NCT02255656

STATISTICAL ANALYSIS PLAN

A long-term follow-up study for Multiple Sclerosis patients who have completed the alemtuzumab Extension Study (CAMMS03409)

Alemtuzumab – LPS13649

GZ402673-LPS13649

STATISTICIAN: [redacted]

DATE OF ISSUE: 09-Mar-2020

Total number of pages: 42

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse events
AESIs:	Adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANCOVA:	ranked analysis of covariance
ARR:	Annualized relapse rate
AST:	aspartate aminotransferase
ATC:	anatomic category
BPF:	Brain parenchymal function
CMQ:	Custom MedDRA queries
DAT:	Delayed alemtuzumab treatment
DMT:	Disease modifying therapy
ECG:	Electrocardiogram
EDSS:	Expanded disability status scale
EQ-5D:	EuroQoL in 5 dimensions
FAMS:	Functional assessment of multiple sclerosis
GEE:	generalized estimating equation
HLGT:	High-level group term
HLT:	High-level term
HRPQ:	Health related productivity questionnaire
HRUQ:	Healthcare resource utilization questionnaire
IAR:	Indusion-associated reaction
IAT:	Immediate alemtuzumab treatment
IFNB-1a:	interferon beta-1a
IMP:	investigational medicinal product
KM:	Kaplan-Meier
LFT:	liver function tests
LLT:	Lower-level term
MedDRA:	Medical dictionary for regulatory activities
MMRM:	mixed model for repeated measures
MRI:	Magnetic resonance imaging
PCSA:	potentially clinical significant abnormality
PH:	proportional hazard
PT:	Perferred term
QoL:	quality of life
SAE:	serious adverse events
SC:	subcutaneous
SF-36:	MOS 36 item short form health survey
SMQ:	standard MedDRA queries
SOC:	System organ class
WHO-DD:	World Health Organization drug dictionary, WHO drug dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This study is a Phase 3B/4, international, multicenter, open-label, noncomparative study to evaluate the long-term safety, efficacy and QoL of alemtuzumab in patients who have completed at least 48 months of the extension study CAMMS03409. In addition, impact of treatment on pharmacoeconomic data will also be evaluated.

Patients treated with alemtuzumab within 48 months prior to enrollment in the LPS13649 study must be followed-up at monthly intervals until 48 months after the last infusion of alemtuzumab.

If the patient is re-treated with additional courses of alemtuzumab, the patient will be followed using the specific recommendations indicated in the IB or in the local approved label (when available). Patients will be followed for 48-months after the last infusion of alemtuzumab received in the current trial setting. During the 48-month period, laboratory safety sampling should be collected every month, in a local laboratory and they must be reviewed in a timely manner by the Study Investigator.

Study duration will be 5 years (plus a window of 6 months) from the day of the enrollment of the first patient.

A pharmacogenomics (PGx) substudy will be conducted for exploratory analysis of genetic variations predictive of autoimmune conditions, including thyroid disorders and immune thrombocytopenia (ITP), related to MS disease and/or the effects of alemtuzumab. The data will be analyzed separately.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective is to evaluate long-term safety of alemtuzumab.

1.2.2 Secondary objectives

The secondary objectives are:

- To evaluate long term efficacy of alemtuzumab.
- To evaluate the safety profile of patients who received other disease modifying therapy (DMT) following alemtuzumab treatment.
- To evaluate patient-reported quality of life (QoL) outcomes and health resource utilization of patients who received alemtuzumab.

- To evaluate as needed re-treatment with alemtuzumab and other DMTs.

1.3 DETERMINATION OF SAMPLE SIZE

There are no sample size calculations for this long-term safety study. Sample size will be based on elective participation of patients who were enrolled (and completed at least 48 months) into the CAMMS03409 extension study.

