EU-RISK MANAGEMENT PLAN FOR LEMTRADA® (ALEMTUZUMAB)

Risk Management Plan (RMP) Version number	Version 13.0
Data Lock Point (DLP)	12-SEP-2024
Date of final sign-off	27-FEB-2025

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	This European Union (EU)-RMP is submitted to answer the Pharmacovigilance Risk Assessment Committee (PRAC) requests to update the RMP with milestones of post-authorization safety study (PASS) studies, in the context of regulatory procedures EMEA/H/C/003718/ANX/009.2 and EMEA/H/C/003718/PSR/S/0051 (Mortality study final study report). As requested, this updated RMP v13.0 includes all relevant updated data, in context of a new type II variation.
Summary of significant changes in this RMP	**Safety Specifications:** All relevant parts of safety concerns are updated with new DLP dated 12-Sep-2024. Part I: Minor wording changes, hyperlink to product information updated. Part II Module SV: Update of post-authorization exposure data as per new DLP. Part II Module SVII: Update of the important risks as per the new DLP. **Pharmacovigilance Plan:** The PASS category 1 studies are updated. The PASS category 3 OBS13434 milestones are updated. **Risk Minimization Measures:** Updated with the main outcomes of the drug utilization study (DUS) and mortality study. Part VI is aligned with all RMP sections. **Annexes:** Annexes 2 and 3 are updated with the updated status of PASS studies. Annex 8 is updated with information on last RMP versions.

DLP: Data Lock Point; DUS: Drug Utilization Study; EMEA: European Medicines Agency; EU: European Union;
PASS: Post-Authorization Safety Study; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	10.1
Approved with procedure	EMEA/H/C/003718/II/0041
Date of approval (opinion date)	Committee for Medicinal Products for Human Use (CHMP) positive opinion 07-Jul-2022

CHMP: Committee for Medicinal Products for Human Use; EMEA: European Medicines Agency; RMP: Risk Management Plan.

Table 4 - QPPV name and signature

Qualified Person Responsible for Pharmacovigilance (QPPV) name	[redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

AAC:	Acute Acalculous Cholecystitis
AE:	Adverse Event
AHA:	Acquired Haemophilia A
AIE:	Autoimmune Encephalitis
AIH:	Autoimmune Hepatitis
ANCA:	Antineutrophil Cytoplastic Antibody
AOSD:	Adult Onset Still's Disease
aRMM:	Additional Risk Minimization Measure
ATC:	Anatomical Therapeutic Chemical
AVM:	Arteriovenous Malformation
B-CLL:	B-cell Chronic Lymphocytic Leukemia
BP:	Blood Pressure
CADASIL:	Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
CBC:	Complete Blood Count
CD:	Cluster of Differentiation
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
CIDP:	Chronic Inflammatory Demyelinating Polyneuropathy
CLL:	Chronic Lymphocytic Leukemia
CMQ:	Customized MedDRA Query
CMV:	Cytomegalovirus
CNS:	Central Nervous System
CPMP:	Committee for Proprietary Medicinal Products
CSF:	Cerebrospinal Fluid
CTCAE:	Common Terminology Criteria for Adverse Event
DDD:	Defined Daily Dose
DLP:	Data Lock Point
DMT:	Disease Modifying Therapy
DNA:	Deoxyribonucleic Acid
EBV:	Epstein-Bar Virus
e-CTD:	Electronic Common Technical Document
EDSS:	Expanded Disability Status Scale
EEA:	European Economic Area
EHR:	Electronic Health Record
EMEA/EMA:	European Medicines Agency
EMSP:	European Multiple Sclerosis Platform
EPAR:	European Public Assessment Report
EU:	European Union
FDA:	Food and Drug Administration
FVIII:	Antihemophilic Factor
GBM:	Glomerular Basement Membrane
GBS:	Guillain Barre Syndrome

GVP:	Good Pharmacovigilance Practices
HBV:	Hepatitis B Virus
HCP:	Healthcare Professional
HCV:	Hepatitis C Virus
HIV:	Human Immunodeficiency Virus
HLH:	Haemophagocytic Lymphohistiocytosis
HPV:	Human Papilloma Virus
HRQoL:	Health Related Quality of Life
HSV:	Herpes Simplex Virus
IAR:	Infusion-Associated Reaction
ICD:	International Classification of Diseases
IFNβ:	Interferon Beta
IgG:	Immunoglobulin G
IgM:	Immunoglobulin M
INN:	International Nonproprietary Name
IRIS:	Immune Reconstitution Inflammatory Syndrome
ISS:	Integrated Summary of Safety
ITP:	Immune Thrombocytopenic Purpura
IV:	Intravenous
JCV:	John Cunningham Virus
LEMS:	Lambert-Eaton Myasthenic Syndrome
LLN:	Lower Limit of Normal
LPLV:	Last Patient Last Visit
MAH:	Marketing Authorization Holder
MARCO:	Margin Consolidated
MAS:	Macrophage Activation Syndrome
Max:	Maximum
MedDRA:	Medical Dictionary for Regulatory Activities
Min:	Minimum
MRI:	Magnetic Resonance Imaging
MS:	Multiple Sclerosis
n:	Number
N:	Total Number of Patient
NA:	Not Applicable
NCA:	National Competent Authority
NCI:	National Cancer Institute
NORD:	National Organization for Rare Disorders
OR:	Odds Ratio
PAH:	Pulmonary Alveolar Haemorrhage
PASS:	Post-Authorization Safety Study
PCR:	Polymerase Chain Reaction
PML:	Progressive Multifocal Leukoencephalopathy
PPMS:	Primary-Progressive Multiple Sclerosis
PRAC:	Pharmacovigilance Risk Assessment Committee
PSUR:	Periodic Safety Update Report
PT:	Preferred Term
Q:	Quarter

QPPV:	Qualified Person Responsible for Pharmacovigilance
REMS:	Risk Evaluation and Mitigation Strategy
RMP:	Risk Management Plan
RMS:	Relapsing Multiple Sclerosis
rRMM:	Routine Risk Minimization Measure
RRMS:	Relapsing Remitting Multiple Sclerosis
RTI:	Respiratory Tract Infection
SC:	Subcutaneous
SD:	Standard Deviation
SmPC:	Summary of Product Characteristics
SOC:	System Organ Class
SPMS:	Secondary Progressive Multiple Sclerosis
T1DM:	Type 1 Diabetes Mellitus
TB:	Tuberculosis
TIA:	Transient Ischemic Attack
TPO:	Thyroid Peroxidase
TSH:	Thyroid Stimulating Hormone
TTO:	Time to Onset
TTP:	Thrombotic Thrombocytopenic Purpura
UK:	United Kingdom
US:	United States
USA:	United States of America
UTI:	Urinary Tract Infection
WHO:	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Alemtuzumab
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	L04AA34
Marketing Authorization Holder (MAH)	Sanofi Belgium
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Lemtrada
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Alemtuzumab is a recombinant deoxyribonucleic acid (DNA)-derived humanized monoclonal antibody that is directed against the cell surface glycoprotein, Cluster of Differentiation (CD)52.
	Summary of mode action: In humans, CD52 is expressed at high levels on T and B lymphocytes and to a lesser extent on natural killer cells, monocytes and macrophages. Alemtuzumab depletes circulating T and B lymphocytes after each treatment course. Lymphocytes begin to repopulate after each depletion course, and the kinetics of repopulation are similar after the first and second courses. B cell recovery is usually complete within 6 months, whilst T lymphocyte counts slowly rise towards normal and may approach Lower Limit of Normal (LLN) by 12 months. Overall, approximately 80% of patients have total lymphocyte counts that reach the LLN within 12 months of each course. Approximately 10% to 20% of patients had CD3+ and CD4+ counts that reached the LLN by 12 months after each treatment course 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 that reached the LLN by 9 months following each course. Almost all patients (≥85%) had CD19+ counts that reached the LLN by 6 months following a treatment course. The mechanism by which alemtuzumab exerts its therapeutic effects in Multiple Sclerosis (MS) is not fully elucidated but may involve immunomodulation through the depletion and repopulation of lymphocytes.
	Important information about its composition: Each vial contains 12 mg alemtuzumab in 1.2 ml (10 mg/ml).
Hyperlink to the product information	Please refer to electronic Common Technical Document (e-CTD) sequence 00167, Module 1.3.1 English clean approved Product Information.

Indication(s) in the EEA	Current: *LEMTRADA is indicated as a single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:* • *Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or;* • *Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.*
	Proposed: Not applicable
Dosage in the EEA	Current: *The recommended dose of alemtuzumab is 12 mg/day administered by intravenous infusion for 2 initial treatment courses, with up to 2 additional courses if needed;* *Initial treatment of 2 courses:* • *First treatment course: 12 mg/day on 5 consecutive days (60 mg total dose);* • *Second treatment course: 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the first treatment course.* *Up to 2 additional treatment courses, as-needed, may be considered:* • *Third or fourth course: 12 mg/day on 3 consecutive days (36 mg total dose) administered at least 12 months after the prior treatment course* in patients with MS disease activity defined by clinical or imaging features.
	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: *Concentrate for solution for infusion (sterile concentrate).* *A clear, colorless to slightly yellow concentrate with pH 7.0-7.4.* *Each vial contains 12 mg alemtuzumab in 1.2 mL (10 mg/mL).*
	Proposed: Not applicable
Is or will the product (be) subject to additional monitoring in the European Union (EU)?	Yes

ATC: Anatomical Therapeutic Chemical; CD: Cluster of Differentiation; DMT: Disease Modifying Therapy; DNA: Deoxyribonucleic Acid; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EU: European Union; INN: International Nonproprietary Name; LLN: Lower Limit of Normal; MAH: Marketing Authorization Holder; MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis; RMP: Risk Management Plan; RRMS: Relapsing Remitting Multiple Sclerosis.

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

LEMTRADA is mainly indicated as a single DMT in adults with highly active RRMS for the following patient groups:

- Patients with highly active disease despite a full and adequate course of treatment with at least one DMT or;
- Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

The epidemiology of the disease is summarized in the following table.

Table 6 - Epidemiology of the Multiple Sclerosis (MS)

Indication	**Multiple Sclerosis (MS)**
Multiple sclerosis is the most common cause of serious neurological disability in young adults. With a prevalence varying from 1 to 300 per 100 000, about 2.3 million people were estimated to live with MS in 2013 worldwide. This estimate represents an increase from the estimated number of 2.1 million patients reported in 2008, (1) which is likely to be due to a better diagnosis and reporting, and to an increase in life expectancy in MS. (2)(3) While MS is present in all regions of the world, its prevalence varies greatly, being highest in North America and Europe (mean prevalence rates of 140 and 108 per 100 000 respectively) and lowest in Sub-Saharan Africa and East Asia, at 2.1 and 2.2 per 100 000 respectively; (1) overall, the pattern of global MS varies according to latitude and ethnicity, with lower rates reported in nonwhite populations (2) and in countries located closer to the equator. (4) However there are exceptions to this rule, which suggest that the presumed increasing gradient of prevalence from equator to poles is an oversimplification.	
Incidence	In Europe the median annual incidence of MS has been estimated as 5.5 cases per 100 000. (1) Incidence data broadly support the distribution observed in prevalence of MS, with some of the highest annual incidence estimates found in the Nordic countries (Iceland [10], Finland [9], and Denmark [8]) and in the Northern regions of the United Kingdom (UK) (Northern Ireland [12], Scotland [15], and the lowest in Romania [1]). Again, annual incidence estimates demonstrated considerable variation within regions, for example, ranging from 0.71 to 9.0 in Malta and Sicily respectively. In some regions the incidence of MS has increased over time, at least in women, which has been attributed to the result of a change in the environment secondary to a change in lifestyle. (5) Overall, the incidence sex ratios (when available) reveal consistently higher rates of women than men with MS across Europe. The average age of newly diagnosed patients is approximately 32 years, or about 5 years lower than for prevalent cases, with female patients exhibiting an earlier age at onset. (5)
Prevalence	Europe is considered a high prevalence region for MS, with a median prevalence of 100 cases per 100 000, and nearly 700 000 patients estimated across the 35 European countries members of the European Multiple Sclerosis Platform (EMSP). (1) Prevalence varies considerably within regions, with the highest prevalence of 227 and 189 per 100 000 in Denmark and Sweden respectively, and the lowest of 22 and 30 per 100 000 in Albania and Romania. Prevalence estimates tend to be higher in the northern regions of the UK and in the Nordic countries, with the highest estimated prevalence per 100 000 seen in

Indication	Multiple Sclerosis (MS)
	Scotland (255) and Northern Ireland (213) in the UK (164), Iceland (140), Germany (149) and Norway (125), implicating the role of latitude. (1) However, this pattern is not uniform, with high estimates originating as far south as in regions of Sicily (127) and Greece (120). (2)(6)
Demographics of the population in the authorized indication	Multiple sclerosis typically begins between the ages of 20 to 40 years. Overall, women are affected approximately twice as often as men, although the female to male MS ratio shows variability across regions (eg, in East Asia and the Americas the female-to-male ratio of MS reaches 3.0), and with calendar time (the female:male sex ratio has increased over recent decades possibly due to increasing incidence of MS in women). (1)(3)(5) <u>Risk factors for the disease</u> Potential risk factors as summarized in a review article by Ascherio et al. (2016): (7) • Latitude: those further from the equator being at higher risk - although this gradient has attenuated in the northern hemisphere; • Gender: women have a higher risk than men. The ratio varies from 1.5:1 to 2.5 to 1 and may differ geographically and by time; • Age: incidence is low in childhood and reaches a peak between 25 and 35 years and then declines; • Race: Whites, especially of Northern European descent, seem to have the highest risk, although incidence may be increasing in United States (US) blacks; • Vitamin D deficiency: inadequate vitamin D increases risk (especially in early life); • Genetic: >100 genes are implicated in MS; • Obesity in early life increases risk; • Epstein-Barr virus that resulted in mononucleosis increases risk. Smoking: Smokers have a higher risk than nonsmokers and MS risk increases as smoking duration and intensity increase.
Main existing treatment options	Teriflunomide, ocrelizumab, cladribine, alemtuzumab, Interferon Beta (IFNβ)-1a, IFNβ-1b, glatiramer acetate, natalizumab, dimethyl fumarate, and fingolimod.
Natural history of the indicated condition in the untreated population including mortality and morbidity	Irrespectively of the world region, in approximately 85% of patients MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery. If left untreated, after 10 years of diagnosis the majority of these patients will transition to a progressive form characterized by worsening neurologic disability, either with or without occasional super-imposed relapses (relapsing or non-relapsing secondary progressive MS. Overall, at any one point in time, about 50-60% patients suffer from RRMS, (5) and at different points in time, RRMS present either active (with relapses and/or evidence of new MRI activity) or not active disease, as well as worsening (a confirmed increase in disability over a specified period of time following a relapse) or not worsening disease forms. Relapsing remitting multiple sclerosis can result in a significant loss of function over the course of a relapse as well as over the long-term course of illness. Physical disability remains the major impact on patients' Health Related Quality of Life (HRQoL). The estimated mean proportions for the Expanded Disability Status Scale (EDSS) 12 groups <4, 4-6.5 and >6.5 have been reported as 55%, 25%, 20% respectively. (6) In RRMS, a median time to reach the disability milestones EDSS4 and EDSS6 from clinical onset of 11 and 23 years (or at a median age of 45 and 55 years respectively) has been reported. (3) Physical disabilities, especially impaired ambulation, and cognitive impairment have great impact on quality of life. Among other frequent and burdensome consequence of the disease are pain and depression, which may limit employability (8) even for MS patients with low levels of physical disability. Among the symptoms, activities of daily living and other issues that are most affected by the disease or pose the greatest problems for patients, fatigue represents a problem for 84% of them, followed by anxiety regarding the evolution of the disease (63%), and ambulation, balance, bowel/bladder symptoms and sensory/motor disturbances for 40-50% of patients. (9)

Indication	Multiple Sclerosis (MS)
	Despite the observed rise in MS survival in recent times, the mortality rate in MS is threefold higher compared with the matched general population. Overall the median time from onset to death ranges from 24 years to >45 years, with a life expectancy reduction by 6 to 14 years. Sex differences in MS mortality, greater risk for younger patients, and better prognosis for RRMS over Primary-Progressive Multiple Sclerosis (PPMS) have been reported across studies. (10) In about 50-70% of deaths, MS is considered either the main cause of death or a main contributing factor. Cardiovascular and cerebrovascular diseases and cancer are, in addition to MS, most frequent (30%), whereas respiratory and infectious causes are recorded in 4%. (3)(10)
Important co-morbidities	Important co-morbidities found in the target population: Depression; urinary tract infections (UTIs); diabetes; hypertension; hypercholesterolemia and arthritis are co-morbidities. (11) Concomitant medications in the target population: It is recommended that patients be pre-treated with corticosteroids immediately prior to the initiation of the alemtuzumab infusion for the first 3 days of any treatment course to ameliorate the effects of infusion reactions. In clinical trials patients were pretreated with 1000 mg of methylprednisolone intravenous (IV) for the first 3 days of each alemtuzumab treatment course. Pretreatment with antihistamines and/or antipyretics prior to alemtuzumab administration may also be considered. Other medications commonly used in the target population are those commonly prescribed in co-morbidities found in the target populations.

EDSS: Expanded Disability Status Scale; EMSP: European Multiple Sclerosis Platform; HRQoL: Health Related Quality of Life; IFNβ: Interferon Beta; IV: Intravenous; MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis; PPMS: Primary-Progressive Multiple Sclerosis; RRMS: Relapsing-Remitting Multiple Sclerosis; UK: United Kingdom; US: United States; UTI: Urinary Tract Infection.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Nonclinical pharmacology, pharmacokinetic, and safety evaluation studies of alemtuzumab in animals have primarily been limited to the cynomolgus monkey and a human CD52 transgenic mouse model due to the lack of expression of the CD52 antigen in other species tested, including mouse, rat, dog, and rabbit. (12)(13)(14) Single- and repeat-dose toxicity studies have been conducted in cynomolgus monkeys, and reproductive toxicity studies have been conducted in human CD52 transgenic mice.

The safety concerns for alemtuzumab from nonclinical studies that have not been adequately addressed by clinical data or are of unknown significance and their possible relevance to human safety are summarized in Table 7.

The key non-clinical findings are presented in the following table.

Table 7 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity	
• Key issues identified from acute or repeat-dose toxicity studies - Repeat-dose toxicity The effects of repeated IV or subcutaneous (SC) administration of alemtuzumab in cynomolgus monkeys were evaluated in 2 studies. In one multi-dose, dose escalation study alemtuzumab was administered at 1, 1.5, 2, and 3 mg/kg on days 1-7, 8-10, 11-14 and 15-30, respectively. No adverse effects that would prevent safe administration of alemtuzumab to humans were observed. Marked and reversible lymphopenia was observed in all treatment groups. An absolute neutropenia (decrease to 3% to 10% of predose levels) was also noted in the 30-day groups only, with lowest values occurring between days 21 through 25. This effect was reversible following cessation of dosing. There were no test article-related changes in other hematologic parameters or noted by pathology. In a second repeat-dose toxicity study, doses of 3, 10 or 30 mg/kg were administered in a 5-day course, similar to the dosing paradigm used in clinical studies of MS. No infusion-related events were noted. Significant depletion of B cells and CD4+ and CD8+ T cells was observed following the first alemtuzumab infusion and the depletion was enhanced as a result of the subsequent 4 days of treatment, similar to the lymphocyte-depletion pattern observed in humans. (15) Serious, antibiotic-resistant, infections were noted in 5 of the 8 animals on study, which resulted in a decision to euthanize these animals. Infections were observed independently of dose level and presumed to be due to the lymphodepletion that is an	Lymphopenia and Infections Alemtuzumab is expected to cause lymphopenia in humans, which may theoretically predispose patients to opportunistic infections during periods when cells counts are low (see [Part II Module SVII.3]). In clinical trials, 72.0% of MS patients experienced infections, predominantly mild to moderate, and serious infections occurred in 4.4% of MS patients (5.3.5.3 ISS Pool -7C [Table 3.3.5.1.1] and Pool C [Table 3.3.5.3.1]). Infections have been typically normal durations and responded to conventional treatments. Among 1188 alemtuzumab-treated patients in MS clinical trials through 2-year follow-up, the incidence of infections was highest in the first month after each course, with the largest increase during the first month following initiation of the first treatment course (5.3.5.3 ISS Pool A [Figure 1.3.5.5]); however, the rate of infections did not increase over time or with subsequent courses, which is consistent with the repopulation kinetics of white blood cell subsets following alemtuzumab treatment and the lack of additive effects on white blood cell depletion with additional treatment courses. There was no evidence for an increased risk of infection among patients with low pre-course neutrophil or lymphocyte counts, nor among patients who had received systemic steroids within the previous 3 months, nor increased risk among patients who had received the second course of alemtuzumab. Despite the theoretical risk for opportunistic infections, in clinical trials of alemtuzumab-treated MS patients, there were only 3 reports of *Clostridium difficile*, 2 reports of active

Key Safety Findings	Relevance to human usage
expected pharmacodynamic effect of alemtuzumab treatment. Additionally, monkeys receiving higher dose levels of alemtuzumab exhibited reductions in red blood cell counts, packed cell volume, and hemoglobin levels. The changes in hematology parameters were variable in direction and timing and generally within historical reference values.	tuberculosis (TB), and 1 report of non-serious (Grade 2) mononucleosis-like cytomegalovirus (CMV), all of which responded to treatment. There was also, 1 report of non-serious, mild chronic hepatitis B. There were no reports of hepatitis C, Progressive Multifocal Leukoencephalopathy (PML), toxoplasmosis, human immunodeficiency virus (HIV), *Pneumocystis jiroveci*, or other viral opportunistic infections. The most frequently reported infections (≥5% of all alemtuzumab 12 mg/day patients) were nasopharyngitis, UTI, upper respiratory tract infection, sinusitis, influenza, oral herpes, and bronchitis (5.3.5.3 Integrated Summary of Safety (ISS) Pool A [Table 1.3.5.1]). Prophylaxis for treatment of MS patients has been limited to aciclovir or an equivalent therapeutic agent. Among 1188 alemtuzumab-treated patients in MS. In clinical trials through 2-year follow-up, in month 1 of Course 1, the incidence of herpes viral infections was 0.9% for the 228 patients who received aciclovir prophylaxis compared to 5.0% for the 960 patients who did not receive aciclovir. Among 1151 patients who received a second course of alemtuzumab treatment, in Month 1 the incidence of herpes viral infections was 1.0% for the 614 patients who received aciclovir compared to 2.2% for 538 patients who did not receive aciclovir (5.3.5.3 ISS Pool A [Table 1.3.5.12.11]; see [Part II Module SVII]). Neutropenia In clinical trials, neutropenia occurred at a frequency of (30.0%) after alemtuzumab treatment, but persistent neutropenia to a clinically significant value <1.0 GI/L occurred less frequently. The incidence of reported neutropenia adverse events (AEs) was 7.0% (5.3.5.3 ISS Pool C [Table 3.5.6.1]). Furthermore, treatment-emergent neutropenia did not appear to be associated with infection risk (5.3.5.3 ISS Pool C [Table 3.3.5.5]). The findings in non-clinical studies relevant to lymphocyte depletion supported the observations in the early clinical trials in humans on the pharmacodynamic effects of alemtuzumab treatment. Therefore, this effect in animals, along with the infections in animals associated with it, were not relevant information in determining the classification of this risk. Serious infections are considered an identified risk with the use of alemtuzumab based on clinical observations.
• Reproductive/developmental toxicity studies - Reproductive toxicity Study 002000227 evaluated the administration of 3 or 10 mg/kg of alemtuzumab in huCD52 transgenic mice during the period of fetal organogenesis (Gestation Day 6 through 10 or Gestation Day 1 through 15). No overt signs of maternal toxicity and, importantly, no gross external, soft tissue or skeletal fetal effects were observed. However, significant increases in the number of dams with all conceptuses dead or resorbed, along	There are no adequate and well-controlled studies of alemtuzumab in pregnant women, but pregnancies have been reported in clinical studies. As noted above, in controlled clinical trials in MS patients treated with alemtuzumab, a total of 140 pregnancies were reported by 101 patients. Of these pregnancies, 79 (59%) were live births, 27 (19%) resulted in spontaneous abortions, 16 (11%) were elective abortions, and 1 was a stillbirth; outcome was unknown in 13 pregnancies.

Key Safety Findings	Relevance to human usage
with a concomitant reduction in the number of dams with viable fetuses occurred in animals exposed to 10 mg/kg/day alemtuzumab during Gestation Day 11 through 15. During pre-/postnatal development studies in huCD52 transgenic mice (Studies 0020002871, 20010591, and DPN0375), there were no statistically significant or biologically important differences in the values for learning, motor activity or on the mating and fertility parameters evaluated in the F1 generation male and female mice. Exposure to alemtuzumab during the gestation and lactation periods evaluated resulted in altered lymphocyte numbers and subpopulations in F1 male and female mice, as well as reduced Immunoglobulin M (IgM) and/or Immunoglobulin G (IgG) responses in F1 pups. Although they were reduced, a majority of the pups did mount antibody responses to antigen challenge. The toxicologic significance of these findings and how they relate to immune system development in humans is uncertain. Binding of alemtuzumab was observed in the female reproductive tract (zona pellucida) of huCD52 transgenic mice. Although specific binding of alemtuzumab to human ovary has not been observed in tissue cross-reactivity studies, human samples containing mature ova and zona pellucida have not been evaluated to date due to challenges in obtaining appropriate samples. During pregnancy, and as pregnancy proceeds, the effect of a changing body composition leads to changes in alemtuzumab pharmacokinetics (Study 11-01187). This is characterized by faster clearance and a concomitant diminishing of overall alemtuzumab exposure. This is likely a result of placental transfer to the fetus, since alemtuzumab was detected in mouse fetuses exposed to alemtuzumab during gestation.	It is generally recognized that the upper limit of the elimination half-life for an IgG monoclonal antibody is approximately 3 weeks. (16) Based on pharmacokinetic data, the concentration of alemtuzumab in patients in the clinical trials generally becomes undetectable at 1 month post-treatment (see Summary of Clinical Pharmacology 2.7.2 [Section 3.2.2] for details). Taken together, a conservative recommendation has been included in the proposed labelling for female patients of childbearing potential to use effective contraception for 4 months following alemtuzumab treatment; see Summary of Product Characteristics (SmPC). Patients treated with alemtuzumab may be at risk for thyroid disorders, which may pose a risk of harm to a pregnant woman, her fetus or newborn. Among 101 alemtuzumab-treated patients who experienced 140 pregnancies in MS controlled clinical trials, 1 patient experienced a pregnancy 4 months after Course 1 of alemtuzumab treatment, and then received Course 2 treatment 2 months after delivery. The patient experienced 3 thyroid serious AEs: Basedow's disease 9 months after the start of alemtuzumab treatment, and thyrotoxic crisis and endocrine ophthalmopathy 23 months after the start of alemtuzumab treatment. Additionally, the patient's newborn infant experienced a serious AE of thyrotoxic crisis (Grade 4). One patient who had a history of hyperthyroidism and was taking propylthiouracil during pregnancy received 2 courses of alemtuzumab 12 mg/day, the patient experienced pregnancy and underwent an elective abortion due to fetal septal cystic hygroma and fetal left hypoplastic heart 27 months after the last dose of alemtuzumab. The non-clinical data were not relevant in determining the risk of thyroid disorders during pregnancy as this was not studied in animals. **As conclusion of non-clinical studies**, Increased numbers of dams with all conceptuses dead or resorbed were observed in an embryo-fetal toxicity study in huCD52 mice. No similar effects on embryo-fetal mortality have been observed in MS patients treated with alemtuzumab. There is limited amount of data from the use of alemtuzumab in pregnant women.
- Effects on Fertility Sanofi Genzyme has performed fertility assessments in male and female human CD52 transgenic mice. No mortality related to the test article occurred. No adverse clinical observations occurred in any mouse during the pre-mating or gestational periods. In female treated mice (Study 0020000815), body weight gains in the 10 mg/kg/day dosage group were significantly reduced during the entire gestation period compared to vehicle control animals. Cesarean-sectioning and litter observations showed that the average number of corpora lutea and implantation sites per mouse was significantly reduced in the 10 mg/kg/day group compared to the	Alemtuzumab is intended for use in patients of childbearing age. The effects of alemtuzumab on human male fertility were intended to be further investigated through a sub-study of patients from the Phase 3 MS trials CAMMS323 and CAMMS324. Male patients at a small number of centers in the US were invited to participate in semen analysis testing trials to analyze sperm count, motility, morphology, and anti-sperm antibodies. Participation in the study was lower than expected (13 alemtuzumab-treated patients). Of the patients studied, there were no adverse effects on sperm quality, quantity, or motility in the alemtuzumab treated patients.

Key Safety Findings	Relevance to human usage
vehicle-treated animals. No other cesarean-sectioning or litter parameters were affected by dosages of the test article as high as 10 mg/kg/day. • In male mice exposed to 3 or 10 mg/kg for five days immediately prior to mating (Study 0020000816), body weights, mating and fertility, reproductive organ weight, sperm motility, and histopathology of the testes were unaffected by dosages of the test article as high as 10 mg/kg/day. Evaluation of sperm morphology revealed that the number of normal sperm was significantly reduced (less than 10% relative to controls) and the number of sperm with detached heads, or no heads (10 mg/kg/day dosage group only), and the percent abnormal sperm were significantly increased in the 3 and 10 mg/kg/day dosage groups compared to the vehicle treated control group values. However, there were no effects on mating and fertility in the alemtuzumab treated mice.	A total of 140 pregnancies in 101 alemtuzumab-treated patients have been reported in the MS clinical program as of 04-Oct-2013 (note this includes patients originally treated with IFNβ-1a who subsequently received alemtuzumab and became pregnant following alemtuzumab exposure): 82 patients in the 12 mg/day alemtuzumab group reported 111 pregnancies, and 19 patients in the 24 mg/day alemtuzumab group reported 29 pregnancies. Of these 140 pregnancies, 27 (19%) resulted in spontaneous abortions, 16 (11%) were elective abortions, and 83 (59%) were live births (79 full-term and 4 pre-term). One pregnancy resulted in a stillbirth, and outcome was unknown in 13 pregnancies. Based on the cumulative experience in the MS clinical program, the most common fetal and neonatal outcome was full-term live birth in the offspring of female alemtuzumab-treated patients. The number of pregnancies observed is higher than expected given the requirement to use effective contraception. While acknowledging limited data are available, alemtuzumab when used as labelled does not appear to be associated with reduced fertility. **As conclusion of non-clinical studies,** Effects on sperm morphology and decreased numbers of corpora lutea and implantation sites were observed in separate male and female fertility studies in huCD52 mice. Similar effects have not been observed in MS patients treated with alemtuzumab.
- Lactation Exposure to alemtuzumab during the gestation and lactation periods (pre-/postnatal development studies in huCD52 transgenic mice 0020002871, 20010591, and DPN0375) resulted in altered lymphocyte numbers and subpopulations in F1 male and female mice, as well as reduced IgM and/or IgG responses in F1 pups. Although they were reduced, a majority of the pups did mount antibody responses to antigen challenge. The toxicologic significance of these findings and how they relate to immune system development in humans is uncertain. There were no statistically significant or biologically important differences in the values for learning, motor activity or on the mating and fertility parameters evaluated in the F1 generation male and female mice.	Pregnant or lactating women have been excluded from alemtuzumab trials. Animal studies indicate exposure of pups to alemtuzumab during gestation and lactation resulted in pharmacodynamic effects on lymphocyte numbers and subpopulations. While reduced IgM and/or IgG responses occurred in the F1 pups, a majority of the pups did mount antibody responses to antigen challenge. The toxicologic significance of these findings and how they relate to immune system development in humans is uncertain. It is unknown whether alemtuzumab could be transferred to human breast milk; there are no data in humans and a risk cannot be excluded. Given the annual dosing regimen, excluding breast feeding is a sensible precaution. The SmPC proposes discontinuing breast feeding within 4 months of alemtuzumab exposure. This recommendation is based on the alpha half-life of 2 days, with serum concentrations became low or undetectable within approximately 30 days after each treatment course (see Summary of Clinical Pharmacology 2.7.2 [Section 3.2.2]) for details, and therefore represents a conservative approach to avoid exposure to the infant. It is noted that there may be some circumstances where the benefits of breast-milk may outweigh the risks, to allow the treating physician to take all factors into account, including the

Key Safety Findings	Relevance to human usage
	timing of the mother's alemtuzumab exposure relative to the timing of breast-feeding, and the health status of the baby. **As conclusion of non-clinical studies,** exposure to alemtuzumab during the gestation and lactation periods evaluated in pre- and postnatal development studies in huCD52 transgenic mice resulted in altered lymphocyte numbers and subpopulations in F1 male and female mice, as well as reduced IgM and/or IgG responses in F1 pups. Although they were reduced, a majority of the pups did mount antibody responses to antigen challenge. The toxicologic significance of these findings and how they relate to immune system development in humans is uncertain. It is not known whether Lemtrada is excreted in human milk. As such, the SmPC Section 4.6 Breast-feeding includes all of these points; • Recommendation to not breast-feed for 4 months. • After exposure to alemtuzumab, since there are no data in humans and a risk cannot be excluded. • Noted that there are benefits of conferred immunity through breast-milk and the benefits may outweigh the risks in some circumstances.
- Genotoxicity, Carcinogenicity As agreed in Scientific Advice received from the EMEA/CPMP/2864/02 and EMEA/CHMP/SAWP/H/SA/64/4/FU/1/ 2008/I, no short- or long-term animal studies were required to assess carcinogenic and mutagenic potential of alemtuzumab; mutagenicity (genotoxicity) studies are generally not applicable to biotechnology-derived pharmaceuticals, because proteins/antibodies are not expected to interact directly with DNA or other chromosomal material, and standard carcinogenicity bioassays in wild-type rodents (International Conference on Harmonization S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, 1997) are not feasible for alemtuzumab since alemtuzumab does not bind to rodent CD52, and a murine-specific antibody surrogate is unavailable.	
Safety pharmacology	
Two studies were conducted in the cynomolgus monkey that evaluated the safety pharmacology of alemtuzumab. Study BPHP/92/0039 was conducted in anesthetized monkeys at dose ranges from 3 to 30 mg/kg of alemtuzumab administered over a 40 minute infusion. No major effects on the cardiovascular and respiratory systems were noted at 3 mg/kg; however, transient and moderate hypotension and tachycardia were noted 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 second, repeat-dose study (5 daily doses) was conducted in conscious monkeys at doses of 3 to 30 mg/kg over a	It is unclear whether the effects noted in study BPHP/92/0039 were due to alemtuzumab administration alone or due to a compounded effect of infusing high dose alemtuzumab in a 40 minute period in anesthetized animals, as animals in study FFA00142 were unconscious and dosed over 180 minutes with no cardiovascular effects observed. Therefore, the non-clinical data are neither conclusive nor relevant.

Key Safety Findings	Relevance to human usage
180 minute infusion (FFA00142). In this study 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. There were no arrhythmias associated with administration of alemtuzumab at any dose level.	
Other toxicity-related information or data	
Not applicable	-

AE: Adverse Event; CD: Cluster of Differentiation; CHMP: Committee for Medicinal Products for Human Use; CMV: Cytomegalovirus; CPMP: Committee for Proprietary Medicinal Products; DNA: Deoxyribonucleic Acid; EMEA: European Medicines Agency; HIV: Human Immunodeficiency Virus; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IFNβ: Interferon Beta-1a; ISS: Integrated Summary of Safety; IV: Intravenous; MS: Multiple Sclerosis; PML: Progressive Multifocal Leukoencephalopathy; SC: Subcutaneous; SmPC: Summary of Product Characteristics; TB: Tuberculosis; UTI: Urinary Tract Infection; US: United States.

No additional non-clinical data have been collected on the use of alemtuzumab in any special populations. Alemtuzumab is not intended for use in additional special populations.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Alemtuzumab development for MS began in a pilot study at Addenbrooke's Hospital, Cambridge, UK, with early observations on the effect on disease activity in secondary progressive multiple sclerosis (SPMS) and RRMS patients. (17)(18)(19) While clinical and surrogate markers of inflammation (ie, relapses and central nervous system [CNS] lesions) were strongly suppressed by alemtuzumab in both the SPMS and RRMS cohorts, RRMS patients appeared to experience a greater benefit on disability outcome measures. This dissociation between the relapsing and progressive forms indicates there may be a window of opportunity for immunotherapy to have an optimal effect on disability outcomes, specifically treatment administered prior to the onset of progressive stage disease. (19) Thus, the subsequent Sanofi Genzyme sponsored development program for alemtuzumab has largely focused on patients with RRMS, but there are also some alemtuzumab studies in patients with progressive MS.

The core of the alemtuzumab development program in MS prior to approval included 3 Sanofi Genzyme sponsored, completed active controlled Phase 2 (15) and Phase 3 studies (20)(21) and an open label, rater-blinded, extension study in patients with RRMS. That extension study is now complete, most patients are participating in continuing open-label follow-up in a separate, ongoing clinical study. Summary of clinical trial exposure from completed studies is presented in Table 8. Subsequent to approval, Sanofi Genzyme has sponsored 3 other interventional clinical trials with alemtuzumab administration to patients with RRMS (2 studies) or progressive multiple sclerosis (1 study), which have been completed.

Clinical trial exposure

Alemtuzumab (12 or 24 mg/day) is administered intravenously in annual courses consisting of 5 consecutive days of treatment at Month 0 and 3 consecutive days of treatment at Month 12. In the Phase 2 study, patients could receive an additional 3-day course at Month 24 at the Investigator's discretion and up to 2 further 3-day (12 mg/day) courses separated by at least 12 months, provided they qualified for each retreatment. In the extension study CAMMS03409, patients who had received alemtuzumab in the Phase 2 and Phase 3 studies could receive additional 3-day (12 mg/day) retreatment courses as needed for resumed disease activity. Patients who had received IFNβ-1a in the Phase 2 and Phase 3 studies also could enroll in the extension study to receive a 5-day (12 mg/day) course of alemtuzumab followed by a 3-day course 12 months later, and could receive additional 3-day (12 mg/day) retreatment courses as needed for resumed disease activity. Of note, studies CAMMS223 and CAMMS324 originally included a 24 mg/day alemtuzumab treatment group. During the course of these studies, the 24 mg/day dose was discontinued, so some patients received 24 mg/day courses followed by 12 mg/day courses. These patients have also been included in the safety evaluation. The approved daily dosage is 12 mg/day. A summary of alemtuzumab exposure in all completed interventional studies is provided in Table 8.

