27 June 2013
EMA/563018/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lemtrada

International non-proprietary name: ALEMTUZUMAB

Procedure No. EMEA/H/C/003718/0000

Note

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

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List of abbreviations

AE: adverse event
AESI: adverse events of special interest
ALT: alanine aminotransferase
ARR: annualised relapse rate
AST: aspartate aminotransferase
BCRP: breast cancer resistant protein
BCS: Biopharmaceutics Classification System
BfArM: Federal Institute for Drugs and Medical Devices
BOD: burden of disease
BP: blood pressure
CHMP: Committee for Medicinal Products for Human Use
CI: confidence interval
CIS: clinically isolated syndrome
CMV: cytomegalovirus
CT: computed tomography
CTD: common technical document
CYP: cytochrome P450
DMT: disease-modifying therapies
EAE: experimental autoimmune encephalomyelitis
EDSS: expanded disability status scale
EMA: European Medicines Agency
EQ-5D: EuroQoL
FIS: Fatigue Impact Scale
FS: functional score
GA: glatiramer acetate
Gd: gadolinium
HLT: high level term
IC50: half maximum inhibitory concentration
IFN: interferon
IgG: immunoglobin G
IgM: immunoglobin M
ILD: interstitial lung disease
IV: intravenous
IVIVC: in vitro/in vivo correlation
LS: least-squares
MAA: Marketing Authorisation Application
MEB: Medicines Evaluation Board
MedDRA: Medical Dictionary for Regulatory Activities
MRI: magnetic resonance imaging

MS: multiple sclerosis
MSFC: multiple sclerosis functional composite
NCT: nerve-conduction test
NOAEL: no-observable-adverse-effect level
OAT: organic anion transporter
OATP: organic anion transporting polypeptide
PCSA: potentially clinically significant abnormality
PDCO: Paediatric Development Committee
PFT: pulmonary function testing
PIP: paediatric investigation plan
PML: progressive multifocal leukoencephalopathy
PPMS: primary progressive multiple sclerosis
PRMS: progressive-relapsing multiple sclerosis
PT: preferred term
QD: once a day
QOL: quality of life
RA: rheumatoid arthritis
RBC: red blood cell
RRMS: relapsing-remitting multiple sclerosis
SAE: serious adverse event
SAWP: Scientific Advice Working Party
SD: standard deviation
SF-36: Short Form (36) Health Survey
SMQ: standardised MedDRA query
SOC: system organ class
SPMS: secondary progressive multiple sclerosis
TEAE: treatment-emergent adverse event
TSQM: Treatment Satisfaction Questionnaire for Medication
ULN: upper limit of normal
WBC: white blood cell
WPAI: work productivity and activities impairment

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Genzyme Therapeutics Ltd submitted on 19 December 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Lemtrada, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Lemtrada is indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) to decrease the frequency of relapses and slow or reverse accumulation of disability.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application. The applicant indicated that alemtuzumab was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/286/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/286/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 27 June 2002, 27 July 2006, 24 May 2007, 25 September 2008 and 17 December 2009. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: Australia, Switzerland, USA, Canada and Brazil.

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of the active substance

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
D-88397 Biberach an der Riss
Germany

Manufacturers responsible for batch release

Genzyme Ltd
37 Hollands Road
Haverhill
Suffolk
CB9 8PU
United Kingdom

Genzyme Ireland Limited
IDA Industrial Park
Old Kilmeaden Road
Waterford
Ireland

1.3. Steps taken for the assessment of the product

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

Rapporteur: Jens Ersbøll Co-Rapporteur: Bengt Ljungberg

This application was received by the EMA on 19 December 2012 as a multiple of Lemtrada (H-2632), for which the steps taken prior to the submission of this application are detailed below:

Lemtrada H-2632 (Genzyme Europe BV)	
Submission date:	28 May 2012
Start of procedure:	20 June 2012
Rapporteur's initial assessment report circulated on:	7 September 2012
CoRapporteur's initial assessment report circulated on:	7 September 2012

Consolidated List of Questions agreed by the CHMP on:	18 October 2012
Consolidated List of Questions sent to MAA on:	22 October 2012
The summary report of the GCP inspection carried out at the following site(s) Zagreb (Croatia), Kiev (Ukraine) and Ramat Gan (Israel) respectively, on 23-26 of October 2012, 30 October-1 of November 2012 and 6-8 of November 2012 was issued on:	14 December 2012

The steps taken for the assessment of this application were the following:

Submission date:	19 December 2012
MAA responses to the CHMP consolidated List of Questions submitted on:	18 January 2013
Start of procedure:	19 January 2013
Joint Rapporteur/Co-Rapporteur Assessment Report on the MAA responses to the CHMP consolidated List of Questions circulated on:	22 February 2013
PRAC RMP advice and assessment overview adopted by PRAC on:	7 March 2013
List of outstanding issues to be addressed in writing and in an oral explanation adopted by the CHMP on:	21 March 2013
MAA responses to the CHMP List of Outstanding Issues submitted on:	29 April 2013
Notification letter dated 29 Apr 2013 from MAA renaming Alemtuzumab Genzyme H-3718 (Genzyme Therapeutics Ltd) as Lemtrada H-3718 (Genzyme Therapeutics Ltd) following withdrawal of Lemtrada H-2632 (Genzyme Europe BV) received on:	7 May 2013
PRAC RMP advice and assessment overview adopted by PRAC on :	13 May 2013
Joint Rapporteur/Co-Rapporteur Assessment Report on the MAA responses to the List of Outstanding Issues circulated on:	14 and 24 May 2013
During a meeting of SAG, experts were convened to address questions raised by the CHMP on:	16 May 2013
During the CHMP meeting, outstanding issues were addressed by the applicant during an oral explanation before the CHMP on:	28 May 2013
2nd List of outstanding issues to be addressed in writing and/or in an oral explanation adopted by the CHMP on:	30 May 2013
MAA responses to the 2nd CHMP List of Outstanding Issues submitted on:	5 June 2013
PRAC RMP advice and assessment overview adopted by PRAC on:	13 June 2013
Joint Rapporteur/Co-Rapporteur Assessment Report on the MAA responses to the 2nd CHMP List of Outstanding Issues circulated on:	17 June 2013
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	24-27 June 2013

a Marketing Authorisation to Lemtrada during the meeting on:	

2. Scientific discussion

2.1. Introduction

MS is a demyelinating disease of the central nervous system (CNS) that affects as many as 2.1 million people worldwide (National Multiple Sclerosis Society, 2011). The prevalence rate varies between races and geographical regions, with reported rates of more than 100 per 100,000 in Northern and Central Europe to 50 per 100,000 in Southern Europe (CPMP/EWP/561/98 Rev. 1). Similar variation in prevalence is also observed by geographical latitude in the United States (US; Noonan, 2010, Prev Chronic Dis). The age of onset ranges from approximately 10 to 60 years, with most cases typically occurring between 20 and 50 years of age. As with most other autoimmune disorders, multiple sclerosis is more common among women than men and has a female predominance of approximately 2:1 (Noseworthy, 2000, N Engl J Med).

Prognosis of multiple sclerosis is highly variable. Its overall prognosis is known, with irreversible limitation in ambulation (EDSS 4), a unilateral aid required for walking (EDSS 6) and patients becoming wheelchair-bound (EDSS 7) after median times of approximately 8, 20 and 30 years of evolution, respectively. It takes longer for cases with an exacerbating-remitting onset than in those with a progressive onset to reach levels of irreversible disability. Life expectancy is only marginally reduced. Another hallmark of the disease is the high degree of variability in the outcome from one patient to another, with the full spectrum of disease ranging from benign and even asymptomatic, to more malignant cases (Confavreux C et al: Brain 2003, Volume 126, Issue 4, 770-782).

Its clinical course is typically characterised by initial episodes of transient neurological compromise (relapses) with recovery, followed by a phase of cumulative deficits that may increase with each new episode. Many relapsing patients eventually develop secondary progression leading to a constellation of chronic sequelae including profound muscle weakness, impaired gait and mobility, bladder and bowel dysfunction, and cognitive and visual impairments. Although patients typically experience some degree of recovery following a relapse, even a single relapse can lead to permanent disability in a substantial number of patients with a sizeable majority being left with disability after two events (Lublin, 2003, Neurology). Furthermore, approximately 70% of those patients with relapsing-remitting MS eventually enter the secondary progressive phase of the disease characterised by continued physical and cognitive decline, with or without relapses, and are often unresponsive to existing treatments.

Pathologically, MS is characterised by focal tissue injury of the brain and spinal cord due to the complex interplay of inflammation, demyelination, axonal injury, astrocytosis and tissue atrophy. Given the central role of inflammation in the pathogenesis of MS, a number of immunological therapies have been studied in patients with this disease, including alemtuzumab.

In addition to symptomatic therapy and therapy for the treatment of acute relapses such as corticosteroids, there are currently eight products (representing 5 different drug classes)

approved as disease-modifying therapies (DMTs) for treatment of relapsing forms of MS in the the European Union (EU) and US.

Four of the approved DMTs are beta-interferon drugs that are typically used as first-line treatments: Betaseron/Betaferon and Extavia (subcutaneous [SC] IFNB-1b 250 µg on alternate days), Avonex (intramuscular [IM] IFNB-1a 30 µg once per week) and Rebif (SC IFNB-1a 22 or 44 µg 3 times per week). Glatiramer acetate (Copaxone; 20 mg/day SC) is also used as first-line therapy while mitoxantrone (Novantrone, Elsep; 12 mg/m² intravenous [IV] infusion every 3 months) is usually confined to aggressive or progressive cases due to associated toxic effects (Compston, 2008, *Lancet*; Pascual, 2009, *Mult Scler*). The most recently approved DMTs are natalizumab (Tysabri; 300 mg IV infusion every 4 weeks) and fingolimod (Gilenya; 0.5 mg capsule once daily).

Clinical experience with the existing approved DMTs indicate a reduction in relapses, slowed accumulation of disability and/or improvement in MRI outcomes to varying extent relative to placebo (Jacobs, 1996, *Ann Neurol*; PRISMS Study Group, 1998, *Lancet*; Johnson, 1995, *Neurology*; Li, 1999, *Ann Neurol*). The pivotal registration studies for the more recently approved natalizumab (as monotherapy) and fingolimod also used placebo as a comparator (Polman, 2006, *N Engl J Med*; Kappos, 2010, *N Engl J Med*) and none of the studies demonstrated in the longer term (e.g., studies of at least 2 years duration) that they are a more appropriate treatment or superior to the existing first-line therapies, particularly with regards to effects on accumulation of disability. A reduction in relapse rate was observed with fingolimod versus low-dose IM IFNB-1a over a 12-month period although there was no difference between treatments with regards to effect on disability progression (Cohen, 2010, *N Engl J Med*). Patients who received low-dose IM IFNB-1a and switched to fingolimod in an extension study showed improvements in relapse rates and MRI outcomes, but not disability progression, relative to the previous IFNB-1a treatment period (Khatri, 2011, *Lancet Neurol*). Fingolimod was not compared to high-dose, high-frequency IFNB-1a, nor was it formally studied in patients experiencing disease activity on another MS treatment.

The active substance, alemtuzumab, is a humanized monoclonal antibody directed against CD52, one of several specific surface antigens acquired by cells of the hematopoietic system during leukocyte differentiation. Alemtuzumab binds to CD52 which is present at high levels on the surface of T and B lymphocytes and at lower levels on natural killer cells, monocytes and macrophages. There is little or no CD52 detected on neutrophils, plasma cells or bone marrow stem cells.

Alemtuzumab was approved until recently as MabCampath for the treatment of B-cell chronic lymphocytic leukemia. The posology, however, is considerably different for MS as compared to B-CLL: the cumulative dose in B-CLL was around 1100 mg, administered in a dose escalation scheme within 12 weeks, while in MS the cumulative dose is much lower: a maximum cumulative dose of 96 mg, administered in two cycles 12 months apart.

The mechanism by which alemtuzumab exerts its therapeutic effects in multiple sclerosis is unknown, but may involve immunomodulation through the depletion and repopulation of lymphocytes. Research suggests that alemtuzumab alters the number, proportions and properties of some lymphocyte subsets on repopulation. The proposed mechanism of action is antibody dependent cell-mediated cytolysis and complement-mediated cytolysis following cell surface binding of alemtuzumab to lymphocytes.

2.2. Quality aspects

2.2.1. Introduction

The active substance of the finished product is alemtuzumab, a genetically engineered human immunoglobulin subclass gamma 1 (IgG1) kappa monoclonal antibody containing 6 complementarity-determining regions derived from an IgG2a rat monoclonal antibody, specific for the cell surface glycoprotein, CD52.

Alemtuzumab binds to CD52, an antigen present at high levels on the surface of B and T lymphocytes, and to a lesser extent on other leukocytes including natural killer (NK) cells, monocytes, and macrophages. Alemtuzumab acts by causing cell lysis through both complement fixation as well as antibody dependent cell-mediated cytolysis following cell surface binding of alemtuzumab to lymphocytes.

The finished product is a concentrate solution for infusion and will be available as 1.2 ml (10 mg/ml) vials.

2.2.2. Active Substance

The alemtuzumab molecule is a genetically engineered human IgG1 kappa monoclonal antibody with a molecular weight of approximately 150 kD. The humanized antibody was made by the insertion of six complementarity-determining regions (CDRs) from an IgG2a rat monoclonal antibody into a human IgG1 immunoglobulin molecule.

The alemtuzumab molecule consists of two ~24 kD small polypeptide chains (light chains, 214 amino acids) and two larger ~49 kD polypeptide chains (heavy chains, 450 amino acids) linked together by two inter (light chain - heavy chain) disulphide bridges and two inter (heavy chain - heavy chain) disulphide bridges to form a Y-shaped molecule, typical for immunoglobulins of the IgG1 subclass. Each molecule also contains a total of 12 intra-chain disulphide bridges and an asparagine residue (301) in each heavy chain which is glycosylated.

Manufacture

Alemtuzumab active substance is manufactured by Boehringer Ingelheim Pharma GmbH & Co. KG.

Source, history and generation of the cell substrate

The source of the antibody and the generation construction of the expression construct are adequately described. The expression construct has been characterized in accordance with ICH Q5B. Alemtuzumab was generated by humanisation of a rat antibody (CAMPATH-1G) directed against the human CD52 antigen.

The cell line development has been described in details, including the animal derived materials used during the culturing and selection procedures. Alemtuzumab is produced in a Chinese Hamster Ovary (CHO) cell line.

The cell banking system, including the procedure for establishment of future working cell banks, is considered properly described. The characterization of the Master Cell Bank (MCB) and Working Cell Bank (WCB) is in accordance with ICH Q5D and Q5B. Viral examination of the WCB and MCB is in accordance with Q5A. The first MCB, designated MCB1, was prepared from the premaster cell line. MCB1 was used to produce WCBs that produced clinical trial material. After the production of MCB1, a second MCB (MCB2) was prepared from a subclone of MCB1 to improve stability. MCB2 was fully characterized and is the source of all WCBs utilised for commercial production. The testing of future WCB includes: viability, cell growth, sterility, mycoplasma, identity (isoenzyme), adventitious virus (*in vitro* and *in vivo*), bovine virus, infectious retroviruses and genetic stability (copy number estimation, restriction enzyme mapping, DNA sequencing and RNA integrity).

Manufacture

The cell culture process consists of four main stages: (1) thawing of vials and expansion of inoculum in spinner flasks, (2) further expansion of the seed train in growth bioreactors, (3) batch production at the bioreactor scale, and (4) clarification of the harvest.

The purification and formulation processes consist of seven unit operations: (1) an initial ultrafiltration/ diafiltration process, (2) an affinity capture chromatography column, (3) a cation exchange chromatography column run in conjunction with an anion exchange chromatography membrane, (4) virus reduction nanofiltration process, (5) a second ultrafiltration / diafiltration process, (6) a size exclusion chromatography column (SEC), and finally (7) formulation.

The harvest from one production bioreactor is purified to provide one active substance batch.

The active substance is defined as the SEC column eluate that has been adjusted for concentration to 10 mg/ml and formulated.

Control of critical steps and intermediates

The overall alemtuzumab process has a planned set of controls, derived from product and process understanding, which ensure consistent process performance and a resulting product of required quality. Each step of the cell culture, purification, and formulation processes is controlled by monitoring critical process parameters (CPPs), intermediate specifications (ISs), and in-process controls (IPCs).

During the evaluation procedure, upon request, further information had been provided on the control strategy.

There is no animal origin components utilised in the alemtuzumab process, with the exception of the CHO cell-line.

The manufacturing process development is considered properly described. It has been demonstrated that the major process changes performed (extension of cell culture duration and change of media component) during the sclerosis clinical trials have not affected the quality of the product.

The manufacturing process was fully validated. The validation data demonstrate a consistent manufacturing process. The validation results were within pre-defined acceptance criteria and comparable to historical data.

Characterisation and Impurities

Alemtuzumab has been characterised structurally by spectroscopic, electrophoretic and chromatographic assays and characterised functionally by enzyme-linked immunosorbent assay (ELISA) and immunoassay. The characterisation is based on studies performed for first product of alemtuzumab (MabCampath), additional testing and release analysis of the present active substance and finished product batches. The characterization data on the active substance batches and finished product batches demonstrate that the manufacturing process results in a consistent product.

The complete primary structure of alemtuzumab has been defined by a combination of protein and cDNA sequencing, amino acid and carbohydrate analysis, carbohydrate structure determination and mass spectroscopy. Carbohydrate moieties are linked to the CH2 domain at a single N-linked site. Mapping of proteolytic digests using reverse phase high-performance liquid chromatography (RP-HPLC), electrospray ionisation mass spectrometry (ESI-MS), and matrix assisted laser desorption ionisation–time of flight (MALDI-TOF) has demonstrated the glycoforms present in alemtuzumab. The secondary and tertiary structure of alemtuzumab has been confirmed using circular dichroism spectroscopy and x-ray crystallography. The results are consistent with an antibody of the IgG class.

Alemtuzumab mediates lysis of CD52+ lymphocytes *in vivo* by both complement mediated cell lysis (CMCL) and antibody dependent cytotoxicity (ADCC) mechanisms.

The alemtuzumab antigen, designated CD52, is acquired by cells during the leukocyte differentiation cascade. With an apparent molecular weight of 21 to 28 kDa the mature CD52 is a small but heavily glycosylated, non-modulating glycophosphatidylinositol (GPI)-anchored glycoprotein. Its length of only 12 amino acids makes it one of the shortest cell-surface glycoproteins ever found.

The potential process-related impurities have been identified and it has been demonstrated that the manufacturing process is capable of consistently reducing these impurities to very low levels. The omission of routine testing for the process-related impurities is considered properly justified by validation and long manufacturing experience.

The potential product-related impurities include alemtuzumab aggregates and alemtuzumab fragments , with the desired active substance composed of alemtuzumab monomer.

Specification

The release specification for alemtuzumab active substance include tests for identity, purity , potency, protein content , safety (endotoxin, bioburden), and physical characteristics (pH, osmolarity, appearance).

Overall, the control tests proposed for active substance are in accordance with ICH Q6B and EMEA/CHMP/BWP/157653/2007 and are considered adequate in order to ensure sufficient quality with regard to identity, purity, quantity, potency and physiochemical properties. The specification acceptance criteria are based on historical release and stability data and data on clinical batches and are considered acceptable. The omission of routine testing for the process related impurities has been properly justified.

The CMCL assay has been justified as suitable for potency testing also for the MS indication.

Stability

The proposed shelf-life for the Alemtuzumab active substance can be accepted based on stability data provided.

In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3. Finished Medicinal Product

Lemtrada is supplied as a sterile, clear, colorless to slightly yellow, concentrate solution that must be diluted prior to IV infusion. It is presented as a single use vial containing 12 mg alemtuzumab in 1.2 ml solution (10 mg/ml). Each 1.0 ml of concentrate solution contains 10 mg of alemtuzumab, along with sodium chloride, dibasic sodium phosphate, potassium chloride, potassium dihydrogen phosphate, polysorbate 80, disodium edetate dihydrate, and water for injections.

Alemtuzumab is administered by I.V. infusion. This route of administration requires that the solution is further diluted with 0.9% Sodium Chloride Injection, or 5% dextrose solution. Studies have been performed to evaluate finished product quality and stability in both of these solutions.

Pharmaceutical Development

Alemtuzumab finished product is an isotonic solution for intravenous infusion. The current formulation for alemtuzumab (10 mg/ml), was based upon the results of cumulative stability studies to determine which formulations were suitable for intravenous administration and exhibited a long term stability profile.

Alemtuzumab finished product was initially manufactured at a concentration of 10 mg/ml and filled into 5 ml Type 1 glass ampoules. In order to improve product handling, a new dosage form was introduced in 2004 by the license holder for alemtuzumab at that time. The concentration of the active ingredient was increased from 10 mg/ml to 30 mg/ml and the container closure was changed from the 5 ml Type I glass ampoule to a 2 ml Type I glass vial/stopper format.

The vial format was maintained when the 12 mg/1.2 ml dosage using the alemtuzumab 10 mg/ml formulation was selected for multiple sclerosis (MS) clinical trials. Subsequent long term stability studies have demonstrated that the 10 mg/ml formulation in the 12 mg vial format exhibits an acceptable stability profile.

There is no formulation overage incorporated into the alemtuzumab 10 mg/ml. However, an overfill is added to the vial to ensure delivery of a nominal 1.2 ml dose to the patient.

Manufacture of the product

The active substance is defined as the formulated product pool containing alemtuzumab, phosphate buffered saline (PBS), disodium edetate dihydrate (EDTA) and polysorbate 80.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

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

1. bulk sterile filtration and aseptic filling,

2. stoppering and capping,

3. labelling and packaging.

The manufacture is acceptably described and the in-process controls are deemed suitable for controlling and monitoring the manufacturing process. The aseptic manufacturing process has been satisfactorily validated. All validation batches complied with the established in-process and release specifications as well as additional process monitoring data. No critical deviations were observed. The results and requirements for the media fill validation is found acceptable and are in line with current EU requirements.

All the excipients comply with Ph Eur requirements.

Product Specification

The proposed finished product specification includes general controls (colour & clarity, particulate matter, pH, osmolality, extractable volume and tests for excipients, as well as controls for safety (endotoxin, sterility), identity, purity/impurity, protein concentration and potency (Complement Mediated Cell Lysis).

The proposed finished product specifications are suitable for control of the finished product. Upon request the limits proposed for potency have been tightened to reflect clinically qualified potency results.

Many tests used for release testing of the finished product are also used for release testing of the active substance.

Batch analysis data from batches used in MS indication clinical trial, non-clinical studies and for process validation are presented. All data comply with the acceptance criteria in the release specification.

Stability of the product

The proposed shelf-life of the finished product is 36 months at 2-8°C and is acceptable based on the submitted data (pilot-scale and large-scale finished product batches).

Chemical and physical In-use stability has been demonstrated for 24 hours, when stored at 2-8ºC or at room temperature, and followed by an infusion period of 8 hours at room temperature. The Applicant recommends that the solution for infusion is prepared just prior to administration to minimize the potential for protein aggregate formation and for microbiological reasons since the product does not contain preservatives. This recommendation is reflected in section 6.3 of the SmPC.

In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

Adventitious agents

The evaluation of adventitious agents demonstrates presence of control for contamination by mycoplasma, bacteria and fungi by adequate methods.

The use of human and animal derived components has been reduced to bovine albumin for establishment of Working Cell Banks. Transmissible spongiform encephalitis (TSE) certificates for these have been provided demonstrating compliance with the TSE guideline.

The cell banks and the manufacturing process are under control for adventitious viruses in that cell banks are tested for presence of viruses, and viral reduction of the manufacturing process has been evaluated using model viruses. The process contains 6 steps contributing to the viral clearance. The results for reduction of viruses are acceptable and the company is actively pursuing future improvements.

GMP

Acceptable GMP status has been verified for the involved manufacturers.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

In the Quality Dossier for Lemtrada the development, characterisation, manufacture and control of the active substance alemtuzumab and the finished product Lemtrada are adequately described. No major objections have been identified that would have precluded a Marketing authorisation. However, a number of other concerns have been raised and satisfactorily addressed by the Applicant during the evaluation procedure. In conclusion, based on the review of the quality data provided, the CHMP considers that the marketing authorisation application for Lemtrada is approvable.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The applicant has acceptably resolved all issues identified during the assessment and there are no remaining quality issues preventing a positive opinion.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP has recommended some future quality developments be considered.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.3. Non-clinical aspects

2.3.1. Introduction

Alemtuzumab is a recombinant DNA-derived humanised monoclonal IgG1 kappa antibody directed against the cell surface glycoprotein CD52. The CD52 antigen is present on the surface of T and B lymphocytes and is expressed to a lesser extent on monocytes, eosinophils and macrophages. Low level expression is also found on mature NK cells and haematological stem cells. CD52 is also present in the human male reproductive tissues such as the epididymis, vas deferens, and in semen.

The majority of the toxicology studies were conducted in compliance with OECD GLP and/or European Community Directives.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The non-clinical pharmacology of alemtuzumab was assessed in a number of *in vitro* and *in vivo* studies.

In vitro

In vitro pharmacology studies were conducted to evaluate the effects of alemtuzumab on human cells, including peripheral blood mononuclear cell (PBMC) subsets and hematopoietic precursors.

In study 10GSTR059 investigating the susceptibility of various myeloid and lymphoid cell populations to alemtuzumab mediated complement-dependent cytolysis (CDC), alemtuzumab had significant cytolytic effects on human B and T cells, with minimal effects on NK cells. This effect correlated with the density of CD52 on these cells. Alemtuzumab did not have significant complement-mediated depleting effects on monocytes, dendritic cells, basophils and lymphoid derived plasmacytoid dendritic cell.

Evaluation of alemtuzumab mediated cytotoxicity on human primary T cells by antibody-dependent cell-mediated cytolysis (ADCC) and CDC in study 10GSTR079 showed significant CDC lysis and ADCC activity in all donors at concentrations as low as 250 ng/ml.

In Study 10GSTR058, following alemtuzumab depletion of normal human T cells through CDC, an increase in the percentage of T cells with a regulatory phenotype (FoxP3+ CD4+ T cells) in the remaining live population was observed compared to control antibody-exposed cells. Furthermore, the alemtuzumab CDC-exposed T cells displayed functional regulatory activity as indicated by their lack of proliferation when stimulated with allogeneic dendritic cells and their ability to suppress the allogeneic response of autologous T cells.

In study BPAT/91/0062, alemtuzumab exposure had no observable effects on bone marrow progenitor cells, which suggested that alemtuzumab was unlikely to impair early hematopoietic development.

In vivo

The primary pharmacodynamic effect evaluated in the *in vivo* pharmacology studies was lymphocyte cell depletion. The studies were conducted in the human CD52 (huCD52) transgenic mouse model and in the cynomolgus monkey. In studies 07-1727 and 10-00373 in the huCD52 transgenic mouse, for both single and repeat dosing and at dose levels ranging from 0.1 to 1 mg/kg, depletion of T and B cells was consistently observed at 24 hours following alemtuzumab administration. Depletion was noted in blood and selected lymphoid tissues (spleen and inguinal lymph nodes).

Lymphocyte depletion was observed also in cynomolgus monkeys at doses 3 mg/kg i.v. or s.c.

Efficacy studies in animal models of MS were not conducted with alemtuzumab, because clinical efficacy data were already available from clinical experience with alemtuzumab for MS at the time huCD52 transgenic mice were developed and characterised.

Secondary pharmacodynamic studies

The secondary pharmacodynamic studies investigated temporal relationship of lymphocyte depletion and repopulation following alemtuzumab administration and were conducted in huCD52 transgenic mouse and the cynomolgus monkey. Studies in the huCD52 transgenic mouse were also performed to characterise the release of cytokines following alemtuzumab.

In study 10-00283, the kinetics of alemtuzumab-mediated depletion and potential repopulation of multiple immune cell subsets was evaluated within a period of 28 days following 5 daily i.v. doses of alemtuzumab in huCD52 transgenic mice. The results showed that depletion of total T cells, T helper cells, T cytotoxic cells and T regulatory cells in whole blood persisted at D28 following a 5-day cycle of dosing. In contrast, T cell levels in the spleen were similar to those observed in control animals at D28, suggesting that depletion in the spleen was shorter-lived. Depletion of B cells was noted in the blood and spleen at Day 7 and Day 14, but no significant decrease compared to control animals was seen at Day 28 for any B cell subset evaluated. In cynomolgus monkeys, following completion of a 5-day cycle of alemtuzumab, both B-cells and CD8+Tcells recovered to levels close to baseline by Day 60. This recovery to baseline levels at the end of the 60-day study period was not observed for CD4+T cells.

The cytokine release was investigated following a single i.v. or s.c. administration of alemtuzumab (0.5 or 3 mg/kg) in heterozygous huCD52 transgenic mice (5/sex/group). The levels of the cytokines IL-6, IL-10, MCP-1 and TNF-α were significantly elevated especially at 2-4 hours post-dosing.

Safety pharmacology programme

Two studies were conducted in the cynomolgus monkey that evaluated the safety pharmacology of alemtuzumab. A single-dose study was conducted in anaesthetised monkeys at doses ranging from 3 to 30 mg/kg of alemtuzumab administered over a 40 minute infusion period (study BPHP/92/0039). No major effects on the cardiovascular and respiratory systems were noted at 3 mg/kg. Transient and moderate hypotension and tachycardia were observed at higher dose levels. A single animal dosed at 30 mg/kg exhibited severe hypotension and

tachycardia, which ultimately resulted in cardiovascular collapse and subsequent respiratory arrest and eventually death.

A repeat-dose study (5 daily doses) was conducted in monkeys at doses of 3 to 30 mg/kg over a 180 minute infusion period (study FFA00142). In this study, a single male animal had 9 ventricular premature complexes. Referring to ventricular premature complexes as a normal variant in cynomolgus monkeys, the applicant concluded that there were no apparent or biologically relevant changes in heart rate, blood pressure or qualitative electrocardiograms associated with administration of alemtuzumab at any of the doses tested in this study.

Pharmacodynamic drug interactions

Pharmacodynamic drug interactions of alemtuzumab were not studied by the applicant (see 2.3.6 Discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

The pharmacokinetic characteristics of alemtuzumab were assessed in single- and repeat-dose studies in huCD52 transgenic mice, wild-type CD-1 mice and cynomolgus monkeys. Alemtuzumab pharmacokinetics was assessed following i.v. and s.c. routes of administration at doses ranging from 0.5 to 10 mg/kg in the huCD52 transgenic mouse and 0.1 to 30 mg/kg in the cynomolgus monkey.

Comparing pharmacokinetics of alemtuzumab following a single i.v. dose of 1 mg/kg in huCD52 transgenic mice vs wild-type CD-1 mice, significant differences were seen for the terminal elimination half-life (~3-fold shorter), the clearance (~9 fold higher), the volume of distribution (~3 fold larger) and the AUC (~5 to 8 fold lower) in huCD52 transgenic mice.

Single dose studies with i.v. and s.c. alemtuzumab administration to transgenic mice and cynomolgus monkeys did not indicate any significant deviations from the dose proportional pharmacokinetics at the dose levels studied (0.5 and 1 mg/kg for transgenic mice and 0.3 and 3 mg/kg for cynomolgus monkeys). The terminal elimination half-life was 34.5 to 45.3 hours in transgenic mice and 4.6 to 6.7 days in cynomolgus monkeys. Bioavailability following s.c. administration ranged from 53.6 to 74.6% in transgenic mice and from 60.3 to 62.9% in cynomolgus monkeys.

The repeat-dose pharmacokinetic analysis of alemtuzumab was performed in huCD52 transgenic mice following one cycle of daily dosing for 5 days and in cynomolgus monkeys following one or two cycles of daily dosing.

In transgenic mice, results of the repeated administration (i.v. dosing of 1 mg/kg for 5 days) indicated time-dependent pharmacokinetics. The systemic exposure ($AUC_{0-\infty}$) on Day 5 was higher than following a single dose. This was related to a decrease in clearance and more than 2-fold decrease in volume of distribution. These changes in pharmacokinetic parameters were suggested to be related to the decreased target availability following sustained lymphocyte depletion resulting from the mechanism of action of alemtuzumab.

The PK of alemtuzumab in cynomolgus monkeys was characterised following repeated i.v. dosing of 3 mg/kg/day in two cycles (administered 28 days apart), with five daily doses in

Cycle 1 and three daily doses in Cycle 2. The results indicated that alemtuzumab exposure was sustained for at least 28 days with a half-life of approximately 5 days following cycles 1 and 2. No apparent differences in half-life, Cmax or systemic exposure were seen in this study between treatment cycles.

No apparent pharmacokinetic differences were observed between female vs male cynomolgus monkeys or female vs male transgenic mice following single or repeated doses of alemtuzumab.

Alemtuzumab pharmacokinetics was also evaluated in pregnant huCD52 transgenic mice to support the reproductive toxicity studies. Results of 5 daily i.v. dosing of 3 and 10 mg/kg to pregnant and non-pregnant transgenic mice indicated that during pregnancy, the effect of a changing body composition (e.g. increase in plasma volume, total body water and placental/foetal growth) led to changes in alemtuzumab pharmacokinetics. This was characterised by faster clearance, larger volume of distribution and lower overall exposure to alemtuzumab. Alemtuzumab was detected in foetuses of dams treated with alemtuzumab during gestation which confirmed transfer across the placental barrier.