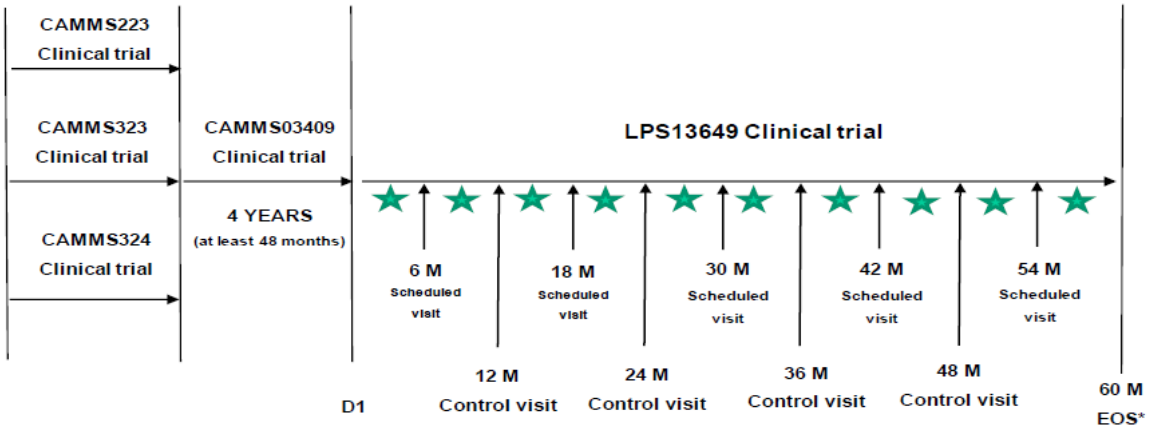
1.4 STUDY PLAN

The whole clinical trial of alemtuzumab consists of three study periods:

CAMMS223/323/324 prior studies (2 years): to compare the efficacy and safety of alemtuzumab to subcutaneous (SC) interferon beta-1a (IFNB-1a, Rebif) in treatment-naïve patients with relapsing-remitting multiple sclerosis (RRMS) who had recent MS disease activity as demonstrated by clinical relapses.

CAMMS03409 extension study (at least 4 years): to examine the long-term efficacy and safety of alemtuzumab in MS patients who received alemtuzumab during prior studies CAMMS223/323/324 and the efficacy and safety of 2 fixed annual alemtuzumab courses in patients who previously received SC IFNB-1a during prior studies.

LPS13649 (TOPAZ) extension study (5 years): to evaluate the long-term safety, efficacy and Quality of life (QoL) of alemtuzumab in patients who have completed at least 48 months of the extension study CAMMS03409.



★ Only for patients treated with alemtuzumab: monthly laboratory safety variables collection for 48 months after last infusion
- For patients who received alemtuzumab in CAMMS03409 study less than 48 months before entering in LPS13649 study, and
- For patients receiving retreatment with alemtuzumab during the LPS13649 study

* After completion of 5 years of the first patient inclusion, the next scheduled visit for any patient will be performed as EOS visit.

Scheduled visits for safety and efficacy assessments will be performed every six months. AEs and concomitant medications will be monitored continuously. Quality of life, pharmaco-economic data and brain imaging will be collected every twelve months (Table 1).

Table 1 – Study flow chart

	Selection visit (D1)	Study assessments each year Scheduled visits		Unscheduled visits	EOS
		6 M	12 M		
Informed consent signature	X				
Inclusion Exclusion criteria verification	X				
AE reporting	X	X	X	X	X
Vital signs	X [a]	X	X	X	X
Physical examination including weight [b]	X [a]		X		X
MS relapse verification	X	X	X	X	X
EDSS	X [a]	X	X	X	X
Brain Imaging	X [c]		X		X [c]
SF-36 - FAMS - EQ-5D	X [a]		X		X
Modified HRUQ/HRPQ	X [d]		X		X
Record concomitant medication	X	X	X	X	X
Collection of blood samples for PGx assessment [e]		X [f]	X [f]	X [f]	X [f]

a If not performed in the previous 3 months.
b Note that weight assessment is included in the vital signs assessment module in the eCRF instead of the physical examinations module. Nevertheless, it is to be performed at baseline and on yearly basis and not every 6 months.
c If not performed in the previous 6 months.
d If the HRUQ questionnaire was administered in the previous 3 months, then only questions 1 through 9 of the Modified HRUQ/HRPQ need to be completed at baseline.
e For consenting patients only.
f Omit if collected at a previous visit.