A total of 1486 patients were exposed to alemtuzumab in completed MS clinical trials sponsored by the MAH. Of these, 1217 received only alemtuzumab 12 mg/day and 269 received at least 1 dose of alemtuzumab 24 mg/day. Follow-up of alemtuzumab treated patients ranged from 8.9 months to 151.8 months, with a mean of 69.7 months follow-up. The total follow-up (in person-years) for alemtuzumab-treated patients in the MS clinical trials was 8634.7.

No study has been conducted with alemtuzumab in special populations.

Table 8 - Summary of alemtuzumab exposure - relapsing remitting multiple sclerosis (RRMS) clinical trials

	Alemtuzumab 12 mg/day	**Alemtuzumab 24 mg/day**	**Alemtuzumab Pooled**
Patients treated	**1217**	**269**	**1486**[a]
Total number of cycles received n (%)			
1 course	41 (3.4)	9 (3.3)	50 (3.4)
2 courses	725 (59.6)	147 (54.6)	872 (58.7)
3 courses	298 (24.5)	71 (26.4)	369 (24.8)
4 courses	108 (8.9)	25 (9.3)	133 (9.0)
5 courses	35 (2.9)	15 (5.6)	50 (3.4)
6 courses	9 (0.7)	1 (0.4)	10 (0.7)
7 courses	1 (0.1)	1 (0.4)	2 (0.1)
Total dose received (mg)			
Mean (standard deviation [SD])	113.9 (31.93)	213.9 (42.31)	132.0 (51.37)
Median	96.0	192.0	96.0
Minimum (Min), Maximum (Max)	36.0, 270.9	58.0, 372.0	36.0, 372.0
Months of follow-up, n (%)			
0 - <6	0	0	0
6 - <12	5 (0.4)	2 (0.7)	7 (0.5)
12 - <18	8 (0.7)	1 (0.4)	9 (0.6)
18 - <24	32 (2.6)	2 (0.7)	34 (2.3)
24 - <30	48 (3.9)	11 (4.1)	59 (4.0)
30 - <36	21 (1.7)	3 (1.1)	24 (1.6)
36 - <42	38 (3.1)	16 (5.9)	54 (3.6)
42 - <48	63 (5.2)	5 (1.9)	68 (4.6)
48 - <60	223 (18.3)	24 (8.9)	247 (16.6)
60 - <72	104 (8.5)	21 (7.8)	125 (8.4)
72 - <84	502 (41.2)	93 (34.6)	595 (40.0)
84 - <96	111 (9.1)	37 (13.8)	148 (10.0)
≥96	62 (5.1)	54 (20.1)	116 (7.8)
Mean (SD)	67.6 (22.39)	79.3 (30.32)	69.7 (24.42)
Median	72.5	78.0	73.0

	Alemtuzumab 12 mg/day	Alemtuzumab 24 mg/day	Alemtuzumab Pooled
Min, Max	8.9, 147.4	10.0, 151.8	8.9, 151.8
Quarter (Q)1, Q3	53.0, 80.0	60.5, 89.2	53.8, 81.4
Total Person-years of follow-up	**6857.91**	**1776.77**	**8634.68**

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL).

Source: CAMMS03409 CSR TABLE 3.2.1.2.1.

CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; Max: Maximum; Min: Minimum; MS: Multiple Sclerosis; n: Number; Q: Quarter; RRMS: Relapsing Remitting Multiple Sclerosis; SD: Standard Deviation.

One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL. Accordingly, that 1 patient has been excluded from some analyses, which are therefore based on a total number of 1485 patients.

Exposure by age, sex, and ethnicity is provided in Table 9. Exposure is presented as the number of MS patients exposed to any dose of alemtuzumab in the RRMS clinical trials. The mean age at entry of patients treated with alemtuzumab was 34.4 years. Approximately two thirds of the patient population was female and >90% were White, which reflects the general RRMS patient population. Patients less than 18 years of age or greater than 55 years of age at enrollment were excluded from all clinical trials.

Table 9 - Exposure to alemtuzumab by age, sex, and race/ethnic origin in all clinical studies of relapsing remitting multiple sclerosis (RRMS)

Total exposed	Age (Yrs) mean (SD)	Sex (N, %)		Race/ethnic origin (N, %)			
		Male	Female	White	Black	Asian	Other
N = 1485	34.4 (8.53)	513 (34.5)	972 (65.5)	1355 (91.2)	64 (4.3)	8 (0.5)	58 (3.9)

Source: 5.3.5.3 ISS Pool C Table 3.1.1

N: Total Number of Patient; RRMS: Relapsing Remitting Multiple Sclerosis; SD: Standard Deviation.

The population approved for treatment is "adult patients with RRMS with active disease defined by clinical or imaging features". This is indeed the population studied in completed clinical trials, to date.

The safety population includes sufficient information to characterize the risk in these patients, in terms of:

- Total number of patients exposed (both number and patient-years of experience);
- Number of patients (number and patient-years of experience) exposed relative to the approved posology (2 courses);
- Duration of follow-up according to the EU guidance for MS (2 years);

- Longer-term follow-up on a significant number of patients (>24 months to ≥96 months);
- Experience of patients receiving courses exceeding the approved number of treatment courses (ie, >2 courses);
- Exposure of patients who have already received first line DMTs.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

An analysis of key exclusion criteria from the Phase 3 studies, and relevance of these exclusion criteria to the proposed population for treatment, is presented in Table 10. Analysis of populations not studied follows thereafter. Note that where an exclusion criterion is already described in detail as a "population not studied", this information is not duplicated in Table 10.

Table 10 - Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Previous treatment with immunosuppressants or cytotoxic therapy other than corticosteroids (or first-line DMTs in CAMMS324).	Concomitant use of alemtuzumab with antineoplastic or immunosuppressive therapies could increase the risk of immunosuppression.	No	Addressed in labelling, in special warnings and precautions for use in the SmPC section 4.4.
Other concomitant disease such as autoimmune diseases including but not limited to immune cytopenias, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue disorders, vasculitis, inflammatory bowel disease, and severe psoriasis.	Exclusion criteria related to avoiding symptoms of other known diseases confounding the interpretation of safety data generated from the study.	No	Warnings and precautions relative to autoimmunity are made in the labelling (SmPC section 4.4).
Presence of anti-thyroid stimulating hormone or anti-thyroid stimulating hormone receptor antibodies (ie, above LLN).	Exclusion criteria related to avoiding symptoms of other known diseases confounding the interpretation of safety data generated from the study.	No	Warnings and precautions relative to thyroid function tests are made in the labelling (SmPC section 4.4).
Previous hypersensitivity reaction to any immunoglobulin product (including monoclonal antibodies).	Good Clinical Practices general clause in clinical trials.	No	Hypersensitivity to the active substance, or to any of the excipients, is contraindicated in the labelling (SmPC section 4.3).
Malignancy History of malignancy (except for basal cell skin carcinoma). Cervical high risk Human Papilloma Virus (HPV) positivity or abnormal	Prior to Phase 3, precautions were taken to exclude patients considered to be at particularly high risk of malignancy.	No	Malignancy is considered an important potential risk. Analysis of clinical trial data on infection has led to special warnings and

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
cervical cytology other than abnormal squamous cells of undetermined significance (in CAMMS324, may be allowed if resolved).			precautions (SmPC section 4.4): • Recommended HPV screening completed annually for female patients. • Caution recommended in initiating therapy in those with pre-existing and/or on-going malignancy.
Illnesses and disorders which could confound analysis of efficacy or safety outcomes Any disability acquired from trauma or another illness that, in the opinion of the Investigator, could have interfered with evaluation of disability due to MS. Major systemic disease or other illness that would have compromised patient safety or interfered with interpretation of study results (eg, peptic ulcer disease or other conditions that predisposed to haemorrhage). Medical, psychiatric, cognitive, or other conditions that could have compromised the patient's ability to understand the patient information, to give informed consent, to comply with the study protocol, or to complete the study. Major psychiatric disorder that is not adequately controlled by treatment. Epileptic seizures inadequately controlled by treatment.	Related to avoiding inclusion of patients with known illnesses, conditions or diseases that could have the potential to confound the interpretation of efficacy or safety data generated from the study.	No	Not applicable: standard medical practice.
Exclusion relative to non-investigational products	This exclusion related to inability of patients to receive protocol required therapies, and as such	No	Not applicable: standard medical practice.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Intolerance of pulsed corticosteroids, especially a history of steroid psychosis. Known allergy or intolerance to interferon beta, human albumin, or mannitol.	is not relevant in itself to labelling recommendations.		
<u>Exclusions relating to infections or infectious risk</u> Active infection (eg, deep-tissue infection sufficiently serious to preclude study participation). At high risk for infection (eg, indwelling catheter, dysphagia with aspiration, decubitus ulcer, and history of prior aspiration pneumonia or recurrent UTI). Latent TB unless effective anti-TB therapy had been completed, or active TB. Past or present Hepatitis B Virus (HBV) infection (positive hepatitis B serology). Infection with Hepatitis C Virus (HCV). History of invasive fungal infections. Seropositivity for HIV. Seropositive for *Trypanosoma cruzi* or human T-lymphotropic virus type I/II. Any other illness or infection (latent or active) that could have been exacerbated by study drug.	Prior to Phase 3 data to aid understanding of the risk infection for alemtuzumab treated MS patients, precautions were taken in relation to patients considered to be at particularly high risk of infections.	No, as per EU-RMP v5.0.	Proposed to be removed from the list of safety concerns as of EU-RMP v5.0 based on Good Pharmacovigilance Practices (GVP) Module V revision 2.
<u>Exclusion criteria relative to Immune Thrombocytopenic Purpura (ITP)</u> CD4+, CD8+, or CD19+ cell count (absolute CD3+CD4+, CD3+, CD8+, or CD19+/mm^3) <LLN at Screening.	Precautions were taken in relation to patients who could be at particularly high risk if treated.	No	Addressed in labelling: • Special warnings and precautions (SmPC [section 4.4]): - Requirement for complete blood counts

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Confirmed platelet count <LLN at screening or documented at <100 000/µL within the past year on a sample without platelet clumping. Absolute neutrophil count <LLN at screening. Known bleeding disorder (eg, dysfibrinogenemia, factor IX deficiency, haemophilia, Von Willebrand's disease, disseminated intravascular coagulation, fibrinogen deficiency, or clotting factor deficiency).			with differential obtained prior to initiation of treatment and at monthly intervals until 48 months after the last infusion. See SmPC for more information.

CD: Cluster of Differentiation; DMT: Disease Modifying Therapy; EU: European Union; GVP: Good Pharmacovigilance Practices; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; HPV: Human Papilloma Virus; ITP: Immune Thrombocytopenic Purpura; MS: Multiple Sclerosis; LLN: Lower Limit of Normal; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics; TB: Tuberculosis; UTI: Urinary Tract Infection.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency. See [Part II Module SV] for detailed exposure data and [Part II Module SVII] for details regarding important risks characterization.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 11 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant or breastfeeding women	It is not known whether alemtuzumab can affect reproductive capacity or cause fetal harm when administered to a pregnant woman. Excretion of alemtuzumab in human breast milk has not been studied. Even though the half-life is an estimated 2 days with no drug detectable within 30 days, MAH decided to use the typical monoclonal antibody half-life of 3 weeks (16) and recommends, with a cautious and reasonable approach, that female patients of childbearing potential use effective contraception for 4 months post-alemtuzumab treatment (5 half-lives, assuming a 3 week half-life). Female patients breastfeeding are recommended to discontinue breast-feeding during each course of treatment with Lemtrada and for 4 months following the last infusion of each treatment course. Patients who become pregnant after alemtuzumab treatment should be closely monitored for autoimmunity that may pose a risk of harm to mother or fetus, such

Type of special population	Exposure
	as thyroid conditions. Sanofi Genzyme has noted the need to educate about specific risks that thyroid disorders could pose in pregnancy and the ability of maternal antibodies to be passed to the fetus in utero, which could be life-threatening (educational materials in [Annex 6]). Additional pharmacovigilance data in the postmarketing setting came from a pregnancy registry to monitor the pregnancy outcomes. This pregnancy registry has been stopped and removed from the pharmacovigilance plan as per European Medicines Agency (EMA) agreement (CHMP adoption of conclusion) dated 20-May-2021 for procedure EMEA/H/C/003718/MEA/006.4.
Patients with relevant comorbidities	
• Patients with hepatic or renal impairment	Alemtuzumab is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by widely distributed proteolytic enzymes. Classical biotransformation studies of alemtuzumab have not been conducted, since hepatic or renal impairment would not be expected to impact the degradation of alemtuzumab. The safety and efficacy of alemtuzumab treatment in patients with hepatic or renal impairment has not been established in controlled clinical studies. Patients with grade 2 or higher hepatic or renal function impairment (with the exception of hyperbilirubinemia due to Gilbert's syndrome) were excluded from the Phase 2 and 3 clinical studies.
• Impact on response to vaccination	Lymphocytes play an essential role in immunizations. The ability to generate an immune response to any vaccine following the lympho-depleting effects of alemtuzumab treatment has not been studied.
• Patients with a disease severity different from inclusion criteria in clinical trials	The alemtuzumab development programme was intended to support the treatment of a population of patients with RRMS across a broad spectrum of disease activity, including those naïve to treatment and those switching to alemtuzumab after an inadequate response (breakthrough disease) to prior first-line therapy. Patients with primary progressive MS characterized by sustained deterioration of neurological function from the outset, were not studied and are not included in the proposed indication. Certain inclusion/exclusion criteria in the study were intended to provide a distinct population for investigation within each study (eg, criteria to differentiate treatment-naive patients and patients with inadequate response to prior therapy), to ensure a population with active disease, and to enable homogeneity for the purposes of analysis and interpretation of the results. These factors are not considered relevant to the currently proposed indication: • Exclusion of patients with an Expanded Disability Status Scale score >3.0 (CAMMS323) or >5.0 (CAMMS324); • Exclusion of patients with an onset of MS >5 years (CAMMS323) or >10 years (CAMMS324) before signing of informed consent form; • Requirement for ≥2 MS attacks occurring in the prior 24 months, with ≥1 MS attack occurring in the prior 12 months (both studies); • Requirement for specific magnetic resonance imaging criteria (CAMMS324).
Populations with relevant different ethnic origin	The Phase 3 clinical studies were conducted in North America, Eastern Europe, Latin America, Israel, and Australia. Patient populations included Caucasians (white), blacks, asians, and "Other races and ethnicities". Although no racial or ethnic groups were excluded from the Phase 3 studies, most patients (91.6%) were White, consistent with the epidemiology for the disease. The Phase 2 and 3 clinical studies did not exclude any racial or ethnic groups of patients. Overall, in clinical trials of MS patients treated with alemtuzumab,

Type of special population	Exposure
	91.2% of patients were White, 4.3% of patients were black, and 4.5% were distributed across other racial categories (5.3.5.3 ISS Pool C [Table 3.1.1]). Therefore, the small number of non-white patients precluded meaningful interpretation of safety and efficacy data by race. However, the racial distribution within the trials is consistent with reports in the literature from randomized controlled clinical trials with other DMTs for MS report that >90% of patients were White. (22)(23)
Subpopulations carrying known and relevant genetic polymorphisms	There is currently no information suggesting the existence of polymorphisms relevant to the efficacy or safety of alemtuzumab in the currently proposed indication. Therefore, patients have not been excluded from clinical trials on the basis of genetic polymorphisms.
Other • Children	The safety and efficacy of alemtuzumab in children with MS aged 0 to 18 years have not been established. Alemtuzumab is not currently intended for use in pediatric MS patients. As such the product is not recommended in the product labelling for use in any subgroup of the pediatric population.
• Elderly	Patients over 61 years of age have not been enrolled in Sanofi Genzyme-sponsored clinical studies of MS. Cumulatively alemtuzumab administration in the elderly population was reported in approximately 1.69% of all postmarketing cases (160 cases) received up to 12-Sep-2016. The new information received to date provides no basis for an update to the characterization of this previously identified missing information.

CHMP: Committee for Medicinal Products for Human Use; DMT: Disease Modifying Therapy; EMEA/EMA: European Medicines Agency; MAH: Marketing Authorization Holder; MS: Multiple Sclerosis; RRMS: Relapsing Remitting Multiple Sclerosis.

Populations with relevant different ethnic origin

Based on CHMP (Day 180 list of outstanding issues) request, “Use in racial categories other than white” is included as missing information.

Use in children

“Pediatric use” of alemtuzumab is considered as missing information.

Use in elderly

“Use in patients aged >55 years (including use in elderly patients aged ≥65 years)” is considered as missing information.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1. Method used to calculate exposure

The MAH has changed the postmarketing exposure data source and methodology utilized for estimating exposure in the interval. Previously, the MAH was utilizing an internal source for reporting of sales data from postmarketing experience. The United States of America (USA) had a unique registration program, Risk Evaluation and Mitigation Strategy (REMS), which tracks unique patients exposed to the product. The patient exposure to alemtuzumab was confirmed by receipt of infusion records as was required by the program. These exposure numbers were recorded and reported to the Food and Drug Administration (FDA) on a periodic basis and therefore used to report postmarket patient exposure in the US. The exposure in the rest of the world (non-US) was calculated utilizing sales figures providing the number of distinct patients treated during the period.

The MAH is currently utilizing the Margin Consolidated (MARCO) application for reporting of sales data from postmarketing experience. The MARCO application collects data monthly, as a result, the data may not correspond precisely to the current reporting interval.

Methodology:

- Total sales in mg was calculated by multiplying counting units for vials of infusion liquid (solution) and injection liquid (solution) with their respective strength in mg.
- Total patient days were calculated by dividing total sales in mg with World Health Organization (WHO) defined daily dose (DDD) of 0.13 mg for parenteral formulations and further dividing by 1 000 000 for conversion in million.
- Total number of patient days were then divided by 365 to calculate total patient exposure in patient years.

SV.1.2. Exposure

Exposure from cumulative experience is available from MARCO for the period from 01 October 2013 through 31 August 2024. Based on the above methodology, the cumulative exposure to alemtuzumab was estimated to be 23.5 million patient days corresponding to 64 504 patient years.

Detailed usage data are not available; presentation of patient exposure by age, sex and indication is not possible. Consequently, it is only presented by country and formulation.

Table 12 - Alemtuzumab (Lemtrada) worldwide sales and estimated patient exposure from 01-Oct-2013 to 31-Aug-2024[a]

		ALEMTUZUMAB[b]		
		INFUSION, LIQUID (SOLUTION)		INJECTION, LIQUID (SOLUTION)
MARKET	COUNTRY	10 MG/1 ML	12 MG/1.2 ML	12 MG/1.2 ML
EEA	[redacted]		938	
	[redacted]		5205	
	[redacted]		97	
	[redacted]		796	
	[redacted]		2005	
	[redacted]		1858	
	[redacted]		260	
	[redacted]		1082	
	[redacted]		2180[c]	
	[redacted]		23 997	
	[redacted]		3781	
	[redacted]		1691	
	[redacted]		724	
	[redacted]		15 304	
	[redacted]		7	
	[redacted]		506	
	[redacted]		3718	
	[redacted]		6345	
	[redacted]		733	
	[redacted]		788	
	[redacted]		224	
	[redacted]		1367	
	[redacted]		1250	
	[redacted]		15 685	
	[redacted]		1185	
	[redacted]		1009	
	[redacted]		34 367	
[redacted]			70 788	
Rest of the world (non-EEA and non-US)		4569	52 948	414
Grand Total		4569	250 838	414

		ALEMTUZUMAB[b]		
		INFUSION, LIQUID (SOLUTION)		INJECTION, LIQUID (SOLUTION)
MARKET	**COUNTRY**	**10 MG/1 ML**	**12 MG/1.2 ML**	**12 MG/1.2 ML**
Total sales in mg		45 690	3 010 056	4968
WHO DDD in mg (parenteral form)		0.13		
Total patient days in million		**23.5**		
Total patient years		**64 504**		

a Sales data is available from Oct-2013 in MARCO database.

b Lemtrada vial is filled to deliver 1.2 mL of 10mg/mL solution (12 mg alemtuzumab).

c [redacted]

DDD: Defined Daily Dose; EEA: European Economic Area; MARCO: Margin Consolidated; US: United States; WHO: World Health Organization.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Potential for misuse of alemtuzumab for illegal purposes is considered very low given the controlled environment and administration by the investigator, nurse, or other healthcare professional (HCP).

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

This section is not applicable since it is not the initial RMP. The first approved RMP was version 1.7.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable.

This EU-RMP v13.0 is submitted to address the PRAC request lastly raised in procedure EMEA/H/C/003718/PSR/S/0051. Several RMP versions were submitted to the PRAC to answer these requests from procedures ANX.009.2, ANX/009.3 and IB/0048. Detailed information regarding these submitted versions are included in Annex 8.

The list of safety concerns is unchanged in this updated RMP v13.0, as compared to the last approved RMP version (v10.1).

The risk tables included in RMP v13.0 include data as of 12 September 2024.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for alemtuzumab:

- Important identified risk:
  - Infusion-associated reactions (IARs)
  - Stroke (including haemorrhagic stroke)
  - Dissection of the cervicocephalic arteries[1]
  - Myocardial infarction and myocardial ischaemia[1]
  - Pulmonary alveolar haemorrhage (PAH)[1]

[1] These risks are temporally associated with Lemtrada infusion.

  - Thrombocytopenia[1]
  - Thyroid disorders
  - Immune thrombocytopenic purpura (ITP)
  - Nephropathies including anti-glomerular basement membrane (anti-GBM) disease
  - Autoimmune hepatitis (AIH)
  - Serious infections
  - Haemophagocytic lymphohistiocytosis (HLH)
  - Acquired Haemophilia A (AHA)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Adult Onset Still's Disease (AOSD)
  - Autoimmune Encephalitis (AIE)
  - Acute acalculous cholecystitis (AAC)
- Important potential risk:
  - Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus [T1DM], Guillain Barre syndrome [GBS], Sarcoidosis)
  - Malignancies
  - Progressive multifocal leukoencephalopathy (PML)
- Missing information:
  - Pediatric use
  - Use in patients aged >55 years (including use in elderly patients aged ≥65 years)
  - Use in racial categories other than white

In the alemtuzumab clinical trials, AEs were graded for severity according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

The classification is provided below:

- Grade 1 mild disease, possibly asymptomatic. No treatment necessary.
- Grade 2 moderate disease. Symptomatic therapy or low risk disease-specific treatment (eg, a short course of oral antibiotics).
- Grade 3 severe disease. Disease modifying treatment with higher risk (eg, IV antibiotics, insulin requiring diabetes).
- Grade 4 very severe disease. Potentially life threatening or disabling. High-risk medical interventions.
- Grade 5 fatal outcome.

SVII.3.1. Presentation of important identified risks and important potential risks

The risk tables included in the RMP v13.0 provide updated data as of 12 September 2024.

Table 13 - Important identified risk: Infusion associated reactions (IARs)

Identified Risk	Infusion-associated reactions (IARs)
Potential mechanism	Infusion-associated reactions with IV administration of alemtuzumab have been reported and are likely due to the rapid release of cytokines. (24)(25) Currently, it is unclear how alemtuzumab mediates this reaction, but with other antibodies this side-effect has been linked to complement fixation. (26)
Evidence source(s) and strength of evidence	Clinical studies and postmarketing.
Characterization of the risk	**Frequency with 95% Confidence Interval (CI)** Infusion-associated reactions refer to AEs that occur between the start and stop of any alemtuzumab infusion plus 24 hours. Infusion-associated reactions are nearly universal.

Table 13a - Number (%) of Alemtuzumab Treated Patients with IARs in MS Clinical Trials

Preferred Term	Alemtuzumab		
	12 mg/day (N = 1217)	24 mg/day (N = 269)	Pooled (N = 1486[a])
Any Event	1107 (91.0)	265 (98.5)	1372 (92.3)
Headache	548 (45.0)	170 (63.2)	718 (48.3)
Pruritis	140 (115)	59 (21.9)	199 (13.4)
Chills	134 (11.0)	42 (15.6)	176 (11.8)
Pyrexia	346 (28.4)	77 (28.6)	423 (28.5)
Nausea	218 (17.9)	74 (27.5)	292 (19.7)
Insomnia	148 (12.2)	36 (13.4)	184 (12.4)
Rash	488 (40.1)	167 (62.1)	655 (44.1)
Rash generalized	142 (11.7)	23 (8.6)	165 (11.1)
Urticaria	181 (14.9)	77 (28.6)	258 (17.4)
Flushing	134 (11.0)	27 (10.0)	161 (10.8)
Fatigue	105 (8.6)	49 (18.2)	154 (10.4)
Dyspnoea	88 (7.2)	32 (11.9)	120 (8.1)
Dysgeusia	80 (6.6)	25 (9.3)	105 (7.1)
Chest discomfort	86 (7.1)	41 (15.2)	127 (8.5)
Tachycardia	99 (8.1)	22 (8.2)	121 (8.1)
Dyspepsia	78 (6.4)	27 (10.0)	105 (7.1)
Dizziness	72 (5.9)	28 (10.4)	100 (6.7)
Pain	76 (6.2)	23 (8.6)	99 (6.7)

Identified Risk	Infusion-associated reactions (IARs)

a There were 1486 alemtuzumab treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

Source: Pool C, Table 3.3.4.7

CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; IAR: Infusion-Associated Reaction; MS: Multiple Sclerosis; N: Total Number of Patient.

Severity and nature of risk

Constitutional symptoms predominate and include fever, chills, palpitations, tachycardia, headache, rash, urticaria, fatigue, asthenia, malaise, and back pain, in addition to gastrointestinal symptoms (eg, dyspepsia, nausea, vomiting, diarrhea, and dysgeusia).

Symptoms are generally mild to moderate in nature. With each subsequent infusion course, the nature of the reported AEs was similar, but fewer patients reported IARs. Similarly, within each course, the number of patients reporting IARs was highest on the first day of the course, decreasing over the next days.

Within the clinical trial experience, serious IARs were infrequent; (2.9% of all IARs) (Source: Pool C, Table 3.3.4.3). To date, no fatal IARs have occurred although 1 case of a severe, life-threatening event consistent with the definition of anaphylaxis has been identified in the MS clinical trials.

Based on the clinical trial data, the occurrence of anaphylactic reactions was rare. However, it is acknowledged that a hypersensitivity type reaction may occur and have important medical implications; physicians should be ready to manage such an event should it occur (as detailed in the SmPC).

Table 13b - Severity of IARs in 1188 Alemtuzumab Treated Patients in MS Clinical Trials (Number [%] of Patients)

Preferred Term	Severity Grade				
	1	2	3	4	5
Any Event	186 (15.7)	791 (66.6)	115 (9.7)	8 (0.7)	0 (0.0)
Headache	206 (17.3)	338 (28.5)	18 (1.5)	0 (0.0)	0 (0.0)
Pruritis	75 (6.3)	91 (7.7)	4 (0.3)	0 (0.0)	0 (0.0)
Chills	61 (5.1)	61 (5.1)	2 (0.2)	1 (0.1)	0 (0.0)
Pyrexia	134 (11.3)	161 (13.6)	2 (0.2)	0 (0.0)	0 (0.0)
Nausea	102 (8.6)	108 (9.1)	3 (0.3)	0 (0.0)	0 (0.0)
Insomnia	68 (5.7)	62 (5.2)	2 (0.2)	0 (0.0)	0 (0.0)
Rash	172 (14.5)	359 (30.2)	24 (2.0)	0 (0.0)	0 (0.0)
Rash generalized	10 (0.8)	60 (5.1)	8 (0.7)	1 (0.1)	0 (0.0)
Urticaria	59 (5.0)	140 (11.8)	8 (0.7)	0 (0.0)	0 (0.0)
Flushing	88 (7.4)	19 (1.6)	2 (0.2)	0 (0.0)	0 (0.0)
Fatigue	82 (6.9)	38 (3.2)	1 (0.1)	0 (0.0)	0 (0.0)
Dyspnoea	47 (4.0)	43 (3.6)	6 (0.5)	2 (0.2)	0 (0.0)
Dysgeusia	78 (6.6)	8 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Chest discomfort	58 (4.9)	39 (3.3)	3 (0.3)	0 (0.0)	0 (0.0)
Tachycardia	59 (5.0)	16 (1.3)	2 (0.2)	1 (0.1)	0 (0.0)
Dyspepsia	45 (3.8)	37 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)

Identified Risk	Infusion-associated reactions (IARs)

Dizziness	63 (5.3)	12 (1.0)	1 (0.1)	0 (0.0)	0 (0.0)
Pain	26 (2.2)	39 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Pool A, Table 1.3.4.5

IAR: Infusion-Associated Reaction; MS: Multiple Sclerosis.

Table 13c - Number (%) of Alemtuzumab-Treated Patients with IARs in MS Clinical Trials by Cycle and Severity

	Alemtuzumab		
	12 mg/day (N = 1217)	**24 mg/day (N = 269)**	**Pooled (N = 1486[a])**
Cycle 1 *Number of Patients Dosed*	*1217*	*269*	*1486*
Patients with IARs	1037 (85.2)	260 (96.7)	1297 (87.3)
Grade 1	680 (55.9)	194 (72.1)	874 (58.8)
Grade 2	793 (65.2)	210 (78.1)	1003 (67.5)
Grade 3	57 (4.7)	30 (11.2)	87 (5.9)
Grade 4	3 (0.2)	3 (1.1)	6 (0.4)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 2 *Number of Patients Dosed*	*1176*	*260*	*1436*
Patients with IARs	810 (68.9)	224 (86.2)	1034 (72.0)
Grade 1	486 (41.3)	165 (63.5)	651 (45.3)
Grade 2	556 (47.3)	144 (55.4)	700 (48.7)
Grade 3	32 (2.7)	13 (5.0)	45 (3.1)
Grade 4	2 (0.2)	0 (0.0)	2 (0.1)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 3 *Number of Patients Dosed*	*451*	*113*	*564*
Patients with IARs	292 (64.7)	85 (75.2)	377 (66.8)
Grade 1	168 (37.3)	54 (47.8)	222 (39.4)
Grade 2	219 (48.6)	62 (54.9)	281 (49.8)
Grade 3	11 (2.4)	6 (5.3)	17 (3.0)
Grade 4	0 (0.0)	1 (0.9)	1 (0.2)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)

Identified Risk	Infusion-associated reactions (IARs)

Cycle 4 *Number of Patients Dosed*	*153*	*42*	*195*
Patients with IARs	92 (60.1)	23 (54.8)	115 (59.0)
Grade 1	58 (37.9)	11 (26.2)	69 (35.4)
Grade 2	63 (41.2)	16 (38.1)	79 (40.5)
Grade 3	1 (0.7)	0 (0.0)	1 (0.5)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 5 *Number of Patients Dosed*	*45*	*17*	*62*
Patients with IARs	19 (60.1)	8 (47.1)	27 (43.5)
Grade 1	12 (26.7)	6 (35.3)	18 (29.0)
Grade 2	17 (37.8)	5 (29.4)	22 (35.5)
Grade 3	0 (0.0)	1 (5.9)	1 (1.6)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)

a There were 1486 alemtuzumab treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

Source: Pool C, Table 3.3.4.6

CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; IAR: Infusion-Associated Reaction; MS: Multiple Sclerosis; N: Total Number of Patient.

Postmarketing experience

The reported cases of IARs following the administration of alemtuzumab were consistent in nature and severity with the clinical features collected during drug development identifying no new safety concerns. Cases of IARs will continue to be monitored.

Seriousness/outcomes

Infusion-associated reactions occurred frequently, but the vast majority were mild or moderate in severity. The most common IARs (≥10% of patients) in the alemtuzumab 12 mg/day group over all available follow up were rash, headache, nausea, pyrexia, urticaria, pruritus, insomnia, and chills. Serious IARs were infrequent (2.9% of all IARs). No fatal IARs have occurred in the MS program.

To date, 1 case of a severe, life-threatening nature consistent with the definition of anaphylaxis has been identified in the MS clinical trials.

Patients in the MS clinical program received pre-treatment with IV steroids (1 gm methylprednisolone) on the first 3 days of any alemtuzumab treatment course.

Identified Risk	Infusion-associated reactions (IARs)

Table 13d - Number (%) of Alemtuzumab Treated Patients (N = 1486[a]) With Serious or Fatal IARs in MS Clinical Trials

Preferred Term	Total	Serious	Fatal
Any Event	1372 (92.3)	36 (3.0)	0 (0.0)
Headache	718 (48.3)	0 (0.00)	0 (0.0)
Pruritis	199 (13.4)	0 (0.0)	0 (0.0)
Chills	176 (11.8)	1 (0.1)	0 (0.0)
Pyrexia	423 (28.5)	3 (0.2)	0 (0.0)
Nausea	292 (19.7)	3 (0.2)	0 (0.0)
Insomnia	184 (12.4)	0 (0.0)	0 (0.0)
Rash	655 (44.1)	1 (0.1)	0 (0.0)
Rash generalized	165 (11.1)	0 (0.0)	0 (0.0)
Urticaria	258 (17.4)	3 (0.2)	0 (0.0)
Flushing	161 (10.8)	0 (0.0)	0 (0.0)
Fatigue	154 (10.4)	0 (0.0)	0 (0.0)
Dyspnoea	120 (8.1)	1 (0.1)	0 (0.0)
Dysgeusia	105 (7.1)	0 (0.0)	0 (0.0)
Chest discomfort	127 (8.5)	2 (0.1)	0 (0.0)
Tachycardia	121 (8.1)	3 (0.2)	0 (0.0)
Dyspepsia	105 (7.1)	0 (0.0)	0 (0.0)
Dizziness	100 (6.7)	0 (0.0)	0 (0.0)
Pain	99 (6.7)	0 (0.0)	0 (0.0)

a There were 1486 alemtuzumab treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

Source: Pool C, Tables 3.3.4.3 and 3.3.4.5

CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; IAR: Infusion-Associated Reaction; MS: Multiple Sclerosis; N: Total Number of Patient.

Background incidence/prevalence

Infusion-associated reactions are specific to the administration of alemtuzumab and do not, per definition, occur in patients who are not exposed to the product.

Impact on individual patient

The most common IARs in the alemtuzumab were rash, headache, nausea, pyrexia, urticaria, pruritus, insomnia, and chills. The majority of these events were non-serious and transient in nature. Impact on quality of life is minimal.

Risk factors and risk groups	Infusion-associated reactions are commonly reported with monoclonal antibody administration (27) and were observed in approximately 90% of patients treated with alemtuzumab in MS clinical trials. A higher than recommended dose and faster infusion rate also increase the risk of IARs. There is no identified pattern in terms of additive or synergistic factors.

Identified Risk	Infusion-associated reactions (IARs)
	While IARs have also been observed with use of alemtuzumab in B-cell chronic lymphocytic leukemia (B-CLL), reporting rates are different than those in MS patients, and AEs tend to be more severe in the B-CLL population. The recommended dosing regimens for B-CLL patients is 10-fold higher than for MS patients: B-CLL patients are dosed chronically for up to 3 months, compared to 2 annual courses for MS patients (5 days at month 0, 3 days at month 12). Alemtuzumab treatment is contraindicated in patients with hypersensitivity to alemtuzumab or its excipients.
Preventability	Preventability measures are described in Part V.1 routine risk minimization measures (rRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of Relapsing Multiple Sclerosis (RMS) remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of IARs in MS patients who have received alemtuzumab is not expected to have any public health impact because it is administered as an IV infusion in hospitals, and not in-home use situations.

AE: Adverse Event; B-CLL: B-cell Chronic Lymphocytic Leukemia; CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; CI: Confidence Interval; DLP: Data Lock Point; IAR: Infusion-Associated Reaction; IV: Intravenous; MS: Multiple Sclerosis; N: Total Number of Patient; PAH: Pulmonary Alveolar Haemorrhage; rRMM: Routine Risk Minimization Measure; RMS: Relapsing Multiple Sclerosis; SmPC: Summary of Product Characteristics.

Table 14 - Important identified risk: Stroke (including haemorrhagic stroke)[a]

Identified risk	Stroke (including haemorrhagic stroke)[a]
Potential mechanism	Strokes are a heterogeneous group of disorders involving sudden, focal interruption of cerebral blood flow that causes neurologic deficit. Strokes can be ischaemic (80%), typically resulting from thrombosis or embolism, or haemorrhagic (20%), resulting from vascular rupture (eg, subarachnoid haemorrhage, intracerebral haemorrhage).
Evidence source(s) and strength of evidence	Postmarketing. There were no nonclinical findings suggestive of stroke in repeat-dose toxicity studies with alemtuzumab.
Characterization of the risk	**Frequency with 95% CI** There were no cases of stroke temporally associated to alemtuzumab infusion identified in clinical trials. **Severity and nature of risk** All cases of temporally associated stroke were severe in intensity and mostly hemorrhagic in nature. **Postmarketing experience** Cases of temporally associated stroke (within 3 days of alemtuzumab administration) have been reported in the postmarketing setting. Most of the events reported were ischemic cerebrovascular accident followed by hemorrhage events. **Seriousness/outcomes** Most of these stroke cases were serious. No fatalities observed in the cases with time to onset (TTO) $\leq$3 days. Majority of the events were recovered. **Background incidence/prevalence** The incidence rate of overall stroke in the general population ranges approximately from 100-300 per 100 000 person-years. (28)(29)

Identified risk	Stroke (including haemorrhagic stroke)[a]
	The incidence rate of overall stroke in the MS population ranges approximately from 245-271 per 100 000 person-years. (28)(29) **Impact on individual patient** Time interval from onset of stroke to treatment plays a vital role in acute ischaemic stroke patients. Admission of patients within window period of 4.5 hours post occurrence of stroke has been linked with better treatment outcome and recovery rates. (30)
Risk factors and risk groups	The major risk factors for stroke include: • High Blood Pressure (BP) • Diabetes • Smoking • Heart disease • Personal or family History of stroke or Transient Ischaemic Attack (TIA) • Brain aneurysms or arteriovenous malformations (AVMs) • It is not clearly identified which patients are at risk of stroke with alemtuzumab use. However, significantly increased BP during infusion may be a risk factor for haemorrhagic stroke, and vital sign should be monitored prior to and during infusion as described in the SmPC. • The reported events followed no particular pattern in terms of risk groups. There was no dose related pattern. The majority of stroke cases temporally associated to alemtuzumab infusion occurred within 3 days of alemtuzumab administration. No pattern of additive or synergistic factors were observed.
Preventability	Preventability measures are described in Part V.1 (rRMMs) and Part V.2 additional risk minimization measure (aRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of stroke in MS patients who have received alemtuzumab is not expected to have any public health impact.

a This risk is temporally associated with Lemtrada infusion.

aRMM: Additional Risk Minimization Measure; AVM: Arteriovenous Malformation; BP: Blood Pressure; CI: Confidence Interval; DLP: Data Lock Point; MS: Multiple Sclerosis; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure; SmPC: Summary of Product Characteristics; TIA: Transient Ischaemic Attack; TTO: Time to Onset.

