycles (192 mg)	Cervix carcinoma (grade 1, serious, not	695 days (23 months)	314 days (10 months)

Sex, age at diagnosis of malignancy	Prior Medical History / Risk Factors	Number of Cycles (or weeks) at Time of Diagnosis (Cumulative Dose)	Preferred Term (Severity Grade, seriousness, relation to study drug)	Time from First Dose to Diagnosis of Malignancy	Days from Last Dose to Diagnosis of Malignancy
			related)		
Female, 51	Hypothyroidism, thyroid neoplasm, thyroidectomy / None	1 cycle (120 mg)	Colon cancer (Grade 3, serious, not related)	116 days (4 months)	112 days (4 months)

The majority of subjects given alemtuzumab developed anti-alemtuzumab antibody. There was no clear relationship between the overall pattern of lymphocyte depletion and repopulation and the presence of anti-alemtuzumab or inhibitory antibody status. Nor were infusion reactions more common in subjects with antibody persisting at the commencement of cycle 2.

Clinical evaluator's recommendation

The clinical evaluator recommended that the following extension of indications be approved [evaluator's modification from the indication proposed by the sponsor in bold text]:

*Alemtuzumab [Lemtrada/Remniq] is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) **in whom treatment with Interferon β -1a or glatiramer is not possible or contraindicated** to reduce the frequency of clinical relapses*

Risk management plan

The TGA OPR recommendations (see above under *Pharmacovigilance findings*) were endorsed.

Risk-benefit analysis

Delegate considerations

Efficacy of the proposed dose regimen of alemtuzumab in the treatment of RRMS has been very clearly demonstrated. Alemtuzumab showed both clinically and statistically superior efficacy compared with Rebif, an active comparator that is widely used for the treatment of RRMS. Superior efficacy with respect to reducing relapse rates was demonstrated in subjects with mostly recently diagnosed RRMS who had little sustained disability at study entry and well as in patients with a longer history of RRMS that included relapses of either an interferon or glatiramer treatment. Superiority in reducing the rate of progression of sustained disability was demonstrated only for patients who had more advanced RRMS. The absolute difference in 6-month SAD was 8% over 2 years for patients with more advanced disease. No statistically significant difference in SAD was demonstrated in the study with more recently diagnosed patients. This is consistent with the natural history of MS because it usually takes some years for SAD to occur therefore fewer recently

diagnosed subjects were likely to meet a SAD endpoint during study in either treatment group.

The major issues associated with use of alemtuzumab in patients with RRMS relate to its safety. Alemtuzumab has substantial infusion-related adverse effects that can be adequately managed with pre-medication. Hospitalisation or at least attendance at an infusion clinic will be required for the period alemtuzumab is to be administered. Patients given alemtuzumab will be more susceptible to infection and autoimmune disease will require monitoring of their haematology, thyroid function, and renal function and careful observation for the development of malignancy for some years after completion of the proposed 2 cycles of alemtuzumab treatment. It is unclear if the increased propensity to develop autoimmune diseases and malignancies post-treatment will recede, persist or escalate. The widespread development of inhibitory antibodies to alemtuzumab is unlikely to have a clinically significant effect given that only 2 treatment cycles have been proposed, however it may affect responses to other monoclonal antibodies that may be administered subsequent to alemtuzumab treatment.

Use of alemtuzumab for the treatment of relapsing MS has substantial risk but also offers efficacy greater than occurs with interferon beta-1a. Patients with RMS given this treatment would require more extensive follow-up than patients receiving most alternative treatments. This suggests alemtuzumab could be considered for patients with markers for more severe RRMS. Cladribine, a cytotoxic agent selective for lymphocytes and monocytes was approved for the treatment of RRMS in September 2010²² but was never marketed in Australia. The sponsor of cladribine (tradenname Movectro) withdrew their application to the EMA for marketing authorisation in February 2011 based on the CHMP's adopted opinion that the data available to date did not allow the Committee to adopt a positive opinion recommending the granting of a marketing authorisation for Movectro.²³

There are similar issues regarding the balance of benefit and risk for alemtuzumab, another product like cladribine, approved at a higher dose for treatment of some leukaemias.