For all the patient retreated with alemtuzumab and for 48 months after last infusion (Table 2).

Table 2 - Re-treatment with Alemtuzumab Flow Chart

	Prior to treatment	During 48 months											
		1 M	2 M	3 M	4 M	5 M	6 M	7 M	8 M	9 M	10 M	11 M	12 M
Pregnancy test (in women of childbearing potential)	X												
ECG	X												
HPV (only in women)	X [a]												X
CBC with differential (including platelet count)	X [b]	X	X	X	X	X	X	X	X	X	X	X	X
Serum Creatinine and LFT (liver function tests)	X [b]	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis with microscopy	X [b]	X	X	X	X	X	X	X	X	X	X	X	X
TSH	X [b]			X			X			X			X
Study Investigator review of labs	X	X	X	X	X	X	X	X	X	X	X	X	X

Monthly safety laboratory assessment will be performed in local laboratories at the patients' convenience.

a If not performed in the previous 12 months. In addition, an HPV screening should be performed approximately 1 year after the last alemtuzumab infusion date, and then every 12 months until the 48 months safety follow-up is completed. For women patients re-treated with alemtuzumab during the study, an HPV screening should be performed prior to re-treatment (if not performed in the previous 12 months) and then every 12 months until the 48 months safety follow-up is completed.

b If not performed in the previous 2 weeks. LFT includes: ALT, AST, ALP, albumin, total protein, total bilirubin, and direct bilirubin.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Not applicable.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The TOPAZ baseline value is defined as the available value assessed on or prior to the V01 Selection visit, unless otherwise specified. The last available value in previous studies can be considered as the baseline if they were evaluated within the pre-specified time window. For brain imaging result, if the last non-missing assessment performed within 6 months prior to the V01 selection visit, it can be considered as baseline. For vital sign, physical examination, EDSS and questionnaires, the time window is 3 months.

For efficacy endpoints (EDSS, MRI), the baseline from prior studies will be considered as long-term baseline, which is defined as last available assessment prior to first dose of alemtuzumab or SC IFNB-1a administration.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic variables are:

- Age (quantitative and qualitative variable: <65, [65 – 75] and >75 years)
- Sex (Male, Female)
- Race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other, Pacific Islander, Other)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino)
- Weight
- Height
- Body Mass Index (BMI)
- Geographic Region (USA/Canada/Australia, Latin America, EU, Non-EU Europe and Israel)
- Time since first dose of alemtuzumab infusion (in years)

Baseline Physical Examination

Baseline physical examination, i.e., number (%) of patients who are normal/abnormal at baseline will be summarized.

Disease characteristics at baseline

Specific disease history includes

- Baseline EDSS (TOPAZ baseline and long-term baseline)
- Time (years) since initial/last clinical episode
- Brain imaging characteristics (e.g. Gadolinium-Enhancing lesion count, T1-Hyperintense Lesion Volumes and T2-Hyperintense Lesion Volumes) (TOPAZ baseline and long-term baseline)

Any technical details related to computation, dates, and imputation for missing dates are described in Section 2.5.

2.1.2 Concomitant medications

A concomitant medication is any treatment received by the patient concomitantly to any investigational medicinal product (IMP)(s) in the current study, all medications received by the patient from the end of the Extension Study CAMMS03409 to Visit 1 of LPS13649 study, and during the TOPAZ study until the last visit will be collected.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

Efficacy endpoints are considered as secondary objective.