Table 15 - Important identified risk: Dissection of the cervicocephalic arteries[a]

Identified risk	Dissection of the cervicocephalic arteries[a]
Potential mechanism	A number of pathophysiological risk factors have been described in the literature that are thought to contribute to the development of dissection of the cervicocephalic arteries. Like trivial events, not all risk factors are present in every patient; and some patients experience dissection of the cervicocephalic arteries without any of them. The most compelling risk factors have to do with connective tissue abnormalities, which may contribute to a weakening of the vascular wall, making it more susceptible to tearing. (31)
Evidence source(s) and strength of evidence	Postmarketing. There were no nonclinical findings suggestive of vascular dissection in repeat-dose toxicity studies with alemtuzumab.

Identified risk	Dissection of the cervicocephalic arteries[a]
Characterization of the risk	**Frequency with 95% CI** Cumulative through the current DLP, no event of dissection of the cervicocephalic arteries was retrieved utilizing the defined search criteria in MS clinical trials. **Severity and nature of risk** Cervicocephalic arterial dissection cases were moderate to severe in severity. **Postmarketing spontaneous individual case safety reports** Cases of dissection of the cervicocephalic arteries in the postmarketing setting at the current DLP were reviewed and were found to be consistent with the known safety profile of alemtuzumab. Multiple cervicocephalic artery involvement has been reported within 3 days of alemtuzumab administration in one case. This case involved a [redacted] patient reported with carotid and vertebral artery dissection. The patient was reported to have prior routine chiropractic therapy. Underlying vasculopathy (fibromuscular dysplasia) and environmental triggers (recent infection, cervical manipulation and a remote history of head or neck surgery) are confounders. **Seriousness/outcomes** All cases of dissection of cervicocephalic arteries were considered serious. There were no fatal cases of cervicocephalic arterial dissection reported in postmarketing setting. **Background incidence/prevalence** No epidemiological study examining the incidence or prevalence of cervicocephalic arterial dissection in the general and MS population was found. **Impact on individual patient** Morbidity and mortality of cervicocephalic dissections vary according to the vessel and location of the dissection. Death rates for extracranial carotid and vertebral dissections are approximately 5-10%. In contrast, mortality rates for intracranial carotid and basilar dissections approach 70% or higher. (32)
Risk factors and risk groups	Dissection of the cervicocephalic arteries are typically associated with “minor” cervical trauma, or torsion of the neck including variety of everyday activities. All of the reported events of arterial dissection appear to be in the extracranial compartment, adjacent to bony structures, which is where traumatic dissection typically occurs. Some of these cases were reported with regular chiropractic manipulations. There was no dose related pattern.
Preventability	Preventability measures are described in Part V.1 (rRMMs) and Part V.2 (aRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of cervicocephalic arterial dissection in MS patients who have received alemtuzumab is not expected to have any public health impact.

a This risk is temporally associated with Lemtrada infusion.

aRMM: Additional Risk Minimization Measure; CI: Confidence Interval; DLP: Data Lock Point; MS: Multiple Sclerosis; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure.

Table 16 - Important identified risk: Myocardial infarction (MI) and myocardial ischaemia[a]

Identified Risk	Myocardial infarction (MI) and myocardial ischaemia[a]
Potential mechanism	Unknown. The etiology of MI is decreased coronary blood flow. The available oxygen supply cannot meet oxygen demand, resulting in cardiac ischaemia. Decreased coronary blood flow is multifactorial. Atherosclerotic plaques classically rupture and lead to thrombosis, contributing to acute decreased blood flow in the coronary. Other etiologies of decreased oxygenation/myocardial ischaemia include coronary artery embolism, which accounts for 2.9% of patients, cocaine-induced ischaemia, coronary dissection, and coronary vasospasm. (33)(34)
Evidence source(s) and strength of evidence	Postmarketing.
Characterization of the risk	**Frequency with 95% CI** There were no events of MI and ischaemia temporally associated with alemtuzumab infusion identified in clinical trials. **Severity and nature of risk** All the cases were predominantly severe. Risk of fatal outcome is possible. **Postmarketing experience** **Myocardial Infarction (MI)**: At the current DLP, there were cases of MI which were reported within 72 hours of last alemtuzumab (Lemtrada) infusion. **Myocardial Ischaemia:** At the current DLP, there were temporarily associated cases of myocardial ischemia reported within 72 hours of last alemtuzumab (Lemtrada) infusion. **Seriousness/outcomes** All MI cases were serious, and more than half of myocardial ischemia were serious. Sign and symptoms of MI may include but are not limited to presence of chest pain, shortness of breath and fatigue. **Background incidence/prevalence** The incidence rate of MI in the general population was estimated to be between 55.2 and 63.1 per 100 000 person-years in Japan (26) and between 190 and 486 per 100 000 person-years conducted by American heart disease community surveillance programs varied. (35) The gap in reported incidences may be explained by the differences in the characteristics of the study population. The prevalence of MI in the general population increased with age and particularly in men then in women. In the US, it ranged from 0.3% to 17.3% (36) and in Germany it was estimated at 4.7% amongst 40-79 years old. (37) The incidence rate of new episodes of MI in MS population was 1.84 (95% CI: 1.28-2.65) times higher than the non-MS population in a Swedish cohort study. Although not specifically presented in the paper, the crude incidence rate of MI in this study can be calculated as 294/100 000 person-years in those with MS and 138/100 000 person-years in the non-MS population. (19) Two prevalence studies in hospitalized patients have not shown an increased prevalence of MI in MS patients. In one study conducted in New York City, the prevalence of hospitalization for MI was 1.4% in MS patients compared to 2.0% in non-MS patients (adjusted odds ratio [OR]: 0.78 (0.64-0.96). (32) In another US study evaluating the prevalence of MI in hospitalized patients an analysis of the 2006 Nationwide Inpatient Sample found that the prevalence of MI in hospital discharge diagnoses among patients with MS was 1.3% compared to 2.1% in non-MS hospitalizations (adjusted OR: 0.70, 95% CI: 0.60-0.80). (38) There is no available data on the prevalence of MI in non-hospitalized MS patients.

Identified Risk	Myocardial infarction (MI) and myocardial ischaemia[a]
	Impact on individual patient Time interval from onset of MI to treatment plays a vital role in MI patient's outcome. The best time to treat MI attack is within one hour of the onset of the first symptoms. When a heart attack occurs, there's a limited amount of time before significant and long-lasting damage occurs to the heart muscle.
Risk factors and risk groups	Risk factors that may cause MI include: • Age (Men age 45 or older, women age 55 or older) • Tobacco • High BP • High blood cholesterol or triglyceride levels • Obesity • Diabetes • Metabolic syndrome • Family history of heart attack • Lack of physical activity • Stress • Illicit drug use • A history of preeclampsia • No particular pattern in terms of risk groups was identified in the reported cases. There was no dose related pattern. Most cases of myocardial ischaemia were reported within 72 hours of last alemtuzumab infusion. No pattern of additive or synergistic factors were observed.
Preventability	Preventability measures are described in Part V.1 (rRMMs) and Part V.2 (aRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of MI in MS patients who have received alemtuzumab is not expected to have any public health impact.

a This risk is temporally associated with Lemtrada infusion.

aRMM: Additional Risk Minimization Measure; BP: Blood Pressure; CI: Confidence Interval; DLP: Data Lock Point; MI: Myocardial Infarction; MS: Multiple Sclerosis; OR: Odds Ratio; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure; US: United States.

Table 17 - Important identified risk: Pulmonary Alveolar Haemorrhage (PAH)[a]

Identified Risk	Pulmonary Alveolar Haemorrhage (PAH)[a]
Potential mechanism	Unknown. Diffuse alveolar haemorrhage results from widespread damage to the pulmonary small vessels, leading to blood collecting within the alveoli. If enough alveoli are affected, gas exchange is disrupted. The specific pathophysiology and manifestations vary depending on cause.
Evidence source(s) and strength of evidence	Postmarketing.
Characterization of the risk	**Frequency with 95% CI** There were no PAH cases reported with alemtuzumab either in active-clinical trials/clinical development program in MS.

Identified Risk	Pulmonary Alveolar Haemorrhage (PAH)[a]
	Postmarketing experience Cumulatively through the DLP, the reported cases of PAH following the administration of alemtuzumab (Lemtrada) were reviewed and were found to be consistent with the known safety profile of alemtuzumab, identifying no new safety concerns. **Severity and nature of risk** Pulmonary alveolar haemorrhage cases were moderate to severe in severity. **Seriousness/outcomes** All cases were considered serious, with one case involving a fatal outcome. For majority of the remaining events, the outcome was reported either as recovered or unknown. Signs and symptoms of alveolar haemorrhage may include presence of hemoptysis, diffuse alveolar, infiltrates, a drop in hematocrit and hypoxemic respiratory failure. **Background incidence/prevalence** No study examining the incidence or prevalence of PAH in the general adult population was found. The frequency of PAH in patients with MS has not been quantified. **Impact on individual patient** Alveolar haemorrhage is a rare but potentially life-threatening condition that is not a specific disorder but a syndrome that suggests a differential diagnosis and a specific sequence of testing. If untreated PAH can be fatal. Impact may be significant.
Risk factors and risk groups	Many disorders can cause alveolar haemorrhage; they include: (39) • Autoimmune disorders (eg, systemic vasculitides, Goodpasture syndrome, antiphospholipid antibody syndrome, connective tissue disorders); • Pulmonary infections (eg, hantavirus infection); • Toxic exposures (eg, trimellitic anhydride, isocyanates, crack cocaine, certain pesticides); • Drug reactions (eg, propylthiouracil, diphenylhydantoin, amiodarone, methotrexate, nitrofurantoin, bleomycin, montelukast, infliximab); • Cardiac disorders (eg, mitral stenosis); • Coagulation disorders caused by diseases or anticoagulant drugs; • Isolated pauci-immune pulmonary capillaritis; • Idiopathic pulmonary hemosiderosis; • Hematopoietic stem cell transplantation or solid organ transplantation • The reported events of PAH followed no particular pattern in terms of risk groups. The reported risk window was between 1 day and 3 days from the last dose. No dose related, or pattern of additive or synergistic risk factors were observed.
Preventability	To date, no marker of increased risk has been identified. The occurrence of PAH cannot be prevented, but the risk of poor outcome of these events can be reduced through early detection methods and subsequent prompt treatment. Preventability measures are described in Part V.1 (rRMMs) and Part V.2 (aRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of PAH in MS patients who have received alemtuzumab is not expected to have any public health impact.

a This risk is temporally associated with Lemtrada infusion.

Identified Risk	Pulmonary Alveolar Haemorrhage (PAH)[a]

aRMM: Additional Risk Minimization Measure; CI: Confidence Interval; DLP: Data Lock Point; IAR: Infusion-Associated Reaction; MS: Multiple Sclerosis; PAH: Pulmonary Alveolar Haemorrhage; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure.

Table 18 - Important identified risk: Thrombocytopenia[a]

Identified Risk	Thrombocytopenia[a]
Potential mechanism	Alemtuzumab leads to a rapid depletion of circulating T and B lymphocytes post-infusion, followed by a distinct pattern of repopulation. Immune thrombocytopenia has been reported (3%) as a secondary autoimmune phenomenon occurring months after alemtuzumab infusion. (40) Non-immune thrombocytopenia during/post-infusion has been sufficiently described in the literature and reported to be transient, reversible, self-limiting acute-onset and can develop during the first treatment course with alemtuzumab. (41)
Evidence source(s) and strength of evidence	Clinical trials and postmarketing.
Characterization of the risk	**Frequency with 95% CI clinical trial setting** There were 28 reports of thrombocytopenia (non-serious) in the clinical trial database. Of the 28 cases with TTO ≤30 days, 9 occurred on the same day as the last alemtuzumab treatment and 7 were within 2 days after the last alemtuzumab treatment. **Postmarketing setting:** Cases of reported thrombocytopenia in the postmarketing setting at the current DLP were reviewed and were found to be consistent with the known safety profile of alemtuzumab, identifying no new safety concerns. **Severity and nature of risk** Immediate thrombocytopenia after alemtuzumab administration is a rare phenomenon, that is mostly mild, occurs shortly after the administration and recovers spontaneously. **Seriousness/outcomes** Thrombocytopenia occurs in most patients in the first week after administration and recovers spontaneously. Most of the thrombocytopenia cases were serious. No fatalities observed in the cases with TTO ≤30 days. Majority of the events were recovered/recovering. **Background incidence/prevalence** Using the Humedica Database (a US electronic health records database) of MS patients and a comparison group consisting of patients matched on age at index date, sex, and calendar-year, crude incidence rate ratios and corresponding 95% CIs were constructed using Poisson regression to compare the incidence rates in the MS cohort relative to the matched comparison group. The incidence rate ratio of thrombocytopenia in an overall MS cohort relative to age, sex and calendar-year matched controls without MS is 2.04, which indicates a 2.04-fold increase. **Impact on individual patient** Temporally associated thrombocytopenia cannot be prevented but are detectable and manageable with conventional treatments.
Risk factors and risk groups	Non-immune thrombocytopenia can occur with a variety of conditions: • Infections (viral, HIV, bacterial infections or sepsis), • Chronic liver disorders, • Hypersplenism,

Identified Risk	Thrombocytopenia[a]
	• Congenital platelet disorders, - Malignancies, - Bone marrow disorders, - Drugs (daptomycin, linezolid, valproic acid), - Over-the counter remedies, supplements, foods, beverages or alcohol consumption. The reported events of non-immune immediate thrombocytopenia followed no particular pattern in terms of risk groups. There was no dose related pattern. No pattern of additive or synergistic factors were observed.
Preventability	To date, no marker of increased risk has been identified. The occurrence of temporally associated thrombocytopenia cannot be prevented, but the risk of poor outcome of these events can be reduced through early detection methods and subsequent prompt treatment. Preventability measures are described in Part V.1 (rRMMs) and Part V.2 (aRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of temporally associated thrombocytopenia in MS patients who have received alemtuzumab is not expected to have any public health impact.

a This risk is temporally associated with Lemtrada infusion.

aRMM: Additional Risk Minimization Measure; CI: Confidence Interval; DLP: Data Lock Point; HIV: Human Immunodeficiency Virus; IAR: Infusion-Associated Reaction; MS: Multiple Sclerosis; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure; TTO: Time to Onset; US: United States.

Table 19 - Important identified risk: Thyroid disorders

Identified Risk	Thyroid disorders
Potential mechanism	The mechanisms responsible for Basedow's disease may include immune response and reduced competition for autoreactive lymphocytes to expand during the time when recovery from lymphopenia commences. (42) Autoimmunity is a known complication of immune reconstitution from lymphocytopenia.
Evidence source(s) and strength of evidence	Clinical studies and postmarketing.
Characterization of the risk	**Frequency with 95% CI** In non-Sanofi Genzyme pilot studies of alemtuzumab for the treatment of MS, thyroid autoimmune disorders were identified as a safety concern associated with alemtuzumab. (19)(35) As a result, thyroid function was monitored every 3 months in Sanofi Genzyme-sponsored clinical studies of alemtuzumab in MS patients and educational materials were provided to both physicians and patients to increase awareness of symptom recognition. These measures facilitated early detection and treatment of thyroid disorders, including appropriate treatment. In active-controlled trials, thyroid AEs occurred in approximately 16.1% of alemtuzumab treated patients compared to approximately 5.2% of IFNβ-1a patients. In longer term follow-up (more than 2 years after first study treatment), thyroid AEs have been observed in an estimated 36.4% of the alemtuzumab pooled dose group through 4 years. Frequency in the recommended post-approval dose.

Identified Risk	Thyroid disorders

The rate of thyroid AEs over the 2-year follow-up period was 0.119 per person-year for the 12 mg/day group compared to 0.036 per person-year in the IFNβ-1a group. In longer-term follow-up, thyroid AEs have been observed in an estimated 36.2% of patients treated with alemtuzumab 12 mg/day; the rate of thyroid AEs over all available follow-up was 0.138 per person-year for the alemtuzumab 12 mg/day group.

Table 19a - Number (%) of Patients with Thyroid Disorders in Phase 2 and Phase 3 MS Clinical Trials Through 2 Year Follow up

Preferred Term	SC IFNβ-1a (N = 496)	Alemtuzumab		
		12 mg/day (N = 919)	24 mg/day (N = 269)	Pooled (N = 1188)
Any Event	26 (5.2)	153 (16.6)	38 (14.1)	191 (16.1)
Hypothyroidism	8 (1.6)	42 (4.6)	7 (2.6)	49 (4.1)
Hyperthyroidism	4 (0.8)	32 (3.5)	9 (3.3)	41 (3.5)
Basedow's disease	0 (0.0)	22 (2.4)	9 (3.3)	31 (2.6)
Autoimmune thyroiditis	2 (0.4)	16 (1.7)	5 (1.9)	21 (1.8)
Goitre	2 (0.4)	13 (1.4)	5 (1.9)	18 (1.5)
Thyroiditis	1 (0.2)	5 (0.5)	2 (0.7)	7 (0.6)
Thyroiditis subacute	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)
Primary hypothyroidism	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Thyroid cyst	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Thyroid mass	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Thyrotoxic crisis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Blood thyroid stimulating hormone decreased	5 (1.0)	21 (2.3)	8 (3.0)	29 (2.4)
Blood thyroid stimulating hormone increased	4 (0.8)	11 (1.2)	3 (1.1)	14 (1.2)
Anti-thyroid antibody positive	0 (0.0)	9 (1.0)	2 (0.7)	11 (0.9)
Thyroxine free decreased	0 (0.0)	6 (0.7)	2 (0.7)	8 (0.7)
Tri-iodothyronine free increased	1 (0.2)	4 (0.4)	3 (1.1)	7 (0.6)
Thyroid function test abnormal	0 (0.0)	3 (0.3)	0 (0.0)	3 (0.3)
Tri-iodothyronine free decreased	0 (0.0)	3 (0.3)	1 (0.4)	4 (0.3)
Thyroxine free increased	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)
Thyroxine decreased	1 (0.2)	1 (0.1)	2 (0.7)	3 (0.3)
Thyroxine increased	1 (0.2)	1 (0.1)	1 (0.4)	2 (0.2)
Tri-iodothyronine increased	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Blood thyroid stimulating hormone abnormal	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Identified Risk	Thyroid disorders

Thyroxin binding globulin increased	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Tri-iodothyronine decreased	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.2)

Source: Pool A, Table 1.3.6.1.
IFNβ-1a: Interferon Beta-1a; MS: Multiple Sclerosis; N: Total Number of Patient; SC: Subcutaneous.

Severity and nature of risk

The risk of experiencing a first thyroid AE was increased between Months 24 and 42 before appearing to stabilize thereafter. The incidence of thyroid AEs was highest in Years 2 (103/1031, 10.0%) and 3 (143/884, 16.2%) in the alemtuzumab 12 mg/day group; starting from Year 4 the annual incidence was similar to that observed in the IFNβ-1a group after 2 years of follow-up. The most frequently reported events (reported for >2% of all alemtuzumab-treated patients) were hypothyroidism, hyperthyroidism, Basedow's disease (Graves' disease), and decreased blood thyroid stimulating hormone (TSH). hypothyroidism and hyperthyroidism were reported in similar frequencies (10.8% and 10.9%, respectively, for the alemtuzumab 12 mg/day group).

Patients can develop anti-TSH receptor antibodies and/or thyroid peroxidase antibodies with or without clinically significant manifestations. As shown in the below Kaplan-Meier graph of the time to first thyroid event, the risk of experiencing a first event increased between 24 and 42 months before appearing to stabilize through month 96; starting from about 48 months, the annual incidence was similar to that observed in the control group.

Thyroid disease poses special risks in pregnancy. Without treatment of hypothyroidism during pregnancy, there is an increased risk for miscarriage and birth defects. A lack of thyroid hormones in the mother can affect the level of thyroid hormones in a developing baby and can lead to mental retardation and dwarfism. Thyroid replacement therapy is safe in pregnancy. Additionally, maternal anti-TSH receptor antibodies can be transferred to a developing fetus and can cause transient neonatal Basedow's disease. In mothers taking anti-thyroid medication, symptoms develop between days 10-20, as anti-thyroid medication is cleared from the neonate. Neonatal Basedow's disease resolves spontaneously in 3-12 weeks as maternal antibodies are cleared. Most infants respond rapidly to treatment but some will have low intelligence quotients at school age. (43)

Table 19b - Number (%) of Alemtuzumab-Treated Patients With Thyroid Events by Maximum Severity in MS Clinical Trials

Preferred Term	Severity Grade				
	1	2	3	4	5
Any Event	144 (9.7)	379 (25.5)	76 (5.1)	6 (0.4)	0 (0.0)
Hypo-thyroidism	29 (2.0)	126 (8.5)	7 (0.5)	1 (0.1)	0 (0.0)
Hyperthyroidism	54 (3.6)	113 (7.6)	7 (0.5)	1 (0.1)	0 (0.0)
Basedow's disease	26 (17)	143 (9.6)	35 (2.4)	2 (0.1)	0 (0.0)
Autoimmune thyroiditis	18 (1.2)	55 (0.7)	3 (0.2)	1 (0.1)	0 (0.0)
Goitre	26 (1.7)	15 (1.0)	2 (0.1)	0 (0.0)	0 (0.0)
Thyroiditis	6 (0.4)	11 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroid disorder	1 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroiditis subacute	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Identified Risk	Thyroid disorders

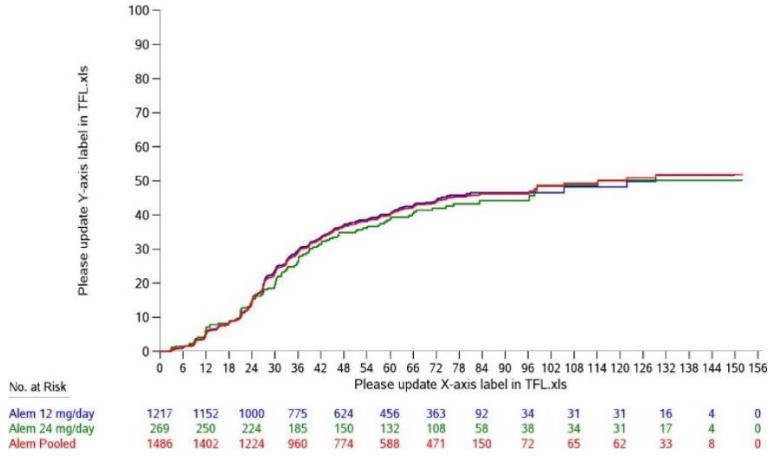
Primary hypothyroidism	2 (0.1)	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroid cyst	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroid mass	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Thyrotoxic crisis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Toxic nodular goitre	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Blood thyroid stimulating hormone decreased	59 (4.0)	20 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Blood thyroid stimulating hormone increased	21 (1.4)	21 (1.4)	3 (0.2)	0 (0.0)	0 (0.0)
Anti-thyroid antibody positive	10 (0.7)	5 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroxine free decreased	9 (0.6)	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroxine free increased	16 (1.1)	8 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Tri-iodothyronine free increased	17 (1.1)	6 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroid function test abnormal	6 (0.4)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Tri-iodothyronine free decreased	4 (0.3)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroxine decreased	3 (0.2)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroxine increased	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Tri-iodothyronine decreased	2 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Tri-iodothyronine increased	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroxin binding globulin increased	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Pool C, Table 3.3.6.2.
MS: Multiple Sclerosis.

The figure below presents a Kaplan-Meier analysis of the time to first thyroid event (ISS Figure below)

Time to First Treatment-Emergent Thyroid Event

Pool C



Identified Risk	Thyroid disorders
	Postmarketing experience Cumulatively through the current DLP, the reported cases of thyroid disorders following the administration of alemtuzumab were consistent in nature and severity with the clinical features collected during drug development identifying no new safety concerns. Cases of thyroid disorders will continue to be monitored. **Seriousness/outcomes** Thyroid disorders are manageable with conventional treatments, including medication, radioactive iodine ablation and, less frequently, thyroidectomy. **Table 19c - Number (%) of Alemtuzumab-Treated Patients (N = 1486[a]) With Serious or Fatal Thyroid Disorders in MS Clinical Trials** Preferred Term / Total / Serious / Fatal Any Event: 606 (40.8) / 77 (5.2) / 0 (0.0) Basedow's disease: 206 (13.9) / 42 (2.8) / 0 (0.0) Hyperthyroidism: 176 (11.8) / 15 (1.0) / 0 (0.0) Hypothyroidism: 163 (11.0) / 6 (0.4) / 0 (0.0) Autoimmune thyroiditis: 77 (5.2) / 4 (0.3) / 0 (0.0) Goitre: 43 (2.9) / 4 (0.3) / 0 (0.0) Thyrotoxic crisis: 1 (0.1) / 1 (0.1) / 0 (0.0) Thyroiditis subacute: 3 (0.2) / 1 (0.1) / 0 (0.0) Thyroxine free increased: 24 (1.6) / 1 (0.1) / 0 (0.0) Tri-iodothyronine free increased: 23 (1.5) / 1 (0.1) / 0 (0.0) *a* There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL. Source: Pool C, Table 3.3.6.1.1 (total), Table 3.3.6.3.1 (serious), Table 3.3.2.3.1 (fatal, Grade = 5). CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; MS: Multiple Sclerosis; N: Total Number of Patient. **Background incidence/prevalence** In the general population, Basedow's (Graves') hyperthyroidism is more prevalent in women, with an annual incidence around 0.5/1000/year and a negligible rate in men. (36)(37) The incidence of hypothyroidism is also more common in women, with an incidence of 3.5/1000/year, and in men, with an incidence of 0.6/1000/year. (36) There is evidence that autoimmune thyroid disease is more common in MS patients than in patients without MS, with odds ratios ranging from 3 to 6. (32)(38)(44)(45) Based on medical records for 404 patients with MS, 38 (9.4%) had autoimmune thyroid disease. (46) In another study, an increased prevalence of both Basedow's (Graves') disease (3.1%) and Hashimoto's disease (5.5%) in the MS population compared to the general population (0.4% and 2.2%, respectively) was noted, although the co-occurrence of Hashimoto's was not statistically significant after age and sex standardization. **Impact on individual patient** Thyroid disorders cannot be prevented but are detectable and manageable with conventional treatments, including medication, radioactive iodine ablation and, less frequently, thyroidectomy.
Risk factors and risk groups	In clinical trials, over all available follow-up of the 1486[a] alemtuzumab treated patients, 1466 had anti-thyroid peroxidase (TPO) antibody testing at baseline. Patients with positive anti-TPO antibodies at baseline also had a higher incidence of abnormal TSH result with simultaneous abnormal T3 or T4 compared to patients with negative

Identified Risk	Thyroid disorders
	antibodies. Of the 1466 patients with anti-TPO testing at baseline, 91.4% tested negative and 8.6% tested positive. Of those who tested negative, 38.2% developed a thyroid AE. Of those who tested positive, 74.8% developed a thyroid AE. Thus, there is a higher risk of developing a thyroid AE in anti-TPO positive patients. However, of the patients with baseline anti TPO antibody testing who developed a thyroid AE, 86% had tested negative for anti-TPO antibodies which underlines the poor predictive value of the measure as a whole. Had anti-TPO positive status been an exclusion to alemtuzumab therapy, only a small number of patients (80 out of 1466, 5.4%) would have been spared a thyroid AE but, based on the lower efficacy observed in the control group, some of them would have experienced additional MS relapses and disability progression that were avoided with alemtuzumab treatment. Maternal transmission of anti-TSH receptor antibodies is associated with higher maternal titres of anti-TSH receptor antibodies in the third trimester. There was no dose related pattern. No pattern of additive or synergistic factors were observed.
Preventability	The occurrence of thyroid disorders cannot be prevented, but poor outcome of thyroid disorders can be prevented through early detection methods and subsequent prompt treatment. Regular monitoring of thyroid function allows for early detection and management implementation. Preventability measures are described in Part V.1 (rRMMs) and Part V.2 (aRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of thyroid disorders in MS patients who have received alemtuzumab is not expected to have any public health impact.

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

AE: Adverse Event; aRMM: Additional Risk Minimization Measure; CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; CI: Confidence Interval; DLP: Data Lock Point; IFNβ: Interferon Beta; MS: Multiple Sclerosis; N: Total Number of Patient; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure; SC: Subcutaneous; TPO: Thyroid Peroxidase; TSH: Thyroid Stimulating Hormone.

Table 20 - Important identified risk: Immune thrombocytopenic purpura (ITP)

Identified Risk	Immune thrombocytopenic purpura (ITP)
Potential mechanism	Autoimmunity is a known complication of immune reconstitution from lymphocytopenia. (47)
Evidence source(s) and strength of evidence	Clinical studies and postmarketing.
Characterization of the risk	**Frequency with 95% CI** There were 28 ITP cases reported with alemtuzumab either in active-clinical trials/clinical development program in MS. In active-controlled trials, ITP occurred in 1.2% of alemtuzumab-treated MS patients compared to 1.6% of IFNβ-1a-treated patients. In longer-term follow-up (more than 2 years after first study treatment), 1.4% of alemtuzumab-treated MS patients had ITP. The overall rate of ITP in alemtuzumab-treated patients was 0.0046 cases per person-year of treatment.

Identified Risk	Immune thrombocytopenic purpura (ITP)

Frequency in the recommended post-approval dose

In the alemtuzumab 12 mg/day group, the incidence of AE or platelet-based ITP was 0.9% (7/8 cases met the AE-based definition and all 8 cases met the platelet-based definition); the annualized rate was 0.0044 per person-year, in active-controlled trials up to 2 years of follow-up; the rate during all available follow-up was 0.0041.

Table 20a - Number (%) of Patients with ITP in Phase 2 and Phase 3 MS Clinical Trials Through 2 Year Follow-up

	SC IFNβ-1a (N = 496)	Alemtuzumab		
		12 mg/day (N = 919)	24 mg/day (N = 269)	Pooled (N = 1188)
Immune thrombocytopenic purpura based on platelet level	8 (1.6)	8 (0.9)	4 (1.5)	12 (1.0)
Any ITP Event	2 (0.4)	7 (0.8)	6 (2.2)	13 (1.1)
Idiopathic thrombocytopenic Purpura	2 (0.4)	2 (0.2)	3 (1.1)	5 (0.4)
Autoimmune Thrombocytopenia	0	5 (0.5)	3 (1.1)	8 (0.7)
Platelet-based or AE-defined ITP	8 (1.6)	8 (0.9)	6 (2.2)	14 (1.2)

Source: Pool A, Table 1.3.7.1

AE: Adverse Event; IFNβ-1a: Interferon Beta-1a; ITP: Immune Thrombocytopenic Purpura; MS: Multiple Sclerosis; N: Total Number of Patient; SC: Subcutaneous.

Table 20b - Number (%) of Alemtuzumab Treated Patients with ITP in MS Clinical Trials

	Alemtuzumab		
	12 mg/day (N = 1217)	24 mg/day (N = 269)	Pooled (N = 1486[a])
Immune thrombocytopenic purpura based on platelet level	28 (2.3)	9 (3.3)	37 (2.5)
Any ITP Event (AE-based definition)	24 (2.0)	10 (3.7)	34 (2.3)
Idiopathic thrombocytopenic Purpura	24 (2.0)	10 (3.7)	34 (2.3)
Platelet-based or AE-defined ITP	28 (2.3)	11 (4.1)	39 (2.6)

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

Source: Pool C Table 3.3.7.1.

AE: Adverse Event; CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; ITP: Immune Thrombocytopenic Purpura; MS: Multiple Sclerosis; N: Total Number of Patient.

Identified Risk	Immune thrombocytopenic purpura (ITP)

Table 20c - Number (Rate) of Adverse Events of ITP in Phase 2 and Phase 3 MS Clinical Trials Through 2 Year Follow-up

	SC IFNβ-1a (N = 496)	Alemtuzumab		
		12 mg/day (N = 919)	24 mg/day (N = 269)	Pooled (N = 1188)
Total Person-years	916.25	1830.81	531.92	2362.73
Any Event	8 (0.0088)	8 (0.0044)	6 (0.0113)	14 (0.0059)

Source: Pool A, Tables 1.2.1 and 1.3.7.1.
Note: Rate = total number of events/total person-years.
IFNβ-1a: Interferon Beta-1a; ITP: Immune Thrombocytopenic Purpura; MS: Multiple Sclerosis; N: Total Number of Patient; SC: Subcutaneous.

Table 20d - Number (Rate) of Adverse Events of ITP in Alemtuzumab-Treated Patients in MS Clinical Trials

	Alemtuzumab		
	12 mg/day (N = 1217)	24 mg/day (N = 269)	Pooled (N = 1486[a])
Total Person-years	6857.91	1776.77	8634.68
Any Event	28 (0.0041)	11 (0.0063)	39 (0.0046)

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

Source: Pool C Tables 3.2.1 and 3.3.7.1
Note: Rate = total number of events/total person-years.
CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; ITP: Immune Thrombocytopenic Purpura; MS: Multiple Sclerosis; N: Total Number of Patient.

Severity and nature of risk

At an early stage of the Sanofi Genzyme-development program, ITP was identified as a risk based on the development of 3 initial cases of ITP in the Phase 2 study CAMMS223, including a fatal index case. Following the identification of these cases, dosing was suspended in the Phase 2 study per Data Safety Monitoring Board recommendation. Sanofi Genzyme introduced education and monitoring measures to facilitate the prompt diagnosis and treatment of ITP. The monitoring program included close monitoring for signs of ITP through patient and investigator education, monthly complete blood counts (CBCs) with differential and platelet counts, and the completion of a monthly symptom monitoring survey. Additionally, a protocol definition of ITP was specified to guide investigators during the conduct of the study. This definition was based upon commonly employed diagnostic criteria for ITP that were similar to those specified by an international working group. (48)

Of the 34 AE reports of ITP among the alemtuzumab-treated patients in the MS clinical trials, most events had a severity of Grade 3 (13 patients) or Grade 4 (14 patients).

Identified Risk	Immune thrombocytopenic purpura (ITP)

Table 20e - Number (%) of Alemtuzumab-Treated Patients (N = 1486[a]) With ITP AEs by Maximum Severity in MS Clinical Trials

	Severity Grade				
	1	2	3	4	5
Any ITP Adverse Event	2 (0.1)	4 (0.3)	13 (0.9)	14 (0.9)	1 (0.1)
Idiopathic thrombo-cytopenic Purpura	2 (0.1)	4 (0.3)	13 (0.9)	14 (0.9)	1 (0.1)

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

Source: Pool C, Pooled Table 3.3.7.2.

AE: Adverse Event; CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; ITP: Immune Thrombocytopenic purpura; MS: Multiple Sclerosis; N: Total Number of Patient.

Postmarketing experience

Cumulatively through the current DLP, the reported cases of ITP following the administration of alemtuzumab were consistent in nature and severity with the clinical features collected during drug development identifying no new safety concerns. Cases of ITP will continue to be monitored.

Seriousness/outcomes

Most cases of ITP were considered serious but resolved with treatment. Of the 1486[a] alemtuzumab-treated patients in clinical trials, 24 (1.6%) patients had serious ITP and 1 patient died. The death was the index case, in which cutaneous symptoms of ITP were noted but their significance went unrecognized until onset of a fatal cerebral haemorrhage. Since 2005, patients in MS clinical trials have been carefully monitored for signs of ITP through patient and investigator education, monthly CBCs with differential and platelet counts, and the completion of a monthly symptom monitoring survey. Following the introduction of these risk minimization provisions for ITP, all cases of ITP after the index case were identified early through CBC monitoring or via symptom identification by the patient or investigator, thus facilitating prompt diagnosis and timely intervention in all subsequent cases.

Table 20f - Number (%) of Alemtuzumab-Treated Patients (N = 1486) With Serious or Fatal ITP in MS Clinical Trials

	Total	Serious	Fatal
Immune thrombocytopenic purpura based on platelet level	37 (2.5)	NA	1 (0.1)
Any ITP Adverse Event (AE-based definition)	34 (2.3)	24 (1.6)	1 (0.1)
Platelet-based or AE-defined ITP	39 (2.6)	24 (1.6)	1 (0.1)

Source: Pool C, Tables 3.3.7.1 and 3.3.7.2 (total AEs and serious AEs), and Table 3.3.2.3.1 (fatal AEs, Grade = 5).

AE: Adverse Event; ITP: Immune Thrombocytopenic Purpura; MS: Multiple Sclerosis
NA: Not Applicable.

Identified Risk	Immune thrombocytopenic purpura (ITP)
	Background incidence/prevalence There is limited information on the frequency of patients with concomitant MS and ITP in the medical literature. Segal et al (49) noted that the prevalence of MS was approximately 25 times higher among patients with ITP than would be expected in the general population. In MS patients treated with beta-interferon, the prevalence of ITP was estimated to be 1.3%. (50) **Impact on individual patient** If undetected, ITP could be fatal. With the currently proposed monitoring activities (ie, monthly blood tests), the impact is considered low.
Risk factors and risk groups	None identified at present. As with other forms of ITP, the data suggest that circulating anti platelet antibody and platelet-bound antibody assays are not predictive of alemtuzumab associated ITP. (51) There was no dose related pattern. No pattern of additive or synergistic factors were observed.
Preventability	After a seemingly distinct form of ITP associated with alemtuzumab treatment in patients with MS was identified during the alemtuzumab clinical development program, a protocol definition of ITP was specified to guide investigators during the conduct of ongoing and future studies. This definition was based upon commonly employed diagnostic criteria for ITP similar to those specified by an international working group. (48) In addition to this protocol definition of ITP, events were also identified based on a platelet-based definition derived from the thrombocytopenia criteria of the protocol definition, or on a review of treatment-emergent AEs coded to a preferred term (PT) of idiopathic thrombocytopenic purpura or autoimmune thrombocytopenia. Data from clinical trials in MS have shown that adherence to blood monitoring recommendations has led to early detection and treatment of ITP onset, with most cases responding to first-line medical therapy or resolved spontaneously. The occurrence of ITP cannot be prevented, but poor outcome of ITP can be prevented through early detection methods and subsequent prompt treatment. Although interleukin-21 has been studied in relation to the pathogenesis of ITP (15) to date, no method to screen for patients at risk has been identified. Preventability measures are described in Part V.1 (rRMMs) and Part V.2 (aRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of ITP in MS patients who have received alemtuzumab is not expected to have any public health impact.