The sponsor had requested that the indication for alemtuzumab include that it can reverse the accumulation of disability. No statistical assessment of reversal of disability was provided in the data package and this claim has subsequently been withdrawn.

Prior to the sponsor of cladribine withdrawing their submission to the EMA, cladribine had been considered for use restricted to patients with high disease activity or patients with persistent disease activity despite treatment with other medicines. The CHMP had recommended against this restricted use and noted that the benefits and the most appropriate dosage for treatment had not been fully established in (high risk) patients who were expected to use the medicine. That committee was concerned about cladribine's long term safety, even if it were to be used in the restricted group of patients.

There are similar issues with alemtuzumab in that:

- the lowest effective dose for the treatment of RMS has not been determined;
- lymphopenia is profound;
- there is no information on ongoing treatment of MS after completion of 2 cycles of alemtuzumab;

²² See AusPAR for Movectro at <<http://www.tga.gov.au/pdf/auspar/auspar-movectro.pdf>>

²³ See European Public Assessment Report (EPAR) for Movectro at: <http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2011/03/WC500104393.pdf>

- there appears to be an increased risk of development of malignancies following treatment, it is not known if an increased propensity to malignancies will persist after completion of the treatment cycles;
- efficacy in patients at high risk of progression has not been examined so there is no basis for limiting use to that population;

In addition to the above concerns which are in common with cladribine, alemtuzumab has a significant risk of autoimmunity and autoimmune related events that have resulted in death. It is not known if this increased risk of auto-immunity will persist following completion of treatment.

Proposed action

Given the evidence submitted to date, the Delegate was inclined to reject alemtuzumab 10 mg/mL for the treatment of relapsing forms of MS. Information on the longer term risks of malignancy, autoimmune disease and serious infection was required to clarify the benefit/ risk of alemtuzumab for its proposed indication.

Subsequent to the above proposed action and prior to this application being considered by the Advisory Committee on Prescription Medicines (ACPM), the TGA reviewed the following additional information provided by the sponsor:

- a summary of information provided during the CHMP assessment and recent specific FDA safety requests that were relevant to concerns raised in the Delegate's Overview over comparisons with cladribine (see *Delegate's considerations*, above)
- the 27 June 2013 EMA summary opinion for Lemtrada which recommended approval for *treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features*.

In view of the above the Delegate proposed to approve the application.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and in addition to request the committee address the following specific issues:

1. Does the committee consider the proposed laboratory monitoring (shown below) is adequate for the identification of adverse effects associated with alemtuzumab?
 - Full blood count (FBC) with differential (prior to treatment initiation and at monthly intervals thereafter).
 - Serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter).
 - Urinalysis with urine cell counts (every 3 months following treatment).
 - A test of thyroid function, such as TSH level (prior to treatment initiation and every 3 months thereafter).
2. Does the committee consider it would be appropriate to permit use of alemtuzumab in a subgroup of patients with relapsing MS, for example, as a second or third line treatment for patients not responding adequately to other treatments or in patients considered at high risk of rapid progression? If this is the case can the committee identify these subgroups?
3. Alemtuzumab as MabCampath is contraindicated during pregnancy and breast feeding. Does the committee consider it appropriate that alemtuzumab as Lemtrada/Remniq also be contraindicated in pregnancy and breast feeding? For

MabCampath, it is advised that males and females of childbearing potential use effective contraceptive measures during treatment and for 6 months following MabCampath therapy. The sponsor is proposing that pregnancy be avoided in women of child bearing potential taking alemtuzumab for 4 months after treatment. No restrictions are proposed for males with RRMS taking alemtuzumab. The committee's view on whether this advice would put fetuses at increased risk of adverse effects from alemtuzumab is requested.

4. The sponsor has not proposed to include information on the risk of malignancy in the PI or CMI. If alemtuzumab were to be approved could the committee suggest an appropriate statement to advise prescribers and patients of this risk?

Response from sponsor

The sponsor's comments on the issues for which the advice of the ACPM was sought, as outlined in the Delegate's Overview, are presented below.

Delegate's question 1: Proposed laboratory monitoring

A comprehensive risk monitoring plan implemented during the clinical development program is the basis for the proposed risk minimisation strategies after the approval of the product. These measures demonstrated to be effective in identifying autoimmune events early in the onset of disease allowing for prompt intervention and favourable outcomes. A brief summary is provided below.