Alemtuzumab was detected in the milk of lactating female mice administered 10 mg/kg for 5 consecutive days postpartum and also in serum of their pups.

No dedicated metabolism, excretion and PK drug interaction studies were submitted.

Anti-alemtuzumab antibodies were detected in one of the studies in transgenic mice and in several of the studies in cynomolgus monkeys. Neutralizing anti-alemtuzumab antibodies were observed in one animal in one of the studies in cynomolgus monkeys.

2.3.4. Toxicology

Single dose toxicity

Alemtuzumab was investigated in 3 single dose toxicity studies in cynomolgus monkeys, using both i.v. and s.c. administrations of alemtuzumab at dose levels ranging from 0.1 to 30 mg/kg. The major findings are summarised in Table 6.

Table 6 Major findings in the single dose toxicity studies

Study ID	Dose (mg/kg)	Duration	Major Findings
BPAT/90/0063	0, 0.1, 1, 3 i.v.	Single 40 min infusion	At ≥1 mg/kg: Dose related lymphocyte depletion (nadirs 8 and 48 hours post dose) Recovery approx. 2 to 5 weeks post dose No adverse clinical signs or morphological changes
BPHP/92/0039 (GLP)	0, 3, 10, 30 i.v.	Single 40 min infusion	10 and 30 mg/kg: Dose related hypotension and tachycardia Males had increased red cell counts (+8-19%), packed cell volume and haemoglobin. Urea elevation (+46-49%), LDH elevation (+79-262%) and glutamic oxaloacetic transaminase elevation (+91-140%) and CPK increased. One 30 mg/kg female monkey died due to cardiovascular collapse 6 h post dose
BPAT/90/0110	1, 2, 3 s.c.	Single dose	At ≥1 mg/kg: Dose related lymphocyte depletion. Recovery approx. 3 to 6 weeks post dose. No adverse clinical signs or morphological changes. At 3 mg/kg: Transient increase in reticulocytes

Repeat dose toxicity

Two repeat dose studies were conducted in cynomolgus monkeys. The first study was a one-month daily dose escalation study in which monkeys were administered 1, 1.5, 2 and 3 mg/kg on days 1 – 7, 8 – 10, 11 – 14 and 15 – 30, respectively. The second study was a dose-ranging pilot study to evaluate the tolerability of 3, 10 and 30 mg/kg of alemtuzumab in the cynomolgus monkey. The major findings are summarised in Table 7.

Table 7 Major findings in the repeated dose toxicity studies

Study ID	Dose (mg/kg)	Duration	Major Findings
TTDR/90/0036-4 (GLP)	1, 1.5, 2, 3, IV or SC	14-30 days dose escalation	Lymphocyte depletion. Absolute neutropenia at 30 days (IV and SC). Neutropenia not observed following 14 days dosing. Slight decrease serum in protein and albumin. No remarkable changes bone marrow.
FFA00142	3, 10, 30 IV slow infusion (180 min)	5 days	B and T cells (CD4+ and CD8+) depleted. No cardiovascular or respiratory effects. Treatment associated with infection in all groups (antibiotic resistant).

Genotoxicity

Studies to assess the genotoxic potential of alemtuzumab were not conducted (see 2.3.6 Discussion on non-clinical aspects).

Carcinogenicity

Studies to evaluate carcinogenicity were not conducted (see 2.3.6 Discussion on non-clinical aspects).

Reproduction Toxicity

The major findings of reproductive and developmental toxicity studies are summarised in Table 8.

Table 8 Reproductive and developmental toxicity studies

Study type / Study ID / GLP	Species; Number / group; Dose & route	Dosing period	Major findings	NOAEL / LOAEL (mg/kg & AUC)
Male fertility				
Tolerability study in male humanised mice/ 09-3315/ Non-GLP	HuCD52 transgenic mice; 10-15♂/group; 0, 3, 10 mg/kg IV	Every 3 to 4 days for 7 weeks	**≥ 3 mg/kg:** 8 deaths following the 3rd or 4th dose due to hypersensitivity reactions *Histopathology:* Moderate to marked lymphoid depletion in lymph nodes and spleen; moderate numbers of multinucleated giant cells and histiocytic infiltrates in lymph nodes; **10 mg/kg:** 3 deaths following the 4th dose due to hypersensitivity reactions 1 death prior to the 9th dose (cause of death was not established) 2 animals had detectable anti-alemtuzumab titers *Histopathology:* Mild thymic lymphoid depletion	ND
Fertility and general reproduction toxicity in male humanised mice/ 0020000816/ GLP	HuCD52 transgenic mice; 25-50♂/group excluding mice used for TK analysis; 0, 3, 10 mg/kg/day IV	Dosing during D1-5 prior to cohabitation	No effects on mating and fertility parameters nor on Caesarean-sectioning and litter parameters **≥ 3 mg/kg:** ↓ percent normal sperm (-4.1%); ↓ sperm density (18% but within historical control) **10 mg/kg:** 1♂ dead on day 3 (cause of death not established; the only adverse observation was a 12% weight loss) ↓ percent normal sperm (-6.7%)	ND / **LOAEL:** 3 mg/kg/day & Cmax at D5 = 94 µg/ml
Female fertility				
Tolerability study in pregnant/non-pregnant female humanised mice/ 09-3680/ Non-GLP	HuCD52 transgenic mice; 12♀/group; 10 mg/kg/day IV for 5 consecutive days	GD6/7 to GD10/11 or GD11/12 to GD15/16	No signs of hypersensitivity No evidence of gross malformations **GD6/7 to GD10/11:** Three confirmed pregnancies; 9 animal had detectable anti-alemtuzumab titres **GD11/12 to GD15/16:** Three confirmed pregnancies; 5 animals had detectable anti-alemtuzumab titres	NA

Study type / Study ID / GLP	Species; Number / group; Dose & route	Dosing period	Major findings	NOAEL / LOAEL (mg/kg & AUC)
Fertility and general reproduction toxicity in female humanised mice/ 0020000815/ GLP	HuCD52 transgenic mice; 25-47♀/group; excluding mice used for TK analysis; 0, 3, 10 mg/kg/day IV for 5 consecutive days	Dosing during D1-5 prior to cohabitation with CD-1 males Scheduled sacrifice at GD13	No effects on oestrous cycle, mating and fertility parameters **10 mg/kg:** 1 dead (clinical signs of general discomfort; the death was documented as being related to an injury sustained during weighing) ↓ Body weight gain and body weight during gestation; ↓ average number of corpora lutea and implantation sites per mouse	**NOAEL:** 3 mg/kg/day & Cmax at D5 = 126 µg/ml **LOAEL:** 10 mg/kg/day & Cmax at D5 = 386 µg/ml
Embryo-fœtal development				
Developmental Toxicity in humanised mice/ 0020002277/ GLP	HuCD52 transgenic mice; 25-50♀/group; 0, 3, 10 mg/kg/day IV	GD6-10 or GD11-15 (control: GD 6-15) Scheduled sacrifice at GD18	No gross external, soft tissue or skeletal fetal alterations (malformations or variations) **10 mg/kg/day (GD11-15):** ↑ Percent preimplantation loss (2.7%); ↑ dams with all conceptuses dead/resorbed (10%); ↓ number of dams with viable foetuses (10%)	**GD6-10:** NOAEL: 10 mg/kg/day & Cmax at GD10 = 192 µg/ml **GD11-15:** NOAEL: 3 mg/kg/day & Cmax at D15 = 74 µg/ml LOAEL: 10 mg/kg/day & Cmax at D15 = 281 µg/ml
Peri- & postnatal				
Perinatal/Postnatal Reproduction Toxicity in humanized mice/ 0020002871/ GLP	HuCD52 transgenic mice; 10-50♀/group; F0: 0, 3, 10 mg/kg/day IV F1: 0, 10 mg/kg/day IV	PPD8-12 or GD6-10 or GD11-15 (control: LD8-12 or GD6-15)	Lymphocyte depletion **F0:** **10 mg/kg/day:** Body weight loss **F1:** None (with respect to cognitive, physical or sexual development)	**F1:** NOAEL 10 mg/kg/day & Cmax = 208 µg/ml at PPD12
Perinatal/Postnatal Immune Toxicity[a] in humanized mice/ 20010591/ GLP	HuCD52 transgenic mice; 8-17♀/group depending on type of assay; 0, 10 mg/kg/day IV	PPD8-12	**F1:** ↓ IgM response to KLH;	**F1:** 10 mg/kg/day & Cmax = 67 µg/ml at PPD13

GD – Gestation day; LD – Lactation day; Post-partum day – PPD

[a] *Pups were either assigned to an evaluation for Serum IgM and IgG Primary Response to Keyhole Limpet Hemocyanin (KLH), Splenocyte Phenotyping, Natural Killer Cell Assay and Anti-CD3 Proliferation Assay*

Local Tolerance

Non-clinical local tolerance studies for alemtuzumab were not performed (see 2.3.6 Discussion on non-clinical aspects). In non-clinical toxicity studies, there were no serious adverse findings related to the injection/infusion of alemtuzumab.

Other toxicity studies

Several tissue cross-reactivity studies were conducted with alemtuzumab using tissues obtained from humans, cynomolgus monkeys and huCD52 transgenic mice. Preliminary data

indicated that alemtuzumab did not bind specifically to monkey spleen and lymphoid tissues. With respect to human tissues, alemtuzumab bound to mononuclear cells, primarily T- and B-cell lymphocytes, NK cells, monocytes, granulocytes and myeloid cells. Mononuclear cell staining was present in all lymphoid organs, mucosal associated lymphoid tissue and mononuclear cell infiltrates in the majority of tissues examined. No binding was observed with either erythrocytes or platelets. Specific binding was also observed in the male reproductive tract (epididymis, sperm, and seminal vesicles) and the skin. Appropriate positive and negative tissue controls, isotype control antibody and tissue staining control were included in GLP-compliant studies. In a study comparing tissue reactivity between human and huCD52 transgenic mice, a generally consistent pattern was observed.

2.3.5. Ecotoxicity / environmental risk assessment

Environmental risk assessment of alemtuzumab was not performed (see 2.3.6 Discussion on non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

Pharmacodynamics

The CHMP considered that in studies testing human peripheral blood mononuclear cells, alemtuzumab induced complement-dependent cytotoxicity of B and T cells, thus supporting the role of complement-dependent cytotoxicity in the mechanism of action of alemtuzumab. Cells expressing high levels of complement-inhibitory proteins, such as monocytes and basophils, may be therefore more resistant to the pharmacological effects of alemtuzumab as observed in the *in vitro* study 10GSTR059. In addition, alemtuzumab induced *in vitro* cytotoxicity of human T cells by induction of antibody-dependent cellular cytotoxicity (ADCC). ADCC and CDC were thus considered mechanisms by which alemtuzumab exerts its cytolytic effect on immune cells.

Furthermore, the CHMP considered that alemtuzumab appeared to lead to an enrichment of T cells with regulatory phenotypes, since the T cell population remaining after CDC *in vitro* displayed functional regulatory activity and was capable of suppressing T cell responses. Similarly, MS patients treated with alemtuzumab in clinical studies showed an increased percentage of T cells with a regulatory phenotype in the reconstituting T cell population. These data indicated that alemtuzumab could potentially act to control autoimmune responses via lymphocyte repopulation.

In vivo, significant depletion of T- and B-cells in huCD52 transgenic mice and cynomolgus monkeys was seen, supporting the pharmacological activity on human mononuclear cells observed *in vitro*. The CHMP considered that several studies were performed to characterise the distribution, expression level and consistency of human CD52 expression in the transgenic mouse to substantiate the suitability of this model. The level of CD52 expression on human PBMCs and huCD52 transgenic mice was similar and the T and B cell responses did not appear to be affected by human CD52 expression in mice. Moreover, in both humans and huCD52 transgenic mice, less depletion of regulatory and memory T-cells was observed when compared to naïve cells. Although functional differences cannot completely be excluded,

heterozygous HuCD52 transgenic mice were considered to be a relevant animal model for studying pharmacology of alemtuzumab. With respect to cynomolgus monkeys, the CHMP considered that although alemtuzumab was pharmacologically active in the species, the relevance of this species was limited due to species differences in the amino acid sequence for the CD52 antigen.

The primary animal model of multiple sclerosis is experimental autoimmune encephalomyelitis (EAE). No proof-of-concept studies in this model were conducted by the applicant. However, as clinical experience with alemtuzumab in the treatment of MS was already available at the time huCD52 transgenic mice were developed and characterised, the lack of these studies was considered acceptable by the CHMP.

No dedicated safety pharmacology studies were conducted by the applicant. Taking into account clinical experience with alemtuzumab in cancer patients, the CHMP was of the view that this was acceptable. Nevertheless, effects on the cardiovascular and respiratory systems were evaluated in a GLP-compliant single-dose toxicity study and a non-GLP-compliant dose-ranging repeat-dose study conducted in cynomolgus monkeys. Cardiovascular effects were observed in both studies at doses of 30 mg/kg, but the effects were only seen in a single animal per study. With respect to the ventricular premature complexes seen in one animal in the repeat-dose study, the CHMP acknowledged that this observation could be a normal variant in cynomolgus monkeys and therefore not treatment-related. None of the findings were considered as clinically relevant.

Pharmacokinetics

The CHMP considered that pharmacokinetic properties of alemtuzumab were appropriately characterized in pharmacologically relevant animal species, i.e. huCD52 transgenic mouse and cynomolgus monkey, following i.v. and s.c. administration of single and repeat doses, and that the results provided adequate exposure information to support interpretation of the toxicology studies.

The pharmacokinetics of alemtuzumab appeared to be dependent on the presence of the human CD52 target. Elimination was faster (higher clearance and shorter terminal elimination half-life) and the volume of distribution was larger in huCD52 transgenic mice than in wild-type CD-1 mice. This suggested that alemtuzumab remained longer in the blood of the wild-type CD-1 mice due to the lack of the human CD52 target, indicating that the primary route of elimination is target-mediated internalisation.

Consistent and significant differences were noted for PK parameters between pregnant and non-pregnant transgenic mice. This was characterized by higher clearance, concomitant diminishing of the overall alemtuzumab exposure and an increase in the volume of distribution in pregnant animals. The CHMP considered that the PK observed during pregnancy was a result of the transfer across the placental barrier to the foetus, as confirmed by detection of alemtuzumab in foetuses of dams treated during gestation.

While it is not known whether alemtuzumab is excreted in human milk, alemtuzumab was detected in the milk and offspring of lactating female mice. Considering that a risk to the breastfed child cannot be excluded, the CHMP was of the view that breast feeding should in general be discontinued during each course of treatment with Lemtrada and for 4 months

following the last infusion of each treatment course, as reflected in section 4.6 of the SmPC. This recommendation was based on the fact that the human serum concentration of alemtuzumab is low or undetectable within approximately 30 days following each treatment course. Therefore, the 4-month window was considered to represent a conservative approach to avoid exposure to the infant.

No metabolism and excretion studies were submitted. As alemtuzumab is a recombinant humanised protein, the expected metabolic pathway is proteolysis. Thus, the CHMP considered lack of these studies acceptable.

There were no studies of pharmacodynamic or pharmacokinetic drug interactions performed with alemtuzumab. Based on its expected metabolism (i.e. proteolysis), alemtuzumab is an unlikely candidate for cytochrome P450 mediated drug-drug interactions and therefore, no drug-drug interaction studies were performed. This was accepted by the CHMP.

Anti-alemtuzumab antibodies were detected in the majority of the animals tested. However, the presence of anti-alemtuzumab antibodies was not considered by the CHMP to have any significant influence on the alemtuzumab pharmacokinetics in the studies conducted.

Toxicology

Single and repeated dose toxicity studies were investigated in cynomolgus monkeys. In a previous CHMP scientific advice, the 30-day toxicity testing was considered sufficient to cover the clinical schedule for alemtuzumab treatment, i.e. administration on 5 consecutive days followed by administration on 3 consecutive days after one year.

With respect to the results of single and repeated dose toxicity studies, the CHMP considered that these should be interpreted with caution due to the low number of animals per group (i.e. 1-2 animals/sex/group), immunogenicity (potentially neutralising the effects and observed in approximately half of the animals), dose-limiting toxicity (increased susceptibility to infections or hypersensitivity leading to lethality/early sacrifice) and limitation of the animal model (decreased affinity of alemtuzumab for CD52 in the cynomolgus monkey). Still, the CHMP was of the view that the repeat-dose toxicity of alemtuzumab was sufficiently addressed from the pre-clinical point of view.

The CHMP considered that the previous CHMP scientific advice focused also on the need for additional toxicity testing. In their advice, the CHMP had acknowledged that evaluating doses corresponding to a 10-fold exposure margin when compared to the exposure in the MS patients would not be feasible due to immunosuppression and severe infections. The resulting need for long-term co-administration of antibiotics had been considered interfering with evaluation of the toxicology profile of alemtuzumab. Overall, the CHMP had concluded that no further long-term repeat dose testing in cynomolgus monkey was warranted.

The lack of genotoxicity testing was considered acceptable, as in accordance with the ICH S6 guideline, the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed. The CHMP also considered acceptable that no carcinogenicity testing was performed, taking into account the lack of an appropriate animal model, the well-established risk of indirect tumorigenicity caused by prolonged immunosuppression and the previous scientific advice provided by the CHMP.

Reproductive and developmental toxicity studies were conducted in the huCD52 transgenic mouse model. This model was characterised in a series of pharmacodynamic studies. Cynomolgus monkey was not considered an appropriate species for reasons of anti-alemtuzumab antibodies developing in proportion of monkeys, which in some cases could exert a neutralizing activity. The CHMP also considered that the studies were conducted in compliance with the CHMP scientific advice.

The female and male reproductive effects were observed at exposures significantly below those observed in the clinical setting, following administration of the recommended therapeutic dose (based on Cmax). Higher exposure margins were established by the applicant based on AUC values obtained in a PK study. The use of these AUC data yielded exposure margins of 1.7- to 7.1-fold.

The applicant proposed that women of child-bearing potential should use effective contraceptive measures when receiving a course of treatment with Lemtrada and for 4 months following that course of treatment. Considering that the human serum concentration of alemtuzumab is low or undetectable within approximately 30 days following each treatment course, this conservative approach, agreed to be applied also to breast-feeding, was considered appropriate by the CHMP.

CD52 is known to be present in human as well as rodent reproductive tissues. The CHMP considered that effects on fertility were seen in humanised mice, but was of the view that a potential impact on human fertility during the period of exposure was unknown based on the available data.

No gross external, soft tissue or skeletal foetal alterations were observed when alemtuzumab was dosed GD6 through 10 or GD11 through 15 to humanized CD52 transgenic pregnant mice mated with wild-type CD-1 male mice. Increase in the number of dams with all conceptuses dead or resorbed and a reduction in the number of dams with viable foetuses occurred in animals exposed to 10 mg/kg/day alemtuzumab during GD 11 through 15. The CHMP was of the opinion that the clinical relevance of these findings in transgenic mice was not known.

The NOAEL for developmental toxicity was 10 mg/kg/day for alemtuzumab when administered for GDs 6 to 10 and 3 mg/kg/day when alemtuzumab on GD11 through 15. Based on Cmax values, the exposures were significantly below those observed in the clinical setting, following administration of the recommended therapeutic dose. Higher exposure margins were established by the applicant based on AUC values obtained in a PK study. The use of these AUC data yielded exposure margins of 0.6- to 4.4-fold.

The effects of peri-natal/post-natal administration of alemtuzumab were evaluated in huCD52 transgenic mice including a post-natal functional immune evaluation. Alemtuzumab was present in serum of both the F0 and F1 generation and in milk from the F0 generation. As expected based on the mode of action of alemtuzumab, alterations in lymphocyte numbers and sub-populations were observed during each period of immune development evaluated. However, only subtle effects on the humoral immune response of unclear clinical relevance (decreased IgM response without an effect on IgG) were observed.

Overall, the CHMP considered that the non-clinical data on reproductive toxicity are adequately reflected in sections 4.6 and 5.3 of the SmPC.

With respect to the local tolerance testing, the CHMP acknowledged that alemtuzumab is administered by i.v. infusion following dilution and does not include concentrations of irritants or corrosive components likely to lead to serious reactions at the injection site. Therefore the lack of dedicated local tolerance toxicity studies was accepted. Furthermore, the absence of serious adverse findings related to the injection/infusion of alemtuzumab in nonclinical toxicity studies was considered re-assuring.

The lack of an environmental risk assessment (ERA) was deemed acceptable in accordance with the current guidance. Alemtuzumab is a monoclonal antibody and therefore, it is exempt from the ERA requirements, as proteins are considered not to pose significant risks to the environment.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical properties of Lemtrada were adequately documented and met the requirements to support this application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 9 Tabular overview of clinical studies

Protocol Number Number of Study Centers (Locations)	First / Last Patient Randomized Enrollment status # Treated	Study Design, Control Type, and Key Objectives	Study & Control Drugs Dose, Route & Regimen	Number of Patients Entered/ Completed by Arm	Duration	Gender[a] Median Age (Range)	Diagnosis	Co-Primary Efficacy Endpoints
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
Ukraine, Israel)								
CAMMS03409 193 (US, EU, Argentina, Brazil, Mexico, Canada, Australia, Serbia, Croatia, Russia, Ukraine, Israel)	05 Aug 2009/ (first patient enrolled)/ NA Ongoing 496[e]	Open-label, rater-blinded, uncontrolled study to evaluate long-term safety and efficacy	Patients previously treated with IFNB-1a: Alem IV 12 mg/day for 2 cycles[f] Patients previously treated with alem: 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 centers that randomized patients.

[a] Demographic characteristics are for all patients in the full analysis set. In CAMMS223, 1 randomized patient was excluded from the full analysis set because after randomization 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 enrollment 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 IFNB-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.

2.4.2. Pharmacokinetics

The pharmacokinetics of alemtuzumab were evaluated in a total of 216 patients (19 in CAMMS223, 57 in CAMMS323 and 140 in CAMMS324) with relapsing remitting multiple sclerosis (RRMS) who received either 12 mg/day (157 patients in studies 223, 323 and 324) or 24 mg/day (59 patients in studies 223 and 324) for 5 days, followed by 3 days of treatment 12 months after the initial treatment cycle. The results of the Phase 2 and 3 studies showed consistent trends in alemtuzumab pharmacokinetics. Serum concentrations increased with each consecutive dose within a treatment course, with the highest observed concentrations occurring following the last infusion of a treatment course. Administration of 12 mg/day resulted in a mean Cmax of 3014 ng/ml on Day 5 of the initial treatment course, and 2276 ng/ml on Day 3 of the second treatment course. The functional half-life approximated 5 days and was comparable between courses leading to low or undetectable serum concentrations within approximately 30 days following each treatment course.

Absorption

No studies of bioavailability were conducted, as alemtuzumab is administered intravenously.

The composition of the to-be-marketed formulation is the same as that used in the clinical trials in multiple sclerosis and the same as the previously approved formulation used in the B-CLL indication. Therefore, no bioequivalence studies were performed by the applicant.

Distribution

Based on the population PK analysis, the central volume of distribution (V1) was proportional to body weight and approximated the extracellular fluid volume (14.1 l), suggesting that alemtuzumab was largely confined to the blood and interstitial space. The inter-subject variability for V1 was approximately 26 %.

The peripheral volume (V2) was estimated to be 16.2 l.

Elimination

Classical biotransformation studies were not conducted. Alemtuzumab is a large-molecule monoclonal antibody and as such it is cleared primarily through target-mediated clearance and through simple non-target specific IgG clearance mechanisms. Alemtuzumab is not excreted renally or eliminated via cytochrome P450 (CYP450) isoenzymes.

Clearance of alemtuzumab ranged from 0.012 – 0.096 l/h depending on study, dose group and anti-alemtuzumab antibody status. The inter-subject variability for clearance was large (58 %). Higher clearance values were observed in cycle 1 compared to cycle 2, the decrease in clearance from cycle 1 to cycle 2 being less than 20%.

Dose proportionality and time dependencies

In studies CAMMS223 and CAMMS 324 which tested doses of 12 mg and 24 mg, the observed alemtuzumab concentrations suggested dose proportionality in both cycle 1 and cycle 2. When

comparing the estimated exposure data in anti-alemtuzumab negative patients, there was a trend towards a less than proportional increase.

Special populations

No dedicated studies in special populations were conducted. The small number of patients with mild renal impairment and absence of patients with more severe renal dysfunction in the clinical programme precluded assessment of the influence of renal impairment on alemtuzumab PK.

75% of the patients had normal values of the hepatic function parameters measured (alkaline phosphatase, alanine aminotransferase and total bilirubin). Several patients had values above the upper limit of normal, but when evaluated as covariates in the population PK analysis, no impact on alemtuzumab PK was found.

No effect on gender and race was observed in the population PK analysis.

The maximum age in the patient population was 53 years, precluding evaluation of impact of higher age on alemtuzumab PK. Alemtuzumab was not investigated in children.

Pharmacokinetic interaction studies

No drug-drug interaction studies have been performed (see Discussion on clinical pharmacology 2.4.4).

2.4.3. Pharmacodynamics

Mechanism of action

Alemtuzumab is a humanised monoclonal antibody (IgG1 kappa) which binds to CD52, a cell surface antigen present at high levels on T (CD3+) and B (CD19+) lymphocytes, and at lower levels on natural killer cells, monocytes and macrophages. There is little or no CD52 detected on neutrophils, plasma cells, or bone marrow stem cells. Alemtuzumab acts through antibody-dependent cellular cytolysis and complement-mediated lysis following cell surface binding to T and B lymphocytes.

The mechanism by which alemtuzumab exerts its therapeutic effects in MS is not fully elucidated. However, research suggests immunomodulatory effects through the depletion and repopulation of lymphocytes, including:

- Alterations in the number, proportions, and properties of some lymphocyte subsets post-treatment

- Increased representation of regulatory T cell subsets

- Increased representation of memory T- and B-lymphocytes

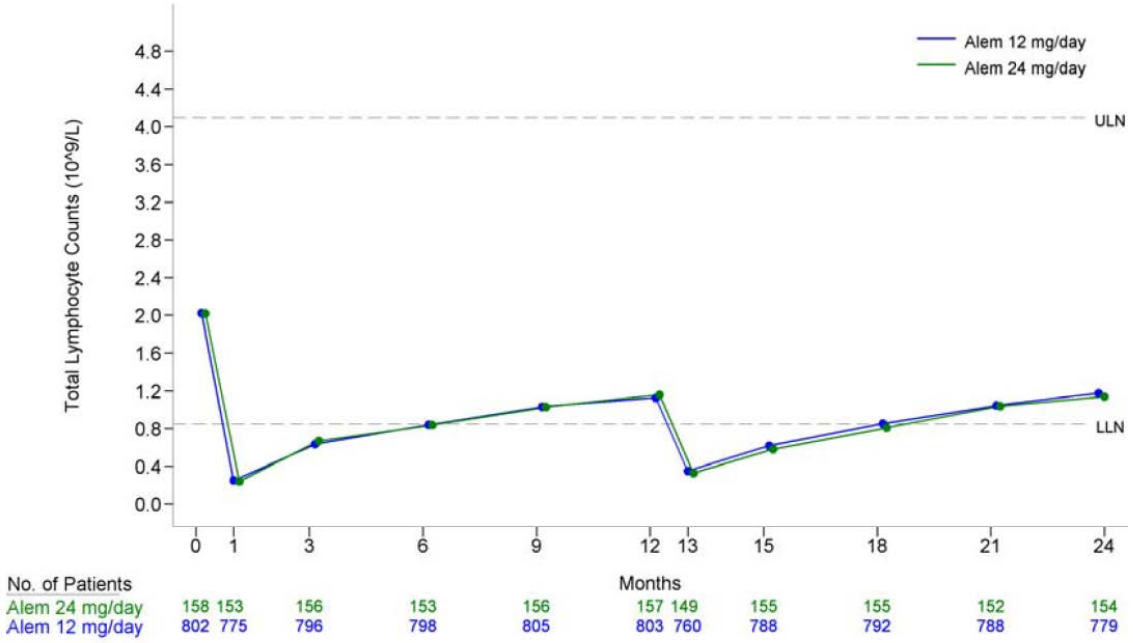
- Transient effects on components of innate immunity (i.e., neutrophils, macrophages, NK cells)

The reduction in the level of circulating B and T cells by alemtuzumab and subsequent repopulation may reduce the potential for relapse, which ultimately delays disease progression.

Primary and Secondary pharmacology

Alemtuzumab depleted circulating T and B cells after each treatment cycle with the lowest values typically occurring at the first post-treatment assessment, which was after one month in the Phase 3 studies (and as early as two days after the end of the first treatment cycle in the phase 2 study). Lymphocyte repopulation appeared to occur at about the same rate after each treatment cycle (Figure 1) and the nadir and degree of repopulation following the second cycle was comparable to the first, with no indication that effects of alemtuzumab on lymphocytes were cumulative. Similar patterns of lymphocyte depletion and repopulation were generally observed for the 24 mg/day dose groups as compared to the 12 mg/day dose groups.

Figure 1 Total lymphocyte depletion and repopulation following treatment with alemtuzumab at month 0 and month 12 in CAMMS323 and CAMMS324



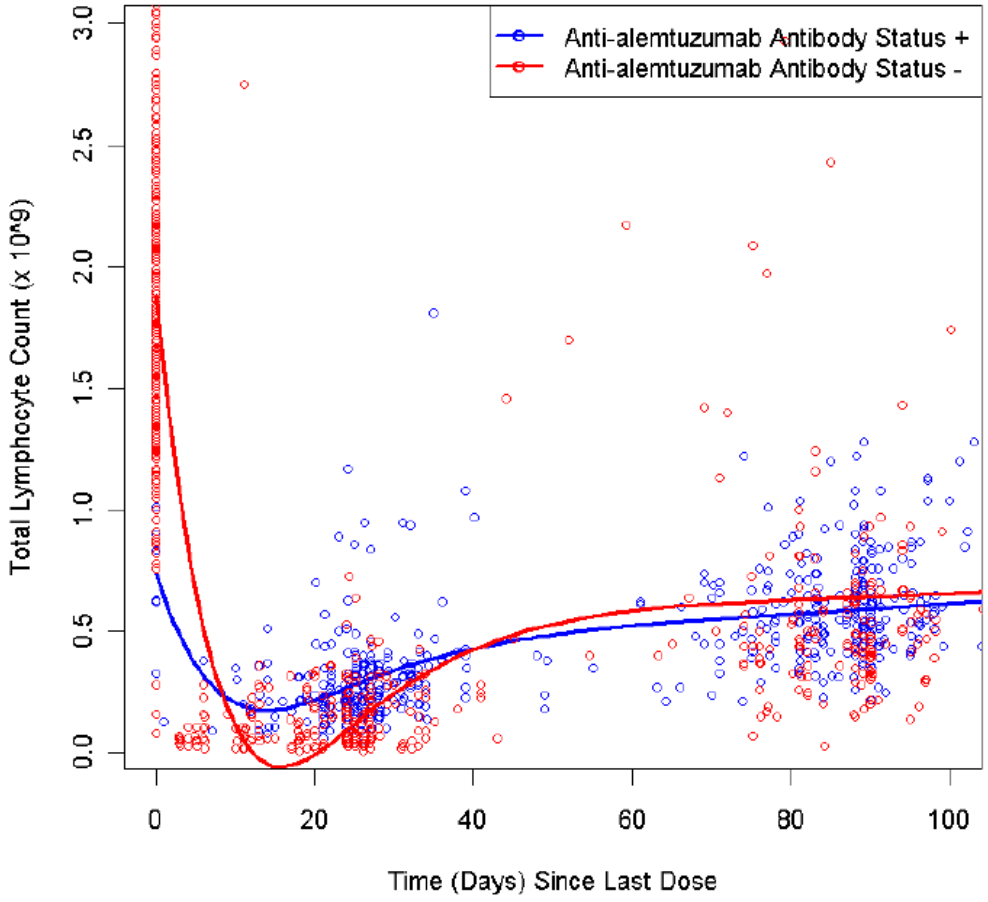
Lymphocytes repopulated after depletion, with the time to reach repopulation milestones varying by lymphocyte subset. Approximately 40% and 80% of patients receiving the 12 mg/day dose had total lymphocyte counts reaching the LLN by 6 and 12 months, respectively, after each treatment cycle. Approximately 10 to 20% of patients had CD3+ and CD4+ counts reaching the LLN by 12 months after each treatment cycle in the Phase 3 studies. The proportion of patients with CD8+ repopulation over time was similar to that for total lymphocytes, with approximately 50% of patients having CD8+ counts reaching the LLN by 9 months following each cycle. Almost all patients (≥85%) had CD19+ counts that reached LLN by 6 months following a treatment cycle. NK cells were reduced to a lesser

extent than T and B cells, with mean cell counts remaining within the normal range, which may relate to the greater expression of CD52 antigen on T and B lymphocytes as compared to NK cells.

PK/PD models were developed for CD3+ lymphocytes, CD19+ lymphocytes and total lymphocytes. Only anti-alemtuzumab antibody status had a significant effect on total lymphocyte count, however the inter-individual variability was large (> 70 %CV).

The observed total lymphocyte count by observed anti-alemtuzumab antibody status for the first 100 days after dosing is presented in Figure 2.