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

AE: Adverse Event; aRMM: Additional Risk Minimization Measure; CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; CBC: Complete Blood Count; CI: Confidence Interval; DLP: Data Lock Point; IFNβ: Interferon Beta; ITP: Immune Thrombocytopenic Purpura; MS: Multiple Sclerosis; N: Total Number of Patient; NA: Not Applicable; PT: Preferred Term; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure; SC: Subcutaneous.

Table 21 - Important identified risk: Nephropathies including anti-glomerular basement membrane (anti-GBM) disease

Identified Risk	Nephropathies including anti-glomerular basement membrane (anti-GBM) disease
Potential mechanism	Autoimmunity is a known complication of immune reconstitution from lymphocytopenia.

Identified Risk	**Nephropathies including anti-glomerular basement membrane (anti-GBM) disease**
Evidence source(s) and strength of evidence	Clinical studies, medical literature, spontaneous reports received by Sanofi Genzyme and postmarketing.
Characterization of the risk	**Frequency with 95% CI** Alemtuzumab has been associated with glomerular disease in MS patients, including membranous nephropathies and anti-GBM disease (a rare autoimmune disorder in which circulating antibodies are directed against an antigen normally present in the renal GBM). Clinical manifestations may include elevations in serum creatinine, hematuria, and/or proteinuria. Overall, 6 (0.4%) of 1486[a] alemtuzumab-treated patients in Sanofi Genzyme-sponsored MS clinical trials had nephropathies including anti-GBM disease. Of these 6 patients, 3 were determined to have glomerular disease associated with alemtuzumab. Interferon Beta-1a treated patients did not develop nephropathies including anti-GBM disease.

Table 21a - Number (%) of Alemtuzumab-Treated Patients with Nephropathies Including Anti GBM Disease in MS Clinical Trials

Preferred Term	Alemtuzumab		
	12 mg/day (N = 1217)	24 mg/day (N = 269)	Pooled (N = 1486[a])
Any Event	6 (0.5)	0 (0.0)	6 (0.4)
Glomerulonephritis	1 (0.1)	0 (0.0)	1 (0.1)
Glomerulonephritis membranous	2 (0.2)	0 (0.0)	2 (0.1)
Goodpasture's syndrome	1 (0.1)	0 (0.0)	1 (0.1)
Tubulointerstitial nephritis	1 (0.1)	0 (0.0)	1 (0.1)
Anti-GBM antibody positive	1 (0.1)	0 (0.0)	1 (0.1)

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

Source: Pool C Table 3.3.8.1.1

CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; GBM: Glomerular Basement Membrane; MS: Multiple Sclerosis; N: Total Number of Patient.

Severity and nature of risk

Nephropathies including anti-GBM disease generally occurred within 39 months following the last alemtuzumab exposure and appear to be unrelated to dose or number of courses.

If untreated, nephropathies including anti-GBM disease can progress to renal failure or death. Treated patients have a significant risk of morbidity and mortality from renal failure, pulmonary haemorrhage, or complications of treatment. Sixty percent (60%) of patients exhibit pulmonary haemorrhage (not seen in alemtuzumab-treated patients to date) related to underlying pulmonary insult (including cigarette smoking, respiratory infection and exposure to hydrocarbons). (52)

Postmarketing experience

Cumulatively through the current DLP, the reported cases of nephropathies including anti-GBM disease following the administration of alemtuzumab were consistent in nature and severity with the clinical features collected during drug development identifying no

Identified Risk	Nephropathies including anti-glomerular basement membrane (anti-GBM) disease
	new safety concerns. Cases of nephropathies including anti-GBM disease will continue to be monitored. **Seriousness/outcomes** Nephropathies including anti-GBM disease (also known as Goodpasture's disease) are rare autoimmune disorders associated with antibodies to Type IV collagen, which is present in the renal GBM and the pulmonary alveoli. Anti-GBM disease was identified in 1 alemtuzumab-treated patient in study CAMMS223 by protocol-specified renal monitoring 39 months after the second annual course of alemtuzumab. Following this event, Sanofi Genzyme convened an external expert advisory panel to review the existing monitoring strategy, and intensified monitoring was incorporated into the safety monitoring program. These measures included monthly serum creatinine and urinalysis testing in alemtuzumab treated patients (while IFNβ-1a treated patients maintained a testing schedule of every 3 months). Additionally, the monitoring program included completion of a monthly symptom monitoring survey. The following AEs within the system organ class (SOC) of renal and urinary disorders were identified in alemtuzumab-treated patients (all available follow-up) for an overall incidence of 0.4% of all alemtuzumab-treated patients with nephropathies and immune renal disorders: glomerulonephritis (1 patient in the extension), glomerulonephritis membranous (2 patients, 1 in CAMMS324 and 1 in the extension study), Goodpasture's syndrome (1 patient in CAMMS223 as previously mentioned), tubulointerstitial nephritis (1 patient in CAMMS324) and anti-GBM antibody positive (1 patient in the extension study). These cases were identified and treated early, and so far, have had positive outcomes. A total of three cases were identified outside of Sanofi Genzyme-sponsored trials (mentioned in the table below). Two cases have been identified late with end-stage renal failure; in one of these cases off-label use was concerned. The third case was identified through periodic monitoring of urine (hematuria and proteinuria) and appropriately diagnosed; however, the patient deferred treatment for social reasons. Treatment usually consists of plasmapheresis, immune suppression (cyclophosphamide), and corticosteroids. This patient deferred treatment with cyclophosphamide and progressed to acute renal failure before full treatment could be initiated. Also, this third patient concerned off-label use; the physician had been treating the patient for MS in the US with product that was commercially available for the oncology indication. All 3 patients became dialysis dependent. Two ultimately required renal transplantation which resulted in no recurrence of the disease. The third case was ongoing at the time of this report and the company continues to actively following up with the reporting physician. Five-year patient and renal survival correlate with renal function at the time of diagnosis. (52) If anti-GBM disease is identified early (Creatinine <5.7 mg/dL), patient and renal survival at 5 years are 94% and 95%, respectively, compared to late identification (Creatinine >7.7 mg/dL but not dialysis dependent), in which 5-year patient and renal survival are 80% and 50%, respectively. If anti-GBM disease is identified when the patient is already dialysis-dependent, 5-year patient and renal survival are 44% and 13%, respectively. In the alemtuzumab MS clinical program, all cases of glomerular disease were identified through the periodic serum creatinine or urinalysis testing performed as part of the safety monitoring program allowing early intervention. All cases were promptly treated and responded.

Identified Risk	Nephropathies including anti-glomerular basement membrane (anti-GBM) disease

Table 21b - Nephropathies Including Anti-GBM Disease in MS Patients Outside Sanofi Genzyme sponsored Clinical Trials (all were serious adverse events) (as of 07-Feb-2013)

Study	Dose/Cycles	Time from First Dose	Treatment	Outcome
Investigator-Sponsored Trials				
CAMMS224 (19)(52)	20 mg/day, 1 cycle (100 mg total dose)	9 months	Plasmapheresis, cyclophosphamide, corticosteroids, renal transplant	No recurrence
Off-Label Use of Alemtuzumab for MS				
NA	20 mg/day, 2 cycles (160 mg total dose)	36 months (24 months from last dose)	Plasmapheresis, corticosteroids, CELLCEPT® (mycophenolate mofetil), renal transplant	No recurrence
Off-Label Use of Alemtuzumab for MS[a]				
NA	12 mg/day, 5 days (60 mg) 24 mg/day, 3 days (72 mg) 12 mg/day, 3 days (36 mg) Total 168 mg	60 months after the first dose (24 months after the last one)	Plasmapheresis, corticosteroids[a], cyclophosphamide, dialysis	Acute renal failure, on-going

a Case #CAMP- 1002377. Case detected through risk monitoring of urine and appropriately diagnosed. Patient deferred treatment (>1 month) with cyclophosphamide for social circumstances (patient getting married) and was started only on plasmapheresis. Patient entered into acute renal failure. Serum creatinine level was 6 mg/dl. The patient ultimately received IV cyclophosphamide and steroids in addition to continued plasmapheresis and is on dialysis.

Source: Postmarketing Summary Report.

GBM: Glomerular Basement Membrane; IV: Intravenous; NA: Not Applicable; MS: Multiple Sclerosis.

Background incidence/prevalence

The incidence of anti-GBM disease in the general population is approximately 0.1 cases per million population. (53)

The frequency of nephropathies including anti-GBM disease in patients with MS has not been quantified.

Impact on individual patient

If untreated, nephropathies including anti-GBM disease can progress to renal failure or death. Impact may be significant.

Identified Risk	Nephropathies including anti-glomerular basement membrane (anti-GBM) disease
Risk factors and risk groups	There is no indication that patients with pre-existing renal conditions are at greater risk of developing an event. There is no dosing related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Preventability	To date, no markers of increased risk have been identified. The occurrence of nephropathies including anti-GBM disease cannot be prevented, but the risk of poor outcome of these nephropathies can be reduced through early detection methods and subsequent prompt treatment. Preventability measures are described in Part V.1 (rRMMs) and Part V.2 (aRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of nephropathies including anti-GBM disease in MS patients who have received alemtuzumab is not expected to have any public health impact.

a There were 1486 alemtuzumab treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

AE: Adverse Event; aRMM: Additional Risk Minimization Measure; CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; CI: Confidence Interval; DLP: Data Lock Point; GBM: Glomerular Basement Membrane; IFNβ-1a: Interferon Beta-1a; MS: Multiple Sclerosis; N: Total Number of Patient; NA: Not Applicable; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure; SOC: System Organ Class; US: United States.

Table 22 - Important identified risk: Autoimmune hepatitis (AIH)

Identified risk	Autoimmune hepatitis (AIH)
Potential mechanism	Autoimmunity is a known complication of immune reconstitution from lymphocytopenia. (45)
Evidence source(s) and strength of evidence	Postmarketing.
Characterization of the risk	**Frequency with 95% CI** There were no AIH cases reported with alemtuzumab either in active-clinical trials/clinical development program in MS. **Postmarketing experience** Cases of reported AIH in the postmarketing setting at the current DLP were reviewed and were found to be consistent with the known safety pattern for this risk for alemtuzumab. **Severity and nature of risk** Autoimmune Hepatitis cases were moderate to severe in intensity. **Seriousness/outcomes** All reported cases were considered serious. Fatal case involved significant history of raised liver function tests prior to starting treatment with alemtuzumab (Lemtrada) and cause of death was reported as colon perforation/perforated bowel, pneumoperitoneum, liver failure, jaundice, worsening hepatic encephalopathy and fecal peritonitis. Autopsy details were unspecified. Symptoms of AIH may include but are not limited to unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice and/or dark urine, or bleeding or bruising more easily than normal.

Identified risk	Autoimmune hepatitis (AIH)
	Background incidence/prevalence Based on a cohort study in the Optum electronic health record (EHR) database conducted by Sanofi Genzyme, the incidence rate of AIH in MS population was observed to be 17 per 100 000 person-years. **Impact on individual patient** If untreated AIH can progress to liver failure. Impact may be with significant impact on individual patients. However, early detection and treatment can result in favorable outcomes.
Risk factors and risk groups	None identified. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Preventability	To date, no marker of increased risk has been identified. The occurrence of AIH cannot be prevented, but the risk of poor outcome of these events can be reduced through early detection methods and subsequent prompt treatment. Preventability measures are described in Part V.1 (rRMMs) and Part V.2 (aRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of AIH in MS patients who have received alemtuzumab is not expected to have any public health impact.

AIH: Autoimmune Hepatitis; aRMM: Additional Risk Minimization Measure; CI: Confidence Interval; DLP: Data Lock Point; EHR: Electronic Health Record; MS: Multiple Sclerosis; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure.

Table 23 - Important identified risk: Serious infections

Identified Risk	Serious infections
Potential mechanism	Lymphocyte depletion occurs as a result of the pharmacodynamic effect of alemtuzumab. However, in clinical trials of alemtuzumab-treated MS patients, there was no evidence for an increased incidence of infections among alemtuzumab-treated patients with low pre-course neutrophil or lymphocyte counts, and the risk of infection did not increase over time with additional courses of alemtuzumab treatment. While the data in Pool C suggest that most infections are not severe or serious, the potential for severe and/or serious infections remains.
Evidence source(s) and strength of evidence	Clinical studies and postmarketing.
Characterization of the risk	**Frequency with 95% CI** Infections were identified as AEs within the Medical Dictionary for Regulatory Activities (MedDRA) SOC of Infections and Infestations and AEs within the MedDRA high level group term of Microbiology and serology investigations under the SOC of Investigations. Analyses for specific infections of interest were also performed and included upper and lower respiratory tract infections (RTIs), UTIs, herpetic, fungal, HPV, TB, and viral hepatitis. There were 142 cases reported with alemtuzumab either in active-clinical trials/clinical development program in MS. **Table 23a - Number (%) of Patients with Selected Infections in Phase 2 and Phase 3 MS Clinical Trials Through 2 Year Follow-up**

	SC IFNβ-1a (N = 496)	Alemtuzumab		
		12 mg/day	24 mg/day	Pooled

Identified Risk	Serious infections

		(N = 919)	(N = 269)	(N = 1188)
Any Infection	264 (53.2)	652 (70.9)	199 (74.0)	851 (71.6)
Candida, fungal, and tinea infections	17 (3.4)	111 (12.1)	36 (13.4)	147 (12.4)
Human Papilloma Virus	7 (1.4)	22 (2.4)	8 (3.0)	30 (2.5)
Cytomegalo Virus	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Respiratory (upper)	182 (36.7)	463 (50.4)	146 (54.3)	609 (51.3)
Urinary Tract Infection	50 (10.1)	189 (20.6)	51 (19.0)	240 (20.2)
Viral hepatitis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Tuberculosis	1 (0.2)	1 (0.1)	3 (1.1)	4 (0.3)
Herpes Simplex Virus	2 (0.4)	17 (1.8)	3 (1.1)	20 (1.7)
Varicella	0 (0.0)	4 (0.4)	2 (0.7)	6 (0.5)

Source: Pool A, Tables 1.3.5.1, 1.3.5.12.1, 1.3.5.12.2, 1.3.5.12.3, 1.3.5.12.4.1, 1.3.5.12.6, 1.3.5.12.8, 1.3.5.12.9, and 1.3.5.12.10.

IFNβ: Interferon Beta; MS: Multiple Sclerosis; N: Total Number of Patient; SC: Subcutaneous.

Table 23b - Number (Rate) of Infections in Alemtuzumab-Treated Patients in MS Clinical Trials

	Alemtuzumab		
	12 mg/day (N = 1217)	24 mg/day (N = 269)	Pooled (N = 1486[a])
Total Person-years	6858	1777	8635
Any Event	6792 (0.990)	1815 (1.022)	8607 (0.997)
Candida, fungal, and tinea infections	332 (0.048)	99 (0.056)	431 (0.050)
Human Papilloma Virus (HPV)	81 (0.012)	29 (0.016)	110 (0.013)
Cytomegalo Virus[b]	1 (0.000)	1 (0.001)	2 (0.000)
Upper respiratory tract infection	2985 (0.435)	777 (0.437)	3762 (0.436)
Urinary Tract Infection	1156 (0.169)	347 (0.195)	1503 (0.174)
Tuberculosis	2 (0.000)	3 (0.002)	5 (0.001)
Herpes Simplex Virus	59 (0.009)	3 (0.002)	62 (0.007)
Varicella	12 (0.002)	2 (0.001)	14 (0.002)

a There were 1486 alemtuzumab treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

b There is 1 additional case reported in the ongoing open label extension study LPS13649.

Identified Risk	Serious infections
	Source: Pool C, Tables 3.3.5.1.3, 3.3.5.6.1, 3.3.5.6.2, 3.3.5.6.3, 3.3.5.6.4.1, 3.3.5.6.6, 3.3.5.6.8, 3.3.5.6.9 and 3.3.5.6.11 CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; HPV: Human Papilloma Virus; MS: Multiple Sclerosis; N: Total Number of Patient. **Severity and nature of risk** Infections are predominantly mild to moderate in severity. Two fatal event of sepsis, one in a patient who developed pancytopenia and one in a patient who developed pneumonia were reported in MS clinical trials. Upper respiratory infections are the most commonly reported type of infection in alemtuzumab treated patients. Primary active TB has occurred in 3 alemtuzumab-treated MS patients in regions of the world with known endemicity, and latent TB has also been reported in 2 patients. The overall incidence of any herpetic infection was higher in the alemtuzumab 12 mg/day group (15.3%) than the IFNβ-1a group (2.8%). Oral herpes simplex infections predominate, and some patients experience recurrent infection with each alemtuzumab course. There have been no events of Herpes Simplex Virus (HSV) encephalitis to date. There was one case of herpes zoster cutaneous disseminated that resolved without sequelae. Based on an analysis of time to first herpes infection for all alemtuzumab dose groups, the risk of experiencing the first herpetic infections tended to be highest after receiving the first course of alemtuzumab treatment before gradually decreasing and remaining at about the same level after 2 years. Herpes prophylaxis during treatment and for 1 month following treatment was recommended by a safety monitoring board that reviewed treatment-emergent safety data. Analysis after completion of the trials shows that the incidence of herpes infections during the first month following the first treatment course of alemtuzumab was lower in patients who received prophylactic aciclovir than in those who did not (0.5% versus 4.9%, respectively); for the second treatment course, similar to the first one, the incidence of herpes infections during the first month following alemtuzumab was lower in patients who received prophylactic aciclovir than in those who did not (0.8% versus 2.4%, respectively). Reactivation of varicella zoster occurs more commonly in alemtuzumab-treated patients than IFNβ-1a patients. There have been events of varicella zoster meningitis and one event of herpes zoster cutaneous disseminated that resolved without sequelae. Primary varicella also occurs more commonly in alemtuzumab-treated patients and has been associated with varicella pneumonia. Three cases of uncomplicated CMV have also been reported in clinical trials; two events were non-serious (Grade 2) and one event was a non-serious (Grade 2) mononucleosis-like condition. Superficial fungal infections, especially oropharyngeal and vaginal candidiasis, occur more commonly in alemtuzumab-treated patients. No systemic fungal infections have been reported in alemtuzumab treated patients. One event of distal esophageal candidiasis that responded well to treatment was reported. Cervical HPV infection and cervical dysplasia occur more commonly in alemtuzumab-treated patients than IFNβ-1a patients. Relatively few alemtuzumab-treated patients had HPV infection events. However, cervical cancer in situ and vulvar cancer in-situ were identified in 1 patient each in the alemtuzumab and IFNβ-1a groups. To date, no events of pneumocystis pneumonia or alemtuzumab related PML have been reported. In the MS clinical trial program, only 5 *C. difficile* events were observed, and opportunistic infections therefore did not appear to be a safety issue in this population. The annualized rates of treatment emergent infections from the first alemtuzumab treatment in the total alemtuzumab group generally decreased during subsequent courses, and the occasional apparent increases in rates could be attributed to the small

Identified Risk	Serious infections

number of patients at risk who received 3 or more courses of treatment. Therefore, it can be concluded that over time, there is no increase in the risk of infection that would be indicative of cumulative immunosuppressive effects.

Table 23c - Number (%) of Patients with Infections by Severity in Phase 2 and Phase 3 MS Clinical Trials Through 2-Year Follow-up

	SC IFNβ-1a (N = 496)	Alemtuzumab		
		12 mg/day (N = 919)	24 mg/day (N = 269)	Pooled (N = 1188)
Any Infection	264 (53.2)	652 (70.9)	199 (74.0)	851 (71.6)
Grade 1	63 (12.7)	124 (13.5)	34 (12.6)	158 (13.3)
Grade 2	195 (39.3)	494 (53.8)	151 (56.1)	645 (54.3)
Grade 3	6 (1.2)	33 (3.6)	14 (5.2)	47 (4.0)
Grade 4	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Pool A, Table 1.3.5.3.

IFNβ: Interferon Beta; MS: Multiple Sclerosis; N: Total Number of Patient; SC: Subcutaneous.

Table 23d - Number (%) of Alemtuzumab-Treated Patients with Infections by Severity in MS Clinical Trials

	Alemtuzumab		
	12 mg/day (N = 1217)	24 mg/day (N = 269)	Pooled (N = 1486[a])
Any Infection	1002 (82.3)	235 (87.4)	1237 (83.2)
Grade 1	100 (8.2)	19 (7.1)	119 (8.0)
Grade 2	802 (65.9)	187 (69.5)	989 (66.6)
Grade 3	91 (7.5)	29 (10.8)	120 (8.1)
Grade 4	7 (0.6)	0 (0.0)	7 (0.5)
Grade 5	2 (0.2)	0 (0.0)	2 (0.1)

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

Source: Pool C, Table 3.3.5.2.

CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; MS: Multiple Sclerosis; N: Total Number of Patient.

Postmarketing experience

Cumulatively through the current DLP, the reported cases of serious infections following the administration of alemtuzumab were consistent in nature and severity with the clinical features collected during drug development identifying no new safety concerns. Cases of serious infections will continue to be monitored.

There were cases of Epstein-Bar Virus (EBV) infections with hepatic involvement reported with confounders in the GPV dataset. Approximately 90% to 95% of the

Identified Risk	Serious infections

worldwide population is seropositive for EBV. Primary EBV infection is common in young children and is frequently asymptomatic. The classical triad of an EBV infection that typically presents in adolescents, is tonsillitis, cervical lymphadenopathy and fever, characteristic of infectious mononucleosis. Approximately one-half of patients with infectious mononucleosis have splenomegaly, only about 14% are reported to have hepatomegaly.

Seriousness/outcomes

Infections occur more commonly in alemtuzumab-treated MS patients (70.9% in 12 mg/day group) than IFNβ-1a patients (53.2%). Serious infections occur infrequently (2.7% and 1.0%, respectively).

Table 23e - Number (%) of Patients With Serious or Fatal Infections in MS Clinical Trials Through 2-year Follow up

	IFNβ-1a (N = 496)	Alemtuzumab		
		12 mg/day (N = 919)	24 mg/day (N = 269)	Pooled (N = 1188)
Any Infection	264 (53.2)	652 (70.9)	199 (74.0)	851 (71.6)
Serious	5 (1.0)	25 (2.7)	10 (3.7)	35 (2.9)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Pool A, Tables 1.3.5.1, 1.3.5.3 and 1.3.5.4.

IFNβ: Interferon Beta; MS: Multiple Sclerosis; N: Total Number of Patient.

Table 23f - Number (%) of Alemtuzumab-Treated Patients (N = 1485) With Serious or Fatal Infections in MS Clinical Trials

	12 mg/day (N = 1217)	24 mg/day (N = 269)	Pooled (N = 1486[a])
Any Infection	1002 (82.3)	235 (87.4)	1237 (83.2)
Serious	93 (7.6)	30 (11.2)	123 (8.3)
Fatal	2 (0.2)	0 (0.0)	2 (0.1)

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

Source: Pool C, Tables 3.3.5.1.1, 3.3.5.3.1 and 3.3.5.2.

CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; MS: Multiple Sclerosis; N: Total Number of Patient.

Table 23g - Number (%) of Alemtuzumab-Treated Patients with Serious Infections in MS Clinical Trials

Preferred Term	Alemtuzumab		
	12 mg/day (N = 1217)	24 mg/day (N = 269)	Pooled (N = 1486[a])
Any Serious Infection	93 (7.6)	30 (11.2)	123 (8.3)
Pneumonia	16 (1.3)	2 (0.7)	18 (1.2)
Appendicitis	6 (0.5)	0 (0.0)	6 (0.4)

Identified Risk	Serious infections			
	Herpes zoster	11 (0.9)	3 (1.1)	14 (0.9)
	Gastroenteritis	6 (0.5)	5 (1.9)	6 (0.4)
	Cellulitis	2 (0.2)	4 (1.5)	4 (0.3)
	Lower respiratory tract infection	2 (0.2)	0 (0.0)	2 (0.1)
	Sepsis	9 (0.7)	0 (0.0)	9 (0.6)
	Subcutaneous abscess	2 (0.2)	0 (0.0)	2 (0.1)
	Tooth infection	2 (0.2)	0 (0.0)	2 (0.1)
	Appendicitis perforated	1 (0.1)	0 (0.0)	1 (0.1)
	Cervicitis	1 (0.1)	0 (0.0)	1 (0.1)
	Disseminated tuberculosis	1 (0.1)	0 (0.0)	1 (0.1)
	Febrile infection	1 (0.1)	0 (0.0)	1 (0.1)
	Gastroenteritis viral	2 (0.2)	0 (0.0)	2 (0.1)
	Infective myositis	1 (0.1)	0 (0.0)	1 (0.1)
	Influenza	2 (0.2)	1 (0.4)	3 (0.2)
	Labyrinthitis	1 (0.1)	0 (0.0)	1 (0.1)
	Oesophageal candidiasis	1 (0.1)	0 (0.0)	1 (0.1)
	Oral herpes	1 (0.1)	0 (0.0)	1 (0.1)
	Pasteurella infection	1 (0.1)	0 (0.0)	1 (0.1)
	Pneumonia legionella	1 (0.1)	0 (0.0)	1 (0.1)
	Postoperative wound infection	1 (0.1)	0 (0.0)	1 (0.1)
	Pyelonephritis	3 (0.2)	2 (0.7)	5 (0.3)
	Sinusitis	1 (0.1)	0 (0.0)	1 (0.1)
	Upper respiratory tract infection	1 (0.1)	0 (0.0)	1 (0.1)
	Urinary tract infection	7 (0.6)	3 (1.1)	10 (0.7)
	Uterine infection	1 (0.1)	0 (0.0)	1 (0.1)
	Varicella	1 (0.1)	0 (0.0)	1 (0.1)
	Viral infection	2 (0.2)	0 (0.0)	2 (0.1)
	Bronchitis	1 (0.1)	2 (0.7)	3 (0.2)
	Cellulitis of male external genital organ	0 (0.0)	1 (0.4)	1 (0.1)
	Diverticulitis	2 (0.2)	1 (0.4)	3 (0.2)
	Furuncle	0 (0.0)	1 (0.4)	1 (0.1)
	Herpes ophthalmic	0 (0.0)	1 (0.4)	1 (0.1)
	Meningitis listeria	0 (0.0)	1 (0.4)	1 (0.1)
	Meningitis viral	0 (0.0)	1 (0.4)	1 (0.1)
	Pulmonary tuberculosis	1 (0.1)	1 (0.4)	2 (0.1)

Identified Risk	Serious infections

Tracheobronchitis	0 (0.0)	1 (0.4)	1 (0.1)

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

Source: Pool C, Table 3.3.5.3.1.

CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; MS: Multiple Sclerosis; N: Total Number of Patient.

Majority of events with PT "EBV" were serious. The outcome was reported as fatal for 1 event with the PT of EBV virus infection. However, blood cultures in this case demonstrated the presence of multiple pathogens.

Background incidence/prevalence

In prospective studies on the relation between systemic infections and MS exacerbations, patients with RRMS were noted to have 1.2-1.4 systemic infections per year. These infections occurred predominantly in the upper respiratory, urinary, and gastrointestinal tracts. (40)(54)

Impact on individual patient

Infections are predominantly mild to moderate in severity; however, two fatal events of sepsis, one in a patient who developed pancytopenia and one in a patient who developed pneumonia were reported. The impact on individual patient may vary depending on the infectious agent and the patient's overall health status.

Risk factors and risk groups	Relapsing remitting MS patients who have been previously treated with immune suppressive agents are theoretically at increased risk for infection if subsequently treated with alemtuzumab, as concomitant use of alemtuzumab with any of these therapies could increase the risk of immunosuppression. In controlled clinical trials, the rate of infections and serious infections is greater in previously treated patients, regardless of treatment (ie, whether alemtuzumab-treated or interferon treated). Interim safety data from CAMMS223 suggested that MS patients treated with alemtuzumab were at an increased risk of developing HSV within 1 month of receiving alemtuzumab. (15) Additionally, patients with mobility restrictions may theoretically be at higher risk for infectious complications due to diminished mobility and functional capacity (eg, aspiration pneumonia, infected decubitus ulcers, presence of indwelling catheter, and dysphagia with aspiration). There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Preventability	Preventability measures are described in Part V.1 (rRMMs) and Part V.2 (aRMMs). Epstein-Barr virus infections have been reported in alemtuzumab-treated patients which can occur at any time after the initial infection.
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	While alemtuzumab was associated with a higher risk of infection in alemtuzumab-treated patients in MS clinical trials, the increase in risk was apparent early and there was no increase in the incidence or rate over time that would indicate cumulative immunosuppressive effects of continued treatment. Neither was there an identified link between lymphocyte levels and risk for infection that would allow for

Identified Risk	Serious infections
	recommendations to be made to the treating physician regarding infection risk and the patient's lymphocyte status. Given the number of MS patients treated with alemtuzumab, infections in these patients are not expected to have a wide public health impact.

AE: Adverse Event; aRMM: Additional Risk Minimization Measure; CI: Confidence Interval; CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; CMV: Cytomegalovirus; DLP: Data Lock Point; EBV: Epstein-Barr virus; GPV: Global Pharmacovigilance; HIV: Human Immunodeficiency Virus; HPV: Human Papilloma Virus; HSV: Herpes Simplex Virus; IFN-β: Interferon Beta; MedDRA: Medical Dictionary for Regulatory Activities; MS: Multiple Sclerosis; N: Total Number of Patient; PML: Progressive Multifocal Leukoencephalopathy; PT: Preferred Term; RRMS: Relapsing Remitting Multiple Sclerosis; RTI: Respiratory Tract Infection; SC: Subcutaneous; SOC: System Organ Class; TB: Tuberculosis; UTI: Urinary Tract Infection; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure.

Table 24 - Important identified risk: Haemophagocytic Lymphohistiocytosis (HLH)

Identified risk	Haemophagocytic Lymphohistiocytosis (HLH)
Potential mechanism	Unknown
Evidence source(s) and strength of evidence	Postmarketing.
Characterization of the risk	**Frequency with 95% CI** There were no cases of HLH identified in clinical trials. **Postmarketing experience** In postmarketing, cases of reported HLH at the current DLP were reviewed and were found to be consistent with the known safety pattern of this risk for alemtuzumab. Acquired or secondary HLH typically occurs in adults with acquired defects in lymphocyte and natural killer cell cytotoxic function. Many triggering infections, malignancies and autoinflammatory or autoimmune diseases have been related to acquired HLH cases. **Severity and nature of risk** Haemophagocytic lymphohistiocytosis cases with known intensity were severe and life-threatening in nature. **Seriousness/outcomes** All HLH cases were considered as serious and the outcome was reported as fatal in 6 cases and majority of other events reported outcomes as recovered/recovering. Signs and symptoms of HLH may include: Persistent fevers, Rash, enlarged liver, enlarged spleen, enlarged lymph nodes, Low blood counts, Jaundice, Hepatitis, Liver failure, Respiratory issues. **Background incidence/prevalence** No study examining the incidence or prevalence of HLH in the general adult population was found. The frequency of HLH in patients with MS has not been quantified. **Impact on individual patient** Haemophagocytic lymphohistiocytosis is a life-threatening condition. It can cause death in weeks or months if not treated. Impact may be significant.
Risk factors and risk groups	None identified. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Preventability	To date, no marker of increased risk has been identified. The occurrence of HLH cannot be prevented, but the risk of poor outcome of these events can be reduced through early detection methods and subsequent prompt treatment. Preventability measures are described in Part V.1 (rRMMs) and Part V.2 (aRMMs).

Identified risk	Haemophagocytic Lymphohistiocytosis (HLH)
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of HLH in MS patients who have received alemtuzumab is not expected to have any public health impact.

aRMM: Additional Risk Minimization Measure; CI: Confidence Interval; DLP: Data Lock Point; HLH: Haemophagocytic Lymphohistiocytosis; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure; MS: Multiple Sclerosis.

Table 25 - Important identified risk: Acquired Haemophilia A (AHA)

Identified Risk	Acquired Haemophilia A (AHA)
Potential mechanism	Acquired Haemophilia A falls within the group of possible autoimmune conditions that could develop following alemtuzumab treatment. The reconstitution of the B-cell population without adequate regulatory control from T cells could explain how autoimmunity arises following alemtuzumab and could potentially contribute to the development of AHA. Alemtuzumab may increase the risk of autoimmune disorders and the known biological mechanism of alemtuzumab induced autoimmunity may be associated with the reported events of AHA.
Evidence source(s) and strength of evidence	Clinical and postmarketing.
Characterization of the risk	**Frequency with 95% CI** There were two cases of AHA identified in the clinical trial setting. **Postmarketing experience** Cases of AHA reported in the postmarketing setting at the current DLP were reviewed and were found to be consistent with the known safety pattern of this risk for alemtuzumab. **Severity and nature of risk** Acquired Haemophilia A cases were moderate to severe in intensity. None of the events reported resulted in death. From the clinical trials, both cases had confounding risk factors (prior treatment with anticoagulation and antiplatelets agents in one case, exposure to IFNβ-1A acting as confounder in the second case). **Seriousness/outcomes** As described above, the cases were predominantly moderate to severe in intensity. Majority of the cases were serious, but none involving fatal outcome. Majority of the event outcomes were reported as recovered/recovering. **Background incidence/prevalence** The incidence of acquired AHA in the general population in North America ranges from 0.1/million/year to 1.98/million/year (55)(56), while in Europe it ranges from 1.34/million/year to 1.48/million/year (57)(58), Asia 0.74/million/year and in Australia 1.2/million/year. (59)(60) The specific AHA rate in the MS population overall, based on US Optum Database (using International Classification of Diseases (ICD)9/ICD10 coding 286.52 and 286.59) is 0.07 per 1000 person-years (95% CI = 0.04 to 0.13) = 71.48 per 1 000 000 person-years. The specific AHA rate in the untreated MS sub-cohort, based on US Optum Database (using ICD9/ICD10 coding 286.52 and 286.59) is 0.175 per 1000 person-years (95% CI = 0.09 to 0.33) = 175.4 per 1 000 000 person-years. **Impact on individual patient** Without correction in mixing studies, low antihemophilic factor (FVIII) activity levels and evidence of a FVIII inhibitor. As AHA is rare, a lack of familiarity of the condition may

Identified Risk	Acquired Haemophilia A (AHA)
	result in delayed diagnosis and prompt haemostatic control is required to reduce morbidity and mortality.
Risk factors and risk groups	Unknown. It is not known whether development of one treatment emergent antibody mediated autoimmune disorder predisposes to development of additional antibody mediated autoimmune diseases. Acquired Haemohilia A is seen more frequently in the non-MS population with increasing age and may be drug-induced or arise in the setting of pregnancy, underlying autoimmune disease or malignancy. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Preventability	To date, no marker of increased risk has been identified. The occurrence of AHA cannot be prevented, but the risk of poor outcome of these autoimmune disorders can be reduced through early detection methods and subsequent prompt treatment. Preventability measures are described in Part V.1 (rRMMs) and Part V.2 (aRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of AHA in MS patients who have received alemtuzumab is not expected to have any public health impact.

aRMM: Additional Risk Minimization Measure; AHA: Acquired Haemophilia A; CI: Confidence Interval; DLP: Data Lock Point; FVIII: Antihemophilic Factor; ICD: International Classification of Diseases; MS: Multiple Sclerosis; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure; US: United States.

Table 26 - Important identified risk: Thrombotic thrombocytopenic purpura (TTP)

Identified Risk	Thrombotic thrombocytopenic purpura (TTP)
Potential mechanism	Autoimmunity is a known complication of immune reconstitution from lymphocytopenia.
Evidence source(s) and strength of evidence	Postmarketing.
Characterization of the risk	**Frequency with 95% CI** There were no thrombotic thrombocytopenic purpura cases reported with alemtuzumab either in active-clinical trials/clinical development program in MS. **Postmarketing experience** Cases of TTP reported in the postmarketing setting at the current DLP were reviewed and were found to be consistent with the known safety profile of alemtuzumab. **Severity and nature of risk** Thrombotic thrombocytopenic purpura cases were moderate to severe in intensity. Thrombotic thrombocytopenic purpura is characterized by a pentad of signs and symptoms, which include thrombocytopenia, microangiopathic hemolytic anemia (±fatigue), neurological sequelae (mental status alteration, seizures, hemiplegia, paresthesia, visual disturbances and aphasia), fever and renal impairment. **Seriousness/outcomes** All cases were reported as serious. Outcome was reported as fatal for one event, recovered/recovering for majority of the events, followed by not recovered and unknown. **Background incidence/prevalence** According to the National Organization for Rare Disorders (NORD), the overall incidence rate of TTP is estimated at 4 in 100 000 persons. (61)

Identified Risk	Thrombotic thrombocytopenic purpura (TTP)
	Impact on individual patient If untreated TTP has a mortality rate of 90%, in the first 10 days and even with appropriate therapy the mortality rate is 20-30% at 6 months. Therefore, there may be significant impact on individual patients. However, early detection and treatment can result in favorable outcomes.
Risk factors and risk groups	None identified.
Preventability	To date, no marker of increased risk has been identified. The occurrence of TTP cannot be prevented, but the risk of poor outcome of these events can be reduced through early detection methods and subsequent prompt treatment. Monthly monitoring of lab parameters and clinical signs or symptoms suggestive of TTP (eg, Purplish spots on the skin or in the mouth due to bleeding under the skin, fatigue, fever, headache, seizures or jaundice and/or dark urine) can facilitate early identification of the rare condition of TTP.
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of TTP in MS patients who have received alemtuzumab is not expected to have any public health impact.

CI: Confidence Interval; DLP: Data Lock Point; MS: Multiple Sclerosis; NORD: National Organization for Rare Disorders; TTP: Thrombotic Thrombocytopenic Purpura; RMS: Relapsing Multiple Sclerosis.

Table 27 - Important identified risk: Adult Onset Still's Disease (AOSD)

Identified Risk	Adult Onset Still's Disease (AOSD)
Potential mechanism	Proinflammatory cytokine induction triggered by activated immune cells is the suspected alemtuzumab-induced pathophysiology.
Evidence source(s) and strength of evidence	Postmarketing.
Characterization of the risk	**Frequency with 95% CI** There were no cases of AOSD reported with alemtuzumab either in active-clinical trials/clinical development program in MS. **Postmarketing experience** Cases of AOSD reported in the postmarketing setting at the current DLP were reviewed and were found to be consistent with known safety profile of alemtuzumab. **Severity and Nature of Risk** Cases meeting the criteria for diagnosis of AOSD were moderate to severe in intensity. A diagnosis of AOSD is most widely made using the Yamaguchi criteria, by meeting at least 5 criteria, of which 2 are major (fever >39˚C for ≥1 week, arthralgia or arthritis ≥2 weeks, rash, leukocytosis >10 000 mm^3 with 80% polymorphonuclear cells) and no exclusions are met (infections, malignancies, rheumatic disease). (62) Minor symptoms include sore throat, lymphadenopathy, hepatomegaly/splenomegaly, abnormal liver function tests, negative test for antineutrophil cytoplasmic antibodies (ANCA) and rheumatoid factor. **Seriousness and Outcomes** Most cases were assessed as serious. The majority of cases were reported as recovering or unknown at the time of report. There were no fatal outcomes reported.