- Following the diagnosis of 3 initial cases of ITP, including the fatal index case in the Phase 2 study (CAMMS223) that led to suspension of alemtuzumab dosing, a safety monitoring program was implemented in the clinical studies. This program included close monitoring for signs of ITP through patient and investigator education, monthly CBCs with platelet counts, and a monthly patient questionnaire about symptoms possibly indicative of severe thrombocytopenia, offset by 2 weeks from the laboratory testing. A protocol definition of ITP was specified to guide investigators during the conduct of the studies. This definition was based upon commonly employed diagnostic criteria for ITP.
- As of 26 November 2012, a total of 27 patients of the 1486 alemtuzumab-treated patients were identified with ITP. Of these 21 (1.4%) were confirmed to meet an international diagnostic criteria and thus, were considered medically confirmed cases. Of the 21 medically confirmed ITP cases as described above, with the exception of the index fatal case which triggered a comprehensive monitoring program including monthly blood counts and surveys around potential signs and symptoms, all cases were detected promptly, either by the monthly platelet counts or the early recognition of signs and symptoms. Most patients achieved prompt platelet count response (within 3 months of diagnosis after treatment with an ITP) with first-line therapy, that is, corticosteroids and/or IV immunoglobulin (IVIG) with or without adjuvant platelet transfusion. Four patients received additional second-line therapies (for example, rituximab, Danazol), and 1 patient recovered spontaneously without treatment. One patient underwent splenectomy for definite treatment of ITP.
- Serum creatinine is the most extensively studied, validated, well characterized, and widely available marker of renal function. It is used consistently across different current guidelines on the diagnosis and treatment of acute kidney injury (Bellomo *et al*, 2004²⁴, Mehta *et al*, 2007²⁵). Limitations of use of serum creatinine have also been

²⁴ Bellomo R *et al*. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004 Aug;8(4):R204-212.

well studied and documented. Measures are available to compensate for some of the limitations such as gender, age, and ethnicity, which can influence the levels of serum creatinine, such as Cockcroft-Gault equation to calculate the glomerular filtration rate, Modification of Diet in Renal Disease formula. With wide accessibility and well-characterised clinical experiences, serum creatinine continues to be the gold standard in the diagnosis of acute kidney injury. Monitoring serum creatinine (changes over time) is currently the recommended method of diagnosing acute kidney injury. Monthly serum creatinine, along with periodic urine analysis is expected to detect renal dysfunction, haematuria and proteinuria, which were the most common presentation of the autoimmune glomerulonephritis cases in alemtuzumab clinical studies in MS; the four cases thus far were detected early in the onset by these methods and successfully managed with favourable outcomes, 1 case was identified through abnormal monthly serum creatinine, 2 through identification of hematuria and proteinuria and 1 case through the patient recognition and reporting of signs and symptoms (awareness/education). These patients responded to timely medical treatment with favourable outcomes.

- Thyroid disorders were defined as a thyroid AE and/or a thyroid laboratory abnormality. The incidence of thyroid disorders was higher in the alemtuzumab 12 mg/day group compared to interferon beta-1a but still occurred in a substantial proportion of interferon beta-1a treated patients (38.6% versus 28.2%, respectively). TSH testing was performed every three months on every patient participating in the clinical trials and the frequency of abnormal results observed was 32.9% in the alemtuzumab 12 mg/day group and 23.4% in the interferon beta-1a. The overall incidence of thyroid AEs was 18.3% in the alemtuzumab 12 mg/day group versus 5.4% in the interferon beta-1a group. The higher frequency of abnormal TSH results compared to reported adverse thyroid events could be plausibly interpreted as an indicator of the high sensitivity of TSH to detect clinically evident thyroid disease. Additionally, in an analysis of time to first thyroid event, it was found that >99% of first events occurred within 48 months following the most recent alemtuzumab dose and only a single event occurred more than 48 months after the last dose of alemtuzumab. This suggests that monitoring of patients for 48 months following the last dose of alemtuzumab is appropriate.