The long-term effects of alemtuzumab will be examined by summarizing from baseline through the last study visit of our study by the following efficacy endpoints:

- Annualized relapse rate (ARR)
- Proportion of patients relapse free
- Change over time in Expanded Disability Status Scale (EDSS) scores
- Change over time in brain imaging characteristics to include:
  - Number of Gadolinium (Gd)-enhancing, and new Gd-enhancing lesions
  - Number of new/enlarging T2 lesions
  - Number of new T1 (and new hypointense T1) lesions
  - T1 and T2 lesion volume
  - Brain Parenchymal Fraction (BPF)

2.1.3.1 Relapse Related Efficacy Endpoints

Relapse is defined as new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination. Symptoms must be attributable to MS, last at least 48 hours, be present at normal body temperature (i.e., no infection, excessive exercise, or excessively high ambient temperature), and be preceded by at least 30 days of clinical stability.

MS relapse will be verified at each visit. On the other hand, patients will be informed to contact the Study Investigator as soon as they observe any sign/symptom compatible with a possible relapse, in order to schedule an extra visit.

2.1.3.1.1 Annualized Relapse Rate

The number of patients with a relapse event, the total number of relapses, and the annualized relapse rate over the years of follow-up will be produced.

2.1.3.1.2 Proportion of Patients who are Relapse Free

Patients will be considered relapse free at each measurement time and at the end of the study if they did not experience a protocol defined relapse in the relevant time period.

2.1.3.2 Expanded Disability Status Scale (EDSS)

Patient disability will be evaluated using the EDSS, which has long been considered the standard for assessing disability in patients with MS.

EDSS will be collected at D1 (if not collected in the previous 3 months) and then at each scheduled visit (every 6 months) and unscheduled visits for MS relapse. For the change from baseline in EDSS analysis, unscheduled EDSS assessments will not be used (except for early study discontinuation assessments).

2.1.3.3 Brain imaging

Brain imaging will be performed at D1 (if not performed in the previous 6 months) and then every 12 months. It will be also performed at the end of study visit, if not performed in the previous 6 months. MRIs will be read and interpreted locally by qualified site personnel and/or designee (e.g., neuroradiologist). MRIs should be reviewed locally by qualified site personnel for signs of Non-MS pathology. For study purposes, per-protocol scans will be also submitted to a central imaging vendor for scan quality control and analysis.

2.1.3.3.1 Number of lesions

The cumulative count is the primary interest, which is defined as the sum of the lesion counts at each successive year from the D1 screening to the end of study. The lesion counts will also be analyzed yearly.

2.1.3.3.2 Volume of lesions and BPF

Percentage change of T1 and T2 volume as well as brain parenchymal function (BPF) are the primary interest, which is defined as absolute difference between post-baseline result and baseline result divided by the baseline times 100%.

2.1.4 Safety endpoints

The safety endpoints are the primary endpoint for this study.

The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data and vital signs.

Observation period

The on-study observation period is defined as the time from start of screening visit until the end of the study (defined as last protocol planned visit or the resolution/stabilization of all serious adverse events and adverse events with prespecified monitoring).

2.1.4.1 Adverse events variables

All adverse events will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock OR specify version if already known from project specifics.

Incidence, duration, grade/intensity, relationship to study drug, and outcome of the AE will be analyzed for serious adverse events (SAEs), adverse events (AEs), infusion-associated reactions (IAR).

Incidence, nature, seriousness, grade/intensity, relationship to study drug, and outcome will be summarized for the project-specific adverse events of special interest (AESIs).

Record the occurrence of adverse events (including serious adverse events and adverse events of special interest) from the time of signed informed consent until the end of the study.

Adverse events of special interest include the following terms:

- Hypersensitivity or anaphylaxis
- Pregnancy of a woman entered in the study;

- Pregnancy occurring in a woman patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria.
- Follow-up of the pregnancy in a woman participant is mandatory until the outcome has been determined.

- Symptomatic overdose (serious or non-serious) with IMP.
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Study Investigator or spontaneously notified by the patient and defined as increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.