Identified Risk	Adult Onset Still's Disease (AOSD)
	Background incidence/prevalence Adult Onset Still's Disease is a rare, systemic, inflammatory disorder of unknown etiology with an estimated incidence of 0.14-0.40 cases per 100 000 people and a prevalence of 1-34 cases per million people. (63) **Impact on individual patient** Adult Onset Still's Disease is a rare and potentially life-threatening secondary inflammatory disease. Severe life-threatening complications like HLH and macrophage activation syndrome (MAS) can occur. Progressive courses cause continuous inflammation that is responsible for chronic and frequently erosive joint involvement with regular system flare. (64)
Risk factors and risk groups	In the general population, AOSD is most often seen in young adults, with a higher prevalence in women. (63)
Preventability	To date, no marker of increased risk has been identified. The occurrence of AOSD cannot be prevented. Diagnosis of AOSD is often difficult and typically delayed due to the presence of several non-specific symptoms and the absence of characteristic serological biomarkers, but an early and accurate diagnosis may lead to better outcomes and would avoid severe life-threatening complications like HLH/MAS.
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of AOSD in MS patients who have received alemtuzumab is not expected to have any public health impact

ANCA: Antineutrophil Cytoplasmic Antibodies; AOSD: Adult Onset Still's Disease; CI: Confidence Interval; DLP: Data Lock Point; HLH: Hemophagocytic Lymphohistiocytosis; RMS: Relapsing Multiple Sclerosis; MAS: Macrophage Activation Syndrome; MS: Multiple Sclerosis.

Table 28 - Important identified risk: Autoimmune Encephalitis (AIE)

Identified Risk	Autoimmune Encephalitis (AIE)
Potential mechanism	Secondary B cell autoimmunity caused by the imbalances and interactions in the different immune cell subsets during the B cell repopulation stage
Evidence source(s) and strength of evidence	Postmarketing.
Characterization of the risk	**Frequency with 95% CI** In clinical studies, four cases were identified; two involving long time to onset making causal association less likely and remaining two had limited information. **Postmarketing experience** Cases of AIE reported in the postmarketing setting at the current DLP were reviewed and were found to be consistent with known safety profile of alemtuzumab. **Severity and Nature of Risk** Majority of autoimmune encephalitis cases with known intensity were moderate. Autoimmune encephalitis is a group of conditions that occur when the body's immune system mistakenly attacks healthy brain cells, leading to inflammation of the brain. Autoimmune encephalitis is confirmed by the presence of neural autoantibodies as well as a variety of clinical manifestations like subacute onset of working memory, altered mental status, psychiatric symptoms, neurological findings and seizures.

Identified Risk	Autoimmune Encephalitis (AIE)
	Seriousness and Outcomes No fatalities were reported. The majority of cases were serious. Out of all cases with known outcome, majority of cases recovered or were in the recovering stage. Autoimmune Encephalitis is a common cause of non-infectious encephalitis, with a variety of clinical manifestation, some of which may mimic an MS relapse such as: difficulty with balance, weakness or numbness, autonomic disturbances, speech or vision changes, behavior changes, impaired memory and understanding. **Background incidence/prevalence** The incidence of autoimmune encephalitis in a general population, defined using the criteria set out by Graus et al, is estimated to be 1.2/100 000 patient-years. (65)(66) **Impact on individual patient** If untreated encephalitis can cause long term neurological sequelae. The clinical evidence suggests that early treatment, with initiation of immunotherapy while other studies and comprehensive antibody tests are processed, improves outcome. Therefore, there may be significant impact on individual patients and early detection and treatment can result in favorable outcomes
Risk factors and risk groups	None identified.
Preventability	To date, no marker of increased risk has been identified. The occurrence of AIE cannot be prevented, but the risk of poor outcome of these events can be reduced through early diagnostic and subsequent prompt treatment. Diagnosis of AIE is often difficult due to the presence of several non-specific symptoms and the delayed detection of the neural autoantibodies but an early and accurate diagnosis may lead to better outcomes and would avoid severe life-long complications.
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of AIE in MS patients who have received alemtuzumab is not expected to have any public health impact.

AIE: Autoimmune Encephalitis; CI; Confidence Interval; DLP: Data Lock Point; MS: Multiple Sclerosis; RMS: Relapsing Multiple Sclerosis.

Table 29 - Important identified risk: Acute acalculous cholecystitis (AAC)

Identified risk	Acute acalculous cholecystitis (AAC)
Potential mechanism	Currently, a plausible pathophysiological mechanism is unknown. The usual risk factors for AAC are infections including sepsis and gallbladder ischaemia due to hypotension or other cardiovascular abnormalities. In addition, drug-induced biliary stasis seems a plausible mechanism. Immunosuppression predisposes to infections, presumably including the gallbladder; and alteration of bile composition resulting in irritation of gallbladder mucosa is a theoretical possibility. However, none of these mechanisms were evident in the reported cases.
Evidence source(s) and strength of evidence	Clinical and postmarketing.
Characterization of the risk	**Frequency with 95% CI** There were 9 cases of AAC identified in clinical trials. In controlled clinical studies, 0.2% of alemtuzumab-treated MS patients developed AAC, compared to 0% of patients treated with IFNβ-1a. In ongoing studies, LPS13649 and

Identified risk	Acute acalculous cholecystitis (AAC)
	TDU14260 studies through 12-Jan-2018, one event was reported with the verbatim term of alithiasic cholecystitis. **Severity and nature of risk** Acute acalculous cholecystitis (AAC) cases were moderate to severe in severity. None of the events reported resulted in death in MS clinical trials. In both cases in controlled clinical trials the patients had confounding risk factors and were assessed as not related to alemtuzumab; definite treatment was cholecystectomy. These cases were reported within 2 months of alemtuzumab dosing. **Postmarketing spontaneous individual case safety reports** Cumulatively through the current DLP, cases of acute cholecystitis have been reported and reviewed. Majority of patients were females. The reported cases of AAC following the administration of alemtuzumab were consistent in nature and severity with the clinical features collected during drug development identifying no new safety concerns. Most patients were treated conservatively with antibiotics and recovered without surgical intervention, whereas others underwent cholecystectomy. Cases of AAC will continue to be monitored. **Seriousness/outcomes** The cases were predominantly moderate to severe in intensity and all were serious. Outcome was reported as recovered for majority of the cases. **Background incidence/prevalence** No study examining the incidence or prevalence of AAC in the general population was found. The frequency of AAC in patients with MS has not been quantified. **Impact on individual patient** If untreated, AAC can progress to perforation or gangrene of the gallbladder and extra biliary abscess formation and subsequent peritonitis. Impact may be significant.
Risk factors and risk groups	None identified. There is no indication that patients with pre-existing gallbladder conditions are at greatest risk of developing an event. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Preventability	To date, no marker of increased risk has been identified. The occurrence of AAC cannot be prevented, but the risk of poor outcome of these events can be reduced through early detection methods and subsequent prompt treatment. Preventability measures are described in Part V.1 (rRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of AAC in MS patients who have received alemtuzumab is not expected to have any public health impact.

AAC: Acute Acalculous Cholecystitis; CI: Confidence Interval; DLP: Data Lock Point; IFNβ: Interferon Beta; MS: Multiple Sclerosis; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure.

Table 30 - Important potential risk: Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus [T1DM], Guillain-Barré syndrome [GBS], Sarcoidosis)

<table>
<tr><td>Potential Risk</td><td>Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus [T1DM], Guillain-Barré syndrome [GBS], sarcoidosis)</td></tr>
<tr><td>Potential mechanism</td><td>Autoimmunity is a known complication of immune reconstitution from lymphocytopenia. Autoimmunity is considered a theoretical risk with alemtuzumab treatment due to the pattern of T-and B-cell depletion and repopulation.</td></tr>
<tr><td>Evidence source(s) and strength of evidence</td><td>Clinical studies and postmarketing.</td></tr>
<tr><td>Characterization of the risk</td><td><u>Frequency with 95% CI</u>
Other autoimmune events were identified using a customized MedDRA query (CMQ) of autoimmune disorders that excluded events of cytopenias, ITP, and thyroid disorders. Additionally, events of cytopenia were medically reviewed and only 2 PT terms met the criteria for autoimmune cytopenias (autoimmune haemolytic anaemia and Autoimmune pancytopenia). These 2 PTs are not included in the table below.
Table 30a - Number (%) of Alemtuzumab-Treated Patients with Other Autoimmune Disorders (excluding Autoimmune Cytopenias and immune thrombocytopenic purpura and Thyroid Adverse Events) in MS Clinical Trials
<table>
<tr><th rowspan="2">Preferred Term</th><th colspan="3">Alemtuzumab</th></tr>
<tr><th>12 mg/day (N = 1217)</th><th>24 mg/day (N = 269)</th><th>Pooled (N = 1486[a])</th></tr>
<tr><td>Any Event</td><td>31 (2.5)</td><td>5 (1.9)</td><td>36 (2.4)</td></tr>
<tr><td>Chronic gastritis</td><td>14 (1.2)</td><td>2 (0.7)</td><td>16 (1.1)</td></tr>
<tr><td>Myelitis transverse</td><td>3 (0.2)</td><td>1 (0.4)</td><td>4 (0.3)</td></tr>
<tr><td>Vitiligo</td><td>4 (0.3)</td><td>0 (0.0)</td><td>4 (0.3)</td></tr>
<tr><td>Alopecia areata</td><td>3 (0.2)</td><td>0 (0.0)</td><td>3 (0.2)</td></tr>
<tr><td>Sjogren's syndrome</td><td>2 (0.2)</td><td>0 (0.0)</td><td>2 (0.1)</td></tr>
<tr><td>Type 1 diabetes mellitus</td><td>2 (0.2)</td><td>0 (0.0)</td><td>2 (0.1)</td></tr>
<tr><td>Autoimmune uveitis</td><td>1 (0.1)</td><td>0 (0.0)</td><td>1 (0.1)</td></tr>
<tr><td>Diabetes mellitus</td><td>0 (0.0)</td><td>1 (0.4)</td><td>1 (0.1)</td></tr>
<tr><td>Goodpasture's syndrome</td><td>1 (0.1)</td><td>0 (0.0)</td><td>1 (0.1)</td></tr>
<tr><td>Neuralgic amyotrophy</td><td>0 (0.0)</td><td>1 (0.4)</td><td>1 (0.1)</td></tr>
<tr><td>Rheumatoid arthritis</td><td>1 (0.1)</td><td>0 (0.0)</td><td>1 (0.1)</td></tr>
</table>
a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.
Source: Pool C, Table 3.3.18.6.2</td></tr>
</table>

Potential Risk	Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus [T1DM], Guillain-Barré syndrome [GBS], sarcoidosis)
	CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; MS: Multiple Sclerosis; N: Total Number of Patient. There was 1 case (0.1%) of autoimmune pancytopenia and 2 cases (0.1%) of autoimmune haemolytic anaemia among the 1486[a] patients in the MS clinical trials. There were 133 autoimmune disorder cases reported with alemtuzumab in clinical trials. Events observed in the postmarketing setting were similar in nature, severity and frequency to those reported in the clinical trial setting and consistent with the known safety profile of alemtuzumab (Lemtrada). The review of the other autoimmune disorder cases did not trigger any validated safety signal. Cases of other autoimmune disorder will continue to be monitored. **Myasthenic syndrome** In the postmarketing setting, cases of reported myasthenic syndrome/myasthenia gravis at the current DLP were reviewed and were found to be consistent with the known safety profile of alemtuzumab. The evidence was considered insufficient to support a causal relationship with alemtuzumab, however based on the potential mechanism of action, the role of alemtuzumab could not be completely ruled out in these cases. **Type 1 Diabetes Mellitus** Cases of T1DM reported in the postmarketing setting at the current DLP were reviewed and were found to be consistent with the known safety profile of alemtuzumab. In these cases, the evidence was insufficient to support a direct causal relationship with alemtuzumab and T1DM. Thyroid disorders were reported a condition that is frequently associated with abnormal glucose metabolism and/or insulin resistance. Alemtuzumab is known to cause autoimmune thyroid disease, and therefore, a secondary effect of alemtuzumab cannot be ruled out in these cases. **Guillain-Barre syndrome** Cases of GBS reported in the postmarketing setting at the current DLP were reviewed and were found to be consistent with the known safety profile of alemtuzumab. In most of the identified cases, bacterial-and/or viral infection was part of the medical history and identified as a relevant risk factor. The exact temporal relationship between infection and GBS debut was not indicated. Whether a recent respiratory or gastrointestinal infection preceded the GBS in most of the cases, or whether these infections appeared as a complication during the course of GBS, was not specified in the vast majority of the reported cases. The evidence was considered insufficient to support a causal relationship with alemtuzumab, however based on the potential mechanism of action, the role of alemtuzumab could not be completely ruled out in these cases. **Sarcoidosis** Cases of sarcoidosis reported in the postmarketing setting at the current DLP were reviewed and were found to be consistent with the known safety pattern of this risk for alemtuzumab. **Severity and nature of risk** Of the events of other autoimmune disorders including cytopenias that were reported in alemtuzumab-treated patients in MS clinical trials, one event of autoimmune pancytopenia was life-threatening (Grade 4), 3 events, 1 each of T1DM, diabetes mellitus, and Goodpasture's syndrome were severe (grade 3) and the remaining events were mild or moderate severity (Grades 1 and 2). All cases of myasthenic syndrome for which intensity is known were moderate to severe in severity. The Lambert-Eaton Myasthenic Syndrome (LEMS) case was considered severe as patient presented to hospital with quadriparesis, dysphagia and areflexia. Multiple prior disease modifying treatments were confounders in this case. Although there

Potential Risk	Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus [T1DM], Guillain-Barré syndrome [GBS], sarcoidosis)
	was insufficient evidence to support a causal association between alemtuzumab and myasthenic syndrome, based on the mechanism of action the role of alemtuzumab cannot be excluded. Majority of events of T1DM were moderate in severity. There is insufficient evidence to support direct causal association between alemtuzumab and T1DM, however the role of preceding alemtuzumab induced thyroid disorders cannot be completely ruled out. Most of the GBS events were unknown in intensity. One event was reported severe and one event was of grade 4. Whether a recent respiratory or gastrointestinal infection preceded the onset of GBS or whether these infections appeared as a complication during the course of GBS was not specified in the vast majority of the reported cases. Although the evidence was considered insufficient to support a causal association between alemtuzumab and GBS, based on the potential mechanism of action, the role of alemtuzumab could not be completely ruled out in these cases. For the events of sarcoidosis with known intensity, two events of sarcoidosis were of Grade 3 severity and rest of the events of sarcoidosis were mild to moderate in severity. In majority of the cases, diagnostic criteria for sarcoidosis were not reported such as laboratory serum angiotensin-converting enzyme, biopsy of lymph nodes and/or imaging data (chest X-ray, computed tomography scan). **Seriousness/outcomes** The occurrence of other autoimmune disorders including cytopenias in alemtuzumab-treated MS patients is rare. Two fatal cases of anaemias haemolytic immune were noted. No fatal outcomes were reported for the events myasthenic syndrome, T1DM and GBS. Majority of events of myasthenic syndrome described in postmarketing setting, were considered serious. There were six cases that required hospitalization and two cases were associated with disability (however confounded with the underlying disorder of MS). Majority of the cases were considered medically significant. Majority of the events were reported with unknown outcome followed by recovered and not recovered. The majority of T1DM cases were considered serious. The outcome was reported as not recovered for majority of the events followed by recovering/resolving. Of the GBS events retrieved, 1 event of chronic inflammatory demyelinating polyneuropathy (CIDP) was considered non-serious while the remaining were all serious. Outcome was reported as not recovered for majority of the events. The majority of events of sarcoidosis were reported as serious. The outcome was reported as not recovered for majority of the events followed by recovering/resolving. **Background incidence/prevalence** Clustering of autoimmune diseases within individuals and families is a well-recognized phenomenon (see also “other antibody-mediated autoimmune diseases” below). The frequency of autoimmune haemolytic anaemia in patients with MS has not been quantified. Incident case reports of MS patients with autoimmune haemolytic anaemia either in combination with autoimmune thrombocytopenia (67) or during IFNβ-1b treatment (68) have been published. To assess the background incidence of autoimmune diseases, Klein et al. (69) studied the incidence of 11 autoimmune diseases in the Kaiser Permanente Northern California population. The incidence of autoimmune haemolytic anaemia was estimated to be 0.8 per 100 000 person-years. **Impact on individual patient** With the currently proposed monitoring activities (ie, monthly blood tests), the impact is considered low.

Potential Risk	Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus [T1DM], Guillain-Barré syndrome [GBS], sarcoidosis)
Risk factors and risk groups	Not identified. It is not known whether development of 1 treatment-emergent antibody mediated autoimmune disorder predisposes to development of additional antibody mediated autoimmune diseases. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Preventability	To date, no markers of increased risk have been identified. The occurrence of other autoimmune disorders including cytopenia cannot be prevented, but poor outcome of these autoimmune disorders can be prevented through early detection methods and subsequent prompt treatment. Preventability measures are described in Part V.1 (rRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of other autoimmune disorders including cytopenias in MS patients who have received alemtuzumab is not expected to have any public health impact.

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

AIH: Autoimmune Hepatitis; CI: Confidence Interval; CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; CMQ: Customized MedDRA Query; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; DLP: Data Lock Point; GBS: Guillain-Barre Syndrome; IFNβ: Interferon Beta; ITP: Immune Thrombocytopenic Purpura; LEMS: Lambert-Eaton Myasthenic Syndrome; MedDRA: Medical Dictionary for Regulatory Activities; MS: Multiple Sclerosis; N: Total Number of Patient; PT: Preferred Term; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure; T1DM: Type 1 Diabetes Mellitus.

Table 31 - Important potential risk: Malignancies

Potential Risk	Malignancies
Potential mechanism	Immune suppression may lead to development of virally induced cancers (eg, lymphoma, cervical cancer) or other cancers resulting from reduced immune surveillance. This is a known risk common to immunosuppressive therapies, likely due to failure of immune surveillance.
Evidence source(s) and strength of evidence	Clinical studies and postmarketing.
Characterization of the risk	**Frequency with 95% CI** To date, there is no evidence of increased risk of malignancy in alemtuzumab-treated MS patients. In active-controlled trials, malignancies occurred in 3.0% of alemtuzumab-treated patients compared to approximately 0.4% of IFNβ-1a patients. Although few in number, thyroid cancer and basal cell carcinoma were the most common types of malignancies reported among alemtuzumab-treated patients. Of the 6 thyroid malignancy cases that occurred in alemtuzumab-treated patients, 2 occurred in patients who reported relevant preexisting conditions prior to the cancer diagnosis, including existing thyroid neoplasm and thyroid nodules. Within the clinical trials, the cases (microcarcinomas) in the alemtuzumab-treated population were all found incidentally during the diagnostic work-up of recently identified underlying thyroid conditions and may be a result of the increased diagnostic scrutiny for alemtuzumab patients compared to the IFNβ-1a patients who did not have a similar thyroid assessment. The incidence of thyroid cancer reported in alemtuzumab studies (0.4%) is within the expected prevalence/incidence reported in published medical

Potential Risk	Malignancies

studies of autopsy studies, screening of general population and diagnostic workup of patients with thyroid disorders as indicated in literature.

The annualized rates of malignancy were similar across all treatment groups in the MS clinical trials (alemtuzumab 12 and 24 mg/day and IFNβ-1a).

Table 31a - Number (%) of Alemtuzumab-Treated Patients with Malignancies in MS Clinical Trials

Preferred Term	Alemtuzumab		
	12 mg/day (N = 1217)	24 mg/day (N = 269)	Pooled (N = 1486[a])
Any Malignancy	31 (2.5)	13 (4.8)	44 (3.0)
Thyroid neoplasm	6 (0.5)	1 (0.4)	7 (0.5)
Basal cell carcinoma	4 (0.3)	5 (1.9)	9 (0.6)
Papillary thyroid cancer	4 (0.3)	1 (0.4)	5 (0.3)
Malignant melanoma in situ	3 (0.2)	0 (0.0)	3 (0.2)
Breast cancer	2 (0.2)	1 (0.4)	3 (0.2)
Neoplasm skin	2 (0.2)	0 (0.0)	2 (0.1)
B-cell lymphoma	1 (0.1)	0 (0.0)	1 (0.1)
Insulinoma	1 (0.1)	0 (0.0)	1 (0.1)
Invasive lobular breast carcinoma	1 (0.1)	0 (0.0)	1 (0.1)
Keratoacanthoma	1 (0.1)	0 (0.0)	1 (0.1)
Malignant melanoma	1 (0.1)	0 (0.0)	1 (0.1)
Metastatic malignant melanoma	1 (0.1)	0 (0.0)	1 (0.1)
Non-small cell lung cancer	1 (0.1)	0 (0.0)	1 (0.1)
Ovarian neoplasm	1 (0.1)	0 (0.0)	1 (0.1)
Pancreatic neuroendocrine tumour	1 (0.1)	0 (0.0)	1 (0.1)
Pituitary tumour	1 (0.1)	0 (0.0)	1 (0.1)
Squamous cell carcinoma	1 (0.1)	0 (0.0)	1 (0.1)
Squamous cell carcinoma of skin	1 (0.1)	0 (0.0)	1 (0.1)
Thyroid cancer	1 (0.1)	0 (0.0)	1 (0.1)
Cervix carcinoma	0 (0.0)	1 (0.4)	1 (0.1)
Cervix carcinoma stage II	0 (0.0)	1 (0.4)	1 (0.1)
Colon cancer	0 (0.0)	1 (0.4)	1 (0.1)

Potential Risk	Malignancies

Granular cell tumour	0 (0.0)	1 (0.4)	1 (0.1)
Invasive ductal breast carcinoma	0 (0.0)	1 (0.4)	1 (0.1)
Vulval cancer stage 0	0 (0.0)	1 (0.4)	1 (0.1)

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

Source: Pool C, 3.3.9.1.1, PT Terms of: Thyroidectomy, Parathyroidectomy, Liver scan abnormal, Carbohydrate antigen 125 increased, and Carbohydrate antigen 19-9 increased were excluded from the analysis.

CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; MS: Multiple Sclerosis; N: Total Number of Patient; PT: Preferred Term.

Table 31b - Number (Rate) of Malignancies in Phase 2 and Phase 3 MS Clinical Trials Through 2-Year Follow-up

Preferred Term	SC IFNβ-1a (N = 496)	Alemtuzumab		
		12 mg/day (N = 919)	24 mg/day (N = 269)	Pooled (N = 1188)
Total Person-Years	916	1831	532	2363
Any Malignancy	3 (0.003)	4 (0.002)	4 (0.008)	8 (0.003)
Thyroid cancer	0 (0.000)	3 (0.002)	0 (0.000)	3 (0.001)
Basal cell carcinoma	2 (0.002)	1 (0.001)	1 (0.002)	2 (0.001)
Acute myeloid leukemia	1 (0.001)	0 (0.000)	0 (0.000)	0 (0.000)
Cervix carcinoma	0 (0.000)	0 (0.000)	1 (0.002)	1 (0.000)
Colon cancer	0 (0.000)	0 (0.000)	1 (0.002)	1 (0.000)
Vulval cancer stage 0	0 (0.000)	0 (0.000)	1 (0.002)	1 (0.000)

Source: Pool A, table 1.3.9.2

IFNβ-1a: Interferon Beta-1a; MS: Multiple Sclerosis; N: Total Number of Patient; SC: Subcutaneous.

Table 31c - Number (Rate) of Malignancies in Alemtuzumab-Treated Patients in MS Clinical Trials

Preferred Term	Alemtuzumab		
	12 mg/day (N = 1217)	24 mg/day (N = 269)	Pooled (N = 1486[a])
Total Person-years	6858	1777	8635
Any Malignancy	38 (0.554)	15 (0.844)	53 (0.614)
Basal cell carcinoma	6 (0.087)	6 (0.338)	12 (0.139)
Thyroid neoplasm	7 (0.102)	1 (0.056)	8 (0.093)

Potential Risk	Malignancies

Papillary thyroid cancer	4 (0.058)	1 (0.056)	5 (0.058)
Breast cancer	2 (0.029)	1 (0.056)	3 (0.035)
Malignant melanoma in situ	3 (0.044)	0 (0.000)	3 (0.035)
Neoplasm skin	2 (0.029)	0 (0.000)	2 (0.023)
Pituitary tumour	2 (0.029)	0 (0.000)	2 (0.023)
B-cell lymphoma	1 (0.015)	0 (0.000)	1 (0.012)
Cervix carcinoma	0 (0.000)	1 (0.056)	1 (0.012)
Cervix carcinoma stage II	0 (0.000)	1 (0.056)	1 (0.012)
Colon Cancer	0 (0.000)	1 (0.056)	1 (0.012)
Granular cell tumour	0 (0.000)	1 (0.056)	1 (0.012)
Insulinoma	1 (0.015)	0 (0.000)	1 (0.012)
Invasive ductal breast carcinoma	0 (0.000)	1 (0.056)	1 (0.012)
Invasive lobular breast carcinoma	1 (0.015)	0 (0.000)	1 (0.012)
Keratoacanthoma	1 (0.015)	0 (0.000)	1 (0.012)
Malignant melanoma	1 (0.015)	0 (0.000)	1 (0.012)
Metastatic malignant melanoma	1 (0.015)	0 (0.000)	1 (0.012)
Non-small cell lung cancer	1 (0.015)	0 (0.000)	1 (0.012)
Ovarian neoplasm	1 (0.015)	0 (0.000)	1 (0.012)
Pancreatic neuroendocrine tumour	1 (0.015)	0 (0.000)	1 (0.012)
Squamous cell carcinoma	1 (0.015)	0 (0.000)	1 (0.012)
Squamous cell carcinoma of skin	1 (0.015)	0 (0.000)	1 (0.012)
Thyroid Cancer	1 (0.015)	0 (0.000)	1 (0.012)
Vulval cancer stage 0	0 (0.000)	1 (0.056)	1 (0.012)

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

Source: Pool C, Table 3.3.9.1.3 PT Terms of: Thyroidectomy, Parathyroidectomy, Liver scan abnormal, Carbohydrate antigen 125 increased, and Carbohydrate antigen 19-9 increased were excluded from the analysis.

Potential Risk	Malignancies

CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; MS: Multiple Sclerosis; N: Total Number of Patient; PT: Preferred Term.

Postmarketing experience

Cumulatively through the current DLP, cases of malignancies in postmarketing setting were retrieved and reviewed. The reported cases of malignancies were found to be similar in nature, severity to those reported in the clinical trial setting and consistent with the known safety profile of alemtuzumab (Lemtrada). The review of the malignancies cases did not trigger any validated safety signal. Cases of malignancies will continue to be monitored.

Severity and nature of risk

Among the reported malignancies, the most common type of malignancies were, malignant neoplasm and basal cell carcinoma. (all with Grade 3 or lower).

Table 31d - Number (%) of Alemtuzumab-Treated Patients (N = 1486[a]) with Malignancies by Maximum Severity in MS Clinical Trials

Preferred Term	Severity Grade				
	1	2	3	4	5
Any Event	8 (0.5)	14 (0.9)	16 (1.1)	5 (0.3)	1 (0.1)
Basal cell carcinoma	0 (0.0)	5 (0.3)	4 (0.3)	0 (0.0)	0 (0.0)
Thyroid neoplasm	5 (0.3)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Papillary thyroid cancer	1 (0.1)	1 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)
Breast cancer	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)	0 (0.0)
Malignant melanoma in situ	0 (0.0)	1 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)
Neoplasm skin	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
B-cell lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Cervix carcinoma	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cervix carcinoma stage II	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Granular cell tumour	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Insulinoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Invasive ductal breast carcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Invasive lobular breast carcinoma	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Keratoacanthoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant melanoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Metastatic malignant melanoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Non-small cell lung cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Ovarian neoplasm	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Potential Risk	Malignancies

Pancreatic neuroendocrine tumour	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pituitary tumour	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Squamous cell carcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Squamous cell carcinoma of skin	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Thyroid cancer	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Vulval cancer stage 0	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

Source: Pool C, Table 3.3.9.2 PT Terms of: Thyroidectomy, Parathyroidectomy, Liver scan abnormal, Carbohydrate antigen 125 increased, and Carbohydrate antigen 19-9 increased were excluded from the analysis.

CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; MS: Multiple Sclerosis; N: Total Number of Patient; PT: Preferred Term.

Seriousness/outcomes

Majority of the malignancies are considered serious. Among the 1486 alemtuzumab-treated patients in MS clinical trials, there were 44 (3.0%) patients who reported events of treatment-emergent malignancies. One event of non-small cell lung cancer was fatal (Grade 5) in a patient who had an extensive history of tobacco use.

Malignancies have also been reported in MS patients who received alemtuzumab outside of Sanofi Genzyme clinical trials. A patient with RRMS who received alemtuzumab at 24 mg/day for 2 courses (192 mg total dose) developed Castleman's disease 31 months after the first course. (70) The patient was treated with chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab) and the disease went into remission. A patient with aggressive relapsing MS who received alemtuzumab at 24 mg/day for 1 course (120 mg total dose) experienced rapid growth and changed appearance of a longstanding melanocytic naevus 6 months after alemtuzumab. The lesion was excised with no residual disease.

Background incidence/prevalence

The current literature does not support an increased frequency of cancers overall in MS patients. Some studies, but not all, found increased risk of brain cancer, breast cancer, and urinary organ cancer. (71)(72)

Impact on individual patient

There is no signal of increased risk of malignancy in alemtuzumab-treated MS patients; the impact, if any, is unknown at this time.

Risk factors and risk groups	Patients with a prior history of basal cell carcinoma are at increased risk for developing subsequent basal cell carcinoma. Women with HPV infections of the uterine cervix are at increased risk for cervical cancer. This risk may increase after immune suppression by alemtuzumab. There was no dose related pattern identified in the reported cases.
Preventability	Preventability measures are described in Part V.1 (rRMMs).

Potential Risk	Malignancies
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	The occurrence of malignancies in MS patients who have received alemtuzumab is not expected to have any public health impact.

CADASIL: Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; CI: Confidence Interval; DLP: Data Lock Point; HPV: Human Papilloma Virus; IFNβ: Interferon Beta; MS: Multiple Sclerosis; N: Total Number of Patient; PT: Preferred Term; rRMM: Routine Risk Minimization Measure; RRMS: Relapsing Remitting Multiple Sclerosis; SC: Subcutaneous.

Table 32 - Important potential risk: Progressive multifocal leukoencephalopathy (PML)

Potential risk	Progressive multifocal leukoencephalopathy (PML)
Potential mechanism	The MAH considers that a risk of developing PML in alemtuzumab treated patients is not supported by current clinical evidence about the product. Moreover, to the best of MAH's knowledge and based on the data presented there is no substantiated mechanism to illustrate such a risk: • Alemtuzumab) is a first-in-class, anti-CD52 immunotherapy. Other MS immune therapies, including those that cause lymphopenia and carry a risk of PML, have important differences in their posology and mechanisms of action that may differentiate from alemtuzumab in their risk profiles; • It is known that patients show lymphopenia in blood tests after alemtuzumab; however, the residual lymphocytes and the cells of the innate immune system appear to have normal functional capacity; • Evidence from clinical studies indicates that lymphocyte counts are not a predictor of infection risk with alemtuzumab.
Evidence source(s) and strength of evidence	Postmarketing.
Characterization of the risk	**Frequency with 95% CI** No case of PML has been reported (in clinical studies of alemtuzumab treated MS patients). PML has been reported in the postmarketing setting in patients with other risk factors, specifically prior treatment with MS products associated with PML. The most relevant literature case describes a [redacted] patient diagnosed with MS who previously received ineffective treatments with interferon-beta, fingolimod, glatiramer acetate and dimethyl fumarate. Two months after receiving the second course of alemtuzumab, a diagnosis of PML was suspected due to clinical and imaging manifestations with the presence of John Cpunningham Virus (JCV) in cerebrospinal fluid (CSF), following Immune Reconstitution Inflammatory Syndrome (IRIS). The diagnosis of PML in this case could not be confirmed. Symptoms gradually improved and the patient was discharged. Treating physician suspected the diagnosis of "encephalitis of indeterminate etiology". **Postmarketing experience** Progressive multifocal leukoencephalopathy has been reported in the postmarketing setting in patients with other risk factors, specifically prior treatment with MS products associated with PML. **Severity and nature of risk** Progressive multifocal leukoencephalopathy is a rare, potentially fatal, demyelinating disease of the human brain due to reactivation of JCV, a human polyomavirus, in immunocompromised hosts.

Potential risk	Progressive multifocal leukoencephalopathy (PML)
	A standardized case definition for PML was designed by Mentzer D, et al to define levels of diagnostic certainty of reported PML cases following treatment with monoclonal antibodies based on the following key elements: clinical symptoms, MRI, virological and histopathological testing. (73) Based on the case definition, PML is diagnosed in: • Cases of evidence of PML from a brain biopsy or autopsy or • Clinical symptoms consistent with PML and brain MRI characteristic of PML described in a radiological report or based on expert review of MRI and Polymerase Chain Reaction (PCR) for JCV DNA in CSF positive; • Clinical symptoms consistent with PML and PCR for JCV DNA in CSF positive; • Clinical symptoms consistent with PML and brain MRI characteristic of PML and PCR for JCV DNA in CSF or PCR assay for JCV DNA in CSF obtained by a laboratory with unknown virological expertise or unknown validation status of assay; • Polymerase chain reaction for JCV DNA in CSF positive and brain MRI characteristic of PML; or • Polymerase chain reaction for JCV DNA in CSF positive and IRIS (eg, after stopping treatment with suspected medicinal product and/or after therapy). **Seriousness/outcomes** All events of PML described in postmarketing setting, were considered serious. A total of 2 fatal cases were reported. Of cases with known outcome, majority of the cases reported outcome as not recovered. **Background incidence/prevalence** Progressive multifocal leukoencephalopathy is a rare disease in both the general population and MS population. Estimates from cohort studies report the incidence of PML to range from 0.0 per 100 000 person-years, 95% CI (0.0-0.4) to 0.27 per 100 000 person years in the general population. (74)(75) Another cohort study from a US medical claims database, that followed MS patients for 57 117 person years did not find any chart-confirmed cases of PML. (74) Until 2013, the only cases of PML in MS patients reported in literature were those who had been treated with Tysabri® (natalizumab). (76) The incidence of PML in MS patients who were taking Tysabri (natalizumab) therapy in the postmarketing setting was 2.129 cases per 1000 patients who were on therapy for at least one month. (77) The risk for PML increased with longer duration of Tysabri (natalizumab) therapy with the greatest increase in risk occurring in those who had therapy for 25-48 months of duration. Progressive multifocal leukoencephalopathy has also been reported among MS patients using fingolimod (78) or dimethyl fumarate (79)(80), but a significantly elevated risk of PML from exposure to these drugs has not been demonstrated, unlike Tysabri (natalizumab) which has shown an increasing risk of PML in patients with longer treatment time. Progressive multifocal leukoencephalopathy also occurs (indeed, was first described) in patients with chronic lymphocytic leukemia (CLL). In a US claims based cohort, CLL patients had an incidence of PML of 11.1 chart-confirmed cases per 100 000 person-years. (74) The incidence of PML among alemtuzumab (CAMPATH, MABCAMPATH treated CLL patients is not increased above the background CLL incidence. **Impact on individual patient** There is no signal of increased risk of PML in alemtuzumab-treated MS patients; the impact, if any, is unknown at this time. However, in general, PML is commonly associated with severe neurologic morbidity and high risk of mortality.

Potential risk	Progressive multifocal leukoencephalopathy (PML)
Risk factors and risk groups	Patients who are seropositive for JCV antibodies or are HIV positive are at increased risk for PML. Chronic lymphocytic leukemia and lymphoproliferative disorders are also associated with increased risk of PML. Prior exposure to immunosuppressive therapies also increases the risk for development of PML. There was no dose related pattern identified in the reported cases.
Preventability	Progressive multifocal leukoencephalopathy is not preventable but early detection may improve outcome. Preventability measures are described in Part V.1 and Part V.2 (rRMMs).
Impact on the benefit-risk balance of the product	At the current DLP, the benefit-risk balance of alemtuzumab (Lemtrada) in the treatment of RMS remains favorable, when prescribed and used in agreement with the updated product information.
Public health impact	No impact on public health is to be expected.

CD: Cluster of Differentiation; CI: Confidence Interval; CLL: Chronic Lymphocytic Leukemia; CSF: Cerebrospinal Fluid; DLP: Data Lock Point; DNA: Deoxyribonucleic Acid; HIV: Human Immunodeficiency Virus; IRIS: Immune Reconstitution Inflammatory Syndrome; JCV: John Cunningham Virus; MAH: Marketing Authorization Holder; MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis; PCR: Polymerase Chain Reaction; PML: Progressive Multifocal Leukoencephalopathy; RMS: Relapsing Multiple Sclerosis; rRMM: Routine Risk Minimization Measure; US: United States.

SVII.3.2. Presentation of the missing information

Table 33 - Missing information: Pediatric use

Missing Information	Pediatric use
Evidence source(s)	No sufficient evidence from clinical studies and postmarketing data reported exists. Following article 20, a product-specific waiver for all subsets of the paediatric population was granted on 17-Jul-2020 (EMEA-001072-PIP01-10-M04), on the grounds that the "specific medicinal product is likely to be unsafe".
Population in need for further characterization	Pediatric MS patients exposed to alemtuzumab.

EMEA: European Medicines Agency; MS: Multiple Sclerosis.

Table 34 - Missing information: Use in patients aged >55 years (including use in elderly patients aged ≥65 years)

Missing Information	Use in patients aged >55 years (including use in elderly patients aged ≥65 years)
Evidence source(s)	No sufficient evidence from clinical studies and postmarketing data reported exists.
Population in need for further characterization	Multiple sclerosis patients aged >55 years (including use in elderly patients aged ≥65 years).

Table 35 - Missing information: Use in racial categories other than white

Missing Information	Use in racial categories other than white
Evidence source(s)	No sufficient evidence from clinical studies and postmarketing data reported exists. Relevant information may become available from PASS OBS13434 to characterize the long-term safety profile of alemtuzumab in patients with RRMS in a real-world setting.

Missing Information	Use in racial categories other than white
Population in need for further characterization	Multiple sclerosis patients with racial categories other than white.