Figure 2 Observed total lymphocyte count versus time by observed anti-alemtuzumab antibody status



Components of the innate immune system such as neutrophils, monocytes, eosinophils, basophils and natural killer cells were only transiently affected by alemtuzumab.

Immunogenicity

The majority of patients (691/811, 85.2%) treated with 12 mg/day alemtuzumab in the pooled Phase 3 studies tested positive for anti-alemtuzumab antibodies. Of the 85.2% of patients who tested positive for anti-alemtuzumab antibodies at any time-point during the course of the study, 92.2% (637/691) tested positive for inhibitory antibodies.

The summary of anti-alemtuzumab antibodies and anti-alemtuzumab inhibitory antibodies is presented in Table 10.

Table 10 Summary of Anti-alemtuzumab Antibodies and Anti-alemtuzumab Inhibitory Antibodies in Alemtuzumab 12 mg/day group in Phase 3 Studies

Statistic	Treatment Cycle 1			Treatment Cycle 2		
	Ever during cycle [a]	Month 1	Month 12 [b]	Ever during cycle [a]	Month 13	Month 24
Patients positive for anti-alemtuzumab antibodies, % (n/N)	71.5% (579/811)	62.4% (486/779)	29.3% (231/789)	84.9% (667/789)	83.2% (594/714)	75.4% (576/764)
Antibody titers, median (range)	NA	400 (30; 102,400)	200 (30; 102,400)	NA	204800 (30; 6,553,600)	1600 (30; 204,800)
Patients positive for anti-alemtuzumab inhibitory antibodies [c], % (n/N)	75.8% (439/579)	86.8% (422/486)	2.2% (5/231)	93.4% (623/667)	94.3% (560/594)	41.5% (239/576)
Inhibitory antibody titers, median (range)	NA	40 (20, 640)	20 (20,640)	NA	640 (20, 81920)	20 (20, 640)

NA = not applicable
a Ever positive at any time during treatment cycle
b Pre-administration of alemtuzumab treatment cycle 2
c Only samples positive for anti-alemtuzumab antibodies were tested for inhibitory antibodies

2.4.4. Discussion on clinical pharmacology

In general, the CHMP was of the view that the data available adequately characterised the pharmacology profile alemtuzumab.

The pharmacokinetics of alemtuzumab was mainly investigated based on a population PK modelling, analysing patient data from one phase II study and two phase III studies (216 patients in total).

The population pharmacokinetics was best described by a linear, 2-compartment model. This was in contrast to what was previously seen with alemtuzumab in B-CLL patients. In those patients, non-linear kinetics was observed, most likely due to their tumour burden and higher numbers of lymphocytes, since the target-mediated elimination of alemtuzumab might change with the tumour burden decrease and lymphocyte concentration decrease over time.

No studies of bioavailability were conducted, as alemtuzumab is to be administered intravenously. Furthermore, since the to-be-marketed formulation is the same as the formulation used in the clinical studies, no bioequivalence studies were performed. This was agreed by the CHMP.

Alemtuzumab is a biotechnologically synthesized IgG1 monoclonal antibody and therefore, its

metabolism is expected to follow the IgG1 metabolism pathway. No investigation of the metabolism was considered necessary by the CHMP.

With respect to elimination, systemic clearance was observed to be influenced by the lymphocyte count: larger clearance values were observed in cycle 1 compared to cycle 2. This decrease in clearance was considered to be attributed to the loss of CD52 antigen in the periphery. However, the decrease from cycle 1 to cycle 2 was less than 20%, despite a larger difference in lymphocyte count. Overall, the CHMP was of the view that this finding would not have any clinically significant impact on the dosing regimen of alemtuzumab.

The large inter-subject variability for clearance was probably due to differences in lymphocyte counts and available CD52+ antigen.

No significant differences in the PK of alemtuzumab were identified in special populations based on the performed covariate analysis. However, several shortcomings were identified in the proposed PK model limiting the possibility to draw conclusions about the PK and potential covariate effects, e.g. effect of gender and race on the pharmacokinetics of alemtuzumab.

The CHMP considered that alemtuzumab was not studied in sufficient numbers of patients with impairment of renal or hepatic function. However, given the metabolism and elimination of alemtuzumab (IgG1 antibody), renal and hepatic impairment were considered to have a limited influence on the pharmacokinetics of alemtuzumab.

While no effect on gender and race was observed in the population PK analysis, the population PK model was not considered qualified by the CHMP and thus, the effect of these two covariates on the PK of alemtuzumab could not be concluded.

With respect to age, the CHMP considered that the pharmacokinetics of alemtuzumab was not studied in patients aged 55 years and older. Nevertheless, given that neither the liver nor kidney are involved in elimination, impact on the PK of alemtuzumab in the older patients was seen as limited. No data in the paediatric population were available at the time of the initial marketing authorisation application. A deferral to performing a clinical trial in patients aged 10 to less than 18 years was granted and a waiver applies to population from birth to less than 10 years of age.

Considering the short duration of drug administration and as no direct P450-mediated drug-drug interactions would be expected with alemtuzumab, the CHMP accepted that no formal interaction studies were conducted. In addition, a wide range of medications were administered concomitantly with alemtuzumab in clinical studies without any apparent drug-drug interactions being observed, which was considered reassuring by the CHMP.

The CHMP considered that the mechanism by which alemtuzumab exerts its therapeutic effects in multiple sclerosis is not fully elucidated. However, the CHMP acknowledged that immunomodulatory effects through the depletion and repopulation of lymphocytes might be involved in mediating the therapeutic activity of alemtuzumab in MS patients. In particular, the reduction in the level of circulating B and T cells by alemtuzumab and subsequent repopulation may reduce the potential for relapse, which could ultimately delay disease progression.

Alemtuzumab was seen to rapidly deplete circulating T and B lymphocytes after each

treatment cycle with the lowest values occurring at the first post-treatment assessment. Lymphocytes repopulated after depletion, with the time to reach repopulation varying by lymphocyte subset. Overall, no apparent differences were seen between the 24 mg/day and 12 mg/day dose levels in the pharmacodynamic response (depletion and repopulation of lymphocytes) as measured in peripheral blood, despite the expectedly higher serum concentrations of alemtuzumab observed after administration of the higher dose.

Approximately 40% and 80% of patients had total lymphocyte counts reaching the LLN by 6 and 12 months, respectively, after each treatment cycle. 50% of patients had CD8+ reaching the lower limit of normal within 9 months. However, CD3+ and CD4+ repopulated slower and did only reach the LLN within 12 months in 10-20 % of patients. The CHMP considered that due to the lack of CD4+ cells, an increase in infections would be expected, but this was not seen in the safety database. Of note, in clinical studies, oral prophylaxis (acyclovir 200 mg BID) for herpes infection was administered 1 month post-treatment. Prophylactic administration of antiviral medication for herpes infection, starting on the first day of each treatment course and continuing for a minimum of one month, was also considered as an appropriate risk minimisation measure and was reflected in sections 4.2 and 4.4 of the SmPC.

The CHMP considered the effect of anti-alemtuzumab antibody status on the total lymphocyte count. The observed total lymphocyte count versus time by antibody status indicated that the decrease in counts was less for patients with positive status. The median individual minimum total lymphocyte count for anti-alemtuzumab antibody positive records was 0.21x109 and 0.08x109 for negative records. Considering that lymphocyte counts started at approximately 1.0x109 to 4.0x109 at time 0, the reduction in lymphocyte count following alemtuzumab administration was substantial regardless of anti-alemtuzumab antibody status. Therefore, despite the large inter-individual variability, the CHMP was of the view that the impact on lymphocyte counts should not pose a problem, as all patients would be expected to have their lymphocytes cleared within one month. During lymphocyte repopulation the profiles of the counts were approximately the same and there was no apparent difference by dose group.

With respect to immunogenicity, the CHMP considered that more than 60 % of patients in cycle 1 and more than 80 % in cycle 2 had detectable anti-alemtuzumab antibodies after 1 month of treatment in the 12 mg dose group. The number had declined to 29 % by month 12 in cycle 1 and to 75 % in cycle 2. Most patients with anti-alemtuzumab antibodies also tested positive for anti-alemtuzumab inhibitory antibodies. Almost 87 % of patients were positive for inhibitory antibodies 1 month after treatment in cycle 1 and almost 94 % after 1 month in cycle 2. Whereas only 2 % of patients were positive for anti-alemtuzumab inhibitory antibodies at month 12, 41.5 % were positive at month 24. While these findings were indicative of some sort of boosting for both the anti-alemtuzumab antibodies and the anti-alemtuzumab inhibitory antibodies in cycle 2 compared to cycle 1, the CHMP was of the view that this had no impact on the depletion or repopulation of the lymphocytes.

In conclusion, no notable differences in T or B lymphocyte depletion by dose-level, treatment cycle, antibody status or titer were seen, suggesting that anti-alemtuzumab or inhibitory antibodies did not impact depletion of these lymphocyte subsets. Lymphocyte repopulation was also unaffected by anti-alemtuzumab or inhibitory antibody status.

With respect to potential pharmacodynamics interactions, the CHMP considered that the ability

to generate an immune response to any vaccine following treatment initiation was not studied and highlighted that patients should complete local immunization requirements at least 6 weeks prior to treatment with alemtuzumab. Furthermore, as alemtuzumab was not administered in MS concomitantly with/ or following antineoplastic or immunosuppressive therapies, the potential combined effects on the patient's immune system should be taken into account when considering administration of alemtuzumab. These considerations were adequately reflected in section 4.4 of the SmPC.

2.4.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology data submitted were considered satisfactory.

2.5. Clinical efficacy

2.5.1. Dose response studies

No formal dose-finding studies in the indication of multiple sclerosis were conducted for alemtuzumab. The dosing in pilot investigator-sponsored MS studies was guided by historical data from oncology use and by pilot studies in patients with rheumatologic disorders. The MS pilot studies suggested that 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 (Coles, 2004, Clin Neurol Neurosurg). The subsequent selection of the dose and dosing regimen used in the later clinical programme of the applicant was based on these empirical observations.

The two alemtuzumab dose levels (12 mg/day and 24 mg/day) used in the initial three-year treatment period of the Phase 2 CAMMS223 study bracketed the 20 mg/day pilot study dose in MS patients and were selected to evaluate any dose-dependent relationship in terms of efficacy or safety. The alemtuzumab cycle 2 dose regimen was calculated as 60% of the initial cycle 1 dose, i.e. a 3-day cycle instead of 5 days. This was done in consideration of the data from the pilot studies where lymphocytes did not repopulate to baseline levels, i.e. at Month 12 after treatment (compared with baseline) reduced lymphocyte levels were seen.

In CAMMS223, both alemtuzumab 12 mg/day and 24 mg/day were more effective than subcutaneous (SC) interferon beta-1a (IFNB-1a). The efficacy results for the alemtuzumab 12 mg/day and 24 mg/day doses were compared for all endpoints. The two doses showed generally comparable efficacy, with non-statistically significant differences in favour of the 24 mg/day dose over the 12 mg/day dose in most clinical endpoints (i.e., relapse reduction, EDSS change from baseline and MSFC), and on reduction in brain atrophy.

Dose selection for the Phase 3 studies was based on the clinical data from CAMMS223. In study CAMMS323, which included a similar treatment-naïve patient population to the Phase 2 study CAMMS223, only the lower 12 mg/day dose was used. Study CAMMS324 was initiated with both the 12 mg/day and 24 mg/day doses, since patients in this study had an inadequate response to prior MS therapy and were considered potentially similarly less responsive to alemtuzumab. Enrolment in the 24 mg/day arm in CAMMS324 was subsequently closed by a

protocol amendment in order to reduce the overall sample size, the duration of the enrolment period and the overall duration of the study, but this decision was not driven by any interim data analysis from the Phase 3 programme and the applicant remained blinded to efficacy data at all times during the decision-making process.

The CHMP conclusions regarding absence of formal dose-finding studies are summarised in section 2.6.3 Discussion on clinical efficacy.

2.5.2. Main studies

CAMMS323 - A phase 3 randomized, rater-blinded study comparing two annual cycles of intravenous alemtuzumab to three-times weekly subcutaneous interferon beta-1a (Rebif) in treatment-naive patients with relapsing-remitting multiple sclerosis (RRMS)

Methods

Study Participants

To be eligible to participate in the study, patients had to present with early, active RRMS. These patients were defined as ambulatory patients with an EDSS score between 0 and 3, who had first onset of MS symptoms within 5 years prior to study entry and at least two clinical episodes of MS in the prior two years and at least one in the prior year. Patients meeting any of the following criteria could not be enrolled: any progressive form of MS, history of malignancy, CD4+, CD8+, B cell or absolute neutrophil count < lower limit of normal (LLN) at screening, known bleeding disorder, significant autoimmune disease, presence of anti-TSHR antibodies and active infection/ high risk of infection. Prior or concomitant use of therapy for MS other than corticosteroid and prior exposure to immunosuppressive agents were not allowed.

Treatments

Alemtuzumab was administered by daily i.v. infusions of approximately 2-4 h duration. At Month 0, alemtuzumab was administered IV over 5 consecutive days at a fixed total dose of 60 mg (12 mg/day), and at Month 12, alemtuzumab was administered over 3 consecutive days at a fixed total dose of 36 mg (12 mg/day). Premedication with methylprednisolone (1 g IV) immediately prior to alemtuzumab administration was required on the first 3 days of any treatment cycle. Further to a protocol amendment, all alemtuzumab patients received acyclovir 200 mg twice daily (or a therapeutic equivalent) starting on the first day of each alemtuzumab cycle and continuing for 28 days after the last day.

The comparator used in the trial was Rebif (IFNB-1a). Following initial dose titration as per the prescribing information, IFNB-1a was self-administered at 44 µg tiw, i.e. in a total weekly dose of 132 µg. The dose could be decreased based on patient tolerance. All patients received IV methylprednisolone (1 g/day) on Days 1, 2 and 3 at Month 0 and 12.

On-study relapses could be treated with corticosteroids at the discretion of the Treating Neurologist. A standardized regimen of methylprednisolone was strongly recommended as follows: 1 g of methylprednisolone administered by IV over approximately 1 hour, daily for 3 consecutive days.

Objectives

The objectives of this study were to compare the safety and efficacy of two annual cycles of intravenous alemtuzumab to 3-times weekly subcutaneous interferon beta-1a in treatment-naïve patients with RRMS who had recent MS disease activity as demonstrated by clinical relapses.

Outcomes/endpoints

The active-controlled phase 3 studies utilized the co-primary efficacy endpoints of MS relapse rate and time to SAD (6-month criteria). Secondary endpoints included imaging findings (MRI) along with additional relapse and disability endpoints. Definitions of the co-primary and secondary endpoints are provided in Table 11.

Table 11 Summary of co-primary and secondary endpoints in studies CAMMS223, -323 and -324

MS Domain Endpoint	Statistic Reported / Endpoint Definition
Relapse	
Relapse Rate (co-primary)	Rate ratio comparing relapse rates across treatment groups. In addition, annualized relapse rate (ARR; number of relapses per person-year) was estimated for each treatment group. A relapse was any new neurological symptom or worsening of previous neurological symptoms with an objective change on neurological examination. Symptoms had to be attributable to MS, last at least 48 hours, be present at normal body temperature (i.e., no infection, excessive exercise, or excessively high ambient temperature), and be preceded by at least 1 month (30 days) of clinical stability. The analysis of relapse rate was based on relapse determinations by the independent, blinded Relapse Adjudication Panel (RAP) in the Phase 3 studies and by blinded raters in the Phase 2 study.
Proportion Relapse Free (secondary)	The proportion of patients who experienced no on-study relapses (2 years for the Phase 3 studies; initial 3-year study period in CAMMS223)
Disability	
Time to 6-month SAD (co-primary) Based on EDSS	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. 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 (i.e., 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 (i.e., 6 consecutive months).
Change in EDSS[a] (secondary)	Change in EDSS score from baseline The change from baseline in EDSS reflects change in disability over time, with increases from baseline representing worsening.
Change in MSFC[a] (secondary)	Change in Multiple Sclerosis Functional Composite (MSFC) score from baseline 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.
Imaging	
Change in T2-hyperintense lesion volume (secondary)	Percent change from baseline in the total volume of T2-hyperintense lesions observed by MRI. The total volume of T2-hyperintense lesions reflect the inflammatory demyelination and edema of active MS lesions, as well as the sclerotic gliosis of end-stage MS plaques, and is indicative of cumulative disease activity.

With respect to imaging, the following endpoints were evaluated as tertiary: % change in T1-hypointense lesion volume, % change in brain parenchymal fraction, new or enlarging T2-

hyperintense lesion counts, Gd-enhancing lesion counts, new T1-hypointense lesion counts and conversion of Gd-enhancing lesions to new T1-hypointense lesions.

The efficacy assessments also comprised a number of additional exploratory and tertiary endpoints, including quality of life parameters (FAMS, SF-36 and EQ-5D).

Sample size

Approximately 525 patients were to be randomized in a 2:1 ratio to 2 annual cycles of 12 mg/day alemtuzumab or tiw s.c. injections of IFNB-1a. This sample size was estimated to provide ≥95% power to detect the expected treatment effect in the 2 co-primary endpoints of relapse rate and time to SAD.

Randomisation

Patients were randomized to alemtuzumab or IFNB-1a using an interactive voice response system (IVRS). Treatment assignment was at a ratio of 2:1 for alemtuzumab or IFNB-1a. The randomisation was stratified by centre using blocks of fixed size (3 in each block). The block size was not revealed to clinical sites until after database lock.

Blinding (masking)

The phase 3 studies were conducted as rater-blinded, since the choice of Rebif (SC IFNB-1a) as an active comparator precluded a double-blinded study design. Rebif 44 µg is commercially available only in proprietary prefilled syringes preventing the possibility to create a matching placebo. Furthermore, there are substantial differences between alemtuzumab and Rebif in timing and mode of administration (yearly i.v. infusions versus s.c. injections 3 tiw) and safety profiles (infusion-associated reactions versus injection site reactions and flu-like symptoms). Therefore, the studies were rater-blinded and designed to minimise the potential impact of treating physicians and patients being aware of treatment assignment. Key efficacy assessments were performed by trained EDSS and MSFC raters who were blinded to treatment assignments and had no access to patient study data. The integrity of rater blinding was preserved by training, specific documentation and procedures regarding the blinding of efficacy assessments and education of patients regarding their role in maintaining the study blind.

Analyses of the relapse co-primary endpoint and all other relapse-related endpoints in the Phase 3 studies were based on relapse determinations made by a blinded Relapse Adjudication Panel (RAP) of independent neurologists with expertise in MS clinical research. All cranial MRIs were evaluated by neuro-radiologists at an independent central facility with no access to patients' treatment assignment and the results of these evaluations were not provided to study sites. Finally, there was limited access to study data for personnel of the study sponsor.

Statistical methods

Efficacy was evaluated using the full analysis set of all patients who were randomized to treatment and who received at least 1 dose of study drug. Patients were compared for efficacy according to the treatment they were randomized to receive, irrespective of the treatment they actually received.

The same endpoints and statistical methodology were used for the primary and secondary efficacy analyses in both of the Phase 3 studies. The primary efficacy analysis (evaluation of the

co-primary efficacy endpoints of relapse rate and time to SAD) was conducted on all patients in the alemtuzumab 12 mg/day and IFNB-1a groups and was adjusted for multiple comparisons via the Hochberg method. Using the Hochberg method, each 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: the maximum of the 2 p-values is ≤0.05; the minimum of the 2 p-values is ≤0.025. Therefore, each study would be considered to have met its primary efficacy objective if a statistically significant difference between alemtuzumab and IFNB-1a was observed in time to SAD or relapse rate.

The comparison of the relapse rate co-primary endpoint used the proportional means model with treatment group indicator and geographic region as covariates. Annualized relapse rate (ARR) was estimated using negative binomial regression.

The comparison of the SAD co-primary endpoint used a Cox proportional hazards regression model with treatment group indicator and geographic region as covariates.

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

(1) Proportion of patients who were relapse free at Year 2

(2) Change from baseline in EDSS

(3) Per cent change from baseline in MRI-T2-hyperintense lesion volume at Year 2

(4) Acquisition of disability as measured by the MSFC.

Hypothesis testing proceeded from the highest rank (1) to lowest rank (4) and if nominal statistical significance ($p \leq 0.05$) was not achieved at an endpoint, then endpoints of lower rank were not formally tested. For descriptive purposes, estimated treatment effects, confidence intervals (CIs) and nominal p-values (i.e. not adjusted for multiple comparisons) were presented and statistical significance was noted when the nominal p-values were <0.05, regardless of the outcome of the closed testing procedure.

The comparison of the proportion of patients relapse free at Year 2 was performed using a Cox proportional hazards regression model with robust variance estimation. Treatment effects with respect to the change from baseline in EDSS and MSFC were compared using the Wei-Lachin method for the non-parametric analysis of repeated measures and the per cent change in T2-hyperintense lesion volume from baseline to Year 2 was compared using a ranked analysis of covariates (ANCOVA) model.

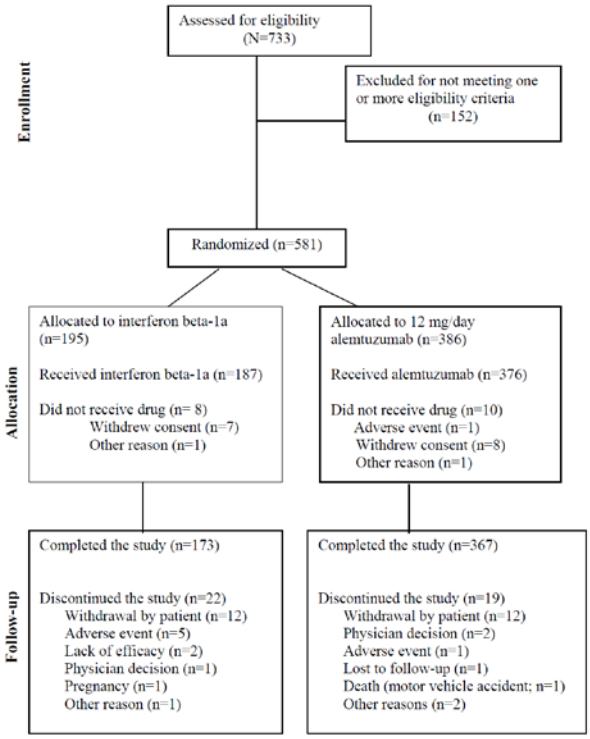
In both phase 3 studies, for assessment of the co-primary efficacy endpoints and other time-to-event endpoints, patients were censored at their last visit if the respective event (e.g. SAD or relapse) had not occurred. For the assessment of continuous, repeated measures efficacy endpoints (e.g. change from baseline in EDSS), missing at random was assumed and methods appropriate to the assumption were used. For the assessment of change from baseline to a specific time-point (e.g., per cent change from baseline in MRI T2-hyperintense lesion volume at Year 2), the last post-treatment observation was used for the analysis if data were missing. For the assessment of binary or categorical efficacy endpoints, the last known post-treatment status of the efficacy measure was used for the analysis if data were missing.

Results

Participant flow

The study participant flow, patient completion rates and reasons for discontinuation are presented in Figure 3.

Figure 3 Participant flow



Recruitment

The study took place between 7 September 2007 and 13 May 2011.

Conduct of the study

There were five amendments to the protocol introduced during the conduct of the study. The key changes included measures implemented in reaction to occurrence of safety events, ensuring patient safety and allowing for collection of information related to risk detection and minimisation activities. Additional measures were implemented to improve blinding.

Baseline data

A summary of the patient population enrolled in the study is presented in the Tables 12 and 13 below:

Table 12 Demographic characteristic

	SC IFNB-1a (N=187)	Alemtuzumab 12 mg/day (N=376)	Total (N=563)
Age (years)			
n	187	376	563
Mean (SD)	33.2 (8.48)	33.0 (8.03)	33.1 (8.18)
Median	33.0	32.0	32.0
Min, Max	18.0, 53.0	18.0, 51.0	18.0, 53.0
Sex, n (%)			
Male	65 (34.8)	133 (35.4)	198 (35.2)
Female	122 (65.2)	243 (64.6)	365 (64.8)
Ethnicity, n (%)			
Hispanic/Latino	7 (3.7)	19 (5.1)	26 (4.6)
Not Hispanic/Latino	180 (96.3)	357 (94.9)	537 (95.4)
Race, n (%)			
White	180 (96.3)	352 (93.6)	532 (94.5)
Black	3 (1.6)	11 (2.9)	14 (2.5)
Asian	0	5 (1.3)	5 (0.9)
American Indian or Alaska Native	0	2 (0.5)	2 (0.4)
Other	4 (2.1)	6 (1.6)	10 (1.8)
Weight (kg)			
n	185	375	560
Mean (SD)	75.2 (19.01)	73.1 (16.95)	73.8 (17.67)
Median	71.4	69.5	70.5
Min, Max	46.1, 166.7	40.0, 141.3	40.0, 166.7
Body Mass Index (kg/m^2)			
n	185	372	557
Mean (SD)	25.7 (5.64)	25.2 (5.38)	25.4 (5.47)
Median	24.4	24.2	24.3
Min, Max	16.2, 54.4	16.0, 53.4	16.0, 54.4

Table 13 Baseline MS Disease Characteristics

Parameter	SC IFNB-1a (N=187)	Alemtuzumab 12 mg/day (N=376)	Total (N=563)
EDSS Score, n(%)			
0	9 (4.8)	15 (4.0)	24 (4.3)
1.0	22 (11.8)	48 (12.8)	70 (12.4)
1.5	38 (20.3)	78 (20.7)	116 (20.6)
2.0	50 (26.7)	87 (23.1)	137 (24.3)
2.5	31 (16.6)	54 (14.4)	85 (15.1)
3.0	34 (18.2)	86 (22.9)	120 (21.3)
3.5[a]	3 (1.6)	6 (1.6)	9 (1.6)
4.0[a]	0	2 (0.5)	2 (0.4)
Mean (SD)	2.0 (0.79)	2.0 (0.81)	2.0 (0.81)
Median	2.0	2.0	2.0
Min, Max	0.0, 3.5	0.0, 4.0	0.0, 4.0
Years Since Initial Episode			
Mean (SD)	2.0 (1.32)	2.1 (1.36)	2.1 (1.35)
Median	1.5	1.7	1.6
Min, Max	0.2, 5.0	0.1, 5.2	0.1, 5.2
Years Since Last Episode			
Mean (SD)	0.38 (0.23)	0.37 (0.23)	0.37 (0.23)
Median	0.33	0.31	0.32
Min, Max	0.05, 1.53	0.04, 1.08	0.04, 1.53
Number of Episodes in Preceding 1 Year, n (%)	187 (100.0)	376 (100.0)	563 (100.0)
0	4 (2.1)	6 (1.6)	10 (1.8)
1	66 (35.3)	145 (38.6)	211 (37.5)
2	94 (50.3)	169 (44.9)	263 (46.7)
≥3	23 (12.3)	56 (14.9)	79 (14.0)
Mean (SD)	1.8 (0.83)	1.8 (0.81)	1.8 (0.82)
Median	2.0	2.0	2.0
Min, Max	0.0, 5.0	0.0, 5.0	0.0, 5.0
Number of Episodes in Preceding 2 Years, n (%)	187 (100.0)	376 (100.0)	563 (100.0)
0	0	0	0
1	3 (1.6)	12 (3.2)	15 (2.7)
2	118 (63.1)	215 (57.2)	333 (59.1)
≥3	66 (35.3)	149 (39.6)	215 (38.2)
Mean (SD)	2.5 (0.76)	2.5 (0.85)	2.5 (0.83)
Median	2.0	2.0	2.0
Min, Max	1.0, 6.0	1.0, 7.0	1.0, 7.0

Numbers analysed

A total of 581 patients (195 IFNB-1a; 386 alemtuzumab) were randomized in this study. 563 patients (187 IFNB-1a; 376 alemtuzumab) were treated and included in both the Full Analysis Set used for the primary efficacy analyses and the Safety set (Table 14).

Table 14 Data sets based on randomised patients, N (%)

	SC IFNB-1a (N=195)	Alemtuzumab 12 mg/day (N=386)	Total (N=581)
Randomized Set, n (%)	195 (100.0)	386 (100.0)	581 (100.0)
Full Analysis Set, n (%)	187 (95.9)	376 (97.4)	563 (96.9)
Patients Excluded	8 (4.1)	10 (2.6)	18 (3.1)
No Study Drug Received	8 (4.1)	10 (2.6)	18 (3.1)
Safety Set, n (%)	187 (95.9)	376 (97.4)	563 (96.9)
Patients Excluded	8 (4.1)	10 (2.6)	18 (3.1)
No Study Drug Received	8 (4.1)	10 (2.6)	18 (3.1)
Per Protocol Set, n (%)	168 (86.2)	362 (93.8)	530 (91.2)
Patients Excluded	27 (13.8)	24 (6.2)	51 (8.8)
No Study Drug Received	8 (4.1)	10 (2.6)	18 (3.1)
Inclusion/Exclusion Criteria Violation	2 (1.0)	5 (1.3)	7 (1.2)
Study Treatment Non-Compliance	13 (6.7)	7 (1.8)	20 (3.4)
Invalid Study Medication	4 (2.1)	0	4 (0.7)
Required Relapse Evaluation Not Done	1 (0.5)	1 (0.3)	2 (0.3)
Received >24 mg of Alemtuzumab in 1 day	0	2 (0.5)	2 (0.3)

Outcomes and estimation

Relapse

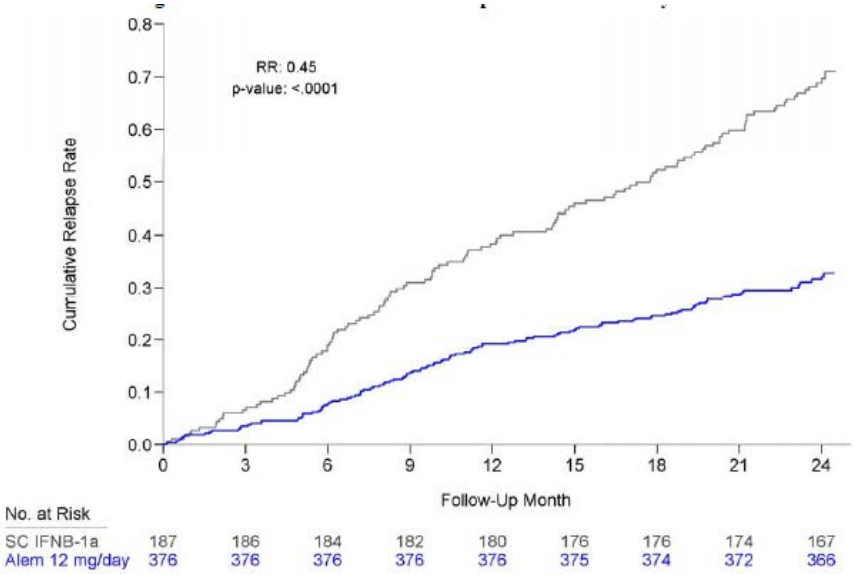
Two annual cycles of alemtuzumab treatment resulted in a statistically significant 55% reduction in relapse rate compared with IFNB-1a ($p<0.0001$), meeting the relapse co-primary endpoint, and satisfying the predefined protocol criteria for declaring that this study met its efficacy objective. The estimated ARR through two years was 0.18 for alemtuzumab versus 0.39 for IFNB-1a (Table 15).

Table 15 Relapse rate and treatment effect summary

Statistic	SC IFNB-1a (N=187)	Alemtuzumab 12 mg/day (N=376)
Patients with event, n	75	82
Total number of events, n	122	119
Annualized rate (95% CI)	0.39 (0.29, 0.53)	0.18 (0.13, 0.23)
Rate ratio (95% CI)		0.45 (0.32, 0.63)
Risk reduction		54.88
p-value		<0.0001

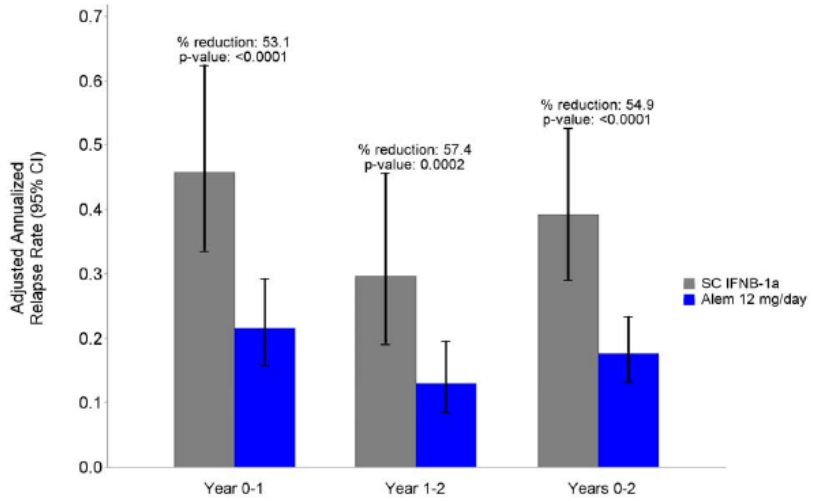
The superior effect of alemtuzumab on relapse reduction was statistically significant within six months of initiating treatment and was maintained throughout the study period (Figure 4).