    Of note, asymptomatic overdose must be reported as a standard AE.
- Increase in alanine transaminase (ALT).
- Other product specific AESIs:
  - Autoimmune mediated conditions including, but not limited to:
    - Immune thrombocytopenic purpura (ITP).
    - Nephropathies including anti-glomerular basement membrane (GBM) disease.
    - Cytopenias.
    - Thyroid disorders.
    - Acquired hemophilia A
    - Autoimmune hepatitis.
  - Hemophagocytic lymphohistiocytosis (HLH).
  - Progressive multifocal leukoencephalopathy (PML)
  - Temporally associated* pulmonary alveolar hemorrhage
  - Temporally associated* myocardial ischemia, myocardial infarction
  - Temporally associated* stroke
  - Temporally associated* cervicocephalic arterial dissection

    (* Temporally associated: 1 to 3 days after the last infusion)
  - Serious infections including serious opportunistic infections (eg, Listeria infections, CMV, EBV), HPV associated with cervical dysplasia
  - Malignancy.
  - Pneumonitis

The standardized MedDRA queries (SMQ) or Custom MedDRA queries (CMQ) will be applied as appropriate to select AESIs.

Infusion-associated reactions (IAR) is defined as any adverse event occurring during and within 24 hours of alemtuzumab infusion. It will be analyzed separately for retreated patients.

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period
- Death poststudy: deaths occurring after the end of the study

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed into standard international units and international units will be used in all listings and tables.

For patients exposed to alemtuzumab within 48 months prior to inclusion in this study, samples for clinical laboratories will be taken at monthly for CBC with differential (including platelet count), serum creatinine, liver function and urinalysis. TSH must be obtained every 3 months and HPV test should be performed yearly until 48 months after the last infusion of alemtuzumab administered in the study CAMMS03409.

For patients exposed to alemtuzumab during this study, pregnancy test, HPV test must be obtained before the infusion in TOPAZ study if they were not done within 12 months prior to the treatment. CBC with differential (including platelet count), serum creatinine, TSH, liver function test (ALT, AST, ALP, albumin, total protein, direct bilirubin and total bilirubin) and urinalysis (minimally including determination of urine protein and red blood cells) with microscopy are also required to be assessed before alemtuzumab infusion if they were not assessed within 2 weeks prior to treatment. Samples for CBC with differential (including platelet count), serum creatinine, liver function and urinalysis will be analyzed monthly. The TSH will be performed quarterly. The HPV test will be performed yearly. In addition, unscheduled liver function tests may be performed at any time if clinically indicated at Investigators' discretion.

The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells and platelets and coagulation**: hemoglobin, hematocrit, red blood cell count, platelet count
  - **White blood cells:** white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry
  - **Renal function**: creatinine, creatinine clearance
  - **Liver function**: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total protein, albumin, direct bilirubin and total bilirubin

- TSH

Urine samples will be collected minimally including determination of urine protein and red blood cells with microscopy.

2.1.4.4 Vital signs variables

Vital signs include systolic and diastolic blood pressure (millimeters of mercury [mmHg]), heart rate (beats/minute [bpm]), respiratory rate (breaths/minute), body temperature (degrees Celsius [°C]) and weight (kg).

- For all the patients: vital signs will be recorded at selection visit (D1) (if not recorded in the previous 3 months) and then every 6 months.
- For patients treated with alemtuzumab: on days when alemtuzumab is infused, vital signs will be recorded before steroid administration, at a time after steroid administration (prior to alemtuzumab infusion), and 1 hour after the start of alemtuzumab infusion and hourly during and after infusion until observation post-infusion has ended (two hours after the end of the infusion).

2.1.4.5 Electrocardiogram variables

ECG is required within 2 weeks prior to alemtuzumab infusion including heart rate, PR, QRS, QT, and corrected QTc (according to Bazett/Fridericia).

2.1.5 Quality-of-life endpoints

Questionnaires including MOS 36-item short-form health survey (SF-36) Version, Functional Assessment of Multiple Sclerosis (FAMS), EuroQoL in 5 dimensions (EQ-5D) will be assessed on selection visit (D1) and every 12 months.

- Change over time in self-reported quality of life (QoL) as assessed by the Medical Outcome Study (MOS) 36-Item Short-Form Health Survey (SF-36) Version 2.
- Change over time in the Functional Assessment of Multiple Sclerosis (FAMS), and
- Change over time in the EuroQoL in 5 Dimensions (EQ-5D).