PASS: Post-Authorization Safety Study; RRMS: Relapsing Remitting Multiple Sclerosis.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 36 - Summary of the safety concerns

Important identified risk	Infusion-associated reactions (IARs)
	Stroke (including haemorrhagic stroke)[a]
	Dissection of the cervicocephalic arteries[a]
	Myocardial infarction (MI) and myocardial ischaemia[a]
	Pulmonary alveolar haemorrhage (PAH)[a]
	Thrombocytopenia[a]
	Thyroid disorders
	Immune thrombocytopenic purpura (ITP)
	Nephropathies including anti-glomerular basement membrane (anti-GBM) disease
	Autoimmune hepatitis (AIH)
	Serious infections
	Haemophagocytic lymphohistiocytosis (HLH)
	Acquired Haemophilia A (AHA)
	Thrombotic thrombocytopenic purpura (TTP)
	Adult Onset Still's Disease (AOSD)
	Autoimmune Encephalitis (AIE)
	Acute acalculous cholecystitis (AAC)
Important potential risk	Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus [T1DM], Guillain Barre syndrome [GBS], sarcoidosis)
	Malignancies
	Progressive multifocal leukoencephalopathy (PML)
Missing information	Pediatric use
	Use in patients aged >55 years (including use in elderly patients aged ≥65 years)
	Use in racial categories other than white

a This risk is temporally associated with Lemtrada infusion.

AAC: Acute Acalculous Cholecystitis; AHA: Acquired Haemophilia A; AIE: Autoimmune Encephalitis; AIH: Autoimmune Hepatitis; AOSD: Adult Onset Still's Disease; GBM: Glomerular Basement Membrane; GBS: Guillain-Barre Syndrome; HLH: Haemophagocytic Lymphohistiocytosis; IAR: Infusion-Associated Reaction; ITP: Immune Thrombocytopenic Purpura; MI: Myocardial infarction; PAH: Pulmonary Alveolar Haemorrhage; PML: Progressive Multifocal Leukoencephalopathy; T1DM: Type 1 Diabetes Mellitus; TTP: Thrombotic Thrombocytopenic Purpura.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

As part of routine surveillance, several specific AEs follow-up forms are set-up to document new cases of some of the important risks for alemtuzumab:

- A "PML questionnaire/checklist" is to be attached to the corresponding completed AE/serious AE form at country level, to document spontaneous or solicited alemtuzumab cases of reported or suspected PML ([Annex 4]).
- As agreed in the context of Article 20 procedure and as requested by the PRAC during the EMEA/H/C/003718/II/0031 procedure, additional specific AE follow-up forms are set up to further assess the important identified risks "Stroke (including haemorrhagic stroke)[2]", "MI and myocardial ischaemia[2]", "Dissection of the cervicocephalic arteries[2]", "PAH[2]", "Thrombocytopenia[2]", "HLH" and "AIH". The forms are available in [Annex 4].

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

As part of the measures taken in the context of the Article 20 referral, the MAH has conducted two additional PASS studies (category 1):

- A non-interventional PASS to investigate drug utilization and safety monitoring patterns for Lemtrada (alemtuzumab). The aim of this study is to assess whether Lemtrada is prescribed in accordance with new risk minimization measures laid out in new EU-SmPC subsequent to Article 20 procedure. The risk minimization measures are inclusive of newly revised indication, additional contraindications, and additional monitoring recommendations. This study is completed.
- A non-interventional PASS to investigate the risk of mortality in MS patients treated with Alemtuzumab (Lemtrada) relative to comparable MS patients using other DMTs. This study is completed.

As part of this RMP v13.0, these two studies are completed. The final milestones have been reached for both studies and the reports have been submitted Q3 2024 as planned (as part of regulatory procedures EMEA/H/C/003718/PSR/S/0050 and EMEA/H/C/003718/PSR/S/0051). Consequently, these two studies are removed from the proposed Pharmacovigilance Plan of this updated RMP v13.0.

- Additionally, as requested in the context of the regulatory procedure EMEA/H/C/003718/MEA/007.17, the MAH takes the opportunity to update the milestone plan of PASS category 3 OBS13434 study.

[2] This risk is temporally associated with Lemtrada infusion.

Table 37 - Additional pharmacovigilance activities (category 1 to 3) summary

PASS OBS13434 (Category 3)
Study short name and title
A Prospective, multicenter, observational cohort study of patients with relapsing forms of MS treated with Lemtrada (alemtuzumab).
Rationale and study objectives
To better characterize the long-term safety profile of alemtuzumab in relapsing MS patients and to determine the incidence of AEs of special interest.
Study design
Prospective, multicenter, observational cohort study of patients with relapsing forms of MS.
Study populations
Patients with relapsing forms of MS.
Milestones
Start of data collection: 2014
End of data collection: 2029
Interim study reports: First: 2020, second: 2026
Final report of study results: 2030
Pediatric Study EFC13429 (Category 3)
Study short name and title
Open-label, rater-blinded, single-arm, before and after efficacy, safety and tolerability study of alemtuzumab in pediatric patients from 10 years to less than 18 years with RRMS with disease activity on prior disease modifying treatment.
Rationale and study objectives
To evaluate the efficacy, safety and tolerability of alemtuzumab (IV) before and after treatment in pediatric subjects with relapsing forms of MS, who have disease activity on prior therapy.
Study design
Open-label, rater-blinded, single-arm, before and after efficacy, safety and tolerability study.
Study populations
Pediatric patients from 10 years to less than 18 years with RRMS with disease activity on prior disease modifying treatment.
Milestones
Protocol status: Version 1 dated 21-Nov-2016
Version 5 dated 15-Dec-2021(current protocol version)
Planned date for submission of final data: within 6 months of completion of the study (Last Patient Last Visit [LPLV]) in accordance with the Article 46 of paediatric regulation.

AE: Adverse Event; IV: Intravenous; LPLV: Last Patient Last Visit; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; RRMS: Relapsing-Remitting Multiple Sclerosis.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 38 - Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization (key to benefit risk)				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances (key to benefit risk)				
Not applicable				
Category 3 - Required additional pharmacovigilance activities (by the competent Authority)				
PASS OBS13434 A prospective, multicenter, observational cohort study of patients with relapsing forms of MS treated with Lemtrada (alemtuzumab). Ongoing	To better characterize the long-term safety profile of alemtuzumab in relapsing MS patients and to determine the incidence of AEs of special interest.	Important risks listed in [Part II Module SVIII]	Start of data collection End of data collection Interim study reports Final report of study results	2014 2029 First: 2020, Second: 2026 2030
Pediatric Study EFC13429 Open-label, rater-blinded, single-arm, before and after efficacy, safety and tolerability study of alemtuzumab in pediatric patients from 10 years to less than 18 years with RRMS with disease activity on prior DMT. Ongoing	To evaluate the efficacy, safety and tolerability of alemtuzumab (IV) before and after treatment in pediatric subjects with relapsing forms of MS, who have disease activity on prior therapy.	Safety and tolerability of alemtuzumab in pediatric patients from ages ≥10 years to less than 18 years with RRMS with disease activity on prior first-line disease modifying treatment.	Protocol status Planned date for submission of final data	Version 1 dated 21-Nov-2016 Version 5 dated 15-Dec-2021 (current protocol version) Within 6 months of completion of the study (LPLV) in accordance with the Article 46 of paediatric regulation.

AE: Adverse Event; DMT: Disease-Modifying Therapy; IV: Intravenous; LPLV: Last Patient Last Visit; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; RRMS: Relapsing Remitting Multiple Sclerosis.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for alemtuzumab.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

The risk minimization plan of EU-RMP v13.0 has been updated to include the final results of the DUS (final protocol submitted in regulatory procedure EMEA/H/C/003718/PSR/S/0050), which was conducted in the context of Article 20 referral, and considered as effectiveness measurement of aRMMs in the RMP, to assess specifically whether Lemtrada is prescribed in accordance with newly revised indication, additional contraindications and additional monitoring recommendations (see Part V.2)

Considering the DUS data detailed in the final report, the MAH concludes that the level of adherence concerning the indication and the contraindications is adequate. Regarding the adherence to monitoring conducted prior and during the Lemtrada course and adherence to the long-term monitoring, some local specificities have been emphasized, as detailed in the final report. Overall, adherence to the entire monitoring schedule can be perceived positively. The results of the DUS reflect, on average, satisfactory monitoring to what is a demanding monitoring schedule for patients especially in the long-term follow-up period.

In general, considering the variation reflecting differences in monitoring practices across the countries, overall adherence above 50% for most monitoring was observed, even in the 3rd and 4th year after course initiation. Consequently, knowing that the current risk minimization measures in place are appropriate and robust, the MAH does not propose any modification to the existing educational materials, nor any new additional risk minimization measure.

Therefore, the MAH is proposing to continue the yearly distribution of the current educational materials to all relevant HCPs. A cover letter will be added to the 2025 distribution highlighting again the monitoring program and the recommended measures to all relevant HCPs.

Furthermore, the MAH plans to share final results of DUS and Mortality with the scientific community through the submission of the manuscripts to scientific journals.

Regarding the Mortality study, this study provided insight into the heterogeneous prescribing patterns for Lemtrada, the differences in underlying exposed populations across European countries, and how these impacted the observed mortality rates. The study did not provide evidence for an increased risk of mortality in Lemtrada treated patients.

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 39 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Infusion associated reactions (IARs)	**Routine risk communication:** Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. Labelled in sections 2 and 4 of PL.

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: Contraindication regarding hypersensitivity to the active substance or excipients are included in SmPC section 4.3 and PL section 2. Recommendations for premedication are included in SmPC sections 4.2 and 4.4 and in PL section 4. How to detect signs and symptoms, the need to seek for immediate medical attention is labelled in PL section 2. Recommendations to exercise caution until IARs (eg, dizziness) are resolved are included in SmPC section 4.7. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Stroke (including haemorrhagic stroke)[a]	**Routine risk communication:** Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. Labelled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication regarding history of stroke is included in SmPC section 4.3 and PL section 2. Instructions for treatment initiation are included in SmPC section 4.2. Instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during infusion, post-infusion) are included in SmPC section 4.4. How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL sections 2 and 4, as well as information on the monitoring which will be done. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Dissection of the cervicocephalic arteries[a]	**Routine risk communication:** Proposed Label in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. Labeled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication regarding history of arterial dissection of the cervicocephalic arteries is included in SmPC section 4.3 and PL section 2. Instructions for treatment initiation are included in SmPC section 4.2.

Safety concern	Routine risk minimization activities
	Instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during infusion, post-infusion) are included in SmPC section 4.4. How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL sections 2 and 4, as well as information on the monitoring which will be done. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Myocardial infarction (MI) and myocardial ischaemia[a]	**Routine risk communication:** Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. Labelled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication regarding history of angina pectoris or MI is included in SmPC section 4.3 and PL section 2. Instructions for treatment initiation are included in SmPC section 4.2. Instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during infusion, post-infusion) are included in SmPC section 4.4. How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL sections 2 and 4, as well as information on the monitoring which will be done. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Pulmonary alveolar haemorrhage (PAH)[a]	**Routine risk communication:** Labelled in sections 4.2, 4.4 and 4.8 of SmPC. Labelled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Instructions for treatment initiation are included in SmPC section 4.2. Instructions to reduce serious reactions temporally associated with Lemtrada. (pre-infusion, during infusion, post-infusion) are included in SmPC section 4.4. How to detect signs and symptoms, the need to seek for immediate medical attention is labelled in PL sections 2 and 4, as well as information on the monitoring which will be done. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to

Safety concern	Routine risk minimization activities
	intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Thrombocytopenia[a]	**Routine risk communication:** Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. Labeled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Instructions for treatment initiation are included in SmPC section 4.2. Platelet count should be obtained before infusion, immediately after infusion on Days 3 and 5 of the first infusion course, as well as immediately after infusion on Day 3 of any subsequent course. Instructions to reduce serious reactions temporally associated with Lemtrada (pre-infusion, during infusion, post-infusion) are included in SmPC section 4.4. How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL section 2 and 4, as well as information on the monitoring which will be done. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Thyroid disorders	**Routine risk communication:** Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. Labelled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. Instructions for treatment initiation are included in SmPC section 4.2. Recommendations for thyroid function monitoring are included in SmPC section 4.4. How to detect signs and symptoms of thyroid disorders and the need to seek for immediate medical attention is labeled in PL section 2 and 4, as well as the summary of the tests to complete. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.

Safety concern	Routine risk minimization activities
Immune thrombocytopenic purpura (ITP)	**Routine risk communication:** Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. Labelled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. Instructions for treatment initiation are included in SmPC section 4.2. Recommendations to complete blood counts are included in SmPC section 4.4, as well as medical conduct to adopt if ITP onset is confirmed. How to detect signs and symptoms of ITP and the need to seek for immediate medical attention is labeled in PL section 2 and 4, as well as the summary of the tests to complete. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Nephropathies including anti-glomerular basement membrane (anti-GBM) disease	**Routine risk communication:** Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. Labelled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. Instructions for treatment initiation are included in SmPC section 4.2. Recommendation to complete serum creatinine levels and urinalysis are included in SmPC section 4.4, as well as medical conduct to adopt in case of clinically relevant changes in these results. How to detect signs and symptoms of kidney disorders and the need to seek for immediate medical attention is labeled in PL sections 2 and 4, as well as the summary of the tests to complete. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Autoimmune hepatitis (AIH)	**Routine risk communication:** Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. Labeled in sections 2 and 4 of PL.

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. Instructions for treatment initiation are included in SmPC section 4.2. The need to perform liver function tests before initial treatment and periodically thereafter are labelled in SmPC section 4.4. How to detect signs and symptoms of liver disorders and the need to seek for immediate medical attention is labeled in PL sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Serious infections	**Routine risk communication:** Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. Labelled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Instructions for treatment initiation are included in SmPC section 4.2. Contraindication regarding severe active infection until complete resolution is included in SmPC section 4.3 and PL section 2. Recommendations regarding screening, prophylaxis and the conduct to adopt in patients with severe active infection is labeled in SmPC section 4.4. Recommendations regarding screening, prophylaxis, treatment and the need to seek for immediate medical attention as well as the summary of tests to complete, for some infections are labeled in PL sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Haemophagocytic Lymphohistiocytosis (HLH)	**Routine risk communication:** Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. Labeled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. Instructions for treatment initiation are included in SmPC section 4.2.

Safety concern	Routine risk minimization activities
	Recommendations provided to identify patients developing early manifestation of pathologic immune activation are labeled in SmPC section 4.4 as well as the need to consider diagnosis of HLH. How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL Sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Acquired Haemophilia A (AHA)	**Routine risk communication:** Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. Labeled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. Instructions for treatment initiation are included in SmPC section 4.2. Recommendation provided to identify patients developing manifestation of acquired haemophilia A as well as the need to complete coagulopathy panel in case a patient presents such symptoms, are included in SmPC section 4.4. Recommendations regarding signs and symptoms of AHA and the need to seek for medical attention are included in PL sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Thrombotic thrombocytopenic purpura (TTP)	**Routine risk communication:** Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. Labeled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. Instructions for treatment initiation are included in SmPC section 4.2. Warning to conduct an urgent evaluation and prompt treatment as well as symptoms to identify TTP are included in SmPC section 4.4. Recommendations regarding signs and symptoms of TTP are included in PL sections 2 and 4. Section 2 of the PL also recommends getting medical help right away if TTP signs or symptoms occur.

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Adult Onset Still's Disease (AOSD)	**Routine risk communication:** Labeled in sections 4.4 and 4.8 of SmPC. Labeled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Warning to conduct an urgent evaluation and treatment as well as symptoms to identify AOSD are included in SmPC section 4.4. The statement to "Consider interruption or discontinuation of treatment with Lemtrada if an alternate etiology cannot be established" is also included in this section. Potential symptoms of AOSD with multi-organ inflammation is described in PL sections 2 and 4. Section 2 of the PL also recommends getting medical help right away if a combination of AOSD symptoms occur. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Autoimmune Encephalitis (AIE)	**Routine risk communication:** Proposed label in sections 4.4 and 4.8 of SmPC. Proposed label in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Acute acalculous cholecystitis (AAC)	**Routine risk communication:** Labeled in sections 4.4 and 4.8 of SmPC. Labeled in sections 2 and 4 of PL.

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: Conduct to adopt in case acalculous cholecystitis is suspected is labeled in SmPC section 4.4. Recommendations regarding signs and symptoms of gall bladder inflammation and the need to seek for medical attention are included in PL sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus [T1DM], Guillain Barre syndrome [GBS], sarcoidosis)	**Routine risk communication:** Labeled in sections 4.3, 4.4 and 4.8 of SmPC. Labeled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. Recommendation to complete blood count is included in SmPC section 4.4, as well as medical conduct to adopt if cytopenia is confirmed. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Malignancies	**Routine risk communication:** Labeled in sections 4.4 and 4.8 of SmPC. Labeled in sections 2 and 4 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Information regarding treatment initiation in patients with pre-existing and/or ongoing malignancy is labeled in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.

Safety concern	Routine risk minimization activities
Progressive multifocal leukoencephalopathy (PML)	**Routine risk communication:** Labeled in section 4.4 of SmPC. Labeled in section 2 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations and exams to be completed in case of signs suggestive of PML are labeled in SmPC section 4.4. Recommendations regarding signs and symptoms of PML and the need to seek for medical attention are included in PL sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Pediatric use	**Routine risk communication:** Labeled in section 5.1 of SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation regarding use in paediatric population is labeled in SmPC section 4.2 and PL section 2. **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Use in patients aged >55 years (including use in elderly patients aged ≥65 years)	**Routine risk communication:** Labeled in sections 4.2 and 5.2 of SmPC**.** **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Use in racial categories other than white	**Routine risk communication:** None

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: None **Other routine risk minimization measures beyond the Product Information:** Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.

a This risk is temporally associated with Lemtrada infusion.

AAC: Acute acalculous cholecystitis; AHA: Acquired Haemophilia A; AIE: Autoimmune Encephalitis; AIH: Autoimmune Hepatitis; AOSD: Adult Onset Still's Disease; GBM: Glomerular Basement Membrane; GBS: Guillain-Barre syndrome; HLH: Haemophagocytic Lymphohistiocytosis; IAR: Infusion-Associated Reaction; ITP: Immune Thrombocytopenic Purpura; MI: Myocardial Infarction; MS: Multiple Sclerosis; PAH: Pulmonary Alveolar Haemorrhage; PL: Package Leaflet; PML: Progressive Multifocal Leukoencephalopathy; SmPC: Summary of Product Characteristics; T1DM: Type 1 Diabetes Mellitus; TTP: Thrombotic Thrombocytopenic Purpura.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Table 40 - Additional risk minimization measures

Healthcare professional education/discussion guide	
Objectives	The safety concerns addressed by the HCP guide are: • Stroke (including haemorrhagic stroke)[a] • Dissection of the cervicocephalic arteries[a] • Myocardial infarction and myocardial ischaemia[a] • Pulmonary alveolar haemorrhage[a] • Thrombocytopenia[a] • Thyroid disorders • Immune thrombocytopenia purpura • Nephropathies including anti-GBM disease • Autoimmune hepatitis • Serious infections • Haemophagocytic lymphohistiocytosis • Acquired Haemophilia A • Thrombotic thrombocytopenic purpura • Adult Onset Still's Disease • Autoimmune encephalitis • Progressive multifocal leukoencephalopathy The primary objectives of the Lemtrada HCP Guide are: • To reinforce education on signs and symptoms of autoimmune disorders, serious infections, temporally associated safety concerns in order to increase their early detection and induce appropriate management to mitigate severity and sequelae of incident of the above-presented risks;

	• Provide infusion instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during infusion, post-infusion); • To reinforce communication about the risks and need and importance of periodic monitoring, to patients and prescribers; • To provide informed benefit risks decisions before each cycle of treatment; • To inform physicians and patients, by increasing awareness about specific information pertaining to the above-presented risks and potential risk of use during pregnancy.
Rationale for the additional risk minimization activity	• Reinforce the education on signs and symptoms of autoimmune disorders, serious infections, temporally associated safety concerns; • Provide infusion instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during infusion, post-infusion); • Emphasize the need to ensure patient compliance with testing and vigilance for symptoms.
Target audience and planned distribution path	• Healthcare professionals including Physicians treating MS, consultant neurologists and MS specialist nurses, hospital pharmacist and other recipients to be agreed with the National Competent Authorities (NCAs); • The educational materials are planned to be distributed on a yearly basis.
Plans to evaluate the effectiveness of the interventions and criteria for success	• Routine effectiveness measurements and monitoring of the distribution; • Drug utilization study: This study assessed specifically whether Lemtrada is prescribed in accordance with newly revised indication, additional contraindications and additional monitoring recommendations. This study is completed as per the RMP v13.0. See below for details: - The DUS data detailed in the final report conclude that the level of adherence concerning the indication and the contraindications is adequate. Regarding the adherence to monitoring conducted prior and during the Lemtrada course and adherence to the long-term monitoring, some local specificities have been emphasized, as detailed in the final report. Overall, adherence to the entire monitoring schedule can be perceived positively. The results of the DUS reflect, on average, satisfactory monitoring to what is a demanding monitoring schedule for patients especially in the long-term follow-up period. Consequently, the current educational materials is considered adequate. The yearly distribution of the current educational materials to all relevant HCPs is maintained, adding a cover letter which will highlight again the monitoring program and reminds all relevant HCPs of the recommended measures. Furthermore, the MAH plans to share the DUS results with the scientific community through the submission of a manuscript to a scientific journal.
Healthcare professional check-list	
Objectives	The safety concerns addressed by the HCP check-list are: • Stroke (including haemorrhagic stroke)[a] • Dissection of the cervicocephalic arteries[a] • Myocardial infarction and myocardial ischaemia[a] • Pulmonary alveolar haemorrhage[a] • Thrombocytopenia[a] • Thyroid disorders • Immune thrombocytopenia purpura

	• Nephropathies including anti-GBM disease • Autoimmune hepatitis • Serious infections • Haemophagocytic lymphohistiocytosis • Acquired Haemophilia A • Progressive multifocal leukoencephalopathy The primary objectives of the Lemtrada HCP checklist are: • To indicate the list of tests and actions to be conducted at the following steps of the treatment (screening of patients, prior to, during and after treatment); • Reinforce communication about the risks and need and importance of periodic monitoring, to patients and prescribers.
Rationale for the additional risk minimization activity	• Reinforce the education on signs and symptoms of autoimmune disorders, serious infections, temporally associated safety concerns; • Provide infusion instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during infusion, post-infusion); • Emphasize the need to ensure patient compliance with testing and vigilance for symptoms.
Target audience and planned distribution path	• Healthcare professionals including Physicians treating MS, consultant neurologists and MS specialist nurses, hospital pharmacist and other recipients to be agreed with the NCAs; • The educational materials are planned to be distributed on a yearly basis.
Plans to evaluate the effectiveness of the interventions and criteria for success	• Routine effectiveness measurements and monitoring of the distribution; • Drug utilization study: This study assessed specifically whether Lemtrada is prescribed in accordance with newly revised indication, additional contraindications and additional monitoring recommendations. This study is completed as per the RMP v13.0. See details above provided for “HCP Guide”.
Patient guide	
Objectives	The safety concerns addressed by the patient guide are: • Stroke (including haemorrhagic stroke)[a] • Dissection of the cervicocephalic arteries[a] • Myocardial infarction and myocardial ischaemia[a] • Pulmonary alveolar haemorrhage[a] • Thrombocytopenia[a] • Thyroid disorders • Immune thrombocytopenia purpura • Nephropathies including anti-GBM disease • Autoimmune hepatitis • Serious infections • Haemophagocytic lymphohistiocytosis • Acquired Haemophilia A • Thrombotic thrombocytopenic purpura • Adult Onset Still’s Disease • Autoimmune encephalitis

	• Progressive multifocal leukoencephalopathy The primary objectives of the Lemtrada patient guide are: • Reinforce the education on signs and symptoms of autoimmune disorders, serious infections, temporally associated safety concerns in order to increase their early detection and induce appropriate management to mitigate severity and sequelae of incident of the above-presented risks; • Reinforce the message about seeking immediate medical attention in case of symptoms associated to these risks; • Provide the information regarding the procedures and tests to be conducted prior, during and after the treatment; • Reinforce communication about the risks and need and importance of periodic monitoring, to patients; • To inform physicians and patients, by increasing awareness about specific information pertaining to of the above-presented risks and potential risk of use during pregnancy.
Rationale for the additional risk minimization activity	• Reinforce the Education on signs and symptoms of autoimmune disorders, serious infections, temporally associated safety concerns Provide infusion instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during infusion, post-infusion); • Emphasize the need to ensure patient compliance with testing and vigilance for symptoms.
Target audience and planned distribution path	Patients with MS being treated with alemtuzumab, through their HCP.
Plans to evaluate the effectiveness of the interventions and criteria for success	• Routine effectiveness measurements and monitoring of the distribution; • Drug utilization study: This study assessed specifically whether Lemtrada is prescribed in accordance with newly revised indication, additional contraindications and additional monitoring recommendations laid out in the Article 20 referral. This study is completed as per RMP v13.0. See details above provided for “HCP Guide”.
Patient alert card	
Objectives	The safety concerns addressed by the patient alert card are: • Stroke (including haemorrhagic stroke)[a] • Dissection of the cervicocephalic arteries[a] • Myocardial infarction and myocardial ischaemia[a] • Pulmonary alveolar haemorrhage[a] • Thrombocytopenia[a] • Thyroid disorders[a] • Immune thrombocytopenia purpura • Nephropathies including anti-GBM disease • Autoimmune hepatitis • Serious infections • Haemophagocytic lymphohistiocytosis • Acquired Haemophilia A • Thrombotic thrombocytopenic purpura • Adult Onset Still’s Disease

	• Autoimmune encephalitis • Progressive multifocal leukoencephalopathy The primary objectives of the Lemtrada patient alert card are: • To provide warning messages for HCPs treating patients including in emergency situations; • To inform the patients regarding signs and symptoms of the important risks, and the need to seek for immediate attention in case they occur; • Reinforce communication about the risks and need and importance of periodic monitoring, to the patients.
Rationale for the additional risk minimization activity	• Reinforce education on signs and symptoms of autoimmune disorders, serious infections, temporally associated safety concerns; • Emphasize the need to ensure patient compliance with testing and vigilance for symptoms.
Target audience and planned distribution path	• The patient (or care givers when appropriate) should carry and show this card at all times to any HCP; • The educational materials will be distributed on a yearly basis.
Plans to evaluate the effectiveness of the interventions and criteria for success	• Routine effectiveness measurements and monitoring of the distribution; • Drug utilization study: This study assessed specifically whether Lemtrada is prescribed in accordance with newly revised indication, additional contraindications and additional monitoring recommendations. recommendations laid out in the Article 20 referral. This study is completed as per RMP v13.0. See details above provided for “HCP Guide”.

a This risk is temporally associated with Lemtrada infusion.

GBM: Glomerular Basement Membrane; HCP: Healthcare Professional; HLH: Haemophagocytic Lymphohistiocytosis; MAH: Marketing Authorization Holder; MS: Multiple Sclerosis; NCA: National Competent Authority; PRAC: Pharmacovigilance Risk Assessment Committee; SmPC: Summary of Product Characteristics.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 41 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infusion-associated reactions (IARs)	**Routine risk minimization measures:** • Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labelled in sections 2 and 4 of PL. • Contraindication regarding hypersensitivity to the active substance or excipients are included in SmPC section 4.3 and PL section 2. • Recommendations for premedication are included in SmPC sections 4.2 and 4.4 and in PL section 4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labelled in PL section 2.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Recommendations to exercise caution until IAR (eg, dizziness) are resolved are included in SmPC section 4.7. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** None	
Stroke (including haemorrhagic stroke)[a]	**Routine risk minimization measures:** • Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labelled in sections 2 and 4 of PL. • Contraindication regarding history of stroke is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during infusion and post-infusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labelled in PL sections 2 and 4, as well as information on the monitoring which will be done. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** As part of routine surveillance, a follow-up form is to be attached to the corresponding completed AE/serious AE form at country level, to document spontaneous or solicited alemtuzumab cases of reported or suspected stroke. **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030

Safety concern	Risk minimization measures	Pharmacovigilance activities
	reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis.	
Dissection of the cervicocephalic arteries[a]	**Routine risk minimization measures:** • Proposed label in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding history of arterial dissection of the cervicocephalic arteries is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during infusion and post-infusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL sections 2 and 4, as well as information on the monitoring which will be done. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card), planned to be distributed on a yearly basis.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** As part of routine surveillance, a follow-up form is to be attached to the corresponding completed AE/serious AE form at country level, to document spontaneous or solicited alemtuzumab cases of reported or suspected dissection of the cervicocephalic arteries. **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030

Safety concern	Risk minimization measures	Pharmacovigilance activities
Myocardial infarction (MI) and myocardial ischaemia[a]	**Routine risk minimization measures:** • Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labelled in sections 2 and 4 of PL. • Contraindication regarding history of angina pectoris or MI is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during infusion and post-infusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL sections 2 and 4, as well as information on the monitoring which will be done. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card), planned to be distributed on a yearly basis.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** As part of routine surveillance, a follow-up form is to be attached to the corresponding completed AE/serious AE Form at country level, to document spontaneous or solicited alemtuzumab cases of reported or suspected myocardial infarction or ischaemia. **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030
Pulmonary alveolar haemorrhage (PAH)[a]	Routine risk minimization measures: • Labelled in sections 4.2, 4.4 and 4.8 of SmPC. • Labelled in sections 2 and 4 of PL. • Instructions for treatment initiation are included in SmPC section 4.2. • Instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** As part of routine surveillance, a follow-up form is to be attached to the corresponding completed AE/serious AE form at country level, to document spontaneous or solicited alemtuzumab cases of reported or suspected PAH.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	infusion and post-infusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labelled in PL sections 2 and 4, as well as information on the monitoring which will be done. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card), planned to be distributed on a yearly basis.	**Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030
Thrombocytopenia[a]	**Routine risk minimization measures:** • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Instructions for treatment initiation are included in SmPC section 4.2. • Platelet count should be obtained before infusion, immediately after infusion on Days 3 and 5 of the first infusion course, as well as immediately after infusion on Day 3 of any subsequent course. • Instructions to reduce serious reactions temporally associated with Lemtrada (pre-infusion, during infusion, post-infusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL section 2 and 4, as well as information on the monitoring which will be done.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** As part of routine surveillance, a follow-up form is to be attached to the corresponding completed AE/serious AE form at country level, to document spontaneous or solicited alemtuzumab cases of reported or suspected thrombocytopenia. **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card), planned to be distributed on a yearly basis.	
Thyroid disorders	**Routine risk minimization measures:** • Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Recommendations for thyroid function monitoring are included in SmPC section 4.4. • How to detect signs and symptoms of thyroid disorders and the need to seek for immediate medical attention is labelled in PL sections 2 and 4 as well as the summary of the tests to complete. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, HCP check list, patient guide, patient card), planned to be distributed on a yearly basis.	
Immune thrombocytopenic purpura (ITP)	**Routine risk minimization measures:** • Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labelled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Recommendations to complete blood counts are included in SmPC section 4.4, as well as medical conduct to adopt if ITP onset is confirmed. • How to detect signs and symptoms of ITP and the need to seek for immediate medical attention is labelled in PL sections 2 and 4, as well as the summary of the tests to complete. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card) planned to be distributed on a yearly basis.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030

Safety concern	Risk minimization measures	Pharmacovigilance activities
Nephropathies including anti-glomerular basement membrane (anti-GBM) disease	**Routine risk minimization measures:** • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Recommendations to complete serum creatinine levels and urinalysis blood counts are included in SmPC section 4.4, as well as medical conduct to adopt in case of clinically relevant changes in these results. • How to detect signs and symptoms of kidney disorders and the need to seek for immediate medical attention is labelled in PL sections 2 and 4, as well as the summary of the tests to complete. Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, HCP checklist, patient guide, patient alert card) planned to be distributed on a yearly basis.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030
Autoimmune hepatitis (AIH)	**Routine risk minimization measures:** • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** As part of routine surveillance, a follow-up form is to be attached to the corresponding completed AE/serious AE form at country level, to document spontaneous or solicited alemtuzumab cases of reported or suspected autoimmune hepatitis.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Instructions for treatment initiation are included in SmPC section 4.2. • The need to perform liver function tests before initial treatment and periodically thereafter are labelled in SmPC section 4.4. • How to detect signs and symptoms of liver disorders and the need to seek for immediate medical attention is labeled in PL sections 2 and 4. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, HCP check list, patient guide, Patient card), planned to be distributed on a yearly basis.	**Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030
Serious infections	**Routine risk minimization measures:** • Labeled in sections 4.2, 4.3, 4.4 ad 4.8 of SmPC • Labeled in sections 2 and 4 of PL. • Instructions for treatment initiation are included in SmPC section 4.2. • Contraindication regarding severe active infection until complete resolution is included in SmPC section 4.3 and PL section 2. • Recommendations regarding screening, prophylaxis and the conduct to adopt in patients with severe active infection are included in SmPC section 4.4. • Recommendations regarding screening, prophylaxis treatment and the need to seek for immediate medical attention as well as the summary of tests to complete, for	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030

Safety concern	Risk minimization measures	Pharmacovigilance activities
	some infections are included in PL sections 2 and 4. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card) planned to be distributed on a yearly basis.	
Haemophagocytic lymphohistiocytosis (HLH)	**Routine risk minimization measures:** • Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labelled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Recommendations provided to identify patients developing early manifestation of pathologic immune activation are labeled in SmPC section 4.4 as well as the need to consider diagnosis of HLH. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL sections 2 and 4. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** As part of routine surveillance, a follow-up form is to be attached to the corresponding completed AE/serious AE form at country level, to document spontaneous or solicited alemtuzumab cases of reported or suspected HLH. **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030

Safety concern	Risk minimization measures	Pharmacovigilance activities
	MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card), planned to be distributed on a yearly basis.	
Acquired Haemophilia A (AHA)	**Routine risk minimization measures:** • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2 • Recommendation provided to identify patients developing manifestation of AHA as well as the need to complete coagulopathy panel in case a patient presents such symptoms, are included in SmPC section 4.4. • Recommendations regarding signs and symptoms of AHA and the need to seek for medical attention are included in PL sections 2 and 4. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, HCP check list, patient guide, patient card), planned to be distributed on a yearly basis.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030

Safety concern	Risk minimization measures	Pharmacovigilance activities
Thrombotic thrombocytopenic purpura (TTP)	**Routine risk minimization measures:** • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Warning to conduct an urgent evaluation and prompt treatment as well as symptoms to identify TTP are included in SmPC section 4.4. • Recommendations regarding signs and symptoms of TTP are included in PL sections 2 and 4. Section 2 of the PL also recommends getting medical help right away if TTP signs or symptoms occur. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, patient guide, patient alert card), planned to be distributed on a yearly basis.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030
Adult Onset Still's Disease (AOSD)	**Routine risk minimization measures:** • Labeled in sections 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Warning to conduct an urgent evaluation and treatment as well as symptoms to identify AOSD are included in SmPC section 4.4. The statement to "Consider interruption or discontinuation of treatment with	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Lemtrada if an alternate etiology cannot be established" is also included in this section. • Potential symptoms of AOSD with multiorgan inflammation is described in PL sections 2 and 4. Section 2 of the PL also recommends getting medical help right away if AOSD symptoms occur. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, patient guide, patient alert card), planned to be distributed on a yearly basis.	
Autoimmune Encephalitis (AIE)	**Routine risk minimization measures:** • Proposed label in sections 4.4 and 4.8 of SmPC. • Proposed label in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome,	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030

Safety concern	Risk minimization measures	Pharmacovigilance activities
	hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, patient guide, patient alert card), planned to be distributed on a yearly basis.	
Acute acalculous cholecystitis (AAC)	**Routine risk minimization measures:** • Labeled in sections 4.4 and 4.8 of SmPC. • Labeled in PL sections 2 and 4. • Conduct to adopt in case acalculous cholecystitis is suspected is included in SmPC section 4.4. • Recommendations regarding signs and symptoms of gall bladder inflammation and the need to seek for medical attention are included in PL sections 2 and 4. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030
Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus [T1DM], Guillain Barre syndrome [GBS], sarcoidosis)	**Routine risk minimization measures:** • Labeled in sections 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Recommendations to complete blood count is included in SmPC section 4.4, as well as medical conduct to adopt if cytopenia is confirmed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** None	
Malignancies	**Routine risk minimization measures:** • Labeled in sections 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Information regarding treatment initiation in patients with pre-existing and/or ongoing malignancy is labelled in SmPC section 4.4. • Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030
Progressive multifocal leukoencephalopathy (PML)	**Routine risk minimization measures:** • Labeled in section 4.4 of SmPC. • Labeled in section 2 of PL. • Recommendations and exams to be completed in case of signs suggestive	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** As part of routine surveillance, a "Progressive Multifocal Leukoencephalopathy questionnaire/checklist" is to be attached

Safety concern	Risk minimization measures	Pharmacovigilance activities
	of PML are labeled in SmPC section 4.4. • Recommendations regarding signs and symptoms of PML and the need to seek for medical attention are included in PL sections 2 and 4. • Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** Educational materials (ie, HCP guide, HCP checklist, patient guide, patient alert card), planned to be distributed on a yearly basis.	to the corresponding completed AE/serious AE form at country level, to document spontaneous or solicited alemtuzumab cases of reported or suspected PML. **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030
Pediatric use	**Routine risk minimization measures:** • Labeled in section 5.1 of SmPC. • Recommendations regarding use in paediatric population are included in SmPC section 4.2 and PL section 2. • Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Pediatric Study EFC13429 Planned date for submission of final data: within 6 months of completion of the study (LPLV) in accordance with the Article 46 of paediatric regulation.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use in patients aged >55 years (including use in elderly patients aged ≥65 years)	**Routine risk minimization measures:** • Labeled in sections 4.2 and 5.2 of SmPC. • Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS OBS13434 Final report: 2030
Use in racial categories other than white	**Routine risk minimization measures:** Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study: PASS OBS13434 Final report: 2030

a This risk is temporally associated with Lemtrada infusion.

AAC: Acute Acalculous Cholecystitis; AE: Adverse Event; AHA: Acquired Haemophilia A; AIE: Autoimmune Encephalitis; AIH: Autoimmune Hepatitis; AOSD: Adult Onset Still's Disease; GBM: Glomerular Basement membrane; GBS: Guillain-Barre syndrome; HCP: Healthcare Professional; HLH: Haemophagocytic Lymphohistiocytosis; IAR: Infusion-Associated Reaction; ITP: Immune Thrombocytopenic Purpura; MS: Multiple Sclerosis; MI: Myocardial Infarction; PAH: Pulmonary Alveolar Haemorrhage; PASS: Post-Authorization Safety Study; PL: Package Leaflet; PML: Progressive Multifocal Leukoencephalopathy; SmPC: Summary of Product Characteristics; T1DM: Type 1 Diabetes Mellitus; TTP: Thrombotic Thrombocytopenic Purpura.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Lemtrada (Alemtuzumab)

This is a summary of the RMP for Lemtrada. The RMP details important risks of Lemtrada how these risks can be minimized, and how more information will be obtained about Lemtrada's risks and uncertainties (missing information).