Figure 4 Cumulative plot of relapse rate



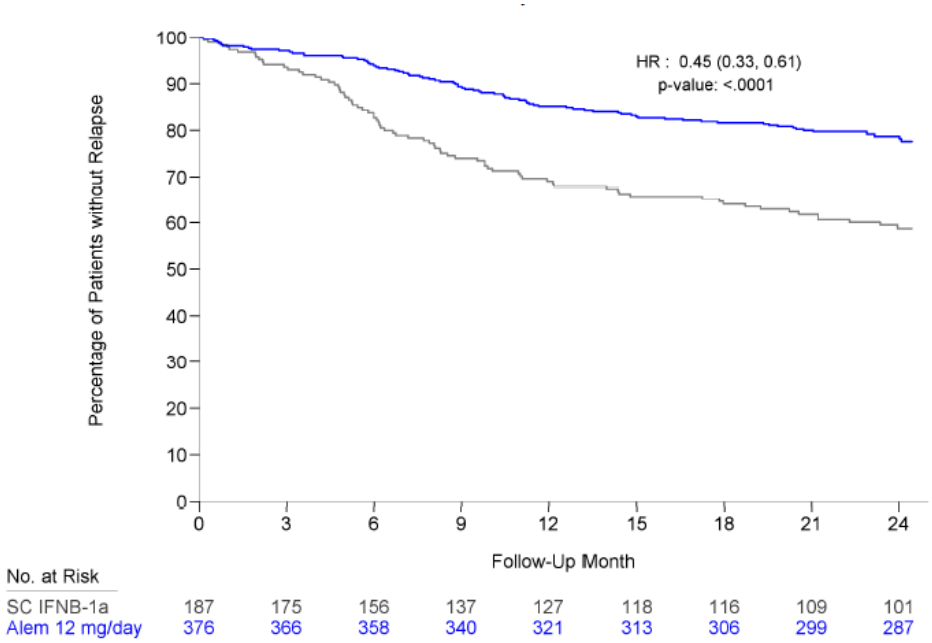
Compared with IFNB-1a, alemtuzumab reduced the relapse rate by 53% in Year 1 and 57% in Year 2 Figure 5.

Figure 5 – Annualised relapse rate (ARR) by time interval: Full analysis set



Alemtuzumab significantly increased the proportion of patients who were relapse free through 2 years compared with IFNB-1a. At Year 2, 78% of alemtuzumab versus 59% of IFNB-1a-treated patients remained relapse free, which represents a 55% reduction in the risk of relapse over 2 years (Figure 6).

Figure 6 Kaplan-Meier plot of time to first relapse: Full analysis set



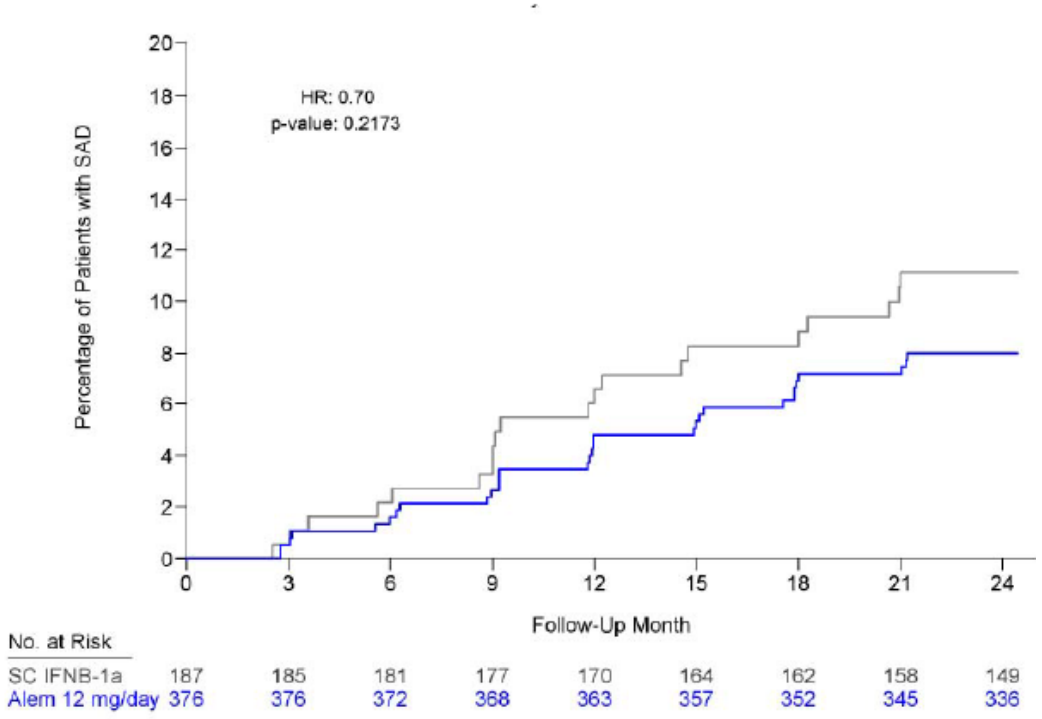
Disability

During the 2-year follow-up, 8.0% of alemtuzumab-treated patients and 11.1% of IFNB-1a-treated patients experienced 6-month SAD, but the difference between the treatment groups in the risk of SAD was not statistically significant (p=0.2173) and therefore, the study did not meet this co-primary endpoint (Table 16, Figure 7)

Table 16 SAD (6-month criteria) event and treatment effect summary

Statistic	SC IFNB-1a (N=187)	Alemtuzumab 12 mg/day (N=376)
Patients with event, n	20	30
KM estimate of event (95% CI)	11.12 (7.32, 16.71)	8.00 (5.66, 11.24)
KM estimate of no event (95% CI)	88.88 (83.29, 92.68)	92.00 (88.76, 94.34)
Hazard ratio (95% CI)		0.70 (0.40, 1.23)
Risk reduction		30
p-value		0.2173

Figure 7 Cumulative plot of time to SAD: Full analysis set



A consolidated summary of efficacy outcomes in the co-primary and secondary endpoints is presented in Table 17.

Table 17 Overview of efficacy results in study CAMMS323 (Full analysis set)

CAMMS323		
Endpoint	**SC IFNB-1a (N=187)**	**Alemtuzumab 12 mg/day (N=376)**
Relapse-Related Endpoints **Primary: Relapse Rate (Proportional Mean/Negative Binomial Regression)**		
Annualized relapse rate (95% CI)	0.39 (0.29, 0.53)	0.18 (0.13, 0.23)
Rate ratio (95% CI)		0.45 (0.32, 0.63)
p-value		< 0.0001
Secondary: Proportion of Patients who are Relapse Free (Proportional Hazards Regression)		
KM estimate of no event (95% CI)	58.69 (51.12, 65.50)	77.59 (72.87, 81.60)
Hazard ratio (95% CI)		0.45 (0.33, 0.61)
p-value		< 0.0001
Disability-Related Endpoints **Primary: Time to SAD, Sustained Over a 6-Month Period (Proportional Hazards Regression)**		
KM estimate of proportion of patients with SAD (95% CI)	11.12 (7.32, 16.71)	8.00 (5.66, 11.24)
Hazard ratio (95% CI)		0.70 (0.40, 1.23)
p-value		0.2173
Secondary Endpoint: Change from Baseline in EDSS (Mixed Model for Repeated Measures)		
Overall p-value (multivariate non-parametric test)		0.4188
Mean change (95% CI)	-0.14 (-0.29, 0.01)	-0.14 (-0.25, -0.02)
Difference (95% CI)		0 (-0.16, 0.17)
p-value		0.9653
Secondary Endpoint: Change from Baseline in MSFC (Mixed Model for Repeated Measures)		
Overall p-value (multivariate non-parametric test)		0.0115
Mean change (95% CI)	0.05 (-0.02, 0.13)	0.12 (0.06, 0.18)
Difference (95% CI)		0.07 (-0.01, 0.15)
p-value		0.0735
Imaging-Related Endpoints **Secondary: Percent Change from Baseline in MRI-T2 Lesion Volume (Ranked ANCOVA)**		
Median percent change	-6.5	-9.3
p-value		0.3080

MRI findings

While alemtuzumab and IFNB-1a were both efficacious in reducing Gd-enhancing lesions and T2 lesion volume compared with baseline, alemtuzumab was significantly more efficacious than IFNB-1a on all MRI measures in the second year of follow-up. In addition, over the duration of follow-up, alemtuzumab significantly reduced the risk of developing Gd-enhancing and new or enlarging T2-hyperintense lesions. Alemtuzumab-treated patients had significant reductions in severe established and ongoing tissue damage as measured by the T1-hypointense lesion volume and significant reductions in the rate of brain atrophy as measured by the brain parenchymal fraction, compared with IFNB-1a-treated patients. Alemtuzumab significantly decreased the odds of experiencing MRI activity (p=0.0388) through 2 years (Table 18).

Table 18 MRI activity – full analysis set

Time Period	SC IFNB-1a (N=187)	Alemtuzumab 12 mg/day (N=376)
Month 12		
n	174	369
Yes, n (%)	83 (47.7)	148 (40.1)
No, n (%)	91 (52.3)	221 (59.9)
Odds Ratio (95% CI)		0.72 (0.49, 1.04)
p-value		0.0824
Month 24		
n	175	362
Yes, n (%)	72 (41.1)	85 (23.5)
No, n (%)	103 (58.9)	277 (76.5)
Odds Ratio (95% CI)		0.43 (0.29, 0.64)
p-value		<.0001
Composite of Months 12 and 24		
n	172	360
Yes, n (%)	100 (58.1)	175 (48.6)
No, n (%)	72 (41.9)	185 (51.4)
Odds Ratio (95% CI)		0.67 (0.46, 0.98)
p-value		0.0388

Quality of life

Alemtuzumab patients showed significantly greater improvements from baseline in self-reported quality of life than IFNB-1a patients on both the FAMS (at all time-points assessed) and the SF-36 PCS (at Year 1 but not Year 2). On both the FAMS and the SF-36, these between-group differences were largely driven by greater improvements on scales pertaining to physical functioning as opposed to mental or social functioning. While there were no significant differences between the treatment groups on EQ-5D utility scores or health states, alemtuzumab patients did show significantly greater improvements from baseline on the EQ-5D VAS at Year 1.

Ancillary analyses

Sensitivity analyses conducted to assess the influence of alternative MS treatments, unblinded EDSS raters and other factors that could potentially affect the primary relapse- and time to SAD-analyses demonstrated that the influence of these factors was minimal and did not alter the estimates of the treatment effects in either of the co-primary endpoints.

Subgroup analyses were conducted to assess the influence of gender, age, geographic region and other baseline or demographic factors on the MS relapse and the time to disability progression sustained for 6 months. Summaries of these analyses are presented in Figures 8 and 9.

Figure 8 Summary of relapse rate subgroup analyses

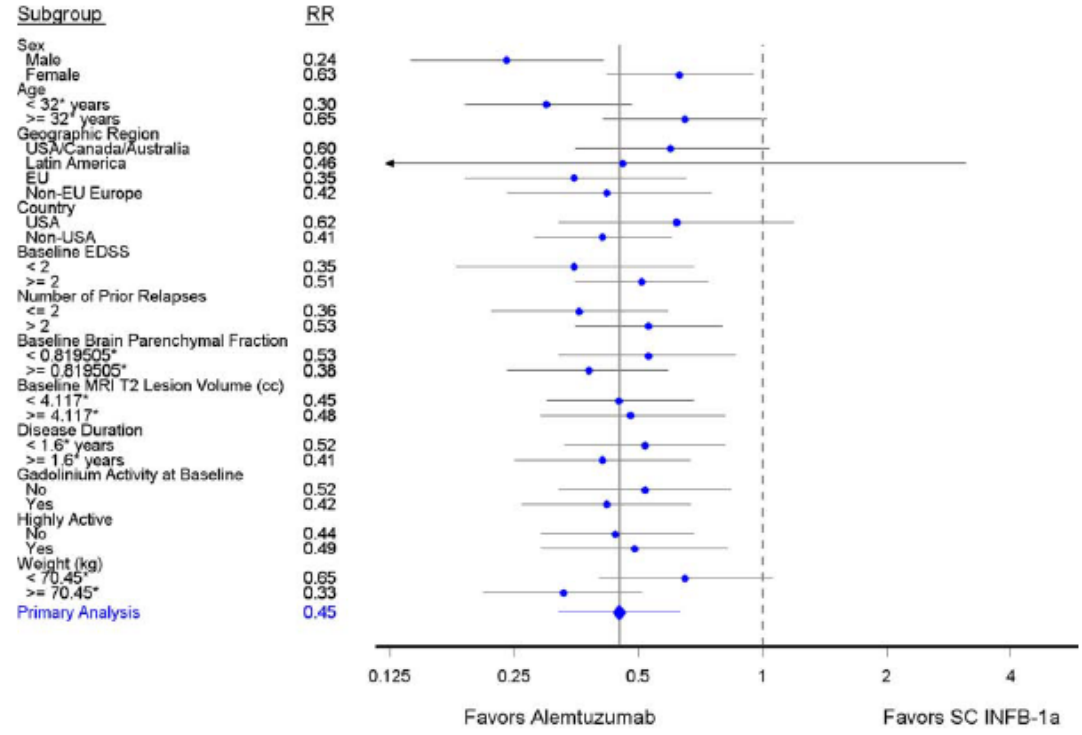
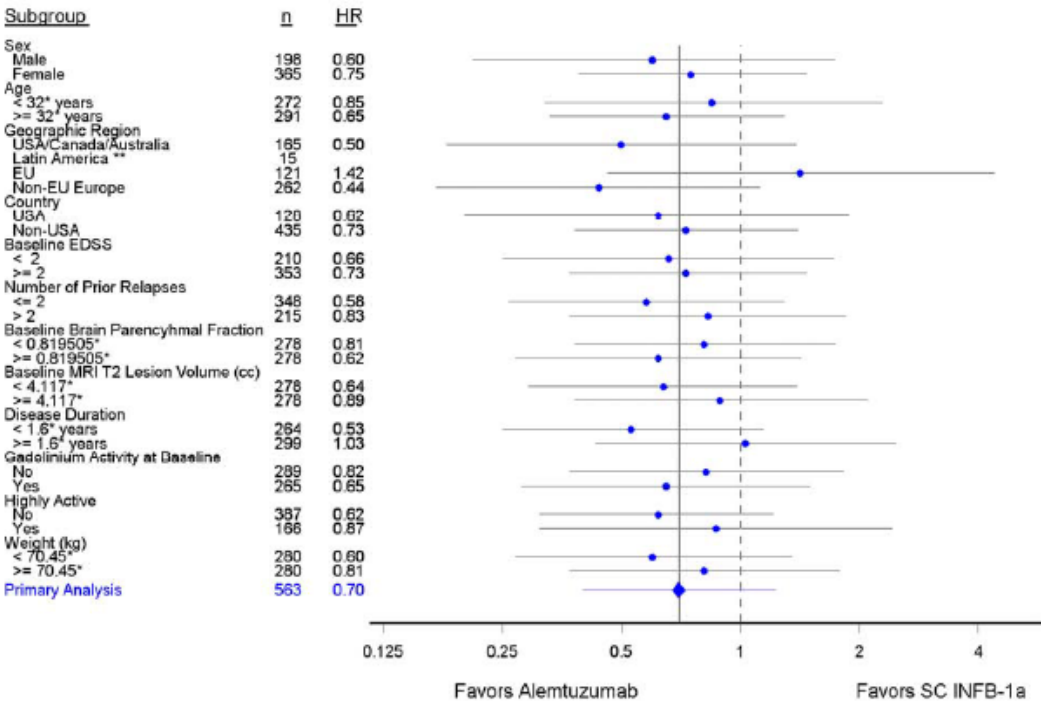


Figure 9 Summary of sustained accumulation of disability subgroup analyses



CAMMS324 - A phase 3 randomized, rater- and dose-blinded study comparing two annual cycles of intravenous low- and high-dose alemtuzumab to three-times weekly subcutaneous interferon beta-1a (Rebif) in patients with relapsing-remitting multiple sclerosis who have relapsed on therapy

Methods

Study Participants

To be eligible to participate in the study, patients (aged 18-55) had to present with active RRMS. These patients were defined as patients with an EDSS score between 0 and 5, who had first onset of MS symptoms within 10 years prior to study entry and at least two clinical episodes of MS in the prior two years, at least one episode in the prior year and at least one MS relapse during treatment with a beta interferon therapy or glatiramer acetate after having been on that therapy for ≥6 months within 10 years prior to study entry. Patients meeting any of the following criteria could not be enrolled: any progressive form of MS, history of malignancy, CD4+, CD8+, CD19+ cell or absolute neutrophil count < lower limit of normal (LLN) at screening, known bleeding disorder, significant autoimmune disease, presence of anti-TSHR antibodies and active infection/ high risk of infection and previous treatment with natalizumab, methotrexate, azathioprine or cyclosporine in the past six months.

Treatments

Alemtuzumab was administered by daily intravenous infusions at 2 dose levels of 12 mg/day and 24 mg/day. Patients in the alemtuzumab 12 mg/day group received daily infusions for 5 consecutive days at Month 0 (Cycle 1; 60 mg total) and for 3 consecutive days at Month 12 (Cycle 2; 36 mg total). Patients in the alemtuzumab 24 mg/day group received daily infusions for 5 consecutive days at Month 0 (Cycle 1; 120 mg total) and for 3 consecutive days at Month 12 (Cycle 2; 72 mg total). Initial infusions were given over a period of at least 4 hours. If the first 2 doses of each annual visit were well tolerated, subsequent daily infusions could be given more rapidly, but never over a period of less than 2 hours. If not well tolerated, the infusion period could be extended at the physician's discretion, but the total infusion period on any day was not to exceed 8 hours. All alemtuzumab-treated patients received IV methylprednisolone (1 g/day) on Days 1, 2 and 3 at Month 0 and 12. Further to a protocol amendment, all alemtuzumab patients received acyclovir 200 mg twice daily (or a therapeutic equivalent) starting on the first day of each alemtuzumab cycle and continuing for 28 days after the last day.

The comparator used in the trial was Rebif (IFNB-1a), administered at 44 µg tiw, i.e. in a total weekly dose of 132 µg. The dose could be decreased based on patient tolerance. All patients received IV methylprednisolone (1 g/day) on Days 1, 2, and 3 at Month 0 and 12.

On-study relapses could be treated with corticosteroids at the discretion of the Treating Neurologist. A standardized regimen of methylprednisolone was strongly recommended as follows: 1 gram of methylprednisolone administered by IV over approximately 1 hour, daily for 3 consecutive days.

Objectives

The objectives of this study were to compare the safety and efficacy of 2 annual cycles of IV alemtuzumab at either 12 mg/day or 24 mg/day versus subcutaneous interferon beta-1a administered 3-times weekly, in patients with RRMS who had experienced at least 1 relapse during prior treatment with interferon beta or glatiramer acetate after having received that therapy for ≥6 months. The alemtuzumab 24 mg/day group was closed by Amendment 2 in order to reduce the overall sample size, the duration of the enrolment period and the overall duration of the study. Efficacy comparisons with alemtuzumab 24 mg/day were considered exploratory.

Outcomes/endpoints

The active-controlled phase 3 studies utilized the co-primary efficacy endpoints of MS relapse rate and time to SAD (6-month criteria). Secondary endpoints included imaging findings (MRI) along with additional relapse and disability endpoints. Definitions of the co-primary and secondary endpoints in studies CAMMS223, CAMMS323 and CAMMS324 are provided in Table 11 (above). With respect to imaging, the same endpoints as in CAMMS323 were deployed: % change in T1-hypointense lesion volume, % change in brain parenchymal fraction, new or enlarging T2-hyperintense lesion counts, Gd-enhancing lesion counts, new T1-hypointense lesion counts and conversion of Gd-enhancing lesions to new T1-hypointense lesions. The efficacy assessments also comprised a number of additional exploratory and tertiary endpoints, including quality of life parameters (FAMS, SF-36 and EQ-5D), as in study CAMMS323.

Sample size

Under the original study protocol, assuming a 2:2:1 randomisation to alemtuzumab 12 mg/day, alemtuzumab 24 mg/day or IFNB-1a, a sample size of 1200 patients was planned in order to provide >80% power to detect a 45% treatment effect in time to SAD, assuming a 2-year SAD rate of 20% for the IFNB-1a patients. Under Amendment 2, the 24 mg/day arm was closed to further enrolment and randomisation continued until approximately 382 patients were assigned to alemtuzumab 12 mg/day and 191 were assigned to IFNB-1a. Approximately 573 patients across the 2 treatment groups should provide >80% power to detect a 50% treatment effect in time to SAD given a 2-year SAD rate of 20% for the IFNB-1a patients.

Randomisation

Patients were randomized to alemtuzumab (12 mg/day or 24 mg/day) or IFNB-1a using an interactive voice response system. Treatment assignment was at a ratio of 2:2:1. After closing the 24 mg/day arm, all patients were randomised at a 2:1 ratio to alemtuzumab 12 mg/day or IFNB-1a. Patients already randomized to the alemtuzumab 24 mg/day arm continued to receive the 24 mg/day dose as originally planned.

Blinding (masking)

The same approach was taken as in study CAMMS 323.

Statistical methods

The same approach was taken as in study CAMMS 323.

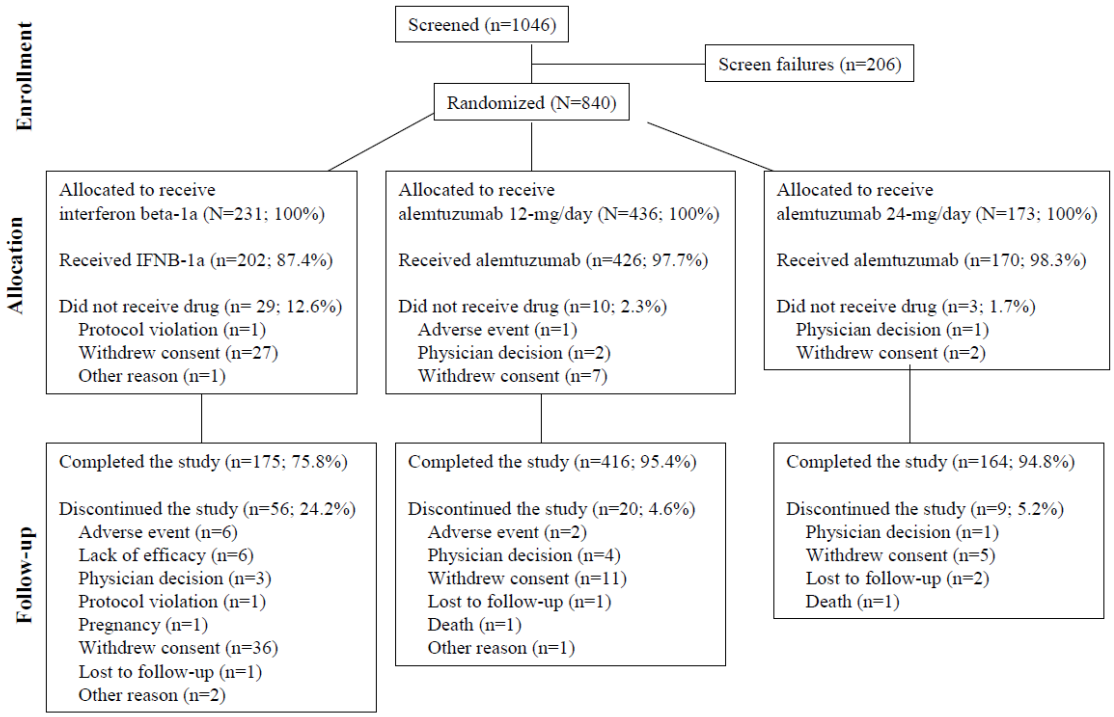
In study CAMMS324, the primary and secondary endpoints were also evaluated in the alemtuzumab 24 mg/day group as exploratory analyses.

Results

Participant flow

The study participant flow, patient completion rates and reasons for discontinuation are presented in Figure 10.

Figure 10



Recruitment

The study took place between 10 October 2007 and 15 September 2011.

Conduct of the study

There were four amendments to the protocol introduced during the conduct of the study. The key changes introduced through Amendment 2 included closing the alemtuzumab 24 mg/day group in order to reduce the overall sample size, the duration of the enrolment period and the duration of the study. The other amendments of the protocol were similar to those implemented for study CAMSS323, i.e. pertained to ensuring patient safety and introducing measures to improve blinding.

Baseline data

A summary of the patient population enrolled in the study is presented in the tables below:

Table 19 Demographic characteristic

Variable	SC IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)	Alemtuzumab 24 mg/day (N=170)	Alemtuzumab Pooled (N=596)	Total (N=798)
Age (years)					
n	202	426	170	596	798
Mean (SD)	35.8 (8.77)	34.8 (8.36)	35.1 (8.40)	34.9 (8.37)	35.1 (8.47)
Median	35.0	34.0	34.0	34.0	34.0
Min, Max	18.0, 54.0	18.0, 55.0	20.0, 54.0	18.0, 55.0	18.0, 55.0
Q1, Q3	30.0, 43.0	29.0, 41.0	29.0, 41.0	29.0, 41.0	29.0, 42.0
Sex, n (%)					
Male	71 (35.1)	145 (34.0)	50 (29.4)	195 (32.7)	266 (33.3)
Female	131 (64.9)	281 (66.0)	120 (70.6)	401 (67.3)	532 (66.7)
Ethnicity, n (%)					
Hispanic/Latino	21 (10.4)	54 (12.7)	29 (17.1)	83 (13.9)	104 (13.0)
Not Hispanic/Latino	181 (89.6)	371 (87.1)	141 (82.9)	512 (85.9)	693 (86.8)
Race, n (%)					
White	187 (92.6)	385 (90.4)	142 (83.5)	527 (88.4)	714 (89.5)
Black	8 (4.0)	24 (5.6)	11 (6.5)	35 (5.9)	43 (5.4)
Asian	0	0	2 (1.2)	2 (0.3)	2 (0.3)
American Indian or Alaska Native	0	2 (0.5)	3 (1.8)	5 (0.8)	5 (0.6)
Other	7 (3.5)	15 (3.5)	12 (7.1)	27 (4.5)	34 (4.3)
Weight (kg)					
n	201	426	169	595	796
Mean (SD)	78.5 (20.22)	76.1 (18.15)	76.8 (20.34)	76.3 (18.78)	76.8 (19.17)
Median	75.0	73.1	72.6	73.0	74.0
Min, Max	44.0, 165.0	42.3, 157.4	48.2, 188.2	42.3, 188.2	42.3, 188.2
Q1, Q3	64.0, 89.8	62.1, 87.1	62.1, 85.0	62.1, 86.9	62.1, 87.1
Height (cm)					
n	200	426	170	596	796
Mean (SD)	169.2 (10.05)	170.1 (9.53)	168.8 (9.02)	169.8 (9.40)	169.6 (9.56)
Median	168.0	170.0	167.6	169.0	169.0
Min, Max	139.7, 193.0	134.6, 198.0	152.4, 197.0	134.6, 198.0	134.6, 198.0
Q1, Q3	162.6, 177.8	163.0, 176.0	162.6, 175.3	162.6, 175.4	162.6, 176.0
Body Mass Index (kg/m^2)					
n	199	426	169	595	794
Mean (SD)	27.5 (7.02)	26.3 (6.11)	26.8 (6.18)	26.4 (6.13)	26.7 (6.38)
Median	25.1	25.0	25.0	25.0	25.1
Min, Max	16.5, 52.0	16.5, 56.4	18.1, 59.5	16.5, 59.5	16.5, 59.5
Q1, Q3	22.5, 31.7	21.8, 29.6	22.7, 29.6	22.0, 29.6	22.2, 29.9

Table 20 Baseline MS Disease Characteristics

Variable	SC IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)	Alemtuzumab 24 mg/day (N=170)	Total (N=798)
Time Since Initial Episode (years)				
n	202	426	170	798
Mean (SD)	4.7 (2.86)	4.5 (2.68)	4.3 (2.77)	4.5 (2.75)
Median	4.1	3.8	3.7	3.8
Min, Max	0.4, 10.1	0.2, 14.4	0.2, 16.9	0.2, 16.9
Q1, Q3	2.2, 7.4	2.3, 6.2	2.0, 5.9	2.2, 6.3
Time Since Last Episode (years)				
n	202	426	170	798
Mean (SD)	0.41 (0.24)	0.40 (0.23)	0.42 (0.22)	0.41 (0.23)
Median	0.34	0.34	0.36	0.34
Min, Max	0.00, 1.22	0.00, 1.16	0.06, 1.05	0.00, 1.22
Q1, Q3	0.24, 0.55	0.22, 0.53	0.24, 0.57	0.23, 0.54
Number of Episodes in the Preceding 1 Year, n (%)	202 (100.0)	426 (100.0)	170 (100.0)	798 (100.0)
0	5 (2.5)	6 (1.4)	3 (1.8)	14 (1.8)
1	107 (53.0)	211 (49.5)	84 (49.4)	402 (50.4)
2	68 (33.7)	151 (35.4)	64 (37.6)	283 (35.5)
≥3	22 (10.9)	58 (13.6)	19 (11.2)	99 (12.4)
Mean (SD)	1.5 (0.75)	1.7 (0.86)	1.6 (0.86)	1.6 (0.83)
Median	1.0	1.0	1.0	1.0
Min, Max	0.0, 4.0	0.0, 5.0	0.0, 6.0	0.0, 6.0
Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0	1.0, 2.0
Number of Episodes in the Preceding 2 Years, n (%)	202 (100.0)	426 (100.0)	170 (100.0)	798 (100.0)
0	0	0	0	0
1	7 (3.5)	15 (3.5)	11 (6.5)	33 (4.1)
2	109 (54.0)	215 (50.5)	94 (55.3)	418 (52.4)
≥3	86 (42.6)	196 (46.0)	65 (38.2)	347 (43.5)
Mean (SD)	2.6 (0.97)	2.8 (1.20)	2.5 (1.02)	2.7 (1.11)
Median	2.0	2.0	2.0	2.0
Min, Max	1.0, 6.0	1.0, 9.0	1.0, 7.0	1.0, 9.0
Q1, Q3	2.0, 3.0	2.0, 3.0	2.0, 3.0	2.0, 3.0
EDSS Score, n (%)				
0	5 (2.5)	16 (3.8)	4 (2.4)	25 (3.1)
1.0	13 (6.4)	24 (5.6)	12 (7.1)	49 (6.1)
1.5	31 (15.3)	65 (15.3)	19 (11.2)	115 (14.4)
2.0	34 (16.8)	63 (14.8)	29 (17.1)	126 (15.8)
2.5	24 (11.9)	53 (12.4)	23 (13.5)	100 (12.5)
3.0	24 (11.9)	59 (13.8)	29 (17.1)	112 (14.0)
3.5	26 (12.9)	55 (12.9)	17 (10.0)	98 (12.3)
4.0	24 (11.9)	43 (10.1)	21 (12.4)	88 (11.0)
4.5	9 (4.5)	17 (4.0)	9 (5.3)	35 (4.4)
5.0	10 (5.0)	25 (5.9)	5 (2.9)	40 (5.0)
5.5	1 (0.5)	4 (0.9)	1 (0.6)	6 (0.8)
6.0	1 (0.5)	1 (0.2)	1 (0.6)	3 (0.4)
6.5	0	1 (0.2)	0	1 (0.1)
n	202	426	170	798
Mean (SD)	2.7 (1.21)	2.7 (1.26)	2.7 (1.17)	2.7 (1.22)
Median	2.5	2.5	2.5	2.5
Min, Max	0.0, 6.0	0.0, 6.5	0.0, 6.0	0.0, 6.5
Q1, Q3	2.0, 3.5	2.0, 3.5	2.0, 3.5	2.0, 3.5

Numbers analysed

A total of 840 patients (231 IFNB-1a; 436 alemtuzumab 12 mg/day; 173 alemtuzumab 24 mg/day) were randomized in this study. 798 patients (202 IFNB-1a; 426 alemtuzumab 12 mg/day; 170 alemtuzumab 24 mg/day) were included in the Full Analysis Set (all patients who were randomised and received at least one dose of the study drug) used for the primary efficacy analyses. The number of patients in each treatment group for the Full Analysis Set and the Safety Set were not the same, because 9 patients were randomised to the alemtuzumab 24 mg/day treatment group but received alemtuzumab 12 mg/day.