2.1.5.1 Medical Outcomes Study Short Form-36, Version 2

The SF-36 is an extensively validated and widely used measure of quality of life (QoL) that assesses patients' perceptions of health status and its impact on their lives (1). It consists of 36 items organized into 8 scales (physical functioning, social functioning, role limitations physical, bodily pain, general medical health, mental health, role limitations emotional, and vitality). Two summary measures of physical and mental health, the Physical Component Summary (PCS) and Mental Component Summary (MCS), respectively, are derived from scale aggregates. Higher scores are associated with better QoL.

SF-36 scores will be transformed using general US population norms so that all scales have a mean of 50 and a standard deviation of 10 as described in the SF-36 Users Manual (2). Therefore, scores can be directly compared across scales, as well as to the general population norm of 50.

2.1.5.2 Functional Assessment of Multiple Sclerosis (FAMS), Version 4

The FAMS is a widely accepted, MS-specific, quality of life questionnaire (3)(4). The FAMS is a self-report multidimensional index comprising a total of 58 items on 7 subscales: mobility (7 items); symptoms (7 items); emotional well-being (7 items); general contentment (7 items); thinking and fatigue (9 items); family/social well-being (7 items); and additional concerns (14 items, these are not scored). Each item (except those for "additional concerns") is rated on a 5-point scale of 0 to 4. The sum of the 44 scored items is the total score, which ranges from 0 to 176. A higher FAMS score reflects a higher quality of life. The total score is the primary criterion by which the effect of treatment on quality of life will be assessed; however, subscale totals will also be evaluated.

2.1.5.3 EuroQoL-5D (EQ-5D)

The EQ-5D is a generic, standardized instrument that provides a simple, descriptive profile and a single index value for health status (4)(5). The EQ-5D comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension consists of 3 levels (some, moderate, extreme problems), generating a total of 243 theoretically possible health states. Country-specific value sets convert these health states into utility scores describing the preference of the population for one health state over another.

Assessments will also be made using the EQ Visual Analogue Scale (EQ-VAS), which captures the self-rating of current health status using a visual "thermometer" with the end points of 100 (best imaginable health state) at the top and zero (worst imaginable health state) at the bottom.

2.1.6 Other endpoints

2.1.6.1 Modified healthcare resource utilization questionnaire (HRUQ) / Health related productivity questionnaire (HRPQ)

Patients' use of healthcare resources, non-medical resources, and informal care as well as their work capacity will be assessed at scheduled study visits using modified healthcare resource utilization questionnaire (HRUQ) and health related productivity questionnaire (HRPQ) designed to evaluate the economic impact of MS.

- The questionnaire addresses the following content areas:
- Employment situation and changes in employment situation due to MS
- Admissions and stays in hospital, rehabilitation centers, or nursing homes
- Typical MS-related investments (eg, stair and bed lift, ramps, rails) and devices (eg, walking aids, wheelchairs)

- Assistance by community or social services (eg, home nurse, transportation), or help from family or friends.
- Patient reported data regarding employment status.

Information on resource use is obtained retrospectively, and each type of resource is collected for a time period that would minimize recall bias.

Each question requires a binary answer (yes/no) followed by details on the type and quantity of the resource. All resources that are expected to be used are prespecified in order to minimize errors due to spelling, and hence no open fields or free text (eg, "other") are permitted.

Modified HRUQ / HRPQ will be collected at D1 (if the HRUQ questionnaire was administered in the previous 3 months, then only questions 1 through 10 of the Modified HRUQ/HRPQ need to be completed at baseline, D1). The modified HRUQ / HRPQ will continue to be collected every 12 months and at the end of study visit.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients who signed the informed consent.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Enrolled patients
- Screen failure patients and reasons for screen failure
- Retreated patients
- Patients who did not complete the study period as per protocol
- Patients who discontinued study period by main reason for permanent treatment discontinuation

For all categories of patients, percentages will be calculated using the number of all enrolled patients as the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages in overall group, retreated group and by subgroups (IAT vs DAT).