Lemtrada's SmPC and its PL give essential information to HCPs and patients on how Lemtrada should be used.

This summary of the RMP for Lemtrada should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Lemtrada's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

LEMTRADA is authorized for use as a single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:

- *Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or;*
- *Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI* (see SmPC for the full indication).

It contains alemtuzumab as the active substance and it is given by IV infusion.

Further information about the evaluation of Lemtrada's benefits can be found in Lemtrada's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/lemtrada

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Lemtrada, together with measures to minimize such risks and the proposed studies for learning more about Lemtrada's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Lemtrada, these measures are supplemented with *additional risk minimization* measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Lemtrada is not yet available, it is listed under 'missing information' outlined in the next section.

II.A List of important risks and missing information

Important risks of Lemtrada are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered or taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lemtrada. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 42 - List of important risks and missing information

Important identified risk	Infusion Associated Reactions (IARs)
	Stroke (including haemorrhagic stroke)[a]
	Dissection of the cervicocephalic arteries[a]
	Myocardial infarction (MI) and myocardial ischaemia[a]
	Pulmonary alveolar haemorrhage (PAH)[a]
	Thrombocytopenia[a]
	Thyroid disorders
	Immune thrombocytopenic purpura (ITP)
	Nephropathies including anti-glomerular basement membrane (anti-GBM) disease

	Autoimmune hepatitis (AIH)
	Serious infections
	Haemophagocytic lymphohistiocytosis (HLH)
	Acquired Haemophilia A (AHA)
	Thrombotic Thrombocytopenic Purpura (TTP)
	Adult Onset Still's Disease (AOSD)
	Autoimmune Encephalitis (AIE)
	Acute Acalculous Cholecystitis (AAC)
Important potential risk	Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus [T1DM], Guillain Barre syndrome [GBS], sarcoidosis)
	Malignancies
	Progressive multifocal leukoencephalopathy (PML)
Missing information	Pediatric use
	Use in patients aged >55 years (including use in elderly patients aged ≥65 years)
	Use in racial categories other than white

a This risk is temporally associated with Lemtrada infusion.

AAC: Acute Acalculous Cholecystitis; AHA: Acquired Haemophilia A; AIE: Autoimmune Encephalitis; AIH: Autoimmune Hepatitis; AOSD: Adult Onset Still's Disease; GBM: Glomerular Basement Membrane; GBS: Guillain-Barre Syndrome; HLH: Haemophagocytic Lymphohistiocytosis; IAR: Infusion-Associated Reaction; ITP: Immune Thrombocytopenic Purpura; MI: Myocardial infarction; PAH: Pulmonary Alveolar Haemorrhage; PML: Progressive Multifocal Leukoencephalopathy; T1DM: Type 1 Diabetes Mellitus; TTP: Thrombotic Thrombocytopenic Purpura.

II.B Summary of important risks

Table 43 - Important identified risk with corresponding risk minimization activities: Infusion associated reactions (IARs)

Important identified risk: Infusion-associated reactions (IARs)	
Evidence for linking the risk to the medicine	Clinical studies and postmarketing.
Risk factors and risk groups.	Infusion-associated reactions are commonly reported with monoclonal antibody administration (27) and were observed in approximately 90% of patients treated with alemtuzumab in MS clinical trials. A higher than recommended dose and faster infusion rate also increase the risk of IARs. There is no identified pattern in terms of additive or synergistic factors. While IARs have also been observed with use of alemtuzumab in B-cell chronic lymphocytic leukemia (B-CLL), reporting rates are different than those in MS patients, and AEs tend to be more severe in the B-CLL population. The recommended dosing regimens for B-CLL patients is 10-fold higher than for MS patients: B-CLL patients are dosed chronically for up to 3 months, compared to 2 annual courses for MS patients (5 days at month 0, 3 days at month 12). Alemtuzumab treatment is contraindicated in patients with hypersensitivity to alemtuzumab or its excipients.

Important identified risk: Infusion-associated reactions (IARs)	
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding hypersensitivity to the active substance or excipients are included in SmPC section 4.3 and PL section 2. • Recommendations for premedication are included in SmPC sections 4.2 and 4.4 and in PL section 4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labelled in PL section 2. • Recommendations to exercise caution until IARs (eg, dizziness) are resolved are included in SmPC section 4.7. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: None

AE: Adverse Event; B-CLL: B-cell Chronic Lymphocytic Leukemia; IAR: Infusion-Associated Reaction; MI: Myocardial Infarction; MS: Multiple Sclerosis; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 44 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Stroke (including haemorrhagic stroke)[a]

Important identified risk: Stroke (including haemorrhagic stroke)[a]	
Evidence for linking the risk to the medicine	Postmarketing. There were no non-clinical findings suggestive of stroke in repeat-dose toxicity studies with alemtuzumab.
Risk factors and risk groups.	The major risk factors for stroke include: • High BP • Diabetes • Smoking • Heart disease • Personal or family History of stroke or TIA • Brain aneurysms or AVMs • It is not clearly identified which patients are at risk of stroke with alemtuzumab use. However, significantly increased BP during infusion may be a risk factor for haemorrhagic stroke, and vital sign should be monitored prior to and during infusion as described in the SmPC. • The reported events followed no particular pattern in terms of risk groups. There was no dose related pattern. The majority of stroke cases temporally associated to alemtuzumab infusion occurred within 3 days of alemtuzumab administration. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labelled in sections 2 and 4 of PL. • Contraindication regarding history of stroke is included in SmPC section 4.3 and PL section 2.

Important identified risk: Stroke (including haemorrhagic stroke)[a]	
	• Instructions for treatment initiation are included in SmPC section 4.2. • Instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during infusion and post-infusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL section 2 and 4, as well as information on the monitoring which will be done. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, HCP check-list, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

a This risk is temporally associated with Lemtrada infusion.

AVM: Arteriovenous Membrane; BP: Blood Pressure; HCP: Healthcare Professional; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics; TIA: Transient Ischaemic Attack.

Table 45 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Dissection of the cervicocephalic arteries[a]

Important identified risk: Dissection of the cervicocephalic arteries[a]	
Evidence for linking the risk to the medicine	Postmarketing. There were no non-clinical findings suggestive of vascular dissection in repeat-dose toxicity studies with alemtuzumab.
Risk factors and risk groups.	Dissection of the cervicocephalic arteries are typically associated with “minor” cervical trauma, or torsion of the neck including variety of everyday activities. All of the reported events of arterial dissection appear to be in the extracranial compartment, adjacent to bony structures, which is where traumatic dissection typically occurs. Of the reported cases, there were 3 cases reported with regular chiropractic manipulations. There was no dose related pattern.
Risk minimization measures	Routine risk minimization measures: • Proposed label in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding history of arterial dissection of the cervicocephalic arteries is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Instructions to reduce serious reactions temporally associated with Lemtrada infusion. (pre-infusion, during infusion and post-infusion) are included in SmPC section 4.4.

Important identified risk: Dissection of the cervicocephalic arteries[a]	
	• How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL sections 2 and 4, as well as information on the monitoring which will be done. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

a This risk is temporally associated with Lemtrada infusion.

HCP: Healthcare Professional; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 46 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Myocardial infarction (MI) and myocardial ischaemia[a]

Important identified risk: Myocardial infarction (MI) and myocardial ischaemia[a]	
Evidence for linking the risk to the medicine	Postmarketing.
Risk factors and risk groups.	Risk factors that may cause myocardial infarction include: • Age (Men age 45 or older, women age 55 or older) • Tobacco • High BP • High blood cholesterol or triglyceride levels • Obesity • Diabetes • Metabolic syndrome • Family history of heart attack • Lack of physical activity • Stress • Illicit drug use • A history of preeclampsia • No particular pattern in terms of risk groups was identified in the reported cases. There was no dose related pattern. Most cases of myocardial ischaemia were reported within 72 hours of last alemtuzumab infusion. No pattern of additive or synergistic factors were observed.

Important identified risk: Myocardial infarction (MI) and myocardial ischaemia[a]	
Risk minimization measures	Routine risk minimization measures: • Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labelled in sections 2 and 4 of PL. • Contraindication regarding history of angina pectoris or MI is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during infusion and post-infusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL Sections 2 and 4, as well as information on the monitoring which will be done. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

a This risk is temporally associated with Lemtrada infusion.

BP: Blood Pressure; HCP: Healthcare Professional; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 47 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Pulmonary alveolar haemorrhage (PAH)[a]

Important identified risk: Pulmonary alveolar haemorrhage (PAH)[a]	
Evidence for linking the risk to the medicine	Postmarketing.
Risk factors and risk groups.	Many disorders can cause PAH; they include: (39) • Autoimmune disorders (eg, systemic vasculitides, Goodpasture syndrome, antiphospholipid antibody syndrome, connective tissue disorders); • Pulmonary infections (eg, hantavirus infection); • Toxic exposures (eg, trimellitic anhydride, isocyanates, crack cocaine, certain pesticides); • Drug reactions (eg, propylthiouracil, diphenylhydantoin, amiodarone; methotrexate, nitrofurantoin, bleomycin, montelukast, infliximab);mCardiac disorders (eg, mitral stenosis);mCoagulation disorders caused by diseases or anticoagulant drugs;mIsolated pauci-immune pulmonary capillaritis; • Idiopathic pulmonary hemosiderosis; • Hematopoietic stem cell transplantation or solid organ transplantation. • The reported events of PAH followed no particular pattern in terms of risk groups. The reported risk window was between 1 day and 3 days from the last

Important identified risk: Pulmonary alveolar haemorrhage (PAH)[a]	
	dose. No dose related, or pattern of additive or synergistic risk factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labelled in sections 4.2, 4.4 and 4.8 of SmPC. • Labelled in sections 2 and 4 of PL. • Instructions for treatment initiation are included in SmPC section 4.2. • Instructions to reduce serious reactions temporally associated with Lemtrada infusion (pre-infusion, during infusion and post-infusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL Sections 2 and 4, as well as information on the monitoring which will be done. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

a This risk is temporally associated with Lemtrada infusion.

HCP: Healthcare Professional; MI: Myocardial Infarction; PASS: Post-Authorization Safety Study; PAH: Pulmonary Alveolar Haemorrhage; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 48 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Thrombocytopenia[a]

Important identified risk: Thrombocytopenia[a]	
Evidence for linking the risk to the medicine	Clinical trials and postmarketing.
Risk factors and risk groups.	Non-immune thrombocytopenia can occur with a variety of conditions: • Infections (viral, HIV, bacterial infections or sepsis) • Chronic liver disorders • Hypersplenism • Congenital platelet disorders - Malignancies - Bone marrow disorders - Drugs (daptomycin, linezolid, valproic acid) - Over-the-counter remedies, supplements, foods, beverages or alcohol consumption. The reported events of non-immune immediate thrombocytopenia followed no particular pattern in terms of risk groups. There was no dose related pattern. No pattern of additive or synergistic factors were observed.

Important identified risk: Thrombocytopenia[a]	
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Instructions for treatment initiation are included in SmPC section 4.2. • Platelet count should be obtained before infusion, immediately after infusion on Days 3 and 5 of the first infusion course, as well as immediately after infusion on Day 3 of any subsequent course. • Instructions to reduce serious reactions temporally associated with Lemtrada (pre-infusion, during infusion, post-infusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL Sections 2 and 4, as well as information on the monitoring which will be done. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

a This risk is temporally associated with Lemtrada infusion.

HCP: Healthcare Professional; HIV: Human Immunodeficiency Virus; MI: Myocardial Infarction; MS: Multiple Sclerosis; PL: Package Leaflet; SmPC: Summary of Product Characteristics; TTO: Time to Onset.

Table 49 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Thyroid disorders

Important identified risk: Thyroid disorders	
Evidence for linking the risk to the medicine	Clinical studies and postmarketing.
Risk factors and risk groups.	In clinical trials, over all available follow-up of the 1486[a] alemtuzumab treated patients, 1466 had anti-TPO antibody testing at baseline. Patients with positive anti-TPO antibodies at baseline also had a higher incidence of abnormal TSH result with simultaneous abnormal T3 or T4 compared to patients with negative antibodies. Of the 1466 patients with anti TPO testing at baseline, 91.4% tested negative and 8.6% tested positive. Of those who tested negative, 38.2% developed a thyroid AE. Of those who tested positive, 74.8% developed a thyroid AE. Thus, there is a higher risk of developing a thyroid AE in anti-TPO positive patients. However, of the patients with baseline anti-TPO antibody testing who developed a thyroid AE, 86% had tested negative for anti-TPO antibodies which underlines the poor predictive value of the measure as a whole. Had anti-TPO positive status been an exclusion to alemtuzumab therapy, only a small number of patients (80 out of 1466, 5.4%) would have been spared a thyroid AE but, based on the lower efficacy observed in the control group, some of them would have experienced

Important identified risk: Thyroid disorders	
	additional MS relapses and disability progression that were avoided with alemtuzumab treatment. Maternal transmission of anti-TSH receptor antibodies is associated with higher maternal titres of anti-TSH receptor antibodies in the third trimester. There was no dose related pattern. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Recommendations for thyroid function monitoring are included in SmPC section 4.4. • How to detect signs and symptoms of thyroid disorders and the need to seek for immediate medical attention is labelled in PL sections 2 and 4 as well as the summary of the tests to complete. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, HCP checklist, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

AE: Adverse Event; CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; HCP: Healthcare Professional; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics; TPO: Thyroid Peroxidase; TSH: Thyroid Stimulating Hormone.

Table 50 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Immune thrombocytopenic purpura (ITP)

Important identified risk: Immune thrombocytopenic purpura (ITP)	
Evidence for linking the risk to the medicine	Clinical studies and postmarketing.
Risk factors and risk groups.	None identified at present. As with other forms of ITP, the data suggest that circulating anti-platelet antibody and platelet-bound antibody assays are not predictive of alemtuzumab associated ITP. (51) There was no dose related pattern. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.

Important identified risk: Immune thrombocytopenic purpura (ITP)	
	• Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Recommendations to complete blood counts are included in SmPC section 4.4, as well as medical conduct to adopt if immune thrombocytopenic purpura onset is confirmed. • How to detect signs and symptoms of ITP and the need to seek for immediate medical attention is labelled in PL sections 2 and 4, as well as the summary of the tests to complete. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. <u>Additional risk minimization measures</u>: Educational materials (ie, HCP guide, HCP check-list, patient guide, patient alert card) planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

HCP: Healthcare Professional; ITP: Immune Thrombocytopenic Purpura; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 51 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Nephropathies including anti-glomerular basement membrane (anti-GBM) disease

Important identified risk: Nephropathies including anti-glomerular basement membrane (anti-GBM) disease	
Evidence for linking the risk to the medicine	Clinical studies, medical literature, spontaneous reports received by Sanofi Genzyme and postmarketing.
Risk factors and risk groups.	There is no indication that patients with pre-existing renal conditions are at greater risk of developing an event. There is no dosing related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Risk minimization measures	<u>Routine risk minimization measures</u>: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Recommendations to complete serum creatinine levels and urinalysis blood counts are included in SmPC section 4.4, as well as medical conduct to adopt in case of clinically relevant changes in these results. • How to detect signs and symptoms of kidney disorders and the need to seek for immediate medical attention is labelled in PL sections 2 and 4, as well as the summary of the tests to complete. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access

Important identified risk: Nephropathies including anti-glomerular basement membrane (anti-GBM) disease	
	to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, HCP check-list, patient guide, patient alert card) planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

GBM: Glomerular Basement Membrane; HCP: Healthcare Professional; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 52 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Autoimmune Hepatitis (AIH)

Important identified risk: Autoimmune Hepatitis (AIH)	
Evidence for linking the risk to the medicine	Postmarketing.
Risk factors and risk groups.	None identified. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • The need to perform liver function test before initial treatment and periodically thereafter are labelled in SmPC section 4.4. • How to detect signs and symptoms of liver disorders and the need to seek for immediate medical attention is labeled in PL sections 2 and 4. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

AIH: Autoimmune Hepatitis; HCP: Healthcare Professional; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 53 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Serious Infections

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Clinical studies and postmarketing.
Risk factors and risk groups.	Relapsing remitting MS patients who have been previously treated with immune suppressive agents are theoretically at increased risk for infection if subsequently treated with alemtuzumab, as concomitant use of alemtuzumab with any of these therapies could increase the risk of immunosuppression. In controlled clinical trials, the rate of infections and serious infections is greater in previously treated patients, regardless of treatment (ie, whether alemtuzumab-treated or interferon treated). Interim safety data from CAMMS223 suggested that MS patients treated with alemtuzumab were at an increased risk of developing HSV within 1 month of receiving alemtuzumab. (15) Additionally, patients with mobility restrictions may theoretically be at higher risk for infectious complications due to diminished mobility and functional capacity (eg, aspiration pneumonia, infected decubitus ulcers, presence of indwelling catheter, and dysphagia with aspiration). There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Instructions for treatment initiation are included in SmPC section 4.2. • Contraindication regarding severe active infection until complete resolution is included in SmPC section 4.3 and PL section 2. • Recommendations regarding screening, prophylaxis and the conduct to adopt in patients with severe active infection are included in SmPC section 4.4. • Recommendations regarding screening, prophylaxis, treatment and the need to seek for immediate medical attention as well as the summary of tests to complete, for some infections are included PL sections 2 and 4. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card) planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

HSV: Herpes Simplex Virus; HCP: Healthcare Professional; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 54 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Haemophagocytic Lymphohistiocytosis (HLH)

Important identified risk: Haemophagocytic Lymphohistiocytosis (HLH)	
Evidence for linking the risk to the medicine	Postmarketing.
Risk factors and risk groups.	None identified. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labelled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Recommendations provided to identify patients developing early manifestation of pathologic immune activation are labeled in SmPC section 4.4 as well as the need to consider diagnosis of HLH. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL Sections 2 and 4. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, HCP check-list, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

HCP: Healthcare Professional; HLH: Haemophagocytic Lymphohistiocytosis; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 55 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Acquired Haemophilia A (AHA)

identified risk: Acquired Haemophilia A (AHA)	
Evidence for linking the risk to the medicine	Clinical and postmarketing.
Risk factors and risk groups.	Unknown. It is not known whether development of one treatment emergent antibody mediated autoimmune disorder predisposes to development of additional antibody mediated autoimmune diseases. Acquired haemophilia A is seen more frequently in the non-MS population with increasing age and may be drug-induced or arise in the setting of pregnancy, underlying autoimmune disease or malignancy. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.

identified risk: Acquired Haemophilia A (AHA)	
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Instructions for treatment initiation are included in SmPC section 4.2. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Recommendation provided to identify patients developing manifestation of AHA as well as the need to complete coagulopathy panel in case a patient presents such symptoms, are included in SmPC section 4.4. • Recommendations regarding signs and symptoms of AHA and the need to seek for medical attention are included in PL sections 2 and 4. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, HCP check-list, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

AHA: Acquired Haemophilia A; HCP: Healthcare Professional; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 56 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Thrombotic thrombocytopenic purpura (TTP)

Important identified risk: Thrombotic thrombocytopenic purpura (TTP)	
Evidence for linking the risk to the medicine	Postmarketing.
Risk factors and risk groups.	None identified.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Warning to conduct an urgent evaluation and prompt treatment as well as symptoms to identify TTP are included in SmPC section 4.4. • Recommendations regarding signs and symptoms of TTP are included in PL sections 2 and 4. Section 2 of the PL also recommends getting medical help right away if TTP signs or symptoms occur. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections,

Important identified risk: Thrombotic thrombocytopenic purpura (TTP)	
	should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics; TTP: Thrombotic Thrombocytopenic Purpura.

Table 57 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Adult Onset Still's Disease (AOSD)

Important identified risk: Adult Onset Still's Disease (AOSD)	
Evidence for linking the risk to the medicine	Postmarketing.
Risk factors and risk groups.	In the general population, AOSD is most often seen in young adults, with a higher prevalence in women. (63)
Risk minimization measures	Routine risk minimization measures: • Labeled in section 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Warning to conduct an urgent evaluation and treatment as well as symptoms to identify AOSD are included in SmPC section 4.4. The statement to "Consider interruption or discontinuation of treatment with Lemtrada if an alternate etiology cannot be established" is also included in this section. • Potential symptoms of AOSD with multi-organ inflammation is described in PL sections 2 and 4. Section 2 of the PL also recommends getting medical help right away if AOSD symptoms occur. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, patient guide, patient alert card) planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

AOSD: Adult Onset Still's Disease; HCP: Healthcare Professional; MS: Multiple Sclerosis; MI: Myocardial Infarction; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC; Summary of Product Characteristics.

Table 58 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Autoimmune Encephalitis (AIE)

Important identified risk: Autoimmune Encephalitis (AIE)	
Evidence for linking the risk to the medicine	Postmarketing studies.
Risk factors and risk groups.	None identified.
Risk minimization measures	Routine risk minimization measures: • Proposed label in sections 4.4 and 4.8 of SmPC. • Proposed label in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

AIE: Autoimmune Encephalitis; CI: Confidence Interval; HCP: Healthcare Professional; MS: Multiple Sclerosis; SmPC: Summary of Product Characteristics; PL: Package Leaflet.

Table 59 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Acute acalculous cholecystitis (AAC)

Important identified risk: Acute acalculous cholecystitis (AAC)	
Evidence for linking the risk to the medicine	Clinical and postmarketing.
Risk factors and risk groups.	None identified. There is no indication that patients with pre-existing gallbladder conditions are at greatest risk of developing an event. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Conduct to adopt in case acalculous cholecystitis is suspected is included in SmPC section 4.4. • Recommendations regarding signs and symptoms of gall bladder inflammation and the need to seek for medical attention are included in PL sections 2 and 4. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections,

Important identified risk: Acute acalculous cholecystitis (AAC)	
	should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: None
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

AAC: Acute Acalculous Cholecystitis; MI: Myocardial Infarction; MS: Multiple Sclerosis; PL: Package Leaflet; PASS: Post-Authorization Safety Study; SmPC: Summary of Product Characteristics.

Table 60 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus [T1DM], Guillain Barre syndrome [GBS], Sarcoidosis)

Important potential risk: Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus [T1DM], Guillain Barre syndrome [GBS], Sarcoidosis)	
Evidence for linking the risk to the medicine	Clinical studies and postmarketing.
Risk factors and risk groups.	Not identified. It is not known whether development of 1 treatment-emergent antibody mediated autoimmune disorder predisposes to development of additional antibody mediated autoimmune diseases. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Recommendations to complete blood count is included in SmPC section 4.4, as well as medical conduct to adopt if cytopenia is confirmed. • Lemtrada treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: None
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

GBS: Guillain-Barre Syndrome; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics; T1DM: Type 1 Diabetes Mellitus.

Table 61 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Malignancies

Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	Clinical studies and postmarketing.
Risk factors and risk groups.	Patients with a prior history of basal cell carcinoma are at increased risk for developing subsequent basal cell carcinoma. Women with HPV infections of the uterine cervix are at increased risk for cervical cancer. This risk may increase after immune suppression by alemtuzumab. There was no dose related pattern identified in the reported cases.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Information regarding treatment initiation in patients with pre-existing and/or ongoing malignancy is labelled in SmPC section 4.4. • Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: None
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

HPV: Human Papilloma Virus; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 62 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Progressive Multifocal Leukoencephalopathy (PML)

Important potential risk: Progressive Multifocal Leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Postmarketing.
Risk factors and risk groups.	Patients who are seropositive for JCV antibodies or are HIV positive are at increased risk for PML. Chronic lymphocytic leukemia and lymphoproliferative disorders are also associated with increased risk of PML. Prior exposure to immunosuppressive therapies also increases the risk for development of PML. There was no dose related pattern identified in the reported cases.
Risk minimization measures	Routine risk minimization measures: • Labeled in section 4.4 of SmPC. • Labeled in section 2 of PL. • Recommendations and exams to be completed in case of signs suggestive of PML are labeled in SmPC section 4.4. • Recommendations regarding signs and symptoms of PML and the need to seek for medical attention are included in PL sections 2 and 4.

Important potential risk: Progressive Multifocal Leukoencephalopathy (PML)	
	• Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Educational materials (ie, HCP guide, HCP checklist, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

HCP: Healthcare Professional; HIV: Human Immunodeficiency Virus; JCV: John Cunningham Virus; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; PML: Progressive Multifocal Leukoencephalopathy; SmPC: Summary of Product Characteristics.

Table 63 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Pediatric use

Missing information: Pediatric use	
Risk minimization measures	Routine risk minimization measures: • Labeled in section 5.1 of SmPC. • Recommendations regarding use in paediatric population are included SmPC section 4.2 and PL section 2. • Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: None
Additional pharmacovigilance activities	Pediatric study EFC13429 Planned date for submission of final data: within 6 months of completion of the study (LPLV) in accordance with the Article 46 of paediatric regulation.

LPLV: Last Patient Last Visit; MI: Myocardial Infarction; MS: Multiple Sclerosis; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 64 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use in patients aged >55 years (including use in elderly patients aged ≥65 years)

Missing information: Use in patients aged >55 years (including use in elderly patients aged ≥65 years)	
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2 and 5.2 of SmPC.

Missing information: Use in patients aged >55 years (including use in elderly patients aged ≥65 years)	
	• Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: None
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; SmPC: Summary of Product Characteristics.

Table 65 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use in racial categories other than white

Missing information: Use in racial categories other than white	
Risk minimization measures	Routine risk minimization measures: Lemtrada treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: None
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2030

MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Lemtrada.

II.C.2 Other studies in post-authorization development plan

Table 66 - Other studies in post-authorization development plan

PASS OBS13434: A prospective, multicenter, observational cohort study of patients with relapsing forms of MS Treated with Lemtrada (alemtuzumab) (cat. 3)
Purpose of the study: To better characterize the long-term safety profile of alemtuzumab in relapsing MS patients and to determine the incidence of adverse events of special interest.
Pediatric Study EFC13429: Open-label, rater-blinded, single-arm, before and after efficacy, safety and tolerability study of alemtuzumab in pediatric patients from 10 years to less than 18 years with RRMS with disease activity on prior disease modifying treatment (cat. 3)
Purpose of the study: To evaluate the efficacy, safety and tolerability of alemtuzumab (IV) before and after treatment in pediatric subjects with relapsing forms of MS, who have disease activity on prior therapy.

IV: Intravenous; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; RRMS: Relapsing Remitting Multiple Sclerosis.

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PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

TABLE OF CONTENTS

ANNEX 4.1 PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY QUESTIONNAIRE

SANOFI

genzyme
A SANOFI COMPANY

Progressive Multifocal Leukoencephalopathy (PML) check list*
Information to be transmitted to Global Pharmacovigilance & Epidemiology Dept.

*** To be attached to the corresponding completed AE/SAE Form**

PROJECT:

Protocol N° if clinical trial: ⌊_⌊_⌊_ ⌊_⌊_⌊_⌊_

Date of this report: ...../...../.....
Day month year

Patient ID: ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_

INVESTIGATOR/REPORTER NAME:

.....

Phone number:.....

GPE case ID (for Sanofi internal use):

⌊_⌊_⌊_⌊_ ⌊_⌊_ ⌊_⌊_⌊_

1. PATIENT INFORMATION

Initials	Age	DOB	Gender: ☐ Male ☐ Female

2. DRUG BEING REPORTED

Name: _____

3. PML-RELATED QUESTIONS

3.1. PML Diagnosis

3.1.1. Please indicate whether the diagnosis of PML is
☐ Suspected ☐ Confirmed ☐ Indeterminate

If indeterminate, what is the differential diagnosis?

_____

_____

3.1.2. Please indicate basis for diagnosis (check all that apply)
☐ Brain biopsy ☐ CSF PCR ☐ MRI

3.2. Causal relationship

Is there a reasonable possibility that PML diagnosis is associated with the use of the drug being reported?
☐ Yes ☐ No ☐ Unable to assess

3.3. Clinical symptoms

Symptoms		Date of onset
Recent changes in personality or mood	☐ Yes ☐ No	
Recent or sudden change in cognitive behaviour Example: confusion, disorientation	☐ Yes ☐ No	
Language or speech disturbances Example: aphasia or dysarthria	☐ Yes ☐ No	
Visual disturbances	☐ Yes ☐ No	
Ataxia/loss of motor coordination/progressive weakness	☐ Yes ☐ No	
New onset of seizures	☐ Yes ☐ No	
Other– if yes, please specify	☐ Yes ☐ No	

3.4. EDSS score

	Date	Score
Prior to the onset of symptoms		
After the onset of symptoms		

3.5. Laboratory and JCV information

Test*		Date	Results
JCV DNA Detection by PCR ☐ Yes ☐ No Laboratory used for detection (please provide name and location)	☐ CSF		
	☐ Plasma		
Brain biopsy ☐ Yes ☐ No Hospital facility (please provide name and location)			
CD4 count ☐ Yes ☐ No			
CD8 count ☐ Yes ☐ No			

*Please provide copies of test results

3.6. Imaging information

	Date	Results
Was Brain MRI performed prior to the start of symptoms? ☐ Yes ☐ No		
Was Brain MRI performed for PML diagnosis? ☐ Yes ☐ No		
Was Brain CT performed prior to the start of symptoms? ☐ Yes ☐ No		
Was Brain CT performed for PML diagnosis? ☐ Yes ☐ No		

3.7. PML treatment

Has any treatment been given to the patient to treat PML? ☐ Yes ☐ No

Medication	Dose	Frequency	Route	Start date	End date

4. MEDICAL HISTORY

4.1. Please indicate if the patient had or has one or more of the following conditions

Relevant medical information		Date	Treatment (if available)
HIV or AIDS	☐ Yes ☐ No		
Leukemia/Lymphoma Other Malignancies Please specify:_____	☐ Yes ☐ No ☐ Yes ☐ No		
Opportunistic infection(s) (e.g CMV) Specify:_____	☐ Yes ☐ No		
Tuberculosis	☐ Yes ☐ No		
Organ transplant Please specify:_____	☐ Yes ☐ No		
Other autoimmune disease (e.g. SLE, Sjogren's, Behcet's, RA, psoriasis….) Please specify: _____	☐ Yes ☐ No		

4.2. Please indicate if the patient had prior JCV testing

Relevant investigations			Date	Results
JCV DNA testing before current illness (please provide the name of laboratory where the test was performed)	□ Yes □ No	□ CSF		
		□ Plasma		
JCV Serology	□ Yes □ No			

5. DRUG HISTORY

5.1. Please indicate any treatment the patient received/receiving for multiple sclerosis

Medication	Date of 1st Course	Date of Last Course	No. of Courses	Dose/ Route	Reason for Discontinuation	Reporter Causality[1]
Lemtrada™ (alemtuzumab) (if not the drug being reported) □ Yes □ No						Related □ Unrelated □ Unknown □

Medication	Start Date	End Date	Dose/ Route	Frequency	Reason for Discontinuation	Reporter Causality[1]
Aubagio® (teriflunomide) (if not the drug being reported) □ Yes □ No						Related □ Unrelated □ Unknown □
Tysabri® (natalizumab) □ Yes □ No						Related □ Unrelated □ Unknown □
Gilenya® (fingolimod) □ Yes □ No						Related □ Unrelated □ Unknown □
Tecfidera® (dimethyl fumarate) □ Yes □ No						Related □ Unrelated □ Unknown □
Interferon beta (any product) □ Yes □ No						Related □ Unrelated □ Unknown □
Copaxone® (glatiramer acetate) □ Yes □ No						Related □ Unrelated □ Unknown □
Novantrone®, Elsep® (mitoxantrone) □ Yes □ No						Related □ Unrelated □ Unknown □
Corticosteroids (most recent course) □ Yes □ No						Related □ Unrelated □ Unknown □
Other MS Therapies □ Yes □ No Specify: _____						Related □ Unrelated □ Unknown □
Other MS Therapies □ Yes □ No Specify: _____						Related □ Unrelated □ Unknown □
Other MS Therapies □ Yes □ No Specify: _____						Related □ Unrelated □ Unknown □
Other MS Therapies □ Yes □ No Specify: _____						Related □ Unrelated □ Unknown □

[1]Physician's assessment of relatedness to PML

5.2. Please indicate if the patient has taken one or more of the following medications

Medication		Start Date	End Date	Dose	Frequency	Reason for Discontinuation	Reporter Causality[1]
Rituxan®, Mabthera® (rituximab)	□ Yes □ No						Related □ Unrelated □ Unknown □
Raptiva® (efalizumab)	□ Yes □ No						Related □ Unrelated □ Unknown □
Arava® (leflunomide)	□ Yes □ No						Related □ Unrelated □ Unknown □
Methotrexate	□ Yes □ No						Related □ Unrelated □ Unknown □
Other immunosuppressive or chemotherapeutic agents (e.g., cyclophosphamide, tacrolimus, azathioprine, mycophenolate, cyclosporine) Please specify:	□ Yes □ No						Related □ Unrelated □ Unknown □

[1]Physician's assessment of relatedness to PML

Abbreviations

AIDS	Acquired immunodeficiency syndrome
CMV	Cytomegalovirus
CT	Computed tomography
DNA	Deoxyribonucleic acid
EDSS	Expanded disability status scale
HIV	Human immunodeficiency virus
JCV	John Cunningham Virus
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction

ANNEX 4.2 HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS FOLLOW-UP QUESTIONNAIRE PROPOSAL

TARGETED FOLLOW-UP QUESTIONNAIRE

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

SUSPECT ADVERSE REACTION INFORMATION			
Sanofi Identification/Country:	Drug Name:	Reaction Onset: Click here to enter a date.	Date of Report: Click here to enter a date.
Report Source: Study ☐ Literature ☐ Health Professional ☐ Other: Unsolicited Non literature ☐			
Clinical trial? Yes ☐ No☐	Study ID:	Patient ID:	
Post Marketing? Yes ☐ No☐	Case ID:	Patient ID:	
Reporter:	Address:	Phone:	
Did Reaction Reappear After Reintroduction Drug? Yes ☐ No ☐ NA☐			

OUTCOME OF AE *Tick more than one box if necessary*	
Emergency Room Treatment: Yes ☐ No☐	Hospital Admission: Yes ☐ No☐
Hospitalization Duration: Weeks ☐ Months ☐ **Additional details:**	Recovery: Yes ☐ No☐ • Resolution of all clinical signs and symptoms: Yes ☐ No☐ • Recovery of the complete blood count: Yes ☐ No☐ • Normalization of abnormal laboratory findings: Yes ☐ No☐ **Additional details:**
Recovered with disability/incapacity: Yes ☐ No☐ • Motor deficits: Yes ☐ No☐ • Cognitive deficits: Yes ☐ No☐ • Other deficits: Yes ☐ No☐ **Additional details:**	
Life threatening: Yes ☐ No☐ • Admitted to CCU: Yes ☐ No☐ • Required supportive ventilation: Yes ☐ No☐ • Required bone marrow transplant: Yes ☐ No☐ **Additional details:**	Patient Died: Yes ☐ No☐ • Reported cause of death: • Date of death Click here to enter a date. **Additional details:**

PATIENT INFORMATION			
Patient initials:	ID number:	Age:	Date of Birth: Click here to enter a date.
Gender:	Weight:	Occupation:	Country:

HLH DIAGNOSIS

Primary HLH: Yes ☐ No☐

- Genetic Testing: Yes ☐ No☐
- Genetic Test Details:

Additional details:

Secondary HLH : Yes ☐ No☐

Additional details:

HLH DIAGNOSTIC CRITERIA

(≥5 of 8 components are required for diagnosis)

Fever: Yes ☐ No☐

- Not Tested: ☐
- Result not available: ☐

Splenomegaly or Hepatomegaly: Yes ☐ No☐

- Not Tested: ☐
- Result not available: ☐

At least 2 of the following 3 blood count criteria: Yes ☐ No☐

- Not Tested: ☐
- Result not available: ☐

  - Hemoglobin <9 g/dL: Yes ☐ No☐
    - Not Tested: ☐
    - Result not available: ☐
  - Platelets <100 x 109/L: Yes ☐ No☐
    - Not Tested: ☐
    - Result not available: ☐
  - Neutrophils <1 x 109/L: Yes ☐ No☐
    - Not Tested: ☐
    - Result not available: ☐

Hypertriglyceridemia (fasting, >265 mg/dL) or hypofibrinogenemia (<150 mg/dL): Yes ☐ No☐

- Not Tested: ☐

- Result not available: ☐

Hemophagocytosis in spleen, bone marrow, lymph nodes or liver: Yes ☐ No☐
- Not Tested: ☐
- Result not available: ☐

Low or absent NK cell activity: Yes ☐ No☐
- Not Tested: ☐
- Result not available: ☐

Ferritin >500 µg/L: Yes ☐ No☐
- Not Tested: ☐
- Result not available: ☐

Elevated soluble CD25 (interleukin 2 receptor alpha): Yes ☐ No☐
- Not Tested: ☐
- Result not available: ☐

RELEVANT FAMILY HISTORY

Tick all that apply and complete additional details section below

☐Parental consanguinity
☐Familial HLH
☐Familial Cancers
☐History of Autoimmune disease
☐Other

Additional details:

PREVIOUS RELEVANT MEDICAL HISTORY AND CONCURRENT DISORDERS

Tick all that apply and complete additional details section below

☐Current pregnancy	☐Cancer	☐Occupational
☐Hepato-biliary	☐Surgical operation	☐Travels Africa
☐Allergic disease	☐Dental operation	☐Travels Asia
☐Allergy to drug	☐Transfusion of blood/derivatives	☐Intravenous drug abuse
☐Auto-immune	☐Alcohol consumption	☐Other
☐Heart/vascular disease	☐Acupuncture	
☐Respiratory		

Additional details:

RELEVANT RISK FACTORS

Tick all that apply and complete additional details section below

Viral Infections

☐ EBV
☐ HIV
☐ HHV8
☐ CMV
☐ HSV
☐ Adenovirus
☐ Rubella
☐ Hepatitis A
☐ Hepatitis B
☐ Hepatitis C
☐ others

Additional details:

Bacterial Infections

☐ Salmonella enterica
☐ Streptococcus pneumonia
☐ Mycobacteria
☐ Spirochaetes
☐ others

Additional details:

Fungal Infections

☐ Mucormycosis
☐ others

Additional details:

Parasitic Infections

☐ Plasmodium vivax
☐ others

Additional details:

Malignancy

☐Lymphoid (lymphomas, leukemias)
☐Myeloid
☐Solid
☐ others

Additional details:

Rheumatologic (known as macrophage activation syndrome, MAS-HLH)

☐Systemic juvenile idiopathic arthritis
☐Adult-onset Still disease
☐Systemic lupus erythematosus to drug
☐Vasculitis
☐ others

Additional details:

Transplantation

☐Bone Marrow Transplantation
☐HCST
☐Other

Additional details:

Past immunomodulatory therapies

☐ Corticosteroids
☐ Janus kinase inhibitors
☐ Calcineurin inhibitors
☐ mTOR inhibitors
☐ IMDH inhibitors
☐ Biologics
☐ Monoclonal antibodies
☐Other

	Additional details:

CLINICAL PRESENTATION AT THE TIME OF HLH DIAGNOSIS (Time point when the treating MD/team defined the patient as having clinical HLH)			
Description- Nature of symptoms (include if present at any point)	**Yes**	**No**	**Onset Date**
Asthenia			
Fever			
Pruritus			
Jaundice			
Joint Pain			
Abdominal Pain			
Vomiting			
Skin Eruption-Details			
Purpura			
Hepatomegaly			
Splenomegaly			
Acalculous Cholecystitis (Acc)			
Lymph Nodes			
Ascites			
Retinal Hemorrhages			
Asterixis			
Seizures			
Ataxia			
Altered Consciousness			
Encephalopathy			
Peripheral Neuropathy			
Headache			
Coma			
Sepsis			
Visual Disturbances			
Optic Nerve Edema			
Hypotonia			
Meningeal Irritation			
Additional details:			

RELEVANT LABORATORY DATA			
Test	**Reference range**	**Patient's value**	
		Most abnormal recorded value / Date of Testing	**Most recent recorded value / Date of Testing**
SGOT/SGPT			
Alkaline Ph.			
GGT			
CPK			
Bilirubin			
Conjugated bilirubin			
IgM			
IgG			
Prothrombin time/international normalized ratio (PT/INR)			
Factor V			
Hemoglobin			
Leukocytes			
Polymorphonuclear cells			
Eosinophils			
Creatinine			
Urea			
Lipid panel with Fasting Triglycerides			
Serum fibrinogen			
Serum Ferritin			
Interleukin-2 (CD25) levels			
Natural Killer cell activity			
Perforin and granzyme B proteins			
SAP and XIAP proteins			
Hemoglobin-haptoglobin scavenger receptor (sCD163)			
B-cell panel			
T-cell panel			
Additional details:			

Genetic mutations associated with HLH			
Genetic mutations tested	**Not tested**	**Absent**	**Present**
PRF1			
UNC13D			
STX11			

STXBP2			
RAB27			
XLP			
LYST			
AP381			
SHD2D1A			
BIRC4			

Additional details:

ULTRASONOGRAPHY NO ☐ YES ☐ Click here to enter a date. Brief result:	LIVER BIOPSY NO ☐ YES ☐ Click here to enter a date. Brief result:
CT/MRI NO ☐ YES ☐ Click here to enter a date. Brief result:	CSF EXAMINATION NO ☐ YES ☐ Click here to enter a date. Brief result:

Brain MRI INFORMATION
T2 lesions in the white matter: Yes ☐ No☐
Basal ganglia T2 abnormality: Yes ☐ No☐
Hemorrhage: Yes ☐ No☐
Features of ischemic stroke: Yes ☐ No☐
Increased ventricle size: Yes ☐ No☐
Loss of brain volume : Yes ☐ No☐
Features consistent with PRES: Yes ☐ No☐
Widening of the ventricle and sulcus: Yes ☐ No☐

Meningeal enhancement: Yes ☐ No☐
Additional details:
CRANIAL CT INFORMATION
Low-density punctate lesions: Yes ☐ No☐
Hemorrhagic infarct: Yes ☐ No☐
Regions of parenchymal calcification: Yes ☐ No☐
Additional details:
CSF ANALYSIS INFORMATION (Date of Exam)
WBC Cell Count :
RBC Cell count:
Protein:
Glucose:
Lactate:
Microbiology result:
Cytospin Findings:
Additional details:

SUSPECTED DRUG INFORMATION		
Drug name (include generic name)	Indication for use	
Route(s) of administration	Daily dose(s)	
Start Date Click here to enter a date.	**Stop Date** Click here to enter a date.	Therapy Duration
Drug name (include generic name)	Indication for use	
Route(s) of administration	Daily dose(s)	
Start Date Click here to enter a date.	**Stop Date** Click here to enter a date.	Duration

ADMINISTRATION OF DRUG *After the beginning of the reaction*			
☐Stopped	☐Continued same dose	☐Reduced dose	☐Other

READMINISTRATION OF DRUG			
☐No ☐Yes **Date:** Click here to enter a date. **Dose:**		Recurrence of reaction? ☐uninterpretable ☐No ☐Yes **Date:** Click here to enter a date.	
Previous therapy with the same drug			
☐No ☐Yes **Date:** Click here to enter a date.		Safety issues:	
CONCOMITANT THERAPY			
Drug **Start Date DD/MM/YYYY**	**Route** **End Date DD/MM/YYYY**	**Daily Dose** **Indication**	
Drug **Start Date** Click here to enter a date.	**Route** **End Date** Click here to enter a date.	**Daily Dose** **Indication**	
Drug **Start Date** Click here to enter a date.	**Route** **End Date** Click here to enter a date.	**Daily Dose** **Indication**	
Drug **Start Date** Click here to enter a date.	**Route** **End Date** Click here to enter a date.	**Daily Dose** **Indication**	
REPORTERS CAUSAL RELATIONSHIP ***Reporters assessment***			
☐Not assessable		☐Not related	
☐Unlikely related		☐Possibly related	
☐Probably related		☐Highly probable	

ANNEX 4.3 AUTOIMMUNE HEPATITIS FOLLOW-UP FORM PROPOSAL

TARGETED FOLLOW-UP QUESTIONNAIRE
AUTOIMMUNE HEPATITIS

Product:	Local case no:	Global case no:
Patient: Initials……..….Gender…….……..Age or date of birth: ……..	Study:	Subject Number:

Pertinent medical history of risk factors: *If yes provide details*
Patient's and family history of autoimmune systemic illness Yes ☐ No ☐
Patient's history of viral hepatitis, alcohol and/or drugs consumption, hepato-biliary disorders Yes ☐ No ☐
……..
……..
Concomitant treatment: *(if not previously reported, please specify)*……
……..

Clinical features
Interval between the last infusion of LEMTRADA and first symptom of hepatitis: ……..days Start date of hepatitis: ……/……/……

Elements confirming diagnosis *If yes, please describe in free narrative text*	**Yes**	**No**	**Elements confirming diagnosis** *Please provide details on page 2*	**Yes**	**No**	**Free Narrative Text** (*Please provide detailed description of reported symptoms, investigations, including onset and stop dates)*
Common sings of hepatitis (abdominal discomfort, vomiting, fever)	☐	☐	1. Liver transaminases increased……	1.☐	☐	
Jaundice	☐	☐	2. Serum immunoglobulin (IgG) increased……	2.☐	☐	
Spider telangiectasia	☐	☐	3. Serum albumin decreased	3.☐	☐	
Amenorrhea	☐	☐	4. Antinuclear antibody (ANA)	4.☐	☐	
Complication to cirrhosis or portal hypertension:	☐	☐	5. Liver –Kidney microsomal antibody (LKM-1)…….	5.☐	☐	
Hepato- and splenomegaly	☐	☐	6. Anti-smooth muscle antibody (ASMA)……	6.☐	☐	
Ascites	☐	☐	7. Diagnosis confirmed by histopathology? *(please detail results on page 2)*	7.☐	☐	
Hepatic Encephalopathy	☐	☐				
Variceal bleedings	☐	☐				
Other concurrent autoimmune illnesses? *(if yes describe in free narrative text)*	☐	☐				
Did symptoms improve with corticosteroids?	☐	☐				

Have alternative etiologies and differential diagnoses been ruled out? *(e.g, viral hepatitis, other drugs or alcohol hepatotoxicity, primary biliary cirrhosis, Wilson disease, hemolytic anemia)*
If yes please specify

Investigations performed *Provide detailed pertinent Positive (+) / Negative (-) or Normal / Abnormal* ***results with units, normal range and date*** *(NA= not available)*

Infectious check-up	**(+) (-) NA**	**Details (IgG, IgM, blood, CSF PCR, serology, culture, value)**	**Blood tests**	**Normal? Yes No NA**	**Anomaly details**
HIV	☐ ☐ ☐		Blood count	☐ ☐ ☐	
Epstein-Barr virus	☐ ☐ ☐		White blood cell formula Platelettes	☐ ☐ ☐ ☐ ☐ ☐	
Hepatitis A virus	☐ ☐ ☐		Serum aminotransferases level	☐ ☐ ☐	***AST*** ***ALT***
Hepatitis B virus	☐ ☐ ☐		Serum bilirubin	☐ ☐ ☐	
Hepatitis C virus	☐ ☐ ☐		Alkaline phosphatase	☐ ☐ ☐	
Hepatitis E virus	☐ ☐ ☐		Serum protein electrophoresis	☐ ☐ ☐	
Hepatitis D virus	☐ ☐ ☐		Prothrombin time (PT)	☐ ☐ ☐	
Rubella	☐ ☐ ☐		Autoantibodies	☐ ☐ ☐	***ANA*** ***ASMA or LKM***
Enteroviruses (polio, echo…)	☐ ☐ ☐		Serum ceruloplasmin	☐ ☐ ☐	
CMV	☐ ☐ ☐		Lupus erythematosus cell test	☐ ☐ ☐	
			Coombs test	☐ ☐ ☐	
Other investigations performed	**Provide detailed pertinent positive and negative results, with dates**				
Biopsy of liver					
Liver Ultrasonography					

Treatment provided *(with dates)*

……

……

Outcome: Recovered ☐ **- Recovered with sequelae** ☐ **- Not Recovered** ☐ **-Incapacity/Disability** ☐ **- Unknown** ☐ **- Lost to follow-up** ☐

Fatal ☐ Date of death:……..Cause of death:……..…Autopsy performed? Yes ☐ No ☐

Date of outcome……..

Date form completion…… **Reporter name**……

ANNEX 4.4 MYOCARDIAL INFARCTION, MYOCARDIAL ISCHEMIA FOLLOW-UP QUESTIONNAIRE PROPOSAL

TARGETED FOLLOW-UP QUESTIONNAIRE
MYOCARDIAL INFARCTION/MYOCARDIAL ISCHEMIA

Product:	Local case no:	Global case no:
Patient: Initials……..….Gender…….……..Age or date of birth: ……..	Study:	Subject Number:

Pertinent medical history*: If yes please provide details*
Patient's family history of coronary artery disease, myocardial infarction, stroke Yes ☐ No ☐
……

Concurrent disorders and risk factors: *If yes please provide details*
Patient's medical history including concurrent disorders and risk factors Yes ☐ No ☐
……..……..

Concomitant therapies and reason for treatment*: (if not previously reported, please specify)*……..
……...

Details of the administration of Lemtrada: *(if not previously reported, please specify: dose, rate, time interval between doses)*
……

Interval between the last infusion of LEMTRADA and first symptom : ……..days Start date of first symptoms: ……/……/……

Vascular Risk factors *If yes, please describe in free narrative text*	**Yes**	**No**	**Were any of the following symptoms/conditions associated with the event:**	**Investigations - please provide detailed results on additional page**	**At Baseline** **Yes**	**No**	**At the time of follow up** **Yes**	**No**
1. History of coronary artery disease	☐	☐	□ Chest pain	1. Serial cardiac enzymes (CPK with isoenzymes, troponin)	1.☐	☐	1.☐	☐
2. History of heart failure (known EF or NYHA classification)	☐	☐	□ Nausea	2. Echocardiogram	2.☐	☐	2.☐	☐
3. Atrial Fibrillation	☐	☐	□ Lightheadedness	3. Nuclear scan	3.☐	☐	3.☐	☐
4. Ventricular arrhythmia	☐	☐	□ Shortness of breath	4. Coronary angiogram	4.☐	☐	4.☐	☐
5. Hypertension	☐	☐	□ Palpitations	5. Telemetry or Holter results	5.☐	☐	5.☐	☐
6. Diabetes	☐	☐	□ Loss of consciousness	6.Serum K/Mg	6.☐	☐	6.☐	☐
7. High BMI index	☐	☐	□ Other symptoms -please specify below	7. Transthoracic echocardiogram(TTE) report	7.☐	☐	7.☐	☐
8. Hyperlipidemia	☐	☐	□ Was the patient diagnosed with an acute myocardial infarction within 1 week of the event?	8. ECG results	8.☐	☐	8.☐	☐
9. Smoking history	☐	☐	□ Does the patient have an implantable cardioverter defibrillator?	9. Fasting lipids/fasting glucose	9.☐	☐	9.☐	☐
			□ Does the patient have a pacemaker?					

10. Family History of stroke/coronary artery disease	☐ ☐	□ Was the patient evaluated by a cardiac specialist?			

Treatment provided for the event *(with dates)*
……
……

Event outcome: Resolved ☐ **Resolution with some sequelae** ☐ **Unknown** ☐ **Lost to follow-up** ☐

Fatal ☐ Date of death:……..Cause of death:……..…Autopsy performed? Yes ☐ No ☐

In the reporter's opinion, what are the causes of this event…….
…….

Date of outcome……..

Date form completion…… **Reporter name**……

ANNEX 4.5 STROKE AND DISSECTION OF CERVICOCEPHALIC ARTERIES FOLLOW-UP QUESTIONNAIRE PROPOSAL

TARGETED FOLLOW-UP QUESTIONNAIRE
STROKE/CERVICOCEPHALIC ARTERIAL DISSECTION

Product:	Local case no:	Global case no:
Patient: Initials……..….Gender…….……..Age or date of birth: ……..	Study:	Subject Number:

Pertinent medical history: *If yes please provide details*
Patient's family history of stroke or cervicocephalic arterial dissection Yes ☐ No ☐
……

Concurrent disorders and risk factors: *If yes please provide details*
Patient's medical history including concurrent disorders and risk factors Yes ☐ No ☐
……..……..
……..……..

Concomitant therapies and reason for treatment: *(if not previously reported, please specify)*……..……..
……..……..

Details of the administration of Lemtrada: *(if not previously reported, please specify: dose, rate, time interval between doses)*
……..……..

Interval between the last infusion of LEMTRADA and first symptom : ……..days Start date of first symptoms: ……/……/……

Vascular Risk factors *If yes, please describe in free narrative text*	**Yes No**	**Description of the symptoms present**	**Investigations - please provide detailed results on additional page**	**At Baseline** **Yes No**	**At the time of follow up** **Yes No**
1. Previous transient ischemic attacks (TIAs) or strokes or cervicocephalic arterial dissection	☐ ☐	Were any of the following symptoms associated with the event:	1. CT head report	1. ☐ ☐	1. ☐ ☐
2. Previous coronary heart disease	☐ ☐	□ Focal deficits	2. MRI head report	2. ☐ ☐	2. ☐ ☐
3. Atrial Fibrillation	☐ ☐	□ Slurred speech	3. Vessels Imaging (CTAngiogram, MRAngiogram) report	3. ☐ ☐	3. ☐ ☐
4. Hypertension	☐ ☐	□ Loss of balance	4. Doppler ultrasound	4. ☐ ☐	4. ☐ ☐
5. Diabetes	☐ ☐	□ Loss of vision	5. Transthoracic echocardiogram(TTE) report	5. ☐ ☐	5. ☐ ☐
6. Hyperlipidemia	☐ ☐	□ Severe headache	6. Telemetry or Holter results	6. ☐ ☐	6. ☐ ☐
7. Smoking history	☐ ☐	□ Loss of consciousness	7. ECG results	7. ☐ ☐	7. ☐ ☐
8. Family History of stroke/coronary artery disease	☐ ☐	□ Other symptoms -please specify below	8. Fasting lipids/fasting glucose	8. ☐ ☐	8. ☐ ☐
9. Head/neck manipulations	☐ ☐		9. High BMI Index	9. ☐ ☐	9. ☐ ☐

procedures or traumas 10. Hyperhomocystenemia 11. Connective tissue conditions: Ehlers- Danlos Syndrome, Marfan;s Syndrome, Osteogenesis Imperfecta, fibromuscular dysplasia	☐ ☐ ☐ ☐				

Treatment provided for the event *(with dates)*
……
……

Event outcome: Resolved ☐ **Resolution with some sequelae** ☐ **Unknown** ☐ **Lost to follow-up** ☐

Fatal ☐ Date of death:……..Cause of death:……..…Autopsy performed? Yes ☐ No ☐

In the reporter's opinion, what are the causes of this event …….
……

Date of outcome……..

Date form completion…… **Reporter name**……

ANNEX 4.6 THROMBOCYTOPENIA FOLLOW-UP QUESTIONNAIRE PROPOSAL

TARGETED FOLLOW-UP QUESTIONNAIRE
THROMBOCYTOPENIA

Product:	Local case no:	Global case no:
Patient: Initials……..….Gender…….……..Age or date of birth: ……..	Study:	Subject Number:

Pertinent medical history: *If yes please provide details*
Patient's family history of any hemorrhagic condition Yes ☐ No ☐
……

Concurrent disorders and risk factors: *If yes please provide details*
Patient's medical history including concurrent disorders and risk factors Yes ☐ No ☐
……..
……..

Concomitant therapies and reason for treatment: *(if not previously reported, please specify)*……
……..

Details of the administration of Lemtrada: *(if not previously reported, please specify: dose, rate, time interval between doses)*
……

Interval between the last infusion of LEMTRADA and first symptom : ……..days Start date of first symptoms: ……/……/……

Other Preexisting Conditions Or Treatments *If yes, please describe in free narrative text*	**Yes No**	**Description of the symptoms present**	**Investigations - please provide detailed results on additional page**	**At Baseline** **Yes No**	**At the time of follow up** **Yes No**
1. Autoimmune syndromes (ITP,antiphospholipid syndrome, SLE, Evans syndrome)	☐ ☐	Were any of the following symptoms associated with the event:	1. Platelet count.	1.☐ ☐	1.☐ ☐
2. History of coagulopathy	☐ ☐	□ Blood in stool	2. Peripheral blood smear.	2.☐ ☐	2.☐ ☐
3. Bone marrow suppression (chemotherapy, infections with CMV, EBV, hepatitis, HIV, VZV, mumps, rubella)	☐ ☐	□ Nose bleeds □ Gum bleeds □ Dehydration □ Blood in urine □ General weakness □ Severe headache □ Pain in joints □ Other symptoms -please specify below	3. Bleeding time. 4. Bone marrow aspiration	3.☐ ☐ 4.☐ ☐	3.☐ ☐ 4.☐ ☐
4. Concomitant treatment with Cephalosporin, penicillin, tetracycline,	☐ ☐				
5. Genetic causes	☐ ☐				

Treatment provided for the event *(with dates)*
……
……

Event outcome: Resolved ☐ **Resolution with some sequelae** ☐ **Unknown** ☐ **Lost to follow-up** ☐

Fatal ☐ Date of death:……..Cause of death:……..…Autopsy performed? Yes ☐ No ☐

In the reporter's opinion, what are the causes of this event…….
…….

Date of outcome……

Date form completion…… **Reporter name**……

ANNEX 4.7 PULMONARY ALVEOLAR HEMORRHAGE FOLLOW-UP QUESTIONNAIRE PROPOSAL

TARGETED FOLLOW-UP QUESTIONNAIRE
PULMONARY ALVEOLAR HEMORRHAGE

Product:	Local case no:	Global case no:
Patient: Initials……..….Gender…….……..Age or date of birth: ……..	Study:	Subject Number:

Pertinent medical history*: If yes please provide details*
Patient's family history of any lung condition Yes ☐ No ☐
……

Concurrent disorders and risk factors: *If yes please provide details*
Patient's medical history including concurrent disorders and risk factors Yes ☐ No ☐
……..……..
……..
Concomitant therapies and reason for treatment*: (if not previously reported, please specify)*……..
……...
Details of the administration of Lemtrada: *(if not previously reported, please specify: dose, rate, time interval between doses)*
……

Interval between the last infusion of LEMTRADA and first symptom : ……..days Start date of first symptoms: ……/……/……

Medical History/Past Medication *If yes, please describe in free narrative text*	**Yes**	**No**	**Description of the symptoms present**	**Investigations - please provide detailed results on additional page**	**At Baseline** **Yes**	**No**	**At the time of follow up** **Yes**	**No**
1. Alveolar Hemorrhage (AH)	☐	☐	Were any of the following symptoms associated with the event:	1. Chest XR	1.☐	☐	1.☐	☐
2. Diffuse Alveolar Hemorrhage	☐	☐		2. CT thorax	2.☐	☐	2.☐	☐
3. Intrapulmonary Hemorrhage	☐	☐	□ Hemoptysis	3. Bronchoscopy	3.☐	☐	3.☐	☐
4. Low hemoglobin and/or hematocrit	☐	☐	□ Cough	4. BAL (Bronchoalveolar lavage)	4.☐	☐	4.☐	☐
5. Hypoxemic respiratory failure	☐	☐	□ Dyspnea	5. CBC	5.☐	☐	5.☐	☐
6. Goodpasture syndrome	☐	☐	□ Chest pain	6. Hematocrit level	6.☐	☐	6.☐	☐
7. Medications causing thrombocytopenia (i.e. pantoprazole, dexchlorpheniramine)	☐	☐	□ Fever	7. Blood gases	7.☐	☐	7.☐	☐
8. Congenital valvular disorder	☐	☐	□ Other symptoms -please specify below					

Treatment provided for the event *(with dates)*
……
……

Event outcome: Resolved ☐ **Resolution with some sequelae** ☐ **Unknown** ☐ **Lost to follow-up** ☐

Fatal ☐ Date of death:……..Cause of death:……..…Autopsy performed? Yes ☐ No ☐

In the reporter's opinion, what are the causes of this event…….
…….

Date of outcome……..

Date form completion…… **Reporter name**……

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Approved key messages of the additional risk minimization measures (aRMMs)

1. Physician educational materials:

- Summary of Product Characteristics
- Guide for healthcare professionals
- Healthcare professional checklist

1.1 Guide for healthcare professionals (HCPs):

This guide is intended for HCPs who initiate and supervise LEMTRADA® treatment. Its purpose is to improve the management of LEMTRADA-treated patients by positively influencing appropriate actions.

LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with multiple sclerosis (MS) in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction (MI), cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available.
Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.

- **Relevant information of the safety concern(s) addressed by the aRMMs**

This educational material has been developed to support the appropriate management of safety events associated with auto-immune disorders (ie, immune thrombocytopenic purpura [ITP], autoimmune thyroid disease, and nephropathies including anti-glomerular basement membrane [GBM] disease, autoimmune hepatitis, haemophagocytic lymphohistiocytosis [HLH], acquired haemophilia A [AHA], thrombotic thrombocytopenic purpura [TTP] and serious infections, including progressive multifocal leukoencephalopathy [PML]) following LEMTRADA treatment. It is also updated with information regarding the newly identified safety events temporally associated with LEMTRADA infusion (ie, myocardial ischaemia and MI, pulmonary alveolar haemorrhage [PAH], haemorrhagic stroke and cervicocephalic arterial dissection, thrombocytopenia). This material describes preventability and measures to mitigate these potential safety events.

The material contains:

A description of potentially serious events associated with the use of LEMTRADA that may occur in a temporally associated manner with LEMTRADA infusion:

- Serious infections
- Progressive multifocal leukoencephalopathy
- Temporally associated adverse events (myocardial ischaemia and MI, PAH, haemorrhagic stroke, cervicocephalic arterial dissection and thrombocytopenia).

- A description of the potentially serious events associated with the use of LEMTRADA that may occur with a delay of months to years after the infusion:
  - Thyroid disorders
  - Immune Thrombocytopenic Purpura
  - Nephropathies including (anti-GBM) disease
  - Autoimmune hepatitis
  - Haemophagocytic lymphohistiocytosis
  - Acquired haemophilia A
  - Thrombotic Thrombocytopenic Purpura
  - Adult Onset Still's disease (AOSD)
  - Autoimmune encephalitis
- Recommendations on how to mitigate these potential safety events through counselling, monitoring and management.
- A Frequently Asked Questions (FAQ) section

- **Details of the population at higher risk for the safety concern addressed by the aRMM**

Patients with MS being treated with alemtuzumab by their HCP.

- **Details on how to minimize the safety concerns addressed by the aRMM through appropriate patient selection, monitoring and management; key messages to convey in patient counselling; instructions on how to handle possible adverse events**

Description of the potentially serious safety events associated with the use of LEMTRADA.

- Risk of serious infections:
  - To educate the patient about requirement for starting treatment, the need to screen for underlying infections regularly (Human Immunodeficiency Virus [HIV], active or inactive [“latent”] tuberculosis risk, hepatitis B virus [HBV] and hepatitis C virus [HCV]), screen for human papilloma virus (HPV) and repeat screening annually. Evaluation of cytomegalo virus (CMV) serostatus could be considered according to local guidelines. Consider vaccination prior to treatment. Complete vaccination program at least 6 weeks prior to start treatment;
  - To recommend listeriosis-prevention diet two weeks prior to, during, and for at least 1 month after infusion.
- Risk of PML:
  - To provide recommendations regarding exams to conduct in case of signs of PML;
  - Advise the patient to seek immediate medical attention in case of sudden onset of progressive weakness or clumsiness of limbs, disturbance of vision, speech difficulties

or changes in thinking, memory, and orientation leading to confusion and personality changes.

- Potentially serious safety events of cardiovascular and cerebrovascular origin that are associated temporally with infusion: myocardial ischaemia and MI, PAH, haemorrhagic stroke and cervicocephalic arterial dissection and thrombocytopenia:
  - To provide recommendations on monitoring vital signs before the infusion and periodically during the infusion;
  - Details of pre-, during-and post-infusion recommendations are detailed in summary of product characteristics (SmPC) section 4.4;
  - To advise the patient to seek immediate medical attention in case of sudden onset of the following symptoms: chest pain, sudden and severe dyspnoea, coughing up blood, sudden severe headache, drooping of parts of the face, weakness on one side, difficulty with speech, neck pain, easy bleeding from mucous membranes, small scattered reddish spots on the skin.
- Serious safety events that may occur with a delay of months to years after the infusion:
  - ***Thyroid disorders:***
    - Provide information on possible symptoms and explain to patients that, depending on the type of thyroid condition, lifelong treatment may be required. Remind patients of the importance of thyroid function tests such as that for thyroid stimulating hormone (TSH), and of the high frequency of LEMTRADA induced thyroidal disorders;
    - Thyroid function tests must be taken quarterly for at least 48 months after the last infusion, but it may be necessary to take them for many years, if clinical findings suggest thyroid dysfunction. Function tests must always be taken in case of pregnancy.
  - ***Immune Thrombocytopenic Purpura:***
    - Provide a definition of the disease (description of clinical signs, delay of onset) and guidelines for monitoring all patients for ITP, including the need to obtain complete blood counts with platelet counts and differential prior to the initiation of treatment and at monthly intervals thereafter for at least 48 months following the last infusion.
  - ***Nephropathies including anti GBM disease:***
    - Provide information on possible symptoms of nephropathies, including anti GBM disease after treatment with LEMTRADA and guidelines for monitoring. Periodic lab tests must be conducted as patients may be asymptomatic; serum creatinine levels should be obtained prior to initiation of treatment and at monthly intervals thereafter until at least 48 months after the last infusion. Urinalysis with microscopy should be obtained prior to initiation and at monthly intervals thereafter until at least 48 months after the last infusion. Reference to a specialist in case of evaluation of nephropathies.

- Give recommendations on how to mitigate these potential safety events through appropriate patient counselling, monitoring, early diagnosis and management.

- ***Autoimmune hepatitis:***
  - Inform patients about the potential occurrence of autoimmune hepatitis;
  - Advise patients to seek medical attention in case of unexplained nausea, vomiting, abdominal pain, fatigue, loss of appetite, yellow skin or eyes or dark urine, or bleeding or bruising that occurs more easily than normal;
  - Prior to infusion: complete liver function test (alanine aminotransferase [ALT] measurement);
  - Post-infusion: liver function test at monthly intervals until at least 48 months after the last infusion.
- ***Haemophagocytic lymphohistiocytosis:***
  - Inform patients about the risk of HLH;
  - Advise patients to seek medical attention in case of persistent fever, rash, enlarged lymph nodes, enlarged liver or spleen, jaundice, seizure or altered mental status.
- ***Acquired haemophilia A:***
  - Inform patients about the risk of AHA:
  - Advise patients to seek immediate medical attention in case of signs or symptoms of unexplained and excessive bleeding from cuts or injuries, or after surgery or dental work, the presence of large or deep bruises, unusual bleeding after vaccinations, pain or swelling in the joints, haematuria or bloody in the stool;
  - A coagulopathy panel including activated partial thromboplastin time (aPTT) must be obtained in all patients that present with such symptoms. In case of a prolonged aPTT the patient should be referred to a haematologist.
- ***Thrombotic Thrombocytopenic Purpura:***
  - Inform patients about the risk of TTP;
  - Advise patient to seek immediate medical attention in case they experience signs and symptoms of TTP.
- ***Adult Onset Still's disease:***
  - Inform patients about the risk of AOSD.
  - Advise patients to seek immediate medical attention in case they experience signs and symptoms of AOSD: fever >39 °C or 102.2 °F lasting more than 1 week, pain, stiffness with or without swelling in multiple joints and/or a salmon pink rash.
- ***Autoimmune encephalitis:***
  - Inform patients about the risk of autoimmune encephalitis. Provide information on possible sign and symptoms, and indicate that they may resemble a MS relapse.

- **Reminder of HCP responsibilities:**
  - Before LEMTRADA is administered, ensure that specialists and equipment required for the timely diagnosis and management of the most frequent adverse reactions (especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections) are available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available;
  - Remind patients to have periodic testing performed and distribute patient educational materials;
  - Review the LEMTRADA patient guide and package leaflet with patients at initial prescription and on a regular basis at follow-up visits;
  - Encourage the patients to carry the patient alert card at all times.
- **Remarks on the importance of reporting adverse reactions**

1.2 Prescriber Checklist:

- **Lists of tests and actions to be conducted for the initial screening of patients**

Reminder to monitor vital signs before the infusion and periodically during the infusion and check infusion reactions after 2 hours of infusion.

Initial screening of patients:

- Contraindications:
  - Hypersensitivity to the active substance (alemtuzumab) or to any of the excipients as listed in the SmPC section 6.1;
  - Human immunodeficiency virus infection;
  - Patients with severe active infections until complete resolution;
  - Uncontrolled hypertension;
  - History of arterial dissection of the cervicocephalic arteries;
  - History of stroke;
  - Known history of angina pectoris or MI;
  - Known coagulopathy, on anti-platelet or anti-coagulant therapy;
  - Concomitant autoimmune diseases (besides MS).
- Precautions for use:
  - Consider the combined effects on the patient's immune system if LEMTRADA is used concomitantly with antineoplastic or immunosuppressive therapies.
- Recommended screening:
  - Evaluate for active and inactive ("latent") tuberculosis (per local guidelines);

- Evaluate magnetic resonance imaging (MRI) scan for any sign suggestive for PML prior to initiation and readministration of alemtuzumab treatment;
- Consider screening patients at high risk of HBV and/or HCV infection. Exercise caution in prescribing LEMTRADA to patients identified as carriers of HBV and/or HCV;
- Human papillomavirus screening recommended prior to treatment and annually after treatment;
- Consider evaluation of CMV serostatus according to local guidelines.

- Baseline tests:
  - Baseline electrocardiogram (ECG), vital signs including heart rate and blood pressure measurement;
  - Complete blood count with differential;
  - Serum transaminases;
  - Serum creatinine levels;
  - Thyroid function tests, such as TSH level;
  - Urinalysis with microscopy.
- Understanding of benefits and risks:
  - The patient has been informed about and understands the potential safety events associated with LEMTRADA, the monitoring requirement and the measures to minimize risk (eg, watching for symptoms, carrying the Patient Alert Card and the need to commit to periodic monitoring for at least 48 months after the last treatment);
  - Vaccination/treatment course to be completed/withdrawn before/after treatment; premedication, general health, and pregnancy and contraception checks immediately before/during/after treatment; monitoring clinical status during treatment and for at least 48 months after last treatment (information regarding the duration of monitoring is underlined reverse printing dark on white to emphasize the message).

Prior to, during and after treatment:

- Vaccinations (6 weeks prior to treatment):
  - It is recommended that patients have completed local immunization requirements;
  - Consider varicella zoster virus vaccination of antibody negative patients before initiating a course of LEMTRADA treatment.
- Diet (two weeks prior to, during, and for at least one month after treatment):
  - Recommend that patients avoid ingesting of uncooked or undercooked meats, soft cheeses and unpasteurized dairy products two weeks prior to, during, and for at least one month after treatment.

Pretreatment:

- Pretreatment for infusion-associated reactions:

- Pretreat with corticosteroids immediately prior to LEMTRADA administration on each of first 3 days of any treatment course;
- Pretreatment with antihistamines and/or antipyretics prior to LEMTRADA administration may also be considered.

- Oral prophylaxis for herpes:
  - Administer 200 mg aciclovir (or equivalent) twice daily from first day of treatment and continuing for a minimum of one month following treatment with LEMTRADA;
- General health:
  - Delay initiation of LEMTRADA administration in patients with active infection until the infection is fully controlled.
- Pregnancy & contraception:
  - Ensure women of childbearing potential use effective contraceptive measures when receiving a course of treatment with LEMTRADA and for up to four months following the last course of treatment.

Infusion administration:

- Pre-infusion measures:
  - Obtain a baseline ECG and record vital signs, including heart rate and blood pressure measurements;
  - Perform laboratory tests (complete blood count with differential, serum transaminases, serum creatinine, thyroid function test and urinalysis with microscopy).
- Measures during infusion:
  - Perform continuous/frequent (at least every hour) monitoring of heart rate, blood pressure and overall clinical status of the patients;
  - In case of a severe adverse event, the infusion should be discontinued and appropriate treatment and investigations provided and investigations performed;
  - If the patient shows clinical symptoms suggesting development of a serious adverse event associated with the infusion (myocardial ischaemia, hemorrhagic stroke, cervicocephalic arterial dissection or PAH), the infusion should be discontinued.

  In case of adverse event, appropriate treatments and investigations should be provided.
- Post-infusion measures:
  - Observation for infusion reactions is recommended for a minimum of 2 hours after LEMTRADA infusion. Patients with clinical symptoms indicating the development of a serious adverse event that may be temporarily associated with the infusion of LEMTRADA (myocardial ischaemia, haemorrhagic stroke, cervicocephalic arterial dissection or PAH) should be closely monitored until complete resolution of the symptoms. The observation time should be extended (hospitalisation) as appropriate. Patients should be educated about the potential for a delayed onset of infusion associated

reactions and instructed to report symptoms immediately and seek appropriate medical care;

- Platelet count should be obtained immediately after infusion on Days 3 and 5 of the first infusion course, as well as immediately after infusion on Day 3 of any subsequent course. Clinically significant thrombocytopenia needs to be followed until resolution. Referral to a haematologist for management should be considered.

2. The patient information pack:

- Patient information leaflet
- Patient guide
- Patient alert card

2.1 Patient Guide:

The patient guide is aligned with labelling information and the HCP guide and includes the following key messages:

- A description of the risks associated with LEMTRADA;
- A reminder for patients that the guide is to be carefully reviewed with the HCP who first prescribes LEMTRADA and on a regular basis at follow up visits;
- Encouragement for patients to call the doctor and/or go to the hospital in case they recognize any of the symptoms described;
- Information to educate the patient:
  - About symptoms of potentially serious events associated with the use of LEMTRADA that may occur in a temporally associated manner with the infusion temporally associated with the infusion or with a delay of months to years after the infusion;
  - About seeking immediate medical attention in case of sudden onset of: Fever, chest pain, drooping of parts of the face, sudden severe headache, weakness on one side, difficulty with speech, difficulty with vision or double vision, dizziness, neck pain, bleeding or bruising more easily than normal, bruising under the skin or inside the mouth, red pinpoint dots with or without unexplained extreme tiredness longer than usual bleeding after minor cuts or injury, nausea, sudden vomiting, shortness of breath, bloody sputum, abdominal pain, fatigue, loss of appetite, yellowing of skin or eyes or dark colored urine, low amount of urine, bloody stool, painful, stiffness or swollen joints, swollen lymph nodes or rash; progressive weakness or clumsiness of limbs, disturbance of vision, speech difficulties or changes in thinking, memory, orientation leading to confusion and personality changes, behavioural and/or psychiatric changes, short-term memory loss, movement disorders, or seizures as well as other symptoms which may resemble an MS relapse.
  - About the need for the procedures/tests before and during LEMTRADA treatment;
  - About LEMTRADA administration: number of courses of treatment, monitoring duration of adverse events (at least 48 months after last course);

- About discussing the recommended diet and checking on vaccinations with their doctor;
- For women of childbearing potential: use effective contraception during each treatment course with LEMTRADA and for at least four months after each course of treatment;
- If female patients are pregnant or plan to become pregnant very soon, they should ask their doctor for advice before being treated with LEMTRADA. Thyroid function tests must always be taken in case of pregnancy;
- Female patients should be reminded to tell their doctor if breastfeeding;
- About the monthly blood and urine tests, continuing for at least 48 months after the last course of treatment with LEMTRADA and recommendations for the planning of the monitoring schedule);
- A figure can be used to help patients visualize the follow-up process and therefore better understand the duration of treatment effects and the length of required monitoring;
- About showing the Patient Education Card to Doctors/HCPs involved with their medical care (especially in the event of medical emergencies and/or if new Doctors/HCPs are involved);

- To encourage the patients to read thoroughly the Patient information leaflet (PIL) thoroughly;
- Remarks on the importance of reporting adverse reactions.

2.2 Patient Alert Card:

The patient alert card contains the following key messages:

- A warning message for HCPs treating the patient at any time, including in emergency situations, that the patient has been treated with LEMTRADA;
- That LEMTRADA treatment may increase the risk of having ITP, nephropathies (including anti-GBM disease), thyroid disorders, autoimmune hepatitis, HLH, AHA, TTP, AOSD, autoimmune encephalitis, serious infections, PML and temporally associated events (myocardial ischaemia and MI, PAH, haemorrhagic stroke, cervicocephalic arterial dissection and thrombocytopenia);
- These side effects could occur many years after receiving a course of treatment with LEMTRADA, meaning that it is very important to continue undergo monthly monitoring tests for at least 48 months after the last course of treatment with LEMTRADA. In addition, patients should be aware of the potential for later onset of autoimmune disorders even after the 48 months monitoring period.