Table 21 Data sets based on randomised patients, N (%)

	SC IFNB-1a (N=231)	Alemtuzumab 12 mg/day (N=436)	Alemtuzumab 24 mg/day (N=173)	Total (N=840)
Randomized Set, n (%)	231 (100.0)	436 (100.0)	173 (100.0)	840 (100.0)
Full Analysis Set, n (%)	202 (87.4)	426 (97.7)	170 (98.3)	798 (95.0)
Patients Excluded	29 (12.6)	10 (2.3)	3 (1.7)	42 (5.0)
No Study Drug Received	29 (12.6)	10 (2.3)	3 (1.7)	42 (5.0)
Safety Set, n (%)	202 (87.4)	435 (99.8)	161 (93.1)	798 (95.0)
Patients Excluded	29 (12.6)	1 (0.2)	12 (6.9)	42 (5.0)
No Study Drug Received	29 (12.6)	1 (0.2)	12 (6.9)	42 (5.0)
PP Set, n (%)	171 (74.0)	398 (91.3)	153 (88.4)	722 (86.0)
Patients Excluded	60 (26.0)	38 (8.7)	20 (11.6)	118 (14.0)
No Study Drug Received	29 (12.6)	10 (2.3)	3 (1.7)	42 (5.0)
Inclusion/Exclusion Criteria Violation	5 (2.2)	10 (2.3)	2 (1.2)	17 (2.0)
Per-Protocol Treatment Non-Compliance	21 (9.1)	12 (2.8)	9 (5.2)	42 (5.0)
Invalid Study Medication	2 (0.9)	0	0	2 (0.2)
Required Relapse Evaluation Not Done	3 (1.3)	7 (1.6)	1 (0.6)	11 (1.3)
Received Incorrect Study Medication	0	0	9 (5.2)	9 (1.1)
Received > 24 mg/day of Alemtuzumab in One Day	0	0	0	0

Outcomes and estimation

Relapse

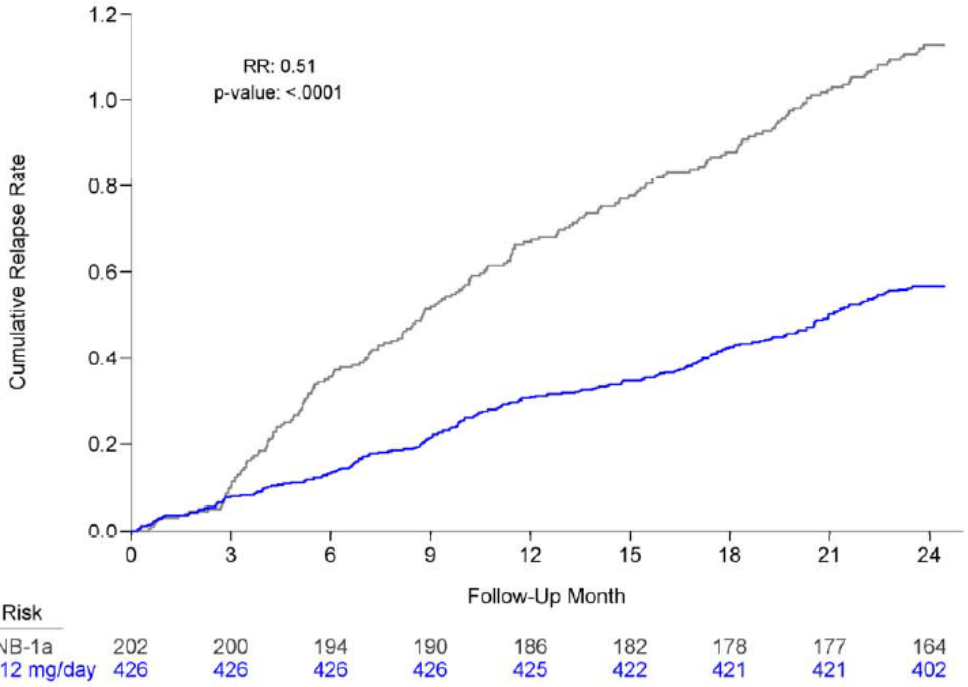
Two annual cycles of alemtuzumab treatment resulted in a statistically significant 49% reduction in relapse rate compared with IFNB-1a ($p<0.0001$), meeting the relapse co-primary endpoint, and satisfying the predefined protocol criteria for declaring that this study met its efficacy objective. The estimated ARR through two years was 0.26 for alemtuzumab versus 0.52 for IFNB-1a (Table 22).

Table 22 Relapse rate and treatment effect summary

Time Period / Statistic	SC IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)
Relapse Rate through 2 Years (Co-primary Efficacy Endpoint)		
Patients with any event (number of events)	104 (201)	147 (236)
Annualized rate (95% CI)	0.52 (0.41, 0.66)	0.26 (0.21, 0.33)
Rate ratio (95% CI)		0.51 (0.39, 0.65)
Risk reduction		49.40
p-value		<0.0001

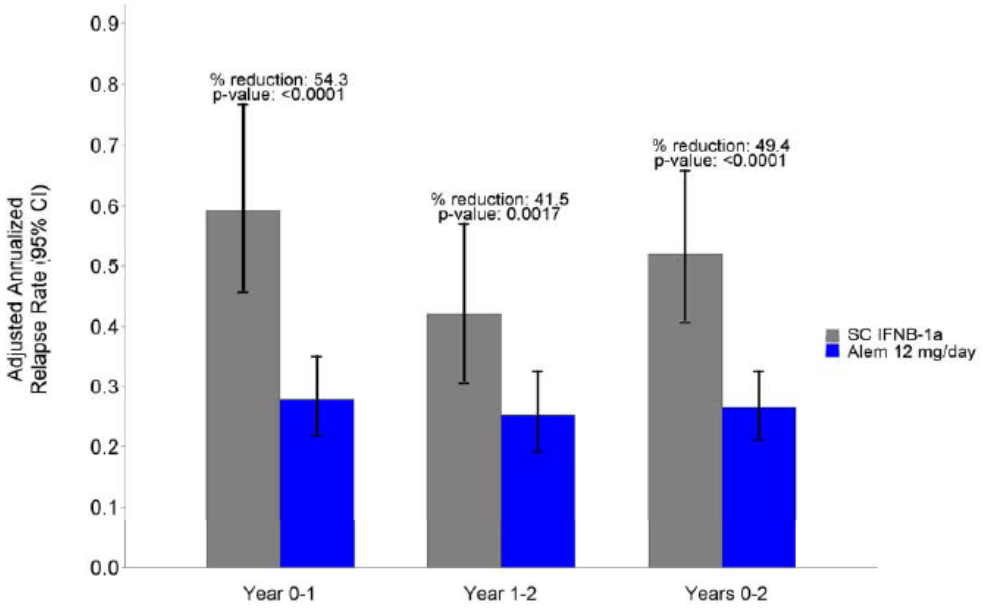
The superior effect of alemtuzumab on relapse reduction was statistically significant within four months of initiating treatment and was maintained throughout the study period (Figure 11).

Figure 11 Cumulative plot of relapse rate



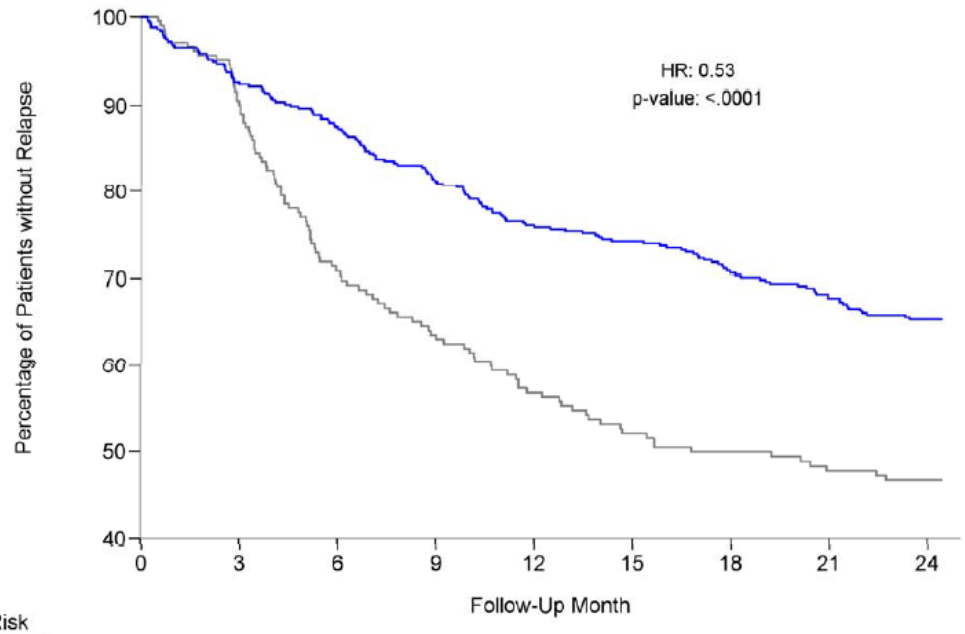
Compared with IFNB-1a, alemtuzumab reduced the relapse rate by 54% in Year 1 and 41% in Year 2 (Figure 12).

Figure 12 Annualised relapse rate (ARR) by time interval: Full analysis set



Alemtuzumab significantly increased the proportion of patients who were relapse free through 2 years compared with IFNB-1a. At Year 2, 65.4% of alemtuzumab versus 46.7% of IFNB-1a-treated patients remained relapse free, which represents a 47% reduction in the risk of relapse over 2 years (Figure 13).

Figure 13 Kaplan-Meier plot of time to first relapse: Full analysis set



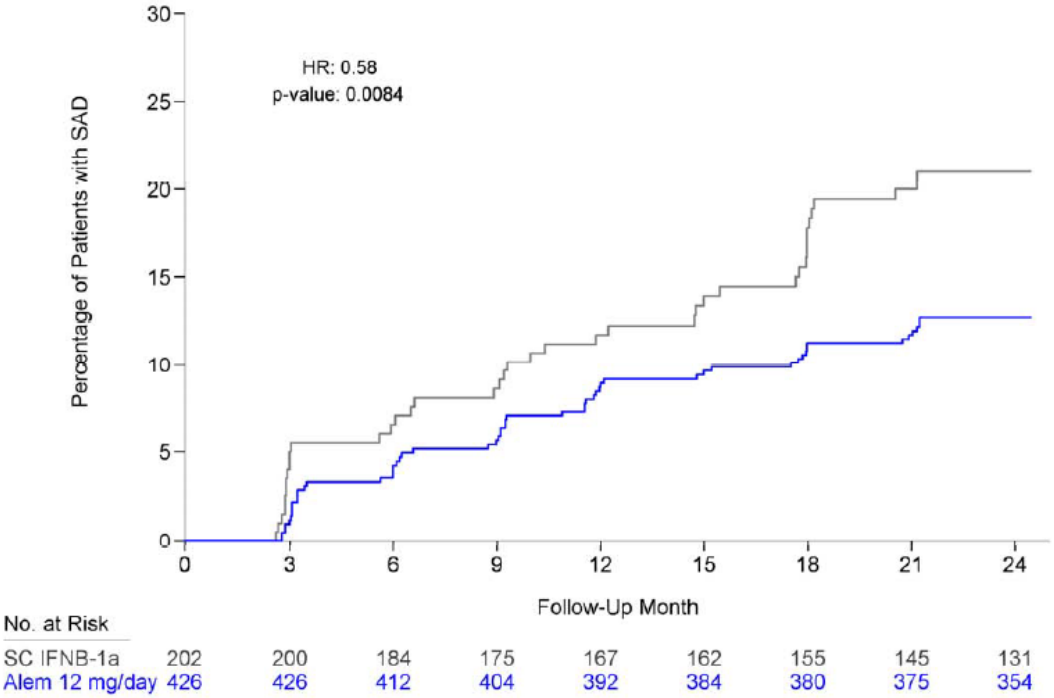
Disability

Alemtuzumab reduced the risk of SAD through 2 years by 42% compared with IFNB-1a (p=0.0084). Thus, the disability co-primary efficacy endpoint was met. The percentage of patients experiencing SAD at 2 years was 12.7% in the alemtuzumab 12 mg/day group and 21.1% in the IFNB-1a group (Table 23, Figure 14).

Table 23 SAD (6-month criteria) event and treatment effect summary

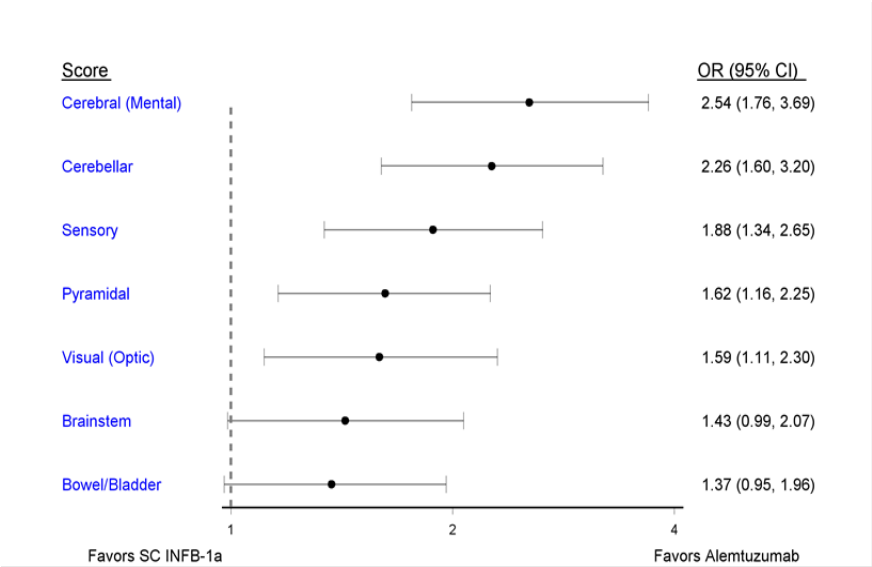
Statistic	SC IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)
Patients with event, n	40	54
KM estimate of event (95% CI)	21.13 (15.95, 27.68)	12.71 (9.89, 16.27)
KM estimate of no event (95% CI)	78.87 (72.32, 84.05)	87.29 (83.73, 90.11)
Hazard ratio (95% CI)		0.58 (0.38, 0.87)
Risk reduction		42
p-value		0.0084

Figure 14 Cumulative plot of time to SAD: Full analysis set



In an analysis of the Function System (FS) scores of the EDSS, improvement of diverse neurological functions was observed in patients treated with alemtuzumab.

Figure 15 Improvements on EDSS Functional Systems



A consolidated summary of efficacy outcomes in the co-primary and secondary endpoints is presented in Table 24.

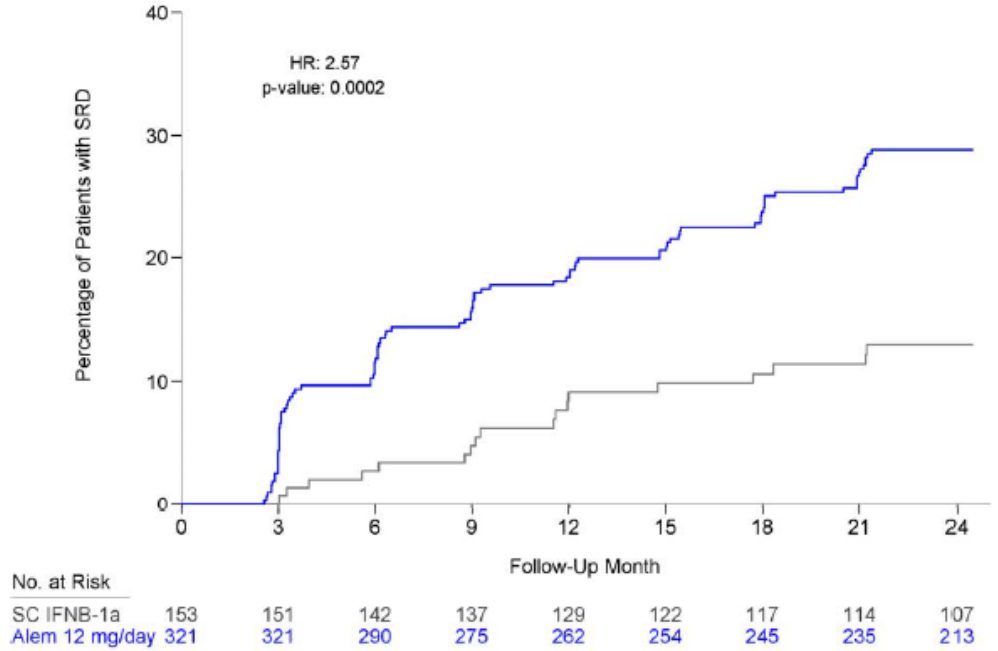
Table 24 Overview of efficacy results in study CAMMS324 (Full analysis set)

CAMMS324			
Endpoint		**SC IFNB-1a (N=202)**	**Alemtuzumab 12 mg/day (N=426)**
Relapse-Related Endpoints **Primary: Relapse Rate (Proportional Means/Negative Binomial Regression)**			
	Annualized relapse rate (95% CI)	0.52 (0.41, 0.66)	0.26 (0.21, 0.33)
	Rate ratio (95% CI)		0.51 (0.39, 0.65)
	p-value		< 0.0001
Secondary: Proportion of Patients who are Relapse Free (Proportional Hazards Regression)			
	KM estimate of no event (95% CI)	46.70 (39.53, 53.54)	65.38 (60.65, 69.70)
	Hazard ratio (95% CI)		0.53 (0.41, 0.69)
	p-value		< 0.0001
Disability-Related Endpoints **Primary: Time to SAD, Sustained Over a 6-Month Period (Proportional Hazards Regression)**			
	KM estimate of proportion of patients with SAD (95% CI)	21.13 (15.95, 27.68)	12.71 (9.89, 16.27)
	Hazard ratio (95% CI)		0.58 (0.38, 0.87)
	p-value		0.0084
Secondary Endpoint: Change from Baseline in EDSS (Mixed Model for Repeated Measures)			
	Overall p-value (multivariate non-parametric test)		< 0.0001
	Mean change (95% CI)	0.24 (0.07, 0.41)	-0.17 (-0.29, -0.05)
	Difference (95% CI)		-0.41 (-0.61, -0.22)
	p-value		< 0.0001
Secondary Endpoint: Change from Baseline in MSFC (Mixed Model for Repeated Measures)			
	Overall p-value (multivariate non-parametric test)		0.0022
	Mean change (95% CI)	-0.04 (-0.10, 0.02)	0.08 (0.04, 0.12)
	Difference (95% CI)		0.12 (0.05, 0.19)
	p-value		0.0009
Imaging-Related Endpoints **Secondary: Percent Change from Baseline in MRI-T2 Lesion Volume (Ranked ANCOVA)**			
	Median percent change	-1.23	-1.27
	p-value		0.1371

Time to sustained reduction in disability

Alemtuzumab-treated patients were more likely to achieve a sustained reduction in disability compared with IFNB-1a-treated patients (92/321 patients [28.8%] versus 18/153 patients [12.9%], respectively; HR [95% CI] = 2.57 [1.57, 4.20], p = 0.0002). (Figure 16)

Figure 16 Cumulative plot of time to sustained reduction in disability



In an additional analysis (Table 25), the applicant also examined the longer-term outcome for individuals who achieved 6-month SRD.

Table 25 Time to 12-Month Sustained Reduction of Disability (SRD)

Statistic	SC IFNB-1a (N=153)	Alemtuzumab 12 mg/day (N=321)
Patients with event, n	12	74
KM estimate of event (95% CI)	8.64 (4.99, 14.76)	23.31 (19.04, 28.37)
KM estimate of no event (95% CI)	91.36 (85.24, 95.01)	76.69 (71.63, 80.96)
Hazard ratio (95% CI)		3.02 (1.65, 5.54)
p-value		0.0003

MRI findings

Alemtuzumab was more effective than IFNB-1a on MRI measures involving all lesion types (T2-hyperintense, Gd-enhancing and T1 hypointense). Alemtuzumab also reduced the risk of developing GD-enhancing lesions, new or enlarging T2-hyperintense lesions and new T1-hypointense lesions at all timepoints. The secondary endpoint of change from baseline in T2 lesion volume at year 2 was not met. However, the T2 lesion volume change from year 1 to year 2 was better with alemtuzumab than with IFNB-1a. Alemtuzumab patients had significant reductions from baseline through Year 2 in the rate of brain atrophy and alemtuzumab significantly reduced the risk that enhancing lesions, which developed during the study, would convert to T1-hypointense black holes. A significant improvement favouring alemtuzumab was seen in the change in T1-hypointense lesion volume during the first year of the study, but there was no difference in the second year between treatment groups.

Alemtuzumab also significantly decreased the odds of experiencing MRI activity at Year 1, Year 2 and for the composite of Year 1 and 2 ($p<0.0001$) (Table 26).

Table 26 MRI activity – full analysis set

Time Period	SC IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)
Month 12		
n	187	405
Yes, n (%)	104 (55.6)	161 (39.8)
No, n (%)	83 (44.4)	244 (60.2)
Odds Ratio (95% CI)		0.49 (0.34, 0.70)
p-value		0.0001
Month 24		
n	187	401
Yes, n (%)	99 (52.9)	98 (24.4)
No, n (%)	88 (47.1)	303 (75.6)
Odds Ratio (95% CI)		0.27 (0.19, 0.39)
p-value		<.0001
Composite of Months 12 and 24		
n	184	395
Yes, n (%)	126 (68.5)	186 (47.1)
No, n (%)	58 (31.5)	209 (52.9)
Odds Ratio (95% CI)		0.39 (0.26, 0.56)
p-value		<.0001

Quality of life

Alemtuzumab patients experienced significant improvement on the SF-36 PCS compared with IFNB-1a. Significant differences favouring alemtuzumab were also noted at Year 1 on the SF-36 MCS, but not at Year 2. In the instrument designed specifically for measuring MS-related impacts on QoL (FAMS), alemtuzumab-treated patients demonstrated significant improvement compared with IFNB-1a-treated patients at all time-points assessed. The significant between-group differences were observed mainly because alemtuzumab-treated patients demonstrated greater improvements on scales pertaining to physical functioning. While there were no significant differences in the health status of the treatment groups as measured by EQ-5D utility scores at Years 1 and 2, alemtuzumab patients showed significantly greater improvements from baseline on the EQ-5D VAS at all time-points.

Ancillary analyses

Sensitivity analyses conducted to assess the influence of alternative MS treatments, unblinded EDSS raters and other factors that could potentially affect the primary relapse- and time to SAD-analyses demonstrated that the influence of these factors was minimal and did not alter the estimates of the treatment effects in either of the co-primary endpoints.

Subgroup analyses were conducted to assess the influence of gender, age, geographic region and other baseline or demographic actors on the MS relapse and the time to disability progression sustained for 6 months. Summaries of these analyses are presented in Figures 17 and 18.

Figure 17 Summary of relapse rate subgroup analyses

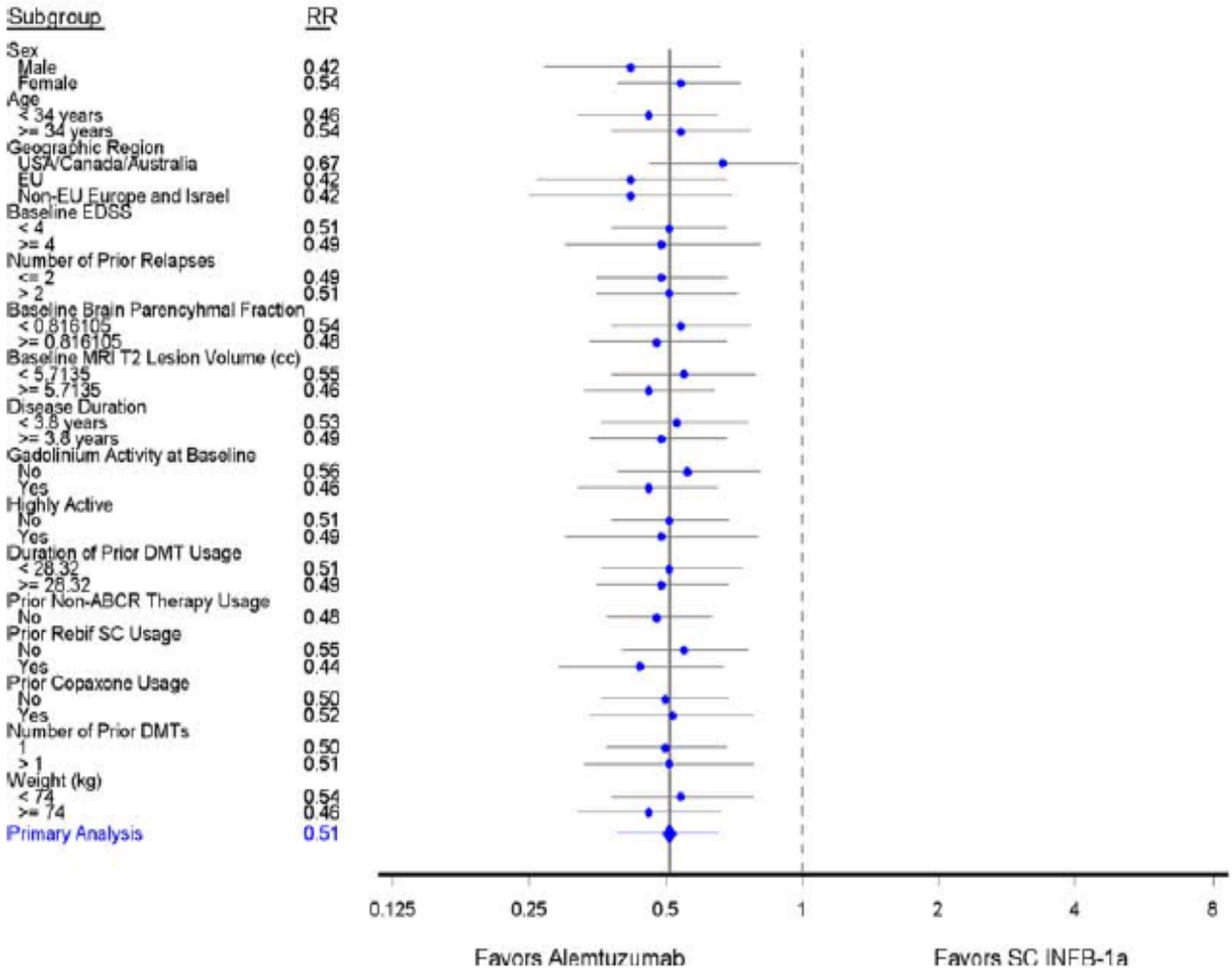
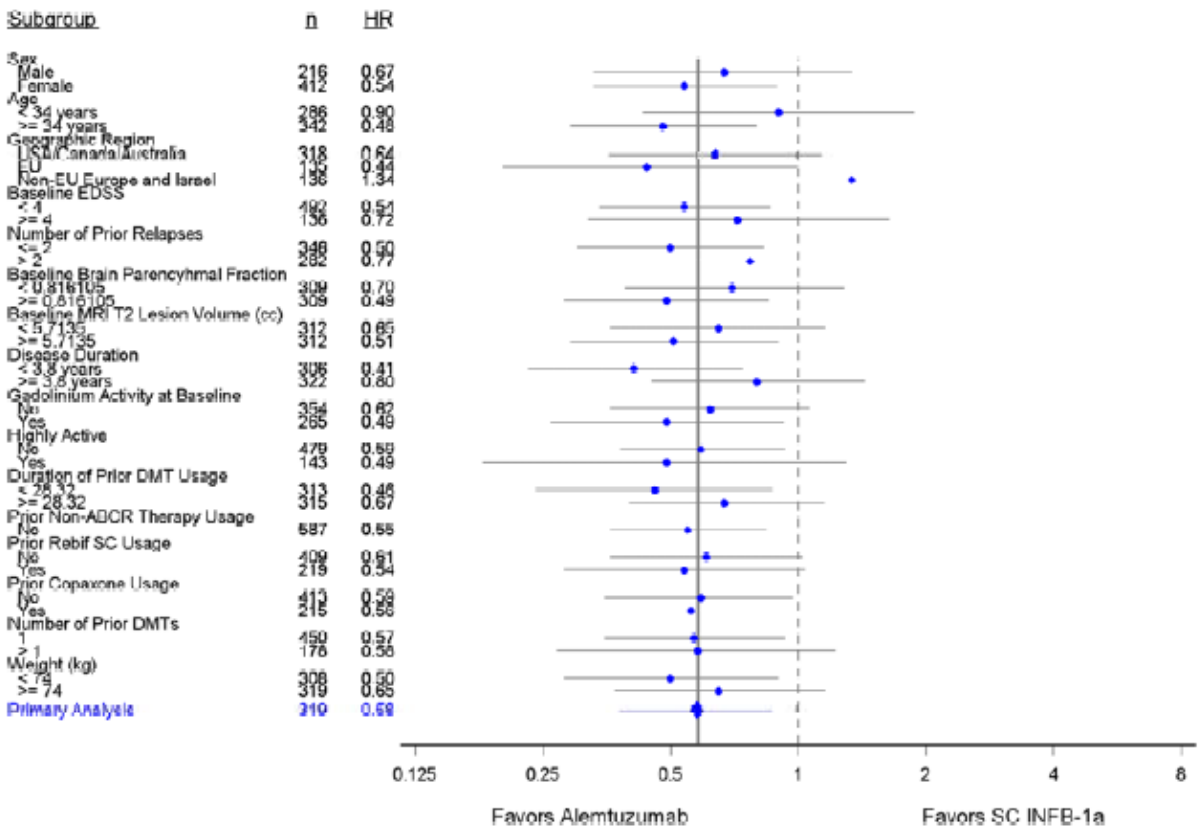


Figure 18 Summary of sustained accumulation of disability subgroup analyses



Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27 Summary of efficacy for trial CAMMS323

Title: A phase 3 randomized, rater-blinded study comparing two annual cycles of intravenous alemtuzumab to three-times weekly subcutaneous interferon beta-1a (Rebif) in treatment-naive patients with relapsing-remitting multiple sclerosis		
Study identifier	CAMMS323	
Design	randomized 2:1, multi-centre, rater-blinded, active-controlled	
	Duration of main phase:	2 years
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable (subject to a separate protocol)
Hypothesis	Superiority	

Treatments groups	Alemtuzumab		At month 0: administered i.v. over 5 consecutive days at a fixed total dose of 60 mg (12 mg/day) At month 12: administered i.v. over 3 consecutive days at a fixed total dose of 36 mg (12 mg/day) N=386 (Randomized) N=376 (Full analysis set)
	Rebif (interferon beta 1-a)		Dose titration per Rebif prescribing information followed by s.c. administration of 44 mcg three times a week N=195 (Randomized) N=187 (Full analysis set)
Endpoints and definitions	Co-primary endpoint	Relapse rate	Relapse was defined as new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination. Symptoms had to be attributable to MS, last at least 48 hours, be present at normal body temperature and be preceded by at least 1 month (30 days) of clinical stability.
	Co-primary endpoint	Time to SAD	Time to sustained accumulation of disability (SAD) For patients with a Baseline EDSS score of 0.0, SAD was defined as an increase of ≥1.5 points sustained over a 6-month consecutive period. For patients with a Baseline EDSS score of ≥1.0, SAD was defined as an increase of ≥1.0 point sustained over a 6-month consecutive period.

Results and Analysis

Analysis description	**Co-Primary Endpoint Analysis**		
Analysis population and time point description	Full analysis set (all treated patients) Time point – year 2		
Descriptive statistics and estimate variability	Treatment group	Alemtuzumab	Rebif
	Number of subject	376	187
	Relapse rate (Annualized relapse rate)	0.18	0.39
	95% CI	0.13; 0.23	0.29; 0.53
	Time to SAD (Kaplan-Meier estimate of event)	8.00	11.12
	95% CI	5.66; 11.24	7.32; 16.71

Effect estimate per comparison	Annualized relapse rate	Comparison groups	Alemtuzumab vs Rebif
		Rate ratio	0.45
		95% CI	0.32; 0.63
		Risk reduction	54.88
		P-value	<0.0001
	Time to SAD	Comparison groups	Alemtuzumab vs Rebif
		Hazard ratio	0.70
		95% CI	0.4; 1.23
		Risk reduction	30
		P-value	0.2173
Notes	The primary efficacy analysis was conducted on the available 2-year follow-up data for all patients in the Full Analysis Set and was adjusted for multiple comparisons via the Hochberg method. The comparison of the relapse rate co-primary endpoint used the proportional means model with treatment group indicator and geographic region as covariates in the model. The comparison of the SAD co-primary endpoint used a Cox proportional hazards regression model with treatment group indicator and geographic region as covariates and robust variance estimation.		

Table 28 Summary of efficacy for trial CAMMS324

Title: A phase 3 randomized, rater- and dose-blinded study comparing two annual cycles of intravenous low- and high-dose alemtuzumab to three-times weekly subcutaneous interferon beta-1a (Rebif) in patients with relapsing-remitting multiple sclerosis who have relapsed on therapy		
Study identifier	CAMMS324	
Design	randomized, multi-centre, rater-blinded, dose-blinded, active-controlled Note: Initial randomization was 2:2:1 (alemtuzumab low dose, high dose and Rebif, respectively). Starting with Amendment 2, the alemtuzumab 24 mg/day arm was closed. All subsequently enrolling patients were randomized in a 2:1 ratio to alemtuzumab 12 mg/day or interferon beta-1a. The primary efficacy comparisons were between alemtuzumab 12 mg/day and IFNB-1a and the efficacy comparisons with 24 mg/day were considered exploratory.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	2 years not applicable not applicable (subject to a separate protocol)
Hypothesis	Superiority	
	Alemtuzumab	At month 0: administered i.v. over 5 consecutive days at a fixed total dose of 60 mg (12 mg/day) At month 12: administered i.v. over 3 consecutive days at a fixed total dose of 36 mg (12 mg/day) N= 436 (Randomized) N= 426(Full analysis set)
	Rebif (interferon beta 1-a)	Dose titration per Rebif prescribing information followed by s.c. administration of 44 mcg three times a week N= 231 (Randomized) N= 202 (Full analysis set)

Endpoints and definitions	Co-primary endpoint	Relapse rate	A relapse was defined as any new neurological symptom or worsening of previous neurological symptoms with an objective change on neurological examination. Symptoms had to be attributable to MS, last at least 48 hours, be present at normal body temperature (i.e., no infection, excessive exercise, or excessively high ambient temperature), and be preceded by at least 1 month (30 days) of clinical stability.
	Co-primary endpoint	Time to SAD	Time to sustained accumulation of disability (SAD) For patients with a Baseline EDSS score of 0.0, SAD was defined as an increase of ≥1.5 points sustained over a 6-month consecutive period. For patients with a Baseline EDSS score of ≥1.0, SAD was defined as an increase of ≥1.0 point sustained over a 6-month consecutive period.