Delegate's question 2. Use of alemtuzumab in a subgroup of patients with relapsing MS

Superior efficacy of alemtuzumab 12 mg/day over interferon beta-1a was demonstrated in 3 randomised, controlled clinical trials in treatment-naïve MS population (studies CAMMS223, CAMMS323) and in patients who relapse on previous MS therapies (study CAMMS324). Alemtuzumab was substantially more effective than a current standard of care (high-dose SC interferon beta-1a) in reducing the relapse rate in all e studies as well as the risk of sustained accumulation of disability in CAMMS223 and CAMMS324. Further, in CAMMS223 and CAMMS324, alemtuzumab-treated patients were more likely to achieve a sustained improvement in disability score. The clinical findings and the MRI results demonstrate that alemtuzumab is effective in a broad range of relapsing MS patients both treatment naïve and previously treated, including those with more severe disease and highly active disease, and support the proposed indication.

The proposed restriction on alemtuzumab use, for example as a second or third line treatment for patients not responding adequately to other treatments or in patients considered at high risk of rapid progression, is similar to the indication granted in EU for natalizumab and fingolimod. However, prescriber experience in Europe suggests that

²⁵ Mehta RL *et al.* Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11(2):R31.

attempts to narrowly specify qualifying criteria (such as those used for the subgroup analyses described below) will inevitably exclude some patients who do not meet those criteria but who nonetheless may require such treatment to adequately control their MS, in the opinion of the treating neurologist. The sponsor proposes that the approved indication should allow treating neurologists (in conjunction with their patients) discretion to make appropriate and informed treatment decisions about use of alemtuzumab based upon a given patient's clinical presentation and after consideration of the benefits and the risks, with proactive risk mitigation according to the conditions for safe use specified in labelling and educational materials. Of note, these materials cite the requirement for patients to be actively monitored for potential risks for a period beginning with initial alemtuzumab treatment and continuing until 4 years after their last dose of alemtuzumab.

Knowledge of alemtuzumab's efficacy and safety in various patient subpopulations may assist the prescriber in making treatment decisions. Analyses in the initial submission demonstrate efficacy across patient subgroups stratified by pre-study relapse history, by MRI burden of disease, and by the presence of enhancing MRI lesions at entry. During the evaluation in the EU which led to a positive CHMP opinion recommending approval of Lemtrada, the applicant upon request of the CHMP, performed additional post-hoc analyses in subgroups described below.

In treatment-naïve patients with active disease, including those with lower disease activity: (CAMMS323 and CAMMS223 pooled, restricted to patients with active disease defined as having had ≥ 2 relapses in the prior 2 years) and analyses further restricting to subsets of this population.

- Both CAMMS223 and CAMMS323 were designed to evaluate the effects of alemtuzumab versus interferon beta-1a in patients with active RRMS. Accordingly, a key element of the eligibility rules was that all patients were required to have had at least 2 relapses in the 2 years prior to entry. In this pooled analysis, alemtuzumab 12 mg/day was significantly more effective than SC interferon beta-1a in its ability to decrease the frequency of relapses ($p < 0.0001$) and slow accumulation of disability ($p = 0.0029$).
- In order to assess the effects of alemtuzumab specifically on patients with relatively lower disease activity, the Applicant performed a pooled analysis of treatment-naïve patients who had 2 relapses in the 2 years prior to entry, excluding patients with more than 2 relapses in 2 years. In this subgroup analysis, as in the overall study population and those with active disease, alemtuzumab 12mg/day was significantly more effective than SC interferon beta-1a in its ability to decrease the frequency of relapses ($p < 0.0001$) and slow accumulation of disability ($p = 0.0059$) which demonstrates that alemtuzumab's superior efficacy relative to interferon beta-1a benefited even study patients with a relatively lower level of prior disease activity.
- **In treatment-naïve patients with highly active, rapidly evolving severe MS** (CAMMS323 and CAMMS223 pooled, restricted to patients with highly active disease defined as having had ≥ 2 relapses in the prior 1 years, ≥ 1 gadolinium-enhancing lesion at baseline, and an EDSS baseline of ≥ 1.5). The results of this analysis support the superior efficacy of alemtuzumab compared with SC interferon beta-1a on relapse ($p = 0.0013$) and disability ($p = 0.0266$) in study patients with rapidly evolving, severe MS.