Results and Analysis

Analysis description	**Co-Primary Endpoint Analysis**		
Analysis population and time point description	Full analysis set (all treated patients) Time point – year 2		
Descriptive statistics and estimate variability	Treatment group	Alemtuzumab	Rebif
	Number of subject	426	202
	Relapse rate (Annualized relapse rate)	0.26	0.52
	95% CI	0.21; 0.33	0.41; 0.66
	Time to SAD (Kaplan-Meier estimate of event)	12.71	21.13
	95% CI	9.89; 16.27	15.95; 27.68
Effect estimate per comparison	Annualized relapse rate	Comparison groups	Alemtuzumab vs Rebif
		Rate ratio	0.51
		95% CI	0.39; 0.65
		Risk reduction	49.4
		P-value	<0.0001
	Time to SAD	Comparison groups	Alemtuzumab vs Rebif
		Hazard ratio	0.58
		95% CI	0.38; 0.87
		Risk reduction	42

		P-value	0.0084
Notes	The primary efficacy analysis was conducted on the available 2-year follow-up data for all patients in the FA Set and was adjusted for multiple comparisons via the Hochberg method. The comparison of the relapse rate co-primary endpoint used the proportional means model with treatment group indicator and geographic region as covariates in the model. The comparison of the SAD co-primary endpoint used a Cox proportional hazards regression model with treatment group indicator and geographic region as covariates and robust variance estimation.		

Clinical studies in special populations

No studies in special populations were performed by the applicant. (See 2.3.6 Discussion on clinical efficacy.)

Supportive studies

Supportive study: CAMMS223 (Phase II study): Phase 2, Randomized, Open-Label, Three-Arm Study Comparing Low- (12 mg) and High-Dose (24 mg) Alemtuzumab and High-Dose Subcutaneous Interferon Beta-1a (Rebif) in Patients With Early, Active Relapsing-Remitting Multiple Sclerosis.

The original study plan called for a 3-year treatment period. The protocol was later amended to add a follow-up period and to enable retreatment with alemtuzumab with up to two additional 12 mg cycles separated by at least 12 months, if patients met qualifying criteria for each retreatment.

Alemtuzumab demonstrated superiority over IFNB-1a on both co-primary endpoints, i.e. relapse rate and time to SAD. For the disability (SAD) component of the co-primary endpoint alemtuzumab 12 mg/day reduced the risk of SAD by 76% as compared to IFNB-1a (hazard ratio of 0.24; 95% CI [0.110, 0.545]; p = 0.0006) over 3 years. Alemtuzumab 24 mg/day also reduced the risk of SAD by 69% as compared to IFNB-1a (HR=0.31; 95% CI [0.151, 0.658]; p = 0.0021). For the relapse rate component, alemtuzumab 12 mg/day significantly reduced the relapse rate by 67% as compared to IFNB-1a (rate ratio=0.33; 95% CI [0.196, 0.552]; p<0.0001) through 3 years. Similarly, alemtuzumab 24 mg significantly reduced the relapse rate by 77% as compared to IFNB-1a (rate ratio=0.23; 95% CI [0.126, 0.431]; p<0.0001). The estimated ARR through 3 years was 0.37 for IFNB-1a, 0.12 for alemtuzumab 12 mg, and 0.09 for alemtuzumab 24 mg. Sensitivity analyses and subgroup analyses were largely consistent and supportive of superiority. Further analyses related to relapse rate, disability and MRI imaging were supportive of the superiority of alemtuzumab 12 mg/day and 24 mg/day over IFNB-1a. Data from the longer-term follow-up indicated that superiority of alemtuzumab over beta-interferon in terms of slowing the disability accumulation may be sustained over 5 years.

Study CAMMS03409 - An Extension Protocol For Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab (ongoing at the time of the initial MAA)

This was an open-label, rater-blinded extension study for patients who participated in studies CAMMS223, CAMMS323 or CAMMS324. The study included collection of additional follow-up data and “as-needed” retreatment with additional cycles of alemtuzumab for patients who received alemtuzumab in the Phase 2 and 3 studies and alemtuzumab treatment and follow-up for patients who received IFNB-1a in the Phase 2 and 3 studies.

As of 31 Dec 2011, 1,320 patients were enrolled in the extension study CAMMS03409, including 305 patients who had received IFNB-1a in a prior study and 1015 patients who had received alemtuzumab in a prior study. As of 31 Dec 2011 cut-off date, 496 patients had received alemtuzumab in this extension study: 199 patients previously treated with alemtuzumab received re-treatment with alemtuzumab and 297 patients previously treated with IFNB-1a. Preliminary efficacy analyses suggested that the relapse rates for patients treated with IFNB-1a in the prior studies, who crossed over to alemtuzumab 12 mg/day, were lower in the extension study than in the prior studies. The CHMP considered that this further supported the assumption that alemtuzumab may also be effective when initiated further in the course of MS.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The main clinical studies submitted to support the claim of efficacy were performed as multicentre, randomised, active-controlled and rater-blinded. The CHMP acknowledged that the applicant complied with the previous CHMP Scientific Advice whereby comparison against a high-dose beta-interferon rather than placebo was encouraged. Thus, the choice of Rebif (interferon beta-1a, administered subcutaneously at 3x 44 µcg/week) as an active control used throughout the clinical studies was considered appropriate by the CHMP.

Of note, the choice of Rebif as an active comparator precluded a double-blinded study design. Rebif 44 µg is commercially available only in proprietary prefilled syringes preventing the possibility of creating a matching placebo. In addition, the CHMP considered the differences between alemtuzumab and Rebif in terms of timing and the mode of administration (yearly i.v. infusions versus s.c. injections 3 tiw) and safety profiles (infusion-associated reactions versus injection site reactions and flu-like symptoms) and acknowledged the difficulties of designing the studies in a double-blind, double dummy fashion. In this context, special attention was paid to taking other appropriate measures to maintain the blind and minimise bias. Specifically, the studies were conducted as rater-blinded and designed to minimise the potential impact of treating physicians and patients being aware of treatment assignment (see Section 2.5.2 Blinding). This approach was considered acceptable by the CHMP.

All three active-controlled studies utilized the co-primary efficacy endpoints of MS relapse rate and time to Sustained Accumulation of Disability. The combination of relapse rate and a disability-related endpoint as co-primary endpoint was acknowledged. The current Guideline on multiple sclerosis (CPMP/EWP/561/98 Rev.1) stipulates that an appropriate disability outcome can be defined based on sustained worsening of relevant magnitude, measured by EDSS as the most widely used scale, and that two consecutive examinations should be carried out at least 6 months apart. The CHMP considered that these requirements were met by Sustained Accumulation of Disability definition used in all three trials, i.e. increase in EDSS score of ≥1.5 points from a baseline score of 0 or an increase of ≥1.0 point from a baseline score of 1 or more, on 3 consecutive quarterly assessments (i.e., for ≥6 months).

Evaluating imaging endpoints as secondary endpoints was considered relevant, since the combination of MRI lesion activity and relapse activity was suggested to correlate with

subsequent accumulation of disability (Sormani et al: Combined MRI lesions and relapses as a surrogate for disability in multiple sclerosis. Neurology. 2011 Nov 1;77(18):1684-90). Other endpoints including the MSFC, an emerging disability assessment tool that involves especially functional aspects, were also considered relevant.

Patients in all three active-controlled studies had active RRMS, in studies CAMMS223 and CAMMS323 treatment-naïve patients were enrolled, whereas relapse on prior therapy (interferon beta or glatiramer acetate taken for at least 6 months) was an inclusion criterion for study CAMSS324. Furthermore, in contrast to CAMMS223 and CAMMS323, patients in CAMMS324 could have had MS symptoms for longer (up to 10 years), a higher EDSS score (up to 5) and were required to have an MRI scan with abnormalities exceeding threshold criteria (at least 1 of the following: ≥9 T2 lesions ≥3 mm in any axis; a gadolinium-enhancing lesion ≥3 mm in any axis plus ≥1 brain T2 lesions; or a spinal cord lesion consistent with MS plus ≥1 brain T2 lesions). Overall, the CHMP was of the view that the patient populations enrolled in the clinical programme were representative of both previously untreated MS patients and MS patients with an inadequate response to prior therapy.

The CHMP considered that the applicant did not perform formal dose-finding studies for alemtuzumab in the MS setting. Nevertheless, the approach to evaluate in phase 2 doses bracketing the 20 mg/day used in the pilot phase (see Section 2.5.1), i.e. doses of 12 mg/day and 24 mg/day, was accepted as well as the resulting choice of doses for the phase 3 trials. Taking into account the generally comparable efficacy of the 12 mg/day and 24 mg/day doses and the issues of tolerability linked to the higher dose, the choice of the lower dose applied for by the applicant was considered acceptable by the CHMP.

With respect to tolerability, especially the infusion associated reactions (Moreau, 1996, Brain), the CHMP also noted that each annual treatment cycle with alemtuzumab is administered in divided doses.

The CHMP considered that protocol violations were assessed by the applicant with respect to their nature and potential impact on the conduct of the studies, including sensitivity analyses on the efficacy outcomes, and agreed that the results suggested the impact was minimal. The majority of deviations fell in the category of a study procedure or assessment not being performed per protocol, primarily attributed to missing laboratory test results or survey responses that were required as part of the intensified surveillance efforts to detect potential events of ITP or anti-GBM disease. A similar pattern of protocol deviations was observed in both phase III studies. The CHMP considered that the intensified safety monitoring was a programme involving more than 30,000 laboratory results, which may include a certain probability of occurrence of such protocol deviations.

The CHMP also discussed the amendments implemented during the conduct of the studies. Whereas measures introduced for safety reasons were accepted by the CHMP, concerns were originally expressed with respect to measures implemented to improve blinding, due to the lack of clarity of their impact on the study conduct, in particular with respect to data collected before implementation of these amendments. Following review of the sensitivity analyses performed by the applicant and presented separately for each of the Phase 3 studies, the CHMP concluded that no impact of the protocol amendments on efficacy outcomes was expected.

No studies in patients with renal or hepatic impairment were performed. Since monoclonal antibodies are neither metabolized by the liver nor excreted by the kidneys, the CHMP considered that studies in these special populations were not needed.

With respect to the paediatric population, the CHMP considered that a waiver was granted for the paediatric subsets in the range from birth to less than 10 years and a deferral was granted for conducting and submitting results of a clinical trial in MS patients 10 to less than 18 years. The CHMP noted that the information is adequately covered in the Product Information.

The clinical studies did not include any patients aged over 55 years and it was not determined whether these patients would respond to the treatment differently than the younger patients. This was appropriately reflected in section 4.2 of the SmPC.

Efficacy data and additional analyses

Efficacy of alemtuzumab in the treatment of multiple sclerosis was supported by results of two phase 3 clinical trials, i.e. CAMMS323 and CAMMS324 as well as by data from a phase II study CAMMS223 and an extension study CAMMS03409, which was ongoing at the time of the initial MAA.

Baseline demographics were in large comparable across the three controlled clinical studies and represented a typical patient population for RRMS. When comparing studies CAMMS223 and CAMMS323 (treatment-naïve patients) with study CAMMS324 (previously treated patients), a more advanced MS population was noted in study CAMMS324, e.g. in terms of the mean EDSS score and MS history. This was in line with the intended study population of previously treated patients who are expected to be more affected than treatment-naïve patients.

Study CAMMS323 (Phase III study in treatment-naïve patients)

The relapse rate component of the primary endpoint was met with a reduction in relapse rate of 55% following alemtuzumab treatment compared to IFNB-1a, with an ARR of 0.18 in the alemtuzumab 12 mg/day group compared with 0.39 in the IFNB-1a group.

Sensitivity analyses and subgroup analyses were generally consistent and supportive of the superiority for relapse rate. Kaplan-Meier plots as well as analysis by time intervals showed that the superior effect of alemtuzumab on relapses was persistent over time.

The disability component Time to Sustained Accumulation of Disability (SAD) showed no significant difference between the treatment groups. The CHMP considered that study CAMMS323 enrolled treatment-naïve patients and, as documented by the baseline and disease characteristics, a less affected patient population. This may explain why statistical significance was reached in the relapse-related parameters (including the relapse-related component of the co-primary endpoint), as opposed to only a trend towards a higher effect in disability-related endpoints, where statistical significance was not reached (including the disability-related component of the co-primary endpoint). Based on the threshold hypothesis in MS, it was considered that within a follow-up of two years, a significant impact on disability separating alemtuzumab from beta-interferon may not yet be observed. The CHMP also considered that the failure to demonstrate effect on the SAD component might be attributed to the lower disability progression in the beta-interferon arm (11.1%) than expected based on

the previous observations (i.e. expected rate of disability progression of 20%).

Alemtuzumab showed a superior effect as compared to high-dose beta-interferon on most MRI parameters. In general, the effect on imaging was more pronounced in the second year of treatment. Given the importance of MRI lesions in conjunction with relapse rate on disability (see discussion above on the threshold hypothesis), the CHMP considered the MRI results relevant and meaningful in terms of alemtuzumab efficacy.

Patients treated with alemtuzumab showed also significantly greater improvements from baseline on two self-report measures of quality of life (FAMS and SF-36), which were largely driven by improvements on scales pertaining to physical functioning. This finding was mirrored in the results on the MSFC.

Study CAMMS324 (Phase III study in previously treated patients)

The proportions of patients previously treated with IFNB-1a, IFNB-1b and glatiramer acetate were balanced across the alemtuzumab 12 mg/day and IFNB-1a groups. Approximately one third of patients in each treatment group had received Rebif prior to entering the study. The mean duration of all prior MS therapies in both treatment groups was approximately 3 years and 25-30% of patients had used two or more prior MS medications. As such, the CHMP was of the view that the study population can be seen as adequately representing the pre-treated MS population.

The Annual Relapse Rate component of the primary endpoint was met: alemtuzumab significantly reduced the relapse rate through 2 years by 49% compared with IFNB-1a. The ARR through 2 years was 0.26 for alemtuzumab-treated patients versus 0.52 for IFNB-1a-treated patients.

In contrast to study CAMMS323, the disability component Time to Sustained Accumulation of Disability (SAD), sustained over a 6-month period, was also met: alemtuzumab significantly reduced the risk of SAD through 2 years by 42% compared with IFNB-1a. The percentage of patients experiencing SAD at 2 years was 12.7% in the alemtuzumab group and 21.1% in the IFNB-1a group.

Sensitivity analyses and subgroup analyses were in large consistent and supportive of superiority. All secondary endpoints, apart from the imaging-related endpoint “Percent change from baseline in MRI T2-hyperintense lesion volume at Year 2”, were highly statistically significant and were considered clinically relevant by the CHMP. The finding that the effect of alemtuzumab on imaging endpoints was more pronounced at year 2 compared to year 1 was consistent with the findings of study CAMMS323 in treatment-naïve patients.

In study CAMMS324, analyses of the EDSS-based endpoints (EDSS change from baseline and sustained reduction in disability) indicated that alemtuzumab treatment might not only reduce the risk of disease progression, but could potentially reverse pre-existing disability. Specifically, alemtuzumab-treated patients experienced significant mean improvement from baseline in EDSS score, suggesting a decrease in disability with alemtuzumab treatment, whereas IFNB-1a-treated patients experienced a significant worsening. The difference in the mean EDSS scores was statistically significant by Month 6 and this difference was maintained throughout the 2-year study period.

In addition, alemtuzumab-treated patients were significantly more likely to achieve a

sustained reduction in disability, defined as improved EDSS scores for at least 6 months, than IFNB-1a-treated patients (28.8% versus 12.9%, p=0.0002). The issue is discussed further under “Claim on reversal of disability”, also reflecting the input from the SAG Neurology.

Similarly to study CAMMS323, patients treated with alemtuzumab showed also significantly greater improvements from baseline on two self-report measures of quality of life (FAMS and SF-36).

Supportive studies

Overall, in study CAMMS223, superiority of alemtuzumab over placebo was observed in all domains considered relevant to treatment of MS, i.e. relapse rate, disability and MRI imaging, as summarised in section 2.5.2. Despite being a phase 2 trial, the study was considered by the CHMP to show features of a phase 3 trial, such as duration or choice of endpoints. Therefore, the CHMP was of the view that the evidence provided by this study contributed to the efficacy dataset of alemtuzumab and hence included considerations regarding these data also in their overall benefit-risk assessment. Of note, the CHMP considered that the applicant provided data over a follow-up period longer than usually expected, i.e. two years. These data indicated that superiority of alemtuzumab over beta-interferon in terms of slowing the disability accumulation may be sustained over 5 years.

The CHMP considered the preliminary efficacy results from the extension study CAMMS3409 provided by the applicant. The data suggested that the relapse rates for patients treated with IFNB-1a in the prior studies, who crossed over to alemtuzumab 12 mg/day, were lower in the extension study than in the prior studies. The CHMP was of the view that this further supported the assumption that alemtuzumab may also be effective when initiated further in the course of MS.

Immunogenicity

Most patients treated with alemtuzumab 12 mg/day (85.2%) in the Phase 3 studies tested positive for anti-alemtuzumab antibodies, with 92.2% of these also testing positive for inhibitory antibodies (see also section 2.4.3). A higher proportion of patients tested positive in Cycle 2 compared to Cycle 1 and peak antibody titres for both types of antibodies were higher following Cycle 2 than Cycle 1. Overall, through either 2 cycles of treatment in the Phase 3 studies (CAMMS323 and CAMMS324) or 3 cycles of treatment in the Phase 2 study (CAMMS223), anti-alemtuzumab or inhibitory antibodies did not appear to diminish the efficacy of alemtuzumab as shown by a number of analyses. This was considered re-assuring by the CHMP.

Reversal of disability

The CHMP discussed the applicant´s claim that the indication should also reflect on the reversal of disability. During their review, the CHMP expressed concerns about the consistency of the data available, i.e. the fact that statistically significant results were obtained only in studies CAMMS223 and CAMMS324, but not in CAMMS323, and questioned the clinical interpretability of the evidence.

In further analyses, the applicant demonstrated that the results were consistent among EDSS and MSFC and supported by the quality of life data (although these data have to be seen as of limited value due to the open-label nature of the clinical studies) and MRI data showing

reduction of brain atrophy-related parameters.

The lack of significant findings on reversal of disability in study CAMMS323 in treatment-naïve patients was attributed by the applicant to the slow disability progression in the active comparator arm. In addition, the CHMP also considered that in the early stage of MS, neurological deficits can still be compensated by the unaffected brain areas.

In an additional analysis (Table 25), the applicant also examined the longer-term outcome for individuals who achieved 6-month SRD during CAMMS324. Around one quarter of patients sustained this effect for at least 12 months.

EDSS improvements in CAMMS223 and CAMMS324 were seen not to be restricted to single or few FSS (functional system scores) but to be consistent within the EDSS scale, including the pyramidal and cerebellar FSS (fig. 15). Improvements after alemtuzumab were also seen in patients who did not experience a relapse in the three months before study entry, thus suggesting that improvements in EDSS were not merely a result of recovery from an MS relapse.

On the other hand, the applicant did not present such analyses for study CAMMS323 where this difference was not observed. In this context, the CHMP also considered the fact that the effect was seen in study CAMMS223, which included the treatment-naïve patients (as in CAMMS323), hence questioning the consistency. Moreover, the CHMP was of the view that the mechanism by which alemtuzumab would initiate and promote repair are not quite elucidated.

As discussed below, the CHMP requested input from the SAG Neurology on this issue. The experts agreed unanimously that the claim was not sufficiently supported by the current data, and may even be misleading for the patient who could expect a healing of the disease, which can currently not be inferred from the data. The CHMP agreed with the SAG Neurology that the claim of reversal of disability should not be part of the indication and concluded that the relevant data on SRD should be reflected in section 5.1 of the SmPC.

Additional expert consultation

In the course of the procedure, the CHMP identified need for input from the SAG Neurology on the two following questions:

- Question 1

How does the SAG see the benefits of Lemtrada in connection with the safety profile, especially autoimmune disorders? Should the indication be restricted like e.g. for Tysabri or Gilenya? How do neurologists see the handling of non-neurological complications that can be rapid and severe (e.g. nephrological complications like glomerulonephritis)?

- Question 2

What is the experts' view on the Applicants claim on reversal of disability, given statistically significant findings on one hand but methodological considerations on the other, e.g. if mean changes in EDSS and MSFC can be clinically interpreted?

Overall, the members of the SAG were in agreement that efficacy of LEMTRADA in patients with RRMS has been demonstrated.

Several provisions to be introduced in the SmPC were proposed by the SAG experts, regarding the therapeutic use of the drug. The following were agreed upon by consensus:

- The initiation of treatment with LEMTRADA should be done by an experienced neurologist, within an appropriate setting, providing the needed specialists and equipment required for the management of the most frequent adverse reactions, as described by the available data.
- Prior to the initiation of treatment, a proactive targeted screening of the patients should be introduced, aiming to minimize the risk of developing opportunistic infections, neoplasms and cytopenic reactions.
- During treatment interphases and after the second administration, patients should be submitted to a very strict clinical and biological follow-up, as described in the RMP proposed by the applicant.

The experts of the SAG were split in their opinion with regard to the most appropriate target population. Some of the experts advocated the position that an unrestricted indication should be granted. They supported their view by the fact that there are positive data on efficacy in both treatment-naïve and pre-treated patients with RRMS, and the expected adverse events can be monitored and managed with a good prognosis for recovery, and even in some cases prevented, if appropriate risk mitigation strategies are put in place.

Others supported the view that the population should be restricted to the patients with highly active disease and the ones that have failed first line treatment with interferon beta and glatiramer acetate, as previously done for other immunomodulators (such as natalizumab and fingolimod). The reasons for that were that the benefit/risk was considered negative in treatment-naïve patients with low disease activity, for whom only limited data on efficacy are available and are insufficient to counter-balance the risk from the already identified serious adverse events.

With respect to the second question, the SAG concluded by consensus that in the proposed indication, the text "…or reverse…" regarding disability progression should be removed, leaving only the mention of slowing of disability progression. The reasons for that are the inconsistency of the data from the pivotal trials on the effect on disability, and also the ambiguity of the wording that could create the impression that a reversal of the clinical course of the disease is to be expected as a result of the treatment with LEMTRADA. The SAG also noted that such claim for reversal of disability cannot be ascertained without additional data. Moreover, it was not considered possible to determine, despite the efforts made by the applicant in this respect, whether the observed effect on disability is due to improved re-myelination and functioning of the neurons, or an artefact from the effect of the drug on the disease activity i.e. on relapses.

2.5.4. Conclusions on the clinical efficacy

Overall, the clinical efficacy data submitted were considered satisfactory and supportive of the indication of alemtuzumab for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

2.6. Clinical safety

Patient exposure

A total of 1,485 alemtuzumab-treated MS patients constituted the safety population. Of these, 972 patients were treated in the phase 3 studies (CAMMS323 and CAMMS324) and 216 patients in the phase 2 study CAMMS223. Alemtuzumab exposure in the active-controlled studies through 2-year follow-up is summarized in Table 29.

297 patients who received IFNB-1a in a prior study were treated with alemtuzumab in the extension study CAMMS03409.

Table 29 Exposure Alemtuzumab in All Active-Controlled Studies (2-Year Follow Up)

Parameter	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1188)
Total Dose Received (mg), n (%)			
<60	1 (0.1)	1 (0.4)	2 (0.2)
60-<96	56 (6.1)	0	56 (4.7)
96-<120	859 (93.5)	0	859 (72.3)
120-<192	3 (0.3)	24 (8.9)	27 (2.3)
≥192	0	244 (90.7)	244 (20.5)
n	919	269	1188
Mean (SD)	94.7 (7.04)	187.6 (16.52)	115.7 (40.18)
Median	96.0	192.0	96.0
Min, Max	42.0, 132.0	58.0, 192.0	42.0, 192.0

SD = standard deviation; Min = minimum; Max = maximum

Patients received between one and five cycles of alemtuzumab and were followed for safety for up to 8.9 years, resulting in a total of 4,262 person-years of follow-up (Table 30).

Table 30 Duration of follow-up in all alemtuzumab-treated patients

	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

Note: Percentages are based on the total number of alemtuzumab-treated patients in the corresponding treatment group and column.

Note: Follow-up duration computed from start of first alemtuzumab treatment cycle to completion/discontinuation or data cut-off.

SD = standard deviation; Min = minimum; Max = maximum; Q = quartile

Source: ISS Pool C Table 3.2.1

Adverse events

Across the active-controlled studies, adverse events (AEs) were reported for 97.5% of patients in the alemtuzumab 12 mg/day group and 94.6% of patients in the IFNB-1a group. The majority of the AEs were reported to be mild or moderate in severity.

The most frequent events reported were rash (48%), urticaria (17%) and pruritus (16.5%) within the SOC "Skin and subcutaneous tissue disorders", headache (52%), MS relapse (26.4%) and paresthesia (12.3%) within the SOC "Nervous System Disorders" and nasopharyngitis (23.5%), urinary tract infection (17.6%) and upper respiratory tract infection (15.3%) within the SOC "Infections and Infestations".

The incidence of the treatment-emergent adverse events (TEAEs) and an overall overview of adverse event categories in all active-controlled studies are presented in Tables 31 and 32, respectively.

Table 31 Incidence of TEAEs by MedDRA SOC in the active-controlled studies (CAMMS223, CAMMS323 and CAMMS324)

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)

Table 32 Overview of Adverse Events in the active-controlled studies (CAMMS223, CAMMS323 and CAMMS324)

	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)

Note: Percentages are based on the number of treated patients in the corresponding treatment group.
Note: Data not available from study CAMMS223 for SAEs leading to study discontinuation due to the design of the CRFs.
SC = subcutaneous; IFNB-1a = interferon beta-1a; AE = adverse event; SAE = serious adverse event

The percentage of patients with treatment-related AEs (as assessed by the investigator) was higher in the alemtuzumab 12 mg/day group than in the IFNB-1a group (94.1% vs with 73.4%). Grade 3 or Grade 4 AEs were reported for a similar proportion of patients in the alemtuzumab 12 mg/day and IFNB-1a groups. The incidence of AEs of Grade 3 or higher was greater in the alemtuzumab pooled dose group compared to the 12 mg/day group.

The overall incidence of AEs in the alemtuzumab 12 mg/day group generally decreased over time through Year 4 (93.6% at Year 1, 86.0% at Year 2, 72.7% at Year 3, 49.7% at Year 4).

Serious adverse event / deaths / other significant events

The incidence of SAEs was 18.3% in both the alemtuzumab 12 mg/day group and the IFNB-1a group. SAEs were assessed by the investigators as related to study drug in 7.1% and 1.6% of patients in the alemtuzumab 12 mg/day and IFNB-1a groups, respectively. The most frequently reported SAEs in the alemtuzumab 12 mg/day group were MS relapse (6.1%), pneumonia (0.4%), autoimmune thrombocytopenia (0.4%), gastroenteritis (0.4%),

appendicitis (0.4%) and urticaria (0.4%). In the pooled alemtuzumab group, in addition to these events, idiopathic thrombocytopenic purpura (ITP) occurred in four patients.

Deaths

There were a total of eight deaths reported in the clinical studies, seven in patients who received alemtuzumab and one patient who received IFNB-1a. The causes of death are listed in Table 33. Fatal events in three alemtuzumab-treated patients were assessed as possibly/likely related to treatment by the investigator.

Table 33 Listing of deaths (all studies)

Study / Patient ID (sex)	Age at Death (years)	Treatment Group	Number of Cycles or Weeks (Total Dose)	Preferred Term for Cause of Death	Days (Months) From First Dose to Death	Days (Months) From Last Dose to Death	Relatedness
Treatment: Alemtuzumab 12 mg							
CAMMS223 / [redacted] (female)	45	12 mg/day	3 Cycles (132 mg)	Cardiovascular disorder	830 days (27 months)	72 days (2 months)	Related
CAMMS323 / [redacted] (male)	32	12 mg/day	2 Cycles (96 mg)	Road traffic accident	670 days (22 months)	281 days (9 months)	Not related
CAMMS324 / [redacted] (female)	28	12 mg/day	2 Cycles (96 mg)	Death (auto-pedestrian accident)	589 days (19 months)	228 (7 months)	Not related
CAMMS324 / [redacted] (male)	30	12 mg/day	2 Cycles (96 mg)	Pneumonia aspiration	701 days (23 months)	312 days (10 months)	Not related
CAMMS03409 / [redacted] (male)	28	12 mg/day	4 Cycles (168 mg)	Wound	2378 days (78 months)	100 days (3 months)	Not related
CAMMS03409 / [redacted] (male)	46	12 mg/day	2 Cycles (96 mg)	Sepsis	957 days (32 months)	590 days (19 months)	Related
Treatment: Alemtuzumab 24 mg							
CAMMS223 / [redacted] (male)	39	24 mg/day	2 Cycles (192 mg)	Idiopathic thrombocytopenic purpura and cerebral haemorrhage	585 days (19 months)	220 days (7 months)	Related
Treatment: IFNB-1a							
CAMMS223 / [redacted] (male)	32	IFNB-1a	156 weeks	Death (train accident)	1609 days (53 months)	521 days (17 months)	Not related

Infusion-Associated Reactions (IARs)

The overall incidence of IARs in the active-controlled studies was 91.1% in the alemtuzumab 12 mg/day group, which was similar to the incidence in the pooled dose group (92.6%). The overall incidence in the 24 mg/day group was 97.8%. The most common IARs (occurring in ≥10% of patients) in the alemtuzumab 12 mg/day group were headache, rash, pyrexia, nausea, urticaria, pruritus and insomnia. Cardiac events had an incidence of approximately 12%. Additional events that occurred in ≥10% of patients in the alemtuzumab 24 mg/day group were fatigue, chills, chest discomfort and dyspnea.

Serious IARs were identified for 2.8% patients in the alemtuzumab 12 mg/day group; the incidence of serious IARs was similar in the pooled dose group (2.7%). The incidence in the 24 mg/day group was 2.2%. Serious IARs included cases of pyrexia, urticaria, atrial fibrillation,

nausea, chest discomfort and hypotension. In addition, one case of a Grade 4 anaphylactic reaction was reported in a patient treated with alemtuzumab 12 mg/day in the extension study. This patient had previously received 2 cycles of alemtuzumab 24 mg/day in CAMMS324 and had experienced non-serious IARs of pruritus and dyspnea. The reaction (redness and swelling of eyes, lips, hands and face, itching and swelling in mouth and throat with cough) occurred on Day 1 of the patient's third treatment cycle and resulted in discontinuation of alemtuzumab treatment. The patient recovered without sequelae.

No events of severe cutaneous reactions, such as Stevens Johnson syndrome, were observed.

The incidence of IARs decreased from Cycle 1 to Cycle 2 for each alemtuzumab dose group. For the alemtuzumab 12 mg/day group, the incidence of IARs in Cycle 1 was 86.2% compared with 69.5% for Cycle 2. Results were similar for the alemtuzumab pooled dose group. For the alemtuzumab 24 mg/day group, the incidence of IARs was 96.7% and 86.2% in Cycle 1 and Cycle 2, respectively. The incidence of IARs decreased over the course of the infusion treatment cycle, with the highest incidence reported on Day 1.

The majority of patients treated with alemtuzumab had detectable anti-alemtuzumab antibodies and anti-alemtuzumab inhibitory antibodies. The presence or level of these antibodies had no apparent effect on the development of IARs or other AEs.

Thyroid disorders

In the active-controlled studies, the incidence of thyroid AEs was higher in the alemtuzumab 12 mg/day group (16.6%) than in the IFNB-1a group (5.2%). The most frequently reported thyroid AEs (reported for >2% of patients) in the alemtuzumab 12 mg/day group were hypothyroidism, hyperthyroidism, Basedow's disease and decreased blood TSH. No thyroid AEs were reported for >2% of the IFNB-1a treated patients. The majority of thyroid AEs (94.9%) in the alemtuzumab 12 mg/day group was mild or moderate in severity. Most thyroid events were managed with conventional medical therapy. Few patients required surgical intervention and few discontinued treatment due to thyroid disorders. Serious thyroid AEs over two years of follow up in the active-controlled studies were reported in 0.8% patients in the alemtuzumab 12 mg/day group including a case of thyrotoxic crisis (Grade 3) and endocrine ophthalmopathy (Grade 2) that occurred 23 months after start of alemtuzumab treatment.

Based on data from all alemtuzumab-treated MS patients, thyroid AEs were observed in 36.2% and 44.7% of patients in the alemtuzumab 12 mg/day group through 4 and 8 years after treatment initiation, respectively. 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. Unlike the general trend observed for AEs, i.e. their decrease with the second cycle, there was an increase of AEs in the SOC 'Endocrine disorders' (4.6% incidence in Year 1 and 9.0% in Year 2). The observed increase in the incidence of 'Endocrine Disorders' at Year 2 was primarily driven by higher incidences of hypothyroidism, hyperthyroidism and Basedow's disease when compared to Year 1. 'Endocrine Disorders' were reported more frequently for females (17.3%) compared to males (5.6%) in the alemtuzumab 12 mg/day group.

Immune Thrombocytopenic Purpura (ITP)

Over the 2-year follow-up in the active-controlled studies, ITP was reported in 0.9% of patients in the alemtuzumab 12 mg/day group, 2.2% of patients in the alemtuzumab 24 mg/day group and 1.6% patients in the IFNB-1a treatment group. Serious ITP AEs were reported for 0.7% patients in the alemtuzumab 12 mg/day group and 1.5% patients in the alemtuzumab 24 mg/day group; no serious ITP events were reported in IFNB-1a-treated patients (Table 34).

Table 34 Incidence and annualized rate of first treatment-emergent immune thrombocytopenic purpura

	SC IFNB-1a (N=496)		Alemtuzumab 12 mg/day (N=919)		Alemtuzumab 24 mg/day (N=269)		Alemtuzumab Pooled (N=1188)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate	n (%)	Rate
Platelet-based or AE-based definition	8 (1.6)	0.0088	8 (0.9)	0.0044	6 (2.2)	0.0113	14 (1.2)	0.0059
Platelet-based definition	8 (1.6)		8 (0.9)		4 (1.5)		12 (1.0)	
AE-based definition	2 (0.4)		7 (0.8)		6 (2.2)		13 (1.1)	
Autoimmune thrombocytopenia	0		5 (0.5)		3 (1.1)		8 (0.7)	
Idiopathic thrombocytopenic purpura	2 (0.4)		2 (0.2)		3 (1.1)		5 (0.4)	
Serious AE	0		6 (0.7)		4 (1.5)		10 (0.8)	
Autoimmune thrombocytopenia	0		4 (0.4)		2 (0.7)		6 (0.5)	
Idiopathic thrombocytopenic purpura	0		2 (0.2)		2 (0.7)		4 (0.3)	

Sixteen of the alemtuzumab-treated patients had confirmed ITP with no alternative etiologies.

The events occurred predominantly between 14 and 36 months after the start of alemtuzumab treatment (range 3 to 85 months after the first alemtuzumab dose). With regards to treatment cycles, the first occurrence of ITP was more common after the second treatment cycle.

Based on data from all alemtuzumab-treated MS patients, platelet counts and/or symptoms indicative of ITP occurred in 22 (1.5%) patients, 13 (1.1%) in the 12 mg/day dose group and 9 (3.3%) in the 24 mg/day dose group. Following medical review, 16 of these alemtuzumab-treated patients had confirmed ITP with no alternative etiologies.

Nephropathy Including Anti-Glomerular Basement Membrane (anti-GBM) Disease

Cases of nephropathies were reported in 5 (0.4%) patients in the 12 mg/day alemtuzumab dose group (0.3% in the pooled dose group, with no additional cases reported in the 24 mg/day group).The events occurred generally within up to 39 months following the last administration of alemtuzumab. These 5 cases included membranous glomerulonephritis and tubulointerstitial nephritis, glomerulonephritis (reported as anti-GBM glomerulonephritis), Goodpasture's syndrome (reported as anti-GBM disease) and nephropathy. Both cases of anti-GBM disease were serious, were identified early through clinical and laboratory monitoring and had a positive outcome after treatment.

Infections

In the active-controlled studies, the incidence of infection AEs for the alemtuzumab 12 mg/day group was 70.9%, compared with 53.2% in the IFNB-1a group (Table 35).

Table 35 Incidence of infections reported in ≥5% of patients in any treatment group in all active-controlled studies

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab Pooled (N=1188)
Preferred Term	**n (%)**	**n (%)**	**n (%)**
Any Event	264 (53.2)	652 (70.9)	851 (71.6)
Nasopharyngitis	82 (16.5)	216 (23.5)	285 (24.0)
Urinary tract infection	40 (8.1)	162 (17.6)	210 (17.7)
Upper respiratory tract infection	57 (11.5)	141 (15.3)	191 (16.1)
Sinusitis	34 (6.9)	100 (10.9)	129 (10.9)
Oral herpes	6 (1.2)	79 (8.6)	95 (8.0)
Influenza	25 (5.0)	77 (8.4)	96 (8.1)
Bronchitis	16 (3.2)	64 (7.0)	89 (7.5)
Herpes zoster[a]	4 (0.8)	38 (4.1)	55 (4.6)
Pharyngitis[a]	7 (1.4)	36 (3.9)	52 (4.4)

The overall incidence of any fungal infection in the active controlled studies was higher in the alemtuzumab 12 mg/day group (12.1%) than in the IFNB-1a group (3.4%). The most commonly reported events (reported for ≥2% of patients) in the alemtuzumab 12 mg/day and IFNB-1a groups were vulvovaginal candidiasis and oral candidiasis. Results were similar in the alemtuzumab pooled and 24 mg/day groups. A serious event of distal oesophageal candidiasis was reported for one patient in the 12 mg/day group. The event occurred following cycle 1 and responded to conventional treatment.

There were no systemic fungal infections.

In all active-controlled studies during the first 2 years of follow up, the overall incidence of any tuberculosis infection was 0.1% (1 patient) in the alemtuzumab 12 mg/day group (reported as disseminated TB) and 0.2% (1 patient) in the IFNB-1a group (recorded as renal TB). Three additional events were identified in the alemtuzumab 24 mg/day group (recorded as latent TB, pulmonary tuberculoma and pulmonary TB), resulting in an incidence of 0.3% (4 patients) in the alemtuzumab pooled dose group. All 4 events occurred in the first 2 years of follow up.

Human papillomavirus (HPV) infections were reported for 2.4% of patients in the alemtuzumab 12 mg/day group and 1.4% in the IFNB-1a group, but these did not appear to lead to an increased risk of cervical pathology, as the incidence of cervical dysplasia was similar in both treatment groups (1.1% and 1.0%, respectively).

Serious infections were reported for 2.7% of patients in the alemtuzumab 12 mg/day group and 1.0% in the IFNB-1a group over 2 years of follow-up in the active-controlled studies (Table 36).

Table 36 Incidence of serious infection (reported in ≥2 patients) in all active-controlled studies (2-year follow-up)

	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)

There were no reports of hepatitis C, progressive multifocal leukoencephalopathy, toxoplasmosis, HIV, P. jiroveci or other opportunistic infections.

Malignancies

In the active-controlled studies (2-year follow up), four patients in the alemtuzumab 12 mg/day and 2 patients in the IFNB-1a treatment groups reported malignant neoplasms. Additionally, 4 patients in the alemtuzumab 24 mg/day group reported malignant neoplasms, for a total of 8 patients in the alemtuzumab pooled group (Table 37).

Table 37 Incidence of treatment-emergent malignancies in the active-controlled trials

Preferred Term	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	2 (0.4)	4 (0.4)	4 (1.5)	8 (0.7)
Thyroid cancer	0 (0.0)	3 (0.3)	0 (0.0)	3 (0.3)
Basal cell carcinoma	1 (0.2)	1 (0.1)	1 (0.4)	2 (0.2)
Acute myeloid leukaemia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Cervix carcinoma	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Colon cancer	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Vulval cancer stage 0	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)

In the alemtuzumab pooled dose group over all available follow-up, 13/1485 (0.88%) patients reported a total of 15 malignancies (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 cancer (5 patients), basal cell carcinoma (3 patients) and breast cancer (2 patients).

Of note, one patient died of sepsis during the course of chemotherapy to treat Burkitt´s lymphoma 40 months after the third annual treatment with alemtuzumab.

Laboratory findings

During 2-year follow up in the active-controlled studies, alemtuzumab was associated with fewer hematologic abnormalities than IFNB-1a with respect to parameters other than lymphocyte depletion. Values below normal for platelets, neutrophils and hemoglobin were observed less frequently in the alemtuzumab 12 mg/day group than in the IFNB-1a group.

Elevations in ALT and AST were less frequently observed in the alemtuzumab 12 mg/day group than in the IFNB-1a group, but elevations in bilirubin were more frequent in the alemtuzumab 12 mg/day group. Three IFNB-1a-treated patients and one patient treated with alemtuzumab 12 mg/day met Hy's Law criteria for potential drug-induced liver injury.

Renal function was monitored by creatinine testing and urinalysis, monthly for alemtuzumab patients and quarterly for IFNB-1a patients. Elevations in serum creatinine at quarterly testing occurred with similar frequency in the alemtuzumab 12 mg/day group and the IFNB-1a group and were of low severity. The proportions of patients with occult blood or urine protein levels flagged as clinically significant or RBCs in the urine were higher in the alemtuzumab 12 mg/day group than in the IFNB-1a group.

During all available follow up in all alemtuzumab patients, there was no apparent increase in the number of patients with low platelets, neutrophils or hemoglobin or high AST, ALT, bilirubin or creatinine or the severity of any abnormal laboratory value with the number of alemtuzumab cycles received or the total alemtuzumab dose. A majority of patients treated with alemtuzumab had detectable anti-alemtuzumab or anti-alemtuzumab inhibitory antibodies, with titers that increased in the 3-month period following each cycle of treatment, but which declined to low levels by the time-point 12 months following treatment. Peak antibody levels were higher after administration of each subsequent treatment cycle.

Safety in special populations

No clinically meaningful differences were seen across age groups in the incidence of AEs, IARs, infections and cytopenias. Alemtuzumab was not specifically investigated in the elderly and the clinical studies did not include any patients aged over 55 years. This was appropriately reflected in section 4.2 of the SmPC.

No patients younger than 18 years were included in the clinical programme.

The overall incidence of AEs was not different in males (94.8% IFNB 1a and 97.8% alemtuzumab 12 mg/day) versus females (94.4% IFNB 1a and 97.3% alemtuzumab 12 mg/day) with the exception of endocrine disorders, which were reported more frequently for females (17.3%) compared to males (5.6%) in the alemtuzumab 12 mg/day group.

No studies in patients with renal or hepatic impairment were performed. Since monoclonal antibodies are neither metabolized by the liver nor excreted by the kidneys, as discussed in the Clinical pharmacology section, the CHMP considered that studies in these special populations were not needed.

Discontinuation due to adverse events

In the active-controlled studies, 2.3% patients in the alemtuzumab 12 mg/day group and 7.9% in the IFNB-1a group discontinued treatment due to an AE during the 2-year study period. SAEs leading to discontinuation of treatment were even less frequent: 0.8% patients in the alemtuzumab 12 mg/day group and 2.0% in the IFNB-1a group.

The AEs leading to discontinuation of treatment in more than one patient in the alemtuzumab 12 mg/day group were non-cardiac chest pain (3 patients), hypothyroidism, infusion-related reaction, MS relapse and dyspnea (2 patients each). Of note, despite the high frequency of

infusion associated reactions (IARs) in alemtuzumab-treated patients, only a small proportion of patients (0.8%) discontinued treatment due to an IAR.

The most frequent AEs leading to discontinuation of IFNB-1a were mainly related to MS factors and the tolerability issues linked to the use of IFNB-1a: MS relapse (5 patients), influenza-like illness (4 patients), hepatic enzyme increased (3 patients) and lymphopenia, thrombocytopenia, injection site erythema, injection site pain, pyrexia, depression and mood altered (2 patients each).

2.6.1. Discussion on clinical safety

Alemtuzumab was previously authorised for the treatment of B-CLL in a more than tenfold higher cumulative dose. The previous experience with alemtuzumab provided important information, e.g. relevant to the use of appropriate pre-medications to avoid cytokine release. Nevertheless, while it could be argued that a higher dose in more than 38,000 patients from the B-CLL safety database should be reassuring and a lower dose should then be considered safer, the safety findings with alemtuzumab used in MS support the hypothesis that for an immunomodulatory biologic, the safety profile is not necessarily dose-dependent but rather only different, as compared to the high dose. For example, the occurrence of autoimmune phenomena with alemtuzumab in MS was not expected from the B-CLL experience and severe opportunistic infections, commonly observed with alemtuzumab in the B-CLL indication, were not observed to that extent in the MS indication.

The clinical development programme for alemtuzumab in MS involved a sufficient number of patients with an adequate follow-up period.

The CHMP considered that data from the completed, active-controlled studies and the ongoing extension were pooled in order to improve the precision of the estimates and gain insight into or identify safety signals for lower frequency events. Pooling of alemtuzumab safety data was accepted as all studies were conducted in patients with RRMS, the alemtuzumab treatment regimen was the same in all studies and all controlled trials used IFNB-1a as an active control. A comparison of baseline characteristics in studies CAMMS223, CAMMS32 and CAMMS324 suggested that the treatment groups were similar across studies with the only notable differences occurring in baseline EDSS score and time since initial MS episode in the CAMMS324 patients, which was expected as a result of study entry criteria.

The safety profiles following alemtuzumab treatment were not different across the individual studies. The majority of AEs in both treatment groups were of mild or moderate severity.

Of note, the overall incidence of AEs in the alemtuzumab 12 mg/day group generally decreased over time through Year 4. The CHMP considered that it was difficult to estimate whether the decrease in AEs over time is driven by the long-term modulation of the immune system, increase of unwanted immunogenicity (thus preventing on-target toxicity), or due to an artifact of the naturally smaller database in longer-term exposed patients.

Nearly all patients in the studies reported at least one AE, although the total number of reported events was higher in the alemtuzumab-treated patients. This was mostly due the higher number of patients randomized to receive alemtuzumab than IFNB-1a, but the number of IARs reported for alemtuzumab-treated patients was also a contributory factor, as

supported by a safety analysis excluding IARs.

The percentage of patients with treatment-related AEs (as assessed by the investigators) was higher in the alemtuzumab 12 mg/day group than in the IFNB-1a group, but this was considered in view of the unblinded design, i.e. treating physicians and patients were aware of the treatment assignment.

With respect to the severity of adverse events, the incidence of AEs of Grade 3 or higher was greater in the alemtuzumab pooled dose group and the 24 mg/day group compared to the 12 mg/day group. A similar trend towards a worse safety profile was observed also with respect to some of the events of special interest, e.g. immune thrombocytopenic purpura (ITP). The CHMP was of the view that these findings were supportive of the applicant´s decision not to pursue the higher dose group based on a less favorable safety profile.

The CHMP discussed the following events more specifically during their review: infusion associated reactions (IARs), thyroid disorders, ITP, nephropathy and infections, ensuring that these safety issues are appropriately addressed in the risk management plan and in the Product Information.

The CHMP considered that the IARs are a known phenomenon with alemtuzumab, as they were previously documented in the B-CLL indication, albeit in a considerably more severe form. Although most MS patients treated with alemtuzumab 12 mg/day reported at least one IAR, these were mostly mild to moderate in severity and manageable with prophylactic corticosteroids, antihistamines and antipyretics. The incidences of IARs were generally higher in the alemtuzumab 24 mg/day group with a higher incidence also of severe (Grade 3 and 4) IARs, suggesting that the tolerability of the alemtuzumab 12 mg/day dose is superior to that of the 24 mg/day dose and supportive of the applicant´s decision to apply for approval of the 12 mg/day dose. Serious IARs were reported in 2.8% of patients in the alemtuzumab 12 mg/day group and included one case of a Grade 4 anaphylactic reaction. The CHMP requested that the information about IARs should be reflected in section 4.4 of the SmPC, including warnings and precautions to be taken, including monitoring of the patient during and for 2 hours after the infusion.

The incidence of IARs was not different between anti-alemtuzumab antibody positive and negative patients, as supported by a number of analyses presented by the applicant. The lack of apparent clinical impact of both binding and neutralizing (“inhibitory”) antibodies could be explained by the strong premedication with methylprednisolone, which is part of any alemtuzumab treatment cycle. The clinical impact of immunogenicity on safety was therefore considered by the CHMP less prominent than in situations where no premedication is foreseen.

Based on the review of the available safety data, the CHMP was of the view that treatment with alemtuzumab may increase the risk of autoimmune conditions, particularly antibody-mediated autoimmunity, including thyroid disorders, ITP or rarely nephropathies (e.g. anti-GBM disease). The mechanisms underlying the increased risk were not fully established. Literature suggested that peripheral T cells proliferate in response to self-antigens in lymphopenic hosts, but proliferation toward these antigens is prevented when T cell numbers are normal; in lymphopenia multiple co-factors could lead to a loss of self-tolerance after the “first hit” of induction of lymphopenia (“two-hit model”, described e.g. by Krupica et al, Clin Immunol (2006) 120, 121-128). Of note, occurrence of autoimmunity was observed in other

settings of immune reconstitution in lymphocytopenic patients (e.g. Graves' disease with HAART or after allogeneic HST) and MS patients have an increased background risk for development of other autoimmune diseases. However, the CHMP considered that autoimmunity should not be seen as an inevitable consequence of lymphopenia. Most lymphopenic subjects do not develop autoimmunity, suggesting that additional co-factors are required. During the clinical development, the applicant implemented several risk identification and minimisation measures for early detection of autoimmune conditions, such as frequent laboratory measures. In literature IL-21 was suggested as a potential predictive biomarker of autoimmunity. The CHMP recommended that the applicant should further investigate its potential usefulness and feasibility as well as continue to explore additional potential biomarkers.

Based on the findings regarding the effect on the thyroid, the CHMP considered that thyroid function tests, such as thyroid stimulating hormone levels, should be obtained prior to initiation of treatment and every 3 months thereafter until 48 months following the last infusion. After this period of time, testing should be performed based on clinical findings suggestive of thyroid dysfunction. This was reflected in section 4.4 of the SmPC.

Serious events of ITP were observed in approximately 1% of patients treated in the controlled clinical trials in MS. Of note, one patient developed ITP that went unrecognised prior to implementation of monthly blood monitoring requirements and died from intracerebral haemorrhage. The CHMP considered that during the development programme, the applicant reacted on the emerging safety issues such as occurrence of ITP by intensifying the safety monitoring in the clinical studies. These monitoring measures formed the basis for the proposed risk minimization strategies. In particular, as part of the risk minimization strategy, complete blood counts (CBC) with differential should be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion. If ITP is suspected, a complete blood count should be obtained immediately. The patient information material explicitly informs about signs and symptoms of ITP, which was endorsed by the CHMP.

Nephropathies, including anti-glomerular basement membrane (anti-GBM) disease, were observed in 0.3% of patients in clinical trials in MS and occurred within up to 39 months following the last administration of alemtuzumab. In clinical trials, there were 2 cases of anti-GBM disease. In order to minimise the risk, the applicant proposed monthly urinalysis and serum creatinine monitoring through to 48 months after the last alemtuzumab dose as a marker to detect anti-GBM disease. Anti-GBM disease is usually rapidly evolving with patients developing terminal renal failure within days, if left untreated and hence, timely diagnosis is important. The measures to minimise the risks were discussed by the CHMP. The CHMP considered that while monthly serum creatinine may not be rapid enough to capture an acute event, it would nevertheless be useful to capture potential other nephropathies developing in a more subacute manner, and also to raise awareness of patients and treating doctors. The Product Information and the educational material were adequately revised to ensure that the patient remains vigilant for symptoms of nephropathies and seek immediate medical help accordingly.

The most frequently reported infections for both the alemtuzumab 12 mg/day and IFNB-1a groups were the types of infections that are commonly described in most MS treatment trials

and included nasopharyngitis, urinary tract infection (UTI), upper respiratory tract infection, sinusitis and influenza. Additionally, in the alemtuzumab 12 mg/day group, oral herpes and bronchitis were listed among the most frequent infections. The CHMP considered that with the implementation of prophylactic acyclovir during the phase 3 studies (starting on the first day of each alemtuzumab cycle and continuing for 28 days after the last day), the risk of herpes simplex infection was substantially reduced as compared to those who did not receive prophylaxis. Fungal infections were also reported more frequently in alemtuzumab-treated patients with none of them being systemic. The most common fungal infections were oral candidiasis and vulvovaginal candidiasis.

Tuberculosis was reported in alemtuzumab-treated patients in the active-controlled clinical trials. The CHMP was of the view that before initiation of therapy, all patients must be evaluated for both active or latent tuberculosis infection, according to local guidelines. This was reflected in section 4.4 of the SmPC.

Given the degree of lymphocyte depletion immediately following alemtuzumab infusion, the CHMP considered noteworthy that the incidence of serious infections on alemtuzumab treatment was not substantially higher than in patients receiving IFNB-1a. Serious infections reported in ≥2 patients in the alemtuzumab 12 mg/day group included appendicitis, gastroenteritis, herpes zoster, tooth infection and pneumonia. Analysis of the incidence of infections by month showed the highest incidence in the first month after each cycle (i.e., Month 1 and Month 13) and the largest increase during the first month after initiation of the first treatment cycle.

Human papillomavirus infections were reported for 2.4% of patients in the alemtuzumab 12 mg/day group and 1.4% in the IFNB-1a group in the active-controlled trials. While there was not an apparent link to an increased risk of cervical pathology, as the incidence of cervical dysplasia was similar in both treatment groups (1.1% and 1.0%, respectively), the applicant proposed routine screening for HPV infection in women treated with alemtuzumab, as reflected in section 4.4 of the SmPC. This was endorsed by the CHMP.

In the active-controlled studies, 4 (0.4%) patients in the alemtuzumab 12 mg/day group and 2 (0.4%) patients in the IFNB-1a group had a malignancy during the 2-year follow-up. The malignancies in the alemtuzumab 12 mg/day group were 3 cases of thyroid cancer and one of basal cell carcinoma, while in the IFNB-1a group were acute myeloid leukemia and basal cell carcinoma. A total of 15 events were reported in 13 (0.9%) patients during all available follow up for all alemtuzumab-treated patients, among them thyroid, basal cell carcinoma and breast cancer, which is in line with the most frequently reported cancers in white, young adults in the general population. The CHMP considered that of the five thyroid malignancies in alemtuzumab-treated patients, three occurred in patients who reported relevant pre-existing conditions, including existing thyroid neoplasm and thyroid nodules. Whether administration of alemtuzumab could have been a trigger or accelerator to a pre-existing dormant malignancy remains unknown. The CHMP was of the view that, given the relatively short observation period in a pre-authorisation setting, firm conclusion as regards the risk of malignancy could not be made. The CHMP considered that malignancy is reflected in the Risk Management Plan as an important potential risk and that the issue will be further monitored in the post-authorisation setting by means of additional pharmacovigilance activities, including a PASS study.

Changes in laboratory parameters were generally consistent with the expected clinical manifestations of RRMS and the known pharmacodynamic effects of the respective treatments, i.e. alemtuzumab (especially lymphopenia) or IFNB-1a. A higher proportion of patients with occult blood, hematuria or proteinuria were flagged as clinically significant during the 2-year follow-up period in the alemtuzumab 12 mg/day group than the IFNB-1a group, which might be a consequence of the more frequent (monthly) testing in the alemtuzumab group versus the quarterly testing in IFNB-1a-treated patients. Elevations in hepatic enzyme ALT and AST levels were more frequent in IFNB-1a-treated patients than in alemtuzumab-treated patients in the 2-year follow-up period in the active-controlled studies. Asymptomatic elevations of hepatic transaminases are described in the Rebif Product Information. Post-baseline bilirubin values ≥1.5 x ULN were more frequent in the alemtuzumab 12 mg/day group (3.5% of patients) than in the IFNB-1a group (1.8%). The laboratory findings with alemtuzumab were in general not accompanied by clinical signs suggestive of impairment of hepatic function. Alemtuzumab was associated with fewer hematologic abnormalities than IFNB-1a with respect to parameters other than lymphocyte depletion.

With respect to safety in women of child-bearing potential, the CHMP considered that human IgG is known to cross the placental barrier and thus, alemtuzumab may potentially pose a risk to the fetus. It is not known whether alemtuzumab can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. Therefore, the CHMP was of the view that women of child bearing potential should use effective contraceptive measures when receiving a course of treatment and for 4 months following that course of treatment. The possibility of administering alemtuzumab during pregnancy was discussed by the CHMP. A total of 72 pregnancies for female patients treated with alemtuzumab were reported as of 31 December 2011. The spontaneous abortion rate was calculated to be approximately 20%. No congenital abnormalities or birth defects have been reported in the MS clinical programme. The CHMP concluded that the use of alemtuzumab during pregnancy should be based on the physician´s assessment of benefit-risk for the individual patient. This was reflected in section 4.6 of the SmPC as follows: LEMTRADA should be administered during pregnancy only if the potential benefit justifies the potential risk to the foetus.

The post-marketing safety data came from alemtuzumab use primarily in the treatment of patients with B-CLL. As discussed above, while the totality of experience in B-CLL provides a useful background to assess events occurring with higher and more frequent doses of alemtuzumab, the applicability of these data to an MS population was seen as limited by the CHMP due to significant differences in the patient populations and dosing regimens for B-CLL and MS.

2.6.2. Conclusions on the clinical safety

Overall, based on the available safety data, the CHMP considered that while several safety concerns were identified, provided that appropriate post-authorisation measures are in place (as summarised in section 2.8 Risk Management Plan), alemtuzumab can be used safely in the proposed indication.

From the safety database all the adverse reactions reported in clinical trials were included in the SmPC.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1.5, the PRAC considered by consensus that the risk management system for alemtuzumab (Lemtrada) was acceptable.

This advice was based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Table 38 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Infusion-associated reactions (IARs) Autoimmune disorders: Thyroid disorders Immune thrombocytopenic purpura Nephropathies incl. anti-GBM-disease Serious infections
Important potential risks	Other autoimmune disorders i.e. cytopenias Malignancies
Missing information	Impact on fertility Use during pregnancy Use during lactation Paediatric use Use in patients aged >55 years (including use in elderly patients aged ≥65 years) Impact on response to vaccination and value of pre-treatment vaccination Use in patients with renal impairment Use in patients with hepatic impairment Use in patients with human immunodeficiency virus(HIV) Use in patients with Hepatitis B virus (HBV) Use in patients with Hepatitis C virus (HCV)

Summary of safety concerns	
	Use in racial categories other than white Modes of administration other than intravenous (IV)

The PRAC agreed.

- **Pharmacovigilance plans**

Table 39 Ongoing and planned studies in the PhV development plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
PASS OBS13434 [category 3]	1. To characterize the long-term safety profile of alemtuzumab in patients with RRMS in a real-world setting; 2. To assess the effectiveness of risk minimisation measures	IARs Thyroid disorders ITP Nephropathies incl anti-GBM-disease Serious infections Malignancy	Planned	Q 4 2024
Pregnancy registry OBS13436 [category 3]	To assess adverse pregnancy outcomes in women exposed to alemtuzumab, including: spontaneous abortion, stillbirth, foetal major malformations, preterm birth, and small for gestational age at birth.	Missing information on safety of alemtuzumab in pregnancy	Planned	Q 4 2021
Paediatric study (CAMMS11910) [category 3] Randomized, parallel group, rater-blinded,	To evaluate the efficacy, safety and tolerability of alemtuzumab (IV) versus appropriate comparator in	Missing information on the efficacy and safety of alemtuzumab in the paediatric population	Planned (pending final agreement with the PDCO)	September 2019

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
efficacy, safety and tolerability study of alemtuzumab compared to an appropriate comparator in paediatric patients from ages ≥10 years to <18 years with RRMS with disease activity on prior first-line disease modifying treatment.	paediatric subjects with relapsing forms of MS, who have disease activity on prior therapy			

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

- **Risk minimisation measures**

Table 40 Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Infusion-associated reactions (IARs)	SmPC 4.4 Special Warnings and Precautions for Use: It is recommended that patients be premedicated with corticosteroids immediately prior to the initiation of the Lemtrada infusion for the first 3 days of any treatment course to ameliorate the effects of infusion reactions. In clinical trials, patients were pretreated with 1,000 mg methylprednisolone for the first 3 days of each Lemtrada treatment course. Pretreatment with	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	antihistamines and/or antipyretics prior to Lemtrada administration may also be considered. Most patients in controlled clinical trials received antihistamines and/or antipyretics before at least 1 Lemtrada infusion. IARs may occur in patients despite pretreatment. Observation for infusion reactions is recommended during and for 2 hours after Lemtrada infusion. Resources for the management of hypersensitivity and/or anaphylactic reactions should be available. If an IAR occurs, provide the appropriate symptomatic treatment, as needed. If the infusion is not well tolerated, the infusion duration may be extended. If severe infusion reactions occur, including anaphylactic reactions immediate discontinuation of the intravenous infusion should be considered.	
Thyroid disorders	SmPC 4.4 Special Warnings and Precautions for Use: Thyroid function tests (TFT's), such as thyroid stimulating hormone (TSH) levels, should be obtained prior to initiation of treatment and every 3 months thereafter until 48 months following the last infusion	Educational materials including: - Patient guide - Patient alert card - HCP guide - HCP check-list
Immune thrombocytopenic purpura (ITP)	SmPC 4.4 Special Warnings and Precautions for Use: Complete blood counts (CBC) with differential should be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion. If ITP is suspected, a CBC with differential should be obtained immediately. If ITP onset is confirmed, appropriate medical intervention should be promptly initiated, including referral to a specialist. Data from clinical trials in MS has shown that adherence to the blood monitoring requirements and education relative to signs and symptoms of ITP has led to early detection and treatment of ITP with most cases responding to first-line medical therapy.	Educational materials including: - Patient guide - Patient alert card - HCP guide - HCP check-list
Nephropathies including anti-GBM disease (Goodpasture's syndrome)	SmPC 4.4 Special Warnings and Precautions for Use: Serum creatinine levels should be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion. Urinalysis with cell counts should be obtained every 3 months until 48 months after the last infusion. The observation of clinically significant changes from baseline in serum	Educational materials include: - Patient Guide - Patient alert card - HCP Guide

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	creatinine, unexplained haematuria, and/or proteinuria, should prompt further evaluation for nephropathies. Early detection and treatment of nephropathies may decrease the risk of poor outcomes.	
Serious infection	SmPC 4.4 Special Warnings and Precautions for Use: It is recommended that HPV screening be completed annually for female patients. Tuberculosis screening should be done according to local guidelines prior to initiation of alemtuzumab. Physicians should consider delaying initiation of alemtuzumab administration in patients with active infection until the infection is fully controlled. Prophylaxis with an oral anti-herpes agent should be initiated starting on the first day of alemtuzumab treatment and continuing for a minimum of 1 month following each course of treatment. Alemtuzumab has not been administered for treatment of MS concomitantly with antineoplastic or immunosuppressive therapies. Concomitant use of alemtuzumab with any of these therapies could increase the risk of immunosuppression. No data are available on the association of alemtuzumab with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) reactivation as patients with evidence of active or chronic infections were excluded from clinical trials. Screening patients at high risk of HBV and/or HCV infection before initiation of alemtuzumab should be considered, and caution should be exercised in prescribing alemtuzumab to patients identified as carriers of HBV and/or HCV, as these patients may be at risk of irreversible liver damage relative to a potential virus reactivation as a consequence of their pre-existing status.	Educational materials including: - Patient guide - HCP check-list
Other autoimmune disorders including cytopenias (autoimmune haemolytic anaemia)	SmPC 4.4 Special Warnings and Precautions for Use: CBC results with differential (see above under ITP) should be used to monitor for cytopenias. If a cytopenia is confirmed, appropriate medical intervention should be promptly initiated, including referral to a specialist.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Fertility	SmPC Special Warnings and Precautions for Use (Section 4.4), and Fertility, Pregnancy and Lactation (Section 4.6): <u>Fertility</u> There are no adequate clinical safety data on the effect of Lemtrada on fertility. In a sub-study in 13 male alemtuzumab-treated patients (treated with either 12 mg or 24 mg), there was no evidence of aspermia, azoospermia, consistently depressed sperm count, motility disorders or an increase in sperm morphological abnormalities. CD52 is known to be present in human and rodent reproductive tissues. Although animal data have not shown a direct effect on fertility in male humanised mice (see section 5.3), a potential impact on human fertility during the period of exposure is unknown based on the collective available data.	None
Pregnancy	SmPC Fertility, Pregnancy and Lactation (Section 4.6): <u>Pregnancy</u> There is a limited amount of data from the use of Lemtrada in pregnant women. No formal studies have been conducted. Lemtrada should be administered during pregnancy only if the potential benefit justifies the potential risk to the foetus. Human IgG is known to cross the placental barrier; alemtuzumab may cross the placental barrier as well and thus potentially pose a risk to the foetus. It is not known whether alemtuzumab can cause foetal harm when administered to pregnant women or whether it can affect reproductive capacity. Thyroid disease (see section 4.4) poses special risks in women who are pregnant. Without treatment of hypothyroidism during pregnancy, there is an increased risk for miscarriage and foetal effects such as mental retardation and dwarfism. In mothers with Graves' disease, maternal thyroid stimulating hormone receptor antibodies can be transferred to a developing foetus and can cause transient neonatal Graves' disease.	None
Lactation	SmPC Fertility, Pregnancy and Lactation (Section 4.6):	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Breast-feeding Lemtrada was detected in the milk and offspring of lactating female mice administered 10 mg/kg for 5 consecutive days postpartum. It is unknown whether Lemtrada is excreted in human milk. A risk to the suckling child cannot be excluded. Breast feeding should be discontinued during each course of treatment with Lemtrada and for 4 months following the last infusion of each treatment course. No data are available on detection of alemtuzumab in breast milk after a course of Lemtrada treatment. Benefits of conferred immunity through breast- milk may outweigh the risks of potential exposure to alemtuzumab for the suckling child.	
Impact on response to vaccination and value of pre-treatment vaccination	SmPC 4.4 Special Warnings and Precautions for use: It is recommended that patients have completed local immunisation requirements at least 6 weeks prior to treatment with alemtuzumab. The ability to generate an immune response to any vaccine following alemtuzumab treatment has not been studied. The safety of immunisation with live viral vaccines following a course of alemtuzumab treatment has not been formally studied in controlled clinical trials in MS and should not be administered to MS patients who have recently received a course of alemtuzumab. Varicella zoster virus antibody testing/vaccination As for any immune modulating drug, before initiating a course of alemtuzumab treatment, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody-negative patients should be considered prior to treatment initiation with alemtuzumab. To allow for the full effect of the VZV vaccination to occur, postpone treatment with alemtuzumab for 6 weeks following vaccination	None
Paediatric use	SmPC Posology and Method of Administration (Section 4.2): Paediatric population The safety and efficacy of Lemtrada in children with MS aged 0 to 18 years have not been established. No data are available.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in patients > 55 years	SmPC Posology and Method of Administration (Section 4.2): <u>Elderly population</u> Clinical studies of Lemtrada did not include sufficient numbers of patients aged over 55 years old to determine whether they respond differently than younger patients	None
Underlying hepatic impairment	SmPC (Section 4.2): Lemtrada has not been studied in patients with renal or hepatic impairment.	None
Underlying renal impairment	SmPC (Section 4.2): Lemtrada has not been studied in patients with renal or hepatic impairment.	None
Use in HIV	SmPC Contraindications (Section 4.3): Human Immunodeficiency Virus (HIV) infection	None
Use in HCV	SmPC Special Warnings and Precautions for Use (Section 4.6): No data are available on the association of alemtuzumab with HBV or HCV reactivation, as patients with evidence of active or chronic infections were excluded from clinical trials. Screening patients at high risk of HBV and/or HCV infection before initiation of alemtuzumab should be considered and caution should be exercised in prescribing alemtuzumab to patients identified as carriers of HBV and/or HCV, as these patients may be at risk of irreversible liver damage relative to a potential virus reactivation as a consequence of their pre-existing status.	None
Use in HBV	SmPC Special Warnings and Precautions for Use (Section 4.6): No data are available on the association of alemtuzumab with HBV or HCV reactivation, as patients with evidence of active or chronic infections were excluded from clinical trials. Screening patients at high risk of HBV and/or HCV infection before initiation of alemtuzumab should be considered and caution should be exercised in prescribing alemtuzumab to patients identified as carriers of HBV and/or HCV, as these patients may be at risk of irreversible liver damage relative to a potential virus reactivation as a consequence of their pre-existing status.	None
Modes of administration other than IV	SmPC (Section 4.2): Alemtuzumab should be administered by IV infusion over a period of approximately 4 hours.	None
GBM = glomerular basement membrane; IV = intravenous; MS = Multiple sclerosis; SmPC = Summary of Product Characteristics.		