Thus, alemtuzumab has efficacy superior to that of SC interferon beta-1a on both relapse and disability endpoints in all analysed treatment-naïve subgroups, with safety outcomes also being similar across subgroups. The risk of alemtuzumab treatment in this population is outweighed by the likelihood of MS-related deterioration during treatment with a less

effective agent and the eventual progression of irreversible disability that would likely result.

Similarly, in patients who relapsed after at least 6 months of either interferon beta-1a or glatiramer acetate (CAMMS324), alemtuzumab has efficacy superior to that of SC interferon beta-1a in all analysed subgroups, with safety outcomes also being similar across subgroups. Of note, patients who relapse despite disease modifying therapy (DMT) or who have subclinical 'breakthrough' disease activity during treatment with first-line DMTs are known to be at high risk for disease progression. Analyses of the "highly active" subgroup and of patients with gadolinium-enhancing lesions at entry (presented in CAMMS324 clinical study report) further demonstrate alemtuzumab's superior efficacy in difficult-to-treat relapsing MS populations.

Benefit-risk

As a leading cause of neurological disability in young adults, MS is a serious disease in which disease activity has a significant long-term impact. Although several medications have been approved for treatment of relapsing MS, there remains an unmet medical need for therapies that more effectively suppress relapses, and prevent (or reduce) the accumulation of disability. This is especially relevant in the treatment of patients with active disease and/or who have experienced disease activity on prior therapies. Relapse rate early in the course of the disease is associated with the time to reach fixed disability with higher numbers of relapses leading to more rapid progression to EDSS-defined milestones (Weinshenker *et al.*, 1989²⁶, Confavreux *et al.*, 2003²⁷). Rudick *et al.*, 2004²⁸ demonstrated that patients who experienced relapse on either placebo or interferon beta-1a were more likely to experience disability progression during 2 years of follow up than patients free of disease activity. While predictive of a poor outcome for placebo treated patients, this finding was particularly true for patients with breakthrough activity in the first 2 years of treatment with interferon beta-1a as these patients had a higher risk of experiencing significant levels of disability even 15 years later (Bermel *et al.*, 2013²⁹). This has led to a more proactive approach to the treatment of the disease where higher efficacy treatments are increasingly used as early as possible in the disease course to allow the greatest chance of favourable long-term outcomes.

The sponsor's studies of alemtuzumab versus subcutaneous interferon beta-1a (SC interferon beta-1a; Rebif) in treatment-naïve patients and in patients who had experienced an inadequate response to prior MS therapy demonstrate that alemtuzumab is effective and superior to SC interferon beta-1a with a clear reduction in the frequency of relapses and improved disability outcomes regardless of disease status. Therefore, these data do not support a restriction of the indication for alemtuzumab to a more advanced population with risk markers, and rather indicate that treatment in an earlier stage of the disease has a similarly favourable benefit/risk balance. In the context of the proposed risk management program with detailed education, frequently lab monitoring and a post-marketing study for long-term assessment of safety, the risks of alemtuzumab treatment in RRMS patients are outweighed, not only by the intrinsic efficacy of the product in such patients, but also by the likelihood of MS-related deterioration if treatment with a less effective agent were implemented. Not all neurologists or patients will choose (or should choose) to use alemtuzumab, but treating physicians should be given the freedom to make

²⁶ Weinshenker BG *et al.* The natural history of multiple sclerosis: a geographically based study. *Brain* 1989;112(6).

²⁷ Confavreux C *et al.* Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain* 2003;Apr;126(Pt 4):770-782.

²⁸ Rudick R, *et al.* Defining interferon beta response status in multiple sclerosis patients. *Ann Neurol* 2004;56(4):548-555.

²⁹ Bermel *et al.* Predictors of long-term outcome in multiple sclerosis patients treated with interferon beta. *Ann Neurol* 2013;73(1);95-103

appropriate treatment recommendations based on individual patient's circumstances, supported by the data which suggest the benefit/risk balance for alemtuzumab is favourable in a broad spectrum of treatment-naïve patients with RRMS, as well as those patients with an inadequate response on prior therapy.

Distinct difference between alemtuzumab and cladribine

While both alemtuzumab and cladribine have an effect on lymphocytes, it is important to note that each achieves its effect through a distinct mechanism of action (MOA) which may result in important differences in the safety profile of each product. Importantly, the effects on immunity following treatment with each drug are quite different, resulting in immune suppression with cladribine versus immune modulation with alemtuzumab. Cladribine's MOA is based on disruption of cellular metabolism by the inhibition of DNA synthesis and repair leading to apoptosis (Giovannoni *et al.*, 2010³⁰). The innate immune system is also negatively affected as evidenced by the observed reduction in neutrophil count (Movectro PI, Australia). Concurrent suppression of adaptive and innate immunity may lead to a broad and durable impairment of immune surveillance. These effects on immunity along with the direct effect of cladribine on DNA synthesis and repair are likely responsible for the increased risk of malignancies.

Alemtuzumab binds to CD52 which is present at high levels on the surface of T and B lymphocytes, and at lower levels on NK cells, monocytes, and macrophages. There is little or no CD52 detected on neutrophils, plasma cells, or bone marrow stem cells.

Alemtuzumab mediates cell lysis through antibody dependent cellular cytotoxicity, complement dependent cytotoxicity and, to a lesser extent, through induction of apoptosis. Clinical studies show lymphopaenia and subsequent lymphocyte repopulation to be the primary pharmacodynamic effect of alemtuzumab in MS. Immunomodulatory effects of alemtuzumab could arise from alterations in the number, proportions, and properties of some lymphocyte subsets during repopulation. While lymphopaenia is an initial and transient effect of alemtuzumab, the increased representation of T regulatory cells and other observed changes in repopulating lymphocyte subsets after alemtuzumab treatment provide an immunologically plausible alternative mechanism that could mediate the therapeutic activity of alemtuzumab in MS patients.

Also in contrast to alemtuzumab, the clinical development program for oral cladribine consisted of a single placebo-controlled study in early RRMS patients, whereas the alemtuzumab clinical development program consisted of 3 head-to-head, active-controlled studies versus one of the most effective MS therapies, high-dose, high frequency interferon beta-1a (Rebif) in two distinct patient populations. Further, taking into account data from extension studies in MS, the safety profile of alemtuzumab has been extensively studied and is very well characterized as described below.

Treatment with alemtuzumab after two cycles

Long-term outcomes in patients who have received > 2 treatment courses show a safety profile that are consistent with, and not worse than, that observed during the first two treatments. As of an updated safety analysis performed for FDA with a data cut-off date of 26 November 2012, a total of 1,486 patients in the clinical studies of MS (including the ongoing Extension Study) have received alemtuzumab in Integrated Summary of Safety (ISS) Pool C (that is, all patients, complete follow up): 1,217 (82%) patients were in the 12 mg/day alemtuzumab group and 269 (18%) were in the 24 mg/day alemtuzumab group. Of these patients, 72.5% received two cycles of treatment, 18.3% received three cycles and 4.4% received four cycles.

³⁰ Giovannoni G *et al.* A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *New Engl J Med* 2010 Feb 4;362(5):416-426.

Overall, the median duration of follow-up for all alemtuzumab-treated patients who received any number of treatment cycles (n = 1,486) was 43.2 months (range: 8.9 to 117.3 months) for a total of 5400.67 person-years of follow-up. A total of 1241 (83.5%) alemtuzumab-treated patients had at least 2 years of follow-up; 1078 (72.5%) had at least 3 years of follow-up; and 444 (29.9%) had at least 4 years of follow-up.

Of the 346 patients who had received 3 or more cycles of treatment, the mean follow-up is 23.5 months following the third cycle. Representing over 20% of the patient pool, the follow-up on these patients is already sufficiently long to enable trends or signals in latent events to have been detected. The time course of lymphocyte recovery after 3 treatment cycles in CAMMS223 patients shows that cells consistently repopulate.

Analysis of the available long-term data found no increased risk for AEs with the administration of a 3rd or 4th cycle of treatment. Importantly, the types of AEs observed did not differ with increasing number of treatment cycles. No meaningful trends were observed with respect to the incidence or rate of AEs including malignancies by number of treatment cycles, years of follow up, or cumulative alemtuzumab dose. Also, the safety profile of alemtuzumab was similar in treatment-naïve patients and patients relapsing on prior therapy.