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice with changes.

With respect to the PASS OBS13434, the CHMP considered that the applicant should target a higher number of sites in order to increase the rate of enrolment. As an additional measure to prompt availability of safety data, the applicant was requested to implement annual reporting from this study and submit an interim report 5 years after study initiation. The applicant amended the PASS study protocol synopsis accordingly.

The changes also concerned the risk minimisation measures pertaining to nephropathies including anti-GBM disease. Specifically, the CHMP concluded that urinalysis with microscopy should be obtained at monthly, rather than quarterly, intervals until 48 months after the last infusion.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

Benefits

Beneficial effects

One active-controlled phase 2 study and two active-controlled phase 3 studies formed the core of the development programme for alemtuzumab in MS. The phase 2 study (CAMS223) and one of the phase 3 studies (CAMMS323) included treatment-naïve RRMS patients and the other phase 3 study (CAMMS324) included RRMS patients who had relapsed on therapy. The three studies shared features such as endpoints, which allowed for an inter-study comparison of results.

The indication initially applied for was: “Lemtrada is indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) to decrease the frequency of relapses and slow or reverse accumulation of disability.”

The clinical programme of alemtuzumab demonstrated a convincing statistical and clinical effect on relapse rate, one of the co-primary end-points, in both treatment-naïve RRMS patients and RRMS patients failing first-line therapy. In studies CAMMS323 and CAMMS324, the relapse rate through 2 years was significantly reduced in the alemtuzumab 12 mg/day group by 55% and 49%, respectively, as compared with IFNB-1a ($p < 0.0001$). The relapse rate through 2 years was significantly reduced by 57% compared with IFNB-1a ($p < 0.0001$) also in the discontinued 24 mg/day group in study CAMMS324. In study CAMMS223, the

relapse rate was reduced in the alemtuzumab 12 mg/day and 24 mg/day groups by 67% and 77%, respectively, compared with IFNB-1a ($p<0.0001$).

The CHMP considered that the applicant´s choice of the active comparator for the clinical programme was made in compliance with the CHMP Scientific Advice and set a higher hurdle in establishing efficacy as compared to placebo. Rebif (INFB-A) is considered to be effective as a first-line treatment of RRMS. Therefore, using this product as an active control was viewed as appropriate to evaluate a product intended as a first-line and second-line treatment.

A superior effect on disability compared to INFB-1a was seen in the 12 mg/day group in study CAMMS324. In this study, alemtuzumab was seen to reduce the risk of SAD through 2 years by 42% compared with IFNB-1a ($p= 0.0084$).

The phase 2 study CAMMS223 including only treatment-naïve RRMS patients also showed a significant effect on SAD between the alemtuzumab arms and the INFB-1a arm, supporting a beneficial effect of alemtuzumab on SAD.

Unlike in studies CAMMS223 and CAMMS324, in the phase 3 study CAMMS323 enrolling treatment-naïve patients, the disability component of the co-primary endpoint was not met. The difference in the effect on SAD between the alemtuzumab 12 mg/day and INFB-1a showed a trend (risk reduction of 30%), but it was not statistically significant ($p=0.2173$).

Nevertheless, the CHMP was still of the view that the trend seen in study CAMMS323 was clinically relevant and supportive of alemtuzumab efficacy. In particular, the CHMP considered that the study was conducted as an actively controlled trial against high-dose beta-interferon, which is expected to have an effect on disability progression, increasing the hurdle to show statistical significance. The CHMP also considered that the failure to demonstrate effect on the SAD component in study CAMMS323 might be attributed to the lower disability progression in the beta-interferon arm (11.1%) than expected based on the previous observations (i.e. expected rate of disability progression of 20%). Lower than expected disease activity in a comparator arm is not unprecedented and was seen for other drugs in MS in the respective placebo groups.

Recent literature suggested that the combination of MRI lesion activity (indicative of ongoing inflammation) and relapse activity (i.e. the clinical manifestation of more severe inflammations or lesions involving functionally relevant white matter areas) correlates with subsequent accumulation of disability (Sormani et al, 2011). The CHMP agreed that mechanistically, this is supported, since continuous inflammation (as measured by MRI), even if not clinically manifesting itself as a relapse, is a known feature of MS, and the literature suggested that MRI imaging correlates with the long-term outcome (Rudick et al, 2006). It was also considered that MS patients show higher recruitment of functional brain areas as compared to healthy controls in order to fulfil the same task as measured by functional MRI (Rachbauer et al, 2006), indicating the need to compensate for existing, but still subclinical brain damage. The CHMP was of the opinion that this suggests that disease activity in MS can lead to brain damage already before becoming clinically detectable as sustained disability, and that a certain threshold is required before disability becomes clinically apparent. Based on this threshold hypothesis, it is plausible that within a follow-up of two years, a significant impact on disability separating alemtuzumab from beta-interferon may not yet be observed. In this respect, the effects seen in more advanced patients (study CAMMS324) were considered of

importance, since the likelihood to detect an impact on disability, if any, is higher in a population which is closer to the threshold of manifesting disability.

Alemtuzumab treatment was superior to beta-interferon in a number of further clinically relevant outcomes, including the increase in the percentage of patients who were relapse-free at Year 2, a reduction in the rate of relapses treated with steroids, the rate of severe relapses and reductions in relapses leading to hospitalisations.

Highly significant outcomes in MRI parameters were observed supporting the claim of superior efficacy of alemtuzumab over beta-interferon. As discussed above, MRI parameters were considered of relevance by the CHMP, since they are a measure of disease activity and there is emerging evidence suggesting their role in predicting further course of the disease. The effect on imaging was more pronounced in the second year of treatment. Alemtuzumab showed a superior effect as compared to high-dose beta-interferon on most MRI parameters, notably in the number of newly emerging gadolinium-enhancing lesions (reflecting active inflammation due to local breakdown of the blood brain barrier at the site of inflammation), the number of newly developing T1-hypointense lesions (reflecting places where axonal density was permanently reduced by MS-related tissue destruction), conversion of Gadolinium-Enhancing lesions to “black holes” (reflecting progression to permanent demyelination) and brain atrophy.

Further analyses on EDSS supported by MSFC, suggested an improvement of the EDSS over time. Therefore, the applicant initially claimed that the indication should also reflect on the reversal of disability. Following input from the SAG Neurology and discussion by the CHMP (see section 2.5.3), it was concluded that such claim was not adequately supported by the current dataset and could be misunderstood by patients in a way that Lemtrada could heal MS. The applicant did not pursue this claim further.

The follow-up efficacy data from the phase 2 trial suggested that the superiority of alemtuzumab over beta-interferon in terms of slowing the accumulation of disability may be sustained over 5 years.

With respect to the ongoing extension study CAMMS3409, the CHMP considered that data from a relevant number of patients were available and that the preliminary efficacy analyses, although considered exploratory, were supportive of a longer lasting efficacy of alemtuzumab in the treatment of MS.

As compared to the active control, high-dose beta-interferon (Rebif), several adverse events typical of interferon beta, such as flu-like symptoms and haematological alterations, occurred to a lesser extent with alemtuzumab.

The CHMP also considered that the dosing schedule of alemtuzumab, i.e. two treatment courses of drug administration, on 5 and 3 consecutive days at Year 1 and 2, respectively, compared to s.c. or i.m. injections once or several times per week with the current first-line therapy can be seen as more convenient and may be a benefit for the individual patient.

Uncertainty in the knowledge about the beneficial effects

A formal dose-finding study was not conducted for alemtuzumab in MS. The dosing in the pilot investigator-sponsored MS studies was guided by historical data from oncology use and by

pilot studies in patients with rheumatologic disorders. The two alemtuzumab dose levels (12 mg/day and 24 mg/day) used in the initial 3-year treatment period of the Phase 2 CAMMS223 study bracketed the 20 mg/day pilot study dose in MS patients and were selected to identify any dose-dependent relationships in terms of efficacy or safety variables.

While the outcomes at two years were not significantly different in clinical terms, the higher dose suppressed the MRI activity more potently, which could have a beneficial long-term impact on the disease course. This stronger effect of the 24 mg/day dose on the MRI could be interpreted such that the higher dose may be more potent and effective in the long run. However, as the safety profile of the higher dose was less favourable compared to the lower dose and the efficacy of the higher dose was not superior over the lower dose, the 12 mg/day dose was considered the preferred option.

The choice of s.c. IFNB-1a (Rebif) as an active comparator precluded a double-blinded study design, as discussed in section 2.5.3. The CHMP acknowledged that the open-label design may have had an influence on the outcomes. However, the applicant followed the CHMP Scientific Advice and implemented a number of measures to improve blinding. In particular, the studies were conducted as rater-blinded and designed to minimise the potential impact of treating physicians and patients being aware of treatment assignment (both patients and raters were trained). Furthermore, sensitivity analyses were performed to evaluate the potential impact of the rater-blinded study design on the co-primary efficacy analyses. Relapse determinations in the phase 3 studies were made by a blinded Relapse Adjudication Panel of independent neurologists. All cranial MRIs were evaluated by neuro-radiologists at an independent central facility with no access to the patients' treatment assignment and the results of these evaluations were not provided to study sites. The CHMP was of the view that these measures were appropriate to ensure blinding to a sufficient extent, and considered that a GCP inspection did not identify any critical findings.

Patients in study CAMMS223 (unlike in the phase III studies) did not participate in training runs of MSFC implemented to reduce practice effects. Therefore, an improvement in MSFC in this study could be attributed to a training effect. However, the CHMP considered that this should not be of major impact, since the effect would apply to both arms.

A superior effect on disability compared to INFB-1a was seen in the 12 mg/day group in study CAMMS324. In this study, alemtuzumab was seen to reduce the risk of SAD through 2 years by 42% compared with IFNB-1a (p= 0.0084). However, it should be noted that alemtuzumab was compared to INFB-1a in patients previously failing first line therapy including the comparator INFB-1a. Consequently, the observed effect of the IFNB-1a comparator on disability and relapse rate could have been less pronounced than would be expected if the study had included exclusively a patient population previously failing a different first line therapy, e.g. glatiramer acetate.

In open-label follow-up of alemtuzumab clinical trials, some patients received additional "as needed" treatment upon documented evidence of resumed MS disease activity. The additional courses were administered at 12 mg/day for 3 consecutive days (36 mg total dose) at least 12 months after the prior treatment course. The benefits of >2 treatment courses were not fully established. The CHMP concluded that the therapy should be recommended as 2 treatment courses, as reflected in section 4.2 of the SmPC. Furthermore, if additional treatment courses

are to be given they must be administered at least 12 months after the prior course, as reflected in section 5.1 of the SmPC.

Risks

Unfavourable effects

Alemtuzumab (MabCampath) was approved from July 2001 until August 2012 as a single agent for the treatment of patients with B-CLL with an estimated exposure of >38,000 patients as of May 2011, and was used in clinical studies in MS since 2002. The marketing authorisation of MabCampath was withdrawn voluntarily by the MAH for commercial reasons.

In view of the CHMP, the experience with previous exposure of patients to alemtuzumab in patients with B-CLL was on one hand relevant, since data were available as regards for example appropriate pre-medications to avoid cytokine release etc. On the other hand, the patient populations for MS and B-CLL are quite different and the dose in B-CLL is likewise considerably higher (the cumulative dose was more than tenfold). The CHMP considered that for a biological immunomodulator, a lower dose is not necessarily safer than a higher dose, but may display a distinct safety profile.

For example, the occurrence of autoimmune phenomena with alemtuzumab in MS was not expected from the B-CLL experience. Pathogenesis of these phenomena is not fully understood, but it may involve repopulation of the B- and T-cells in predisposed patients. During the conduct of the clinical studies, the applicant reacted to occurrence of these events by intensifying the safety monitoring and evaluating effectiveness of the measures with respect to early detection of emerging adverse events and their treatment. This formed the basis for strengthening the risk management strategies.

Several risks were identified, including infections and infusion-associated reactions. The risk of infections, including re-activation of latent infections, is one of the main safety concerns for immunomodulating agents/ monoclonal antibodies. The serious infections reported in the MS population included amongst others herpes/varicella, HPV and tuberculosis infections. Some of them occurred months after initiation of treatment.

The most common adverse events related to treatment with alemtuzumab were infusion-associated reactions occurring between start and stop of infusion +24 hrs, such as rash, pyrexia and urticaria, and infections such as nasopharyngitis, urinary tract infections and upper respiratory infections. Of note, a relatively high number of cardiac events (around 12%) were labelled as infusion-associated (including seven cases considered as serious adverse events). However, in general the IARs were manageable and their frequency decreased after the first cycle.

The cumulative proportion of patients experiencing thyroid events (including hypo- and hyperthyroidism, Basedow´s disease, laboratory abnormalities and anti-TPO antibodies) over a follow-up of 8 years was 44.7%. No clear mechanisms of these effects were found. The CHMP considered that this effect will have a major impact on the MS population treated with alemtuzumab and that appropriate monitoring needs to be put in place. To this end, the CHMP was of the view that thyroid function test, such as thyroid stimulating hormone levels, should be obtained prior to initiation of treatment and every 3 months thereafter until 48 months

following the last infusion. The 4-year timeframe was based on the median time that the events were observed. After this period, it was considered sufficient to perform the tests based on clinical findings suggestive of thyroid dysfunction, as reflected in section 4.4 of the SmPC.

Contraindication of alemtuzumab in patients with thyroid disorders was not considered appropriate by the CHMP, given the intensive follow-up in place and the fact that these patients could still benefit from the treatment. The CHMP concluded that the use of alemtuzumab in patients with ongoing thyroid disorder should be based on the physician´s assessment of benefit-risk for the individual patient. This was reflected in section 4.4 of the SmPC as follows: LEMTRADA in patients with ongoing thyroid disorder should be administered if the potential benefit justifies the potential risks.

Further autoimmune conditions confirmed as important identified risks by the CHMP were immune thrombocytopenic purpura and nephropathies.

ITP was medically confirmed in 16 out of 22 identified patients, one of which died of ITP and cerebral haemorrhage prior to implementing CBC into the study schedules. Nephropathies occurred in 5 patients treated with alemtuzumab, including 2 patients with the anti-GBM disease.

Importantly, the treatments of adverse events such as ITP or infusion reactions were not expected to negatively impact the underlying condition (RRMS). For example, ITP is normally treated with intravenous immunoglobulin and corticosteroids, both of which were described as having favourable impact on RRMS. Likewise the anti-inflammatory premedication (methylprednisolone) is the same as used in treatment of an MS relapse and thus was not expected to be harmful to the course of RRMS. Finally, antiviral prophylaxis with acyclovir was also not expected to adversely impact on MS, since data in literature suggested a potential beneficial and at least not harmful effect of some antivirals such as gancyclovir on the course of MS.

In the alemtuzumab pooled dose group over all available follow-up, a total of 15 malignancies was reported. The most common malignancies reported in more than 1 alemtuzumab-treated patient were thyroid cancer (5 patients), basal cell carcinoma (3 patients) and breast cancer (2 patients). The CHMP considered that there were also cases of cancer of viral or potentially viral origin, including a case of cervical carcinoma (HPV+), vulvar carcinoma (HPV+) and Burkitt´s lymphoma. The patient with Burkitt´s lymphoma died of sepsis during the course of chemotherapy to treat the underlying malignancy. The CHMP considered that malignancies are adequately reflected in the RMP as an important potential risk. The issue is discussed further in section “Uncertainty in the knowledge about the unfavourable effects”.

Immunogenicity

Most patients in the phase 3 studies tested positive for anti-alemtuzumab antibodies and also inhibitory antibodies, and both the occurrence of antibodies against alemtuzumab and their titer increased upon re-exposure, i.e. cycle 2. The occurrence of an immune response per se is not necessarily a problem and can be expected for a biological; it is the clinical consequences which should guide the clinical assessment. Following the CHMP Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use

EMA/CHMP/BMWP/86289/2010, a risk-based approach is recommended considering also the clinical context and availability of alternative treatments.

Usually, the immunogenicity of humanised antibodies is observed in around 5-10% of patients (in chronic and continuous treatment, depending on the clinical indication etc.), but the immunogenicity of alemtuzumab was considerably higher. MS is an autoimmune disease, and patients with a pre-activated immune system may thus be at higher risk of developing an unwanted immune response.

Alemtuzumab depletes B and T cells, thus potentially eliminating the effector cells which would be capable of mounting an immune response. On the other hand, alemtuzumab was also considered to be involved in triggering of other autoimmune phenomena such as anti-GBM glomerulonephritis or thyroid autoimmune conditions. Therefore, the mechanistic impact of alemtuzumab on a predisposition to mounting an unwanted immune response is difficult to estimate. Alemtuzumab is administered as a cyclic treatment where every new treatment cycle could be recognised by the immune system as a kind of a “vaccination”. This may explain the considerable triggering of an immune response with cycle 2 and is most probably the likely explanation of the high immunogenicity.

The CHMP considered that the following aspects are important for a risk-based approach to the observed high incidence of an unwanted immune response:

- The efficacy of alemtuzumab is considerable across studies including relevant subgroups. Analysis by presence or absence of inhibitory antibodies did not suggest relevant impact of anti-alemtuzumab antibodies. This might be explained by the fact that the B and T cell depletion with alemtuzumab could be that rapid that any immune response would take longer to be triggered or reactivated again.
- MS is a disease, where loss of efficacy (reoccurrence of disease activity) would be detected by regular MRI scans that are normally part of routine clinical management or by occurrence of relapses.
- There are numerous treatment alternatives including other monoclonal antibodies in case alemtuzumab shows reduced or diminished efficacy; immune responses against monoclonal antibodies are normally anti-idiotypic and therefore product-specific, thus not expected to interfere with administration of other monoclonal antibodies. If such other treatments can be given to a patient, will have to be decided on a case-by-case basis considering additive immunosuppressive effects.
- Infusion reactions, normally a main concern, are effectively curbed by methylprednisolone treatment that is administered to every patient.

Uncertainty in the knowledge about the unfavourable effects

The lack of information about the pathogenetic mechanisms as well as clearly elaborated time course of events for developing the various thyroid disorders was initially seen as an area of uncertainty. While there is still a lack of full understanding of the mechanisms, the CHMP considered that the safety of alemtuzumab can be adequately controlled in the post-authorisation setting by the risk management strategies, including a post-authorisation safety study, and by the regular PSUR reporting.

The potential for re-activation of infections was seen as another area of uncertainty. The applicant put in place safety measures such as prophylactic medication (oral anti-herpes agents) and laboratory assessments after a few cases of serious infections occurred in the clinical studies. The CHMP was of the view that the risk of infections is of considerable clinical importance and should be one of the key areas for follow-up in the post-authorisation setting. The CHMP considered that this objective would also be pursued in the context of a post-authorisation safety study.

At the time of the CHMP opinion, there were no confirmed predictive biomarkers that could help identifying patients at higher risk of developing an autoimmune condition. Interleukin-21 was reported in scientific literature as a potential predictor of autoimmunity following alemtuzumab treatment, which was detectable even before treatment; however, these results could not reproduced by the applicant. The CHMP recommended the applicant to further investigate potential biomarkers predictive of safety concerns and report back to the CHMP within the PSURs.

One of the safety concerns for this type of disease modifying drug, apart from induction of certain forms of autoimmunity, is the potential risk of malignancies. With respect to thyroid cancer, the CHMP considered that the primary focus should be risk management strategies that focus on thyroid conditions in order to detect any thyroid condition in time, together with intensive physician and patient education. The fact that all thyroid malignancies observed in alemtuzumab treated patients were found during the diagnostic work-up of recently identified underlying thyroid conditions could suggest that the existing risk minimization measures for thyroid conditions are sufficient mechanisms by which a thyroid malignancy could be identified. The CHMP also considered that malignancies will be closely monitored in the post-authorisation study.

Anti-GBM disease is a potentially severe and rapidly developing condition. The long-term prognosis of patients affected by the condition and treated is currently unknown, due to the lack of long-term outcome data. However, although not seen in Lemtrada studies, even small permanent changes of serum creatinine were suggested in medical literature to negatively impact the cardiovascular prognosis. Anti-GBM disease is usually rapidly evolving with patients developing terminal renal failure within days if left untreated highlighting the need for a timely diagnosis. The CHMP considered that monthly analyses of serum creatinine and urine status could be used as a basic screening tool, but acknowledged the concern of potentially higher rate of false positives, triggering unnecessary diagnostic procedures, as well as the fact that even monthly serum creatinine measurement may not be able to capture a rapidly evolving event. In this context, the CHMP was of the view that the most important risk minimisation activity is awareness of the patient and any doctor that will see the patient with an acute renal failure, underlining the importance of the educational programme, including the patient alert card, as an additional risk minimisation measure.

At the time of the CHMP opinion, it was not known whether there could be an increased incidence of infections, including opportunistic infections, and malignancies after a longer time following treatment. This was considered as a common concern for immunosuppressants/immunomodulators and not necessarily specific of alemtuzumab. Nevertheless, the long-term follow-up data available for a considerable number of patients were considered reassuring by the CHMP.

The safety concern of using alemtuzumab during pregnancy was considered as missing information and thus as an uncertainty, particularly when seen in the context of a condition affecting women of child-bearing potential. The CHMP considered that this issue was adequately addressed in the risk management plan by setting up a pregnancy registry in order to assess adverse pregnancy outcomes in women exposed to alemtuzumab.

Lemtrada was not administered for treatment of MS concomitantly with or following antineoplastic or immunosuppressive therapies. As with other immunomodulating therapies, potential combined effects on the patient´s immune system should be taken into account when considering administration of the product. The CHMP considered that concomitant use of alemtuzumab with any of these therapies could increase the risk of immunosuppression. This was reflected in section 4.4 of the SmPC.

The risks of >2 treatment courses were not fully established, but the results suggested that the safety profile did not appear to change with additional courses. Overall, the CHMP concluded that the therapy should be recommended as 2 treatment courses with safety follow-up of patients from initiation of treatment and until 48 months after the last infusion, as reflected in section 4.2 of the SmPC. Furthermore, if additional treatment courses are to be given they must be administered at least 12 months after the prior course, as reflected in section 5.1 of the SmPC.

Benefit-risk balance

Importance of favourable and unfavourable effects

An improved effect compared to first line therapy on relapse rate and disability progression can be considered of importance in light of the limited effects of the current first line therapies. In addition, the dosing schedule of alemtuzumab, i.e. two treatment courses of maximum 5 days of drug administration, one year apart, compared to s.c. or i.m. injections once or several times per week could be seen as more convenient and beneficial for an individual patient.

Although there are several licensed treatments for RRMS, there is still unmet medical need, since the current first-line treatments (beta-interferons and glatiramer acetate) are not sufficiently effective in all patients, and further lines of treatments such as fingolimod or natalizumab are accompanied with significant safety issues that require careful treatment decisions by the treating physician.

On the other hand, clinically significant unfavourable effects were observed, most noteworthy the occurrence of autoimmune diseases (especially thyroid disease which occurred relatively frequently). While patients can be monitored by means of clinical observation and laboratory values, the adverse events can nevertheless be severe and require medical treatment.

The CHMP was of the opinion that adverse events occurring with alemtuzumab in the indication of multiple sclerosis should be assessed in view of the typical MS patient population, i.e. predominantly young and otherwise healthy women of child-bearing potential. In this context, particularly the occurrence of autoimmune diseases such as thyroid disease (Graves' disease, hypo- and hyperthyroidism), anti-GBM renal disease and ITP were seen as significant. Adverse events such as infusion-related reactions can effectively be clinically managed with

appropriate pre-medication.

Discussion on the benefit-risk balance

In the clinical programme, alemtuzumab was seen to have consistent efficacy both in previously untreated RRMS patients and RRMS patients failing first-line therapy, also across various subgroups analysed. The CHMP considered that the benefits in terms of effects observed on the relapse- and disability-related endpoints were clinically meaningful and that the efficacy was further supported by relevant MRI-related outcomes.

As discussed above, the SAG-Neurology was consulted as to whether the safety profile would warrant a restriction of the indication. In general, the SAG-Neurology experts were positive towards efficacy of alemtuzumab, but highlighted that the safety issues observed and the risk management required special attention. The SAG-Neurology experts were split with respect to the issue of restricting the indication versus leaving the decision up to the treating physician and the patient. In either case, however, the SAG-Neurology felt that physicians and doctors need to be well-trained and educated about the risks of alemtuzumab treatment.

This was taken up by the CHMP in their discussion regarding the importance of the physician and patient education and risk management. The CHMP considered that the applicant proposed a specific and pro-active risk management plan that was developed in the clinical studies and that builds on regular medical surveillance including monthly complete blood counts, monthly serum creatinine measurements and monthly urinalysis. A patient alert card was proposed alongside the patient and physician educational material in order to inform physicians about the adverse events that might occur on treatment with alemtuzumab. This was agreed by the CHMP, particularly considering that the physicians diagnosing and treating the complications, i.e. endocrinologists, nephrologists etc., would not be the same as the physicians treating the underlying disease, i.e. neurologists.

The CHMP also acknowledged that the patient information material includes information on key symptoms the patients need to be aware of in order to allow for timely diagnosis and treatment of potentially serious adverse reactions.

Based on their evaluation of the benefits and risks of alemtuzumab in the MS population, as detailed in the sections above, the CHMP discussed the appropriate indication of alemtuzumab.

Overall, it was concluded that patients with inactive disease or stable on current therapy should not be treated with alemtuzumab. At the same time, the CHMP was of the view that the treating physicians should have sufficient flexibility to reach more individualized treatment decisions in patients showing activity as documented by clinical or imaging features, and concluded on the following indication:

"LEMTRADA is indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features. (See Section 4.4 and 5.1)"

The CHMP made the following considerations:

- The reference to "active disease" was considered to ensure that patients being stable on treatment, patients with currently "benign" course or patients with low disease activity are not treated. Furthermore, the following wording added to section 4.4 of the SmPC

was considered to add further clarity to the prescriber: “Lemtrada is not recommended for patients with inactive disease or stable on current therapy.”

- The reference to “as defined by clinical or imaging features” was considered to ensure that the diagnosis for “activity” is based on commonly used criteria. It was considered to refer to “or” instead of “and”, since a clinical presentation may already be sufficiently severe to trigger treatment (e.g., certain cerebellar or pyramidal symptoms causing severe disability), but also MRI evidence of continuing disease activity without corresponding clinical symptoms could equally qualify, on a case-by-case basis, for active treatment.
- The reference to section 4.4 was considered useful to ensure that the treatment decision is made in full awareness of the safety profile of Lemtrada, thus addressing the safety concerns.
- The reference to section 5.1 was considered useful in raising awareness of the prescribers to the inclusion criteria of the clinical trials, thus strengthening the recommendation for “active” disease only.

The CHMP was of the view that this indication would avoid restricting alemtuzumab to patients with high disease activity only. Thus, such approach was seen as allowing for disease modification also for patients, whose disease course is not yet highly active, but is still disabling or likely to become highly active or may later result in higher cumulative disability.

The CHMP concluded that this indication, when read in conjunction with the entire physician and patient documentation, would facilitate a more individualised treatment decision for a given patient by the prescribing specialist neurologist, while at the same time preventing treatment of patients with inactive disease (benign course) or those stable on an alternative treatment.

Divergent positions are appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Lemtrada in the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme for Health Care Professionals (HCP) and patients with the National Competent Authority.

The MAH shall ensure that, following agreement with the National Competent Authorities in each Member State where LEMTRADA is marketed, at launch and after launch, all physicians who intend to prescribe LEMTRADA are provided with an updated physician educational pack containing the following elements:

- The Summary of Product Characteristics
- HCP guide
- Prescriber checklist

- Patient guide
- Patient alert card

The HCP guide shall contain the following key messages:

1. A description of the risks associated with the use of LEMTRADA namely:
    - Immune Thrombocytopenic Purpura (ITP)
    - Nephropathies including anti-Glomerular Basement Membrane (anti-GBM) disease
    - Thyroid disorders
2. Recommendations on how to mitigate these risks through appropriate patient counselling, monitoring and management.
3. A “Frequently asked questions” section

The **prescriber checklist** shall contain the following key messages:

1. Lists of tests to be conducted for the initial screening of the patient
2. Vaccination course to be completed 6 weeks before treatment
3. Premedication, general health, and pregnancy and contraception checks immediately before treatment
4. Monitoring activities during treatment and for 4 years after last treatment
5. A specific reference to the fact that the patient has been informed and understands the risks of serious autoimmune disorders, infections and malignancies, and the measures to minimize them

The **patient guide** shall contain the following key messages:

1. A description of the risks associated with the use of LEMTRADA namely:
    - Immune Thrombocytopenic Purpura (ITP)
    - Nephropathies, including anti-Glomerular Basement Membrane (anti-GBM) disease
    - Thyroid disorders
    - Serious infections
2. A description of the sign and symptoms of autoimmune risks
3. A description of the best course of action if sign and symptoms of those risks present themselves (e.g. How to reach your doctors)
4. Recommendations for the planning of the monitoring schedule

The **patient alert card** shall contain the following key messages:

1. A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient has been treated with LEMTRADA
2. That LEMTRADA treatment may increase the risk of:
    - Immune Thrombocytopenic Purpura (ITP)
    - Nephropathies, including anti-Glomerular Basement Membrane (anti-GBM) disease
    - Thyroid disorders
    - Serious infections
3. Contact details of the prescriber of LEMTRADA

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Divergent positions to the majority recommendation are appended to this report.

APPENDIX

DIVERGENT POSITIONS

The undersigned members of the CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for Lemtrada.

The reasons for divergent positions were as follows:

It is agreed that efficacy of alemtuzumab has been shown in patients with relapsing remitting multiple sclerosis (RRMS). However, there are serious safety concerns with the use of the product.

While the benefit/risk in a limited indication in patients with RRMS with high disease activity defined by clinical and imaging features could be considered positive, the benefit in a population with less active disease is considered not to outweigh the risks.

Therefore the benefit/risk is deemed negative in the broader indication, as proposed by the MAH.

Daniela Melchiorri	Pierre Demolis
Barbara van Zwieten-Boot	Sol Ruiz
Karsten Bruins Slot	Concepcion Prieto Yerro
Reynir Arngrimsson	