Alemtuzumab dose and dosing regimen

The selection of the dose and dosing regimen for Phase II Study CAMMS223 was based on experience in pilot studies in MS patients treated with alemtuzumab at cumulative dosages ranging from 60 mg to 120 mg administered over 10 days. Doses of 12 mg/day and 24 mg/day were selected to bracket the 20 mg pilot study daily dose to examine possible dose-response relationships. Dose selection for the Phase III studies was based on the clinical data from CAMMS223. Both regimens used in Study CAMMS223 provided clear efficacy signals: alemtuzumab 12 mg and 24 mg were significantly more effective than SC interferon beta-1a; (decreasing the frequency of relapses p-values for 12mg/day and 24 mg/day p < 0.0001 and slowing accumulation of disability p-values for 12mg/day and 24 mg/day p = 0.0006 and p = 0.0021 respectively); additionally, the 12 mg and 24 mg doses had similar overall safety profiles.

Data from CAMMS223 and CAMMS324 suggest that reduction from the 24 mg dose to the 12 mg dose leads to reduced efficacy, particularly on MRI endpoints (although still better than interferon beta-1a). Since the MRI endpoints are a more sensitive measure of disease activity than clinical endpoints (Martinelli Boneschi, 2004³¹, *Mult Scler*), the consistently smaller effect on MRI outcomes with the 12 mg/day dose compared with 24 mg/day suggests there could be a further waning of efficacy, with potential impact on clinical outcomes, at doses below 12 mg/day. Analysis of the safety data show that the 12 mg infusions were better tolerated than 24 mg, but that the risk of autoimmune disorders did not differ by dose. Therefore, the 12 mg/day dose appears to be optimal from a benefit-risk standpoint and is thus the proposed dose for licensing. It is the recommended dose for use in the EU per the recent CHMP positive opinion.

Delegate's question 3. Alemtuzumab use during pregnancy and breast feeding

At the time of the MabCampath registration, no animal studies on fertility, embryofetal development, or lactation had been conducted, nor were they considered necessary (given the indication of B-CLL, which occurs predominantly in the elderly population) and as such the contraindication was based on an absence of data. Human IgG is known to cross the placental barrier, and alemtuzumab may cross the placental barrier potentially causing fetal T and B cell lymphocyte depletion. Based on pharmacokinetic data, the concentration of alemtuzumab in patients in the clinical trials generally becomes undetectable at 1

³¹ Martinelli Boneschi F *et al.* The use of magnetic resonance imaging in multiple sclerosis: lessons learned from clinical trials. *Multiple Sclerosis* 2004; 10(4):341-347.

month post treatment. As presented in the ISS, reproductive toxicology studies in the human CD52 transgenic mouse demonstrated placental transfer and potential pharmacologic activity of alemtuzumab (that is, alterations in lymphocyte counts) in the offspring exposed during gestation and post-partum (ISS). These observations in mice were not considered adverse and no functional effects on the immune system of the offspring were observed following exposure to alemtuzumab during lactation. The relevance to humans is unknown. Taken together, the PI includes a conservative recommendation for female patients of childbearing potential to use effective contraception during treatment and for 4 months post alemtuzumab treatment.

In nonclinical studies, alemtuzumab was detected in the milk and offspring of lactating female mice administered 10 mg/kg alemtuzumab for 5 consecutive days postpartum (ISS). No data are available on detection of alemtuzumab in the breast milk of patients after a course of alemtuzumab treatment. Therefore, the PI recommends breast-feeding be discontinued during treatment and for 4 months following the last infusion of each treatment course. In clinical studies of alemtuzumab in MS, a total of 99 pregnancies in 78 alemtuzumab-treated patients have been reported as of 26 November 2012 with most of the pregnancies ending in live births. Anecdotal reports of partners of male patients treated with alemtuzumab demonstrate similar outcomes. Based on the available information the PI recommends that alemtuzumab should be administered during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. Such a decision would lie with the patient's physician who would be able to make an informed benefit-risk assessment based on an individual's circumstances as to whether alemtuzumab treatment should be administered or not and thus does not require pregnancy to be contraindicated.

Delegate's question 4. Information on the risk of malignancy

Clinical studies have not shown an increased risk of malignancy for alemtuzumab treated patients when compared with Rebif (interferon beta-1a). The annualized rates of malignancies reported through 2 years of follow up were 0.002, 0.003, and 0.003 per person-year for the alemtuzumab 12 mg/day, alemtuzumab pooled, and interferon beta-1a treatment groups, respectively. Over all available follow-up for all alemtuzumab treated patients through 26 November 2012, a total of 22 malignancies have been reported for 19 patients treated with alemtuzumab in the clinical trials. The annualised rate was 0.407 per 100 person-years, which is within the range of the background population (0.151 to 0.834, Surveillance, Epidemiology and End Results (SEER) program 2009 in 20-49 and 50-64 years old in the US). The most common malignancies reported were thyroid cancer (5 patients), breast cancer (5 patients) and basal cell carcinoma (4 patients), which are among the most frequent cancers reported for white, young adults.

Considering that for immunomodulatory products there is a theoretical risk of malignancy, the following statements are proposed to be included in the *Precautions* section of the PI and in the CMI.

PI: Malignancy *As with other immunomodulatory therapies, caution should be exercised in initiating Lemtrada therapy in patients with pre-existing and/or an on-going malignancy.*

CMI: Previously diagnosed cancer *If you have been diagnosed with cancer in the past, please inform your doctor about it.*

Advisory committee considerations

The ACPM having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Lemtrada/Remniq concentrated injection containing 10 mg/mL of

alemtuzumab to have an overall marginally positive benefit–risk profile for the amended indication;

Lemtrada/Remniq is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) who failed previous treatment or are unsuitable for other treatments.

The risk-benefit profile of Lemtrada/Remniq does not support use as a first-line disease-modifying agent

The ACPM agreed with the proposed laboratory monitoring.

Proposed conditions of registration:

The ACPM advised that the conditions of registration should include the following:

- Subject to satisfactory negotiation of the RMP most recently approved by the TGA; and
- Negotiation of PI and CMI to the satisfaction of the TGA.

Proposed PI and CMI amendments:

The ACPM advised that the amendments to the PI and CMI should include:

- A statement in the *Dosage and Administration* and *Contraindications* sections of the PI and relevant sections of the CMI classifying Lemtrada/Remniq as a pregnancy category C medicine, contraindicated in pregnancy and breastfeeding;
- The current contraindication in patients with HIV should be replaced with a statement contraindicating use in patients with increased risk for opportunistic infections, including those immunocompromised due to current or recent immunosuppressive therapies or systemic medical conditions resulting in significantly compromised immune system function (for example, HIV, organ transplant, active malignancy).
- The PI and CMI for Lemtrada/Remniq and MabCampath should be harmonised in accordance with latest available evidence
- A statement in the *Precautions* section of the PI and relevant sections of the CMI clarifying the risk of malignancy and providing greater detail.
- A statement in the *Precautions* section of the PI and relevant sections of the CMI similar to;
 - There is limited information of the efficacy and safety of Lemtrada beyond two years. Observation over longer treatment periods is required before any effect of Lemtrada/Remniq on malignancies can be excluded.
- The CMI formatting is inconsistent with guidelines.
- The CMI *Contraindications* section requires revision.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, and considering matters raised during post-ACPM negotiations of the PI, TGA approved the registration of Lemtrada/Remniq injection concentrate containing alemtuzumab 10 mg/mL, indicated for:

Lemtrada/Remniq is indicated for the treatment of relapsing forms of multiple sclerosis (MS) for patients with active disease defined by clinical or imaging features

to slow the accumulation of physical disability and reduce the frequency of clinical relapses.

Specific conditions applying to this therapeutic good

- The Lemtrada and Remniq injection containing alemtuzumab 10 mg/mL European Risk Management Plan Version; 1.6 (dated 25 June 2013) with an Australian Specific Annex Version: 1.2 (dated December 2013), included with submission PM-2012-02297-3-1, and any subsequent revisions, as agreed with the TGA must be implemented in Australia.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

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