All critical or major deviations will be summarized in tables giving numbers and percentages of deviations in overall group and by subgroups (IAT vs DAT).

Additionally, the analysis populations for safety, efficacy, and subgroup population (see Section 2.3) will be summarized in a table by number of patients on the enrolled population.

- Safety population

  - Retreated population
  - 48 months follow-up population
- Efficacy population
- Subgroup population
  - IAT population
  - DAT population

2.2.1 Randomization and drug dispensing irregularities

Not applicable.

2.3 ANALYSIS POPULATIONS

2.3.1 Safety populations

All patients who have signed the ICF will be included in the safety population.

2.3.1.1 Retreated population

The population is defined as safety patients who have received study drug in TOPAZ study.

2.3.1.2 48 months follow-up population

The population is defined as all safety patients who have received study drug in CAMMS223, CAMMS323, CAMMS324 or CAMMS03409, that didn't complete 48 months of follow-up at the screening visit in TOPAZ study.

2.3.2 Efficacy populations

The population on which efficacy analyses will be performed consists of all enrolled patients who have received study drug in CAMMS223, CAMMS323, CAMMS324 or CAMMS03409.

2.3.3 Subgroup population

All subgroup populations are subgroup of enrolled patients.

Immediate alemtuzumab treatment (IAT) subgroup: Patients who received alemtuzumab 12 mg/day from CAMMS323 or CAMMS324 study.

Delayed alemtuzumab treatment (DAT) subgroup: Patients who received SC IFNB-1a from CAMMS323 or CAMMS324 and then received alemtuzumab 12 mg/day in CAMMS03409 study.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum and maximum. Categorical and ordinal data will be summarized using the number and percentage of patients.

Parameters will be summarized on the enrolled population analyzed in overall group and by subgroups (IAT vs DAT).

Parameters described in Section 2.1.1 will be summarized b in overall group and by subgroups (IAT vs DAT) using descriptive statistics.

2.4.2 Prior or concomitant medications

The concomitant medications will be presented for the enrolled population. All the medication that taken in TOPAZ study will be considered as concomitant medications.

Medications will be summarized in overall group and by subgroups (IAT vs DAT) according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several time for the same medication.

The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the overall group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories and/or generic names), alphabetical order will be used.

In addition, the alternative MS therapies will be summarized separately. Alternative MS medication will be determined based on the anatomic or therapeutic categories and generic name.

2.4.3 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed and summarized within safety population (Section 2.3.1.1).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure in TOPAZ study for retreated patients.

Duration of IMP exposure is defined as last dose date – first dose date + 1 day, regardless of unplanned intermittent discontinuations (see Section 2.5.1 for calculation in case of missing or incomplete data).

Alemtuzumab exposed duration will also be summarized in exposed person-years and total number of courses in overall group and by subgroups (IAT vs DAT) for all safety population. Person-years are estimated as the date of first study treatment in prior studies minus the date when the patient is determined to have ended the TOPAZ study.

2.4.4 Analyses of efficacy endpoints

The efficacy population will be used for all efficacy analyses.

For MRI endpoints, EDSS, questionnaires endpoints, only data collected in TOPAZ study will be used for analysis in addition of baseline information from previous studies. The long-term baseline is defined as the last available assessment prior to first dose of alemtuzumab or SC IFNB-1a administration in prior studies. It will be applied to long-term efficacy analysis.

For relapse endpoints, data from prior studies (CAMMS323, CAMMS324 and CAMMS03409) should be obtained.

The main long-term analysis for efficacy endpoints is IAT versus DAT comparison. The efficacy of immediate alemtuzumab treatment (Subgroup IAT defined in Section 2.3.3) and delayed alemtuzumab treatment (Subgroup DAT defined in Section 2.3.3) groups will be compared for relapse related endpoints, EDSS assessment as well as MRI endpoints.

The analysis in reference of long-term baseline in prior studies by total number of alemtuzumab courses (i.e. <=3 vs >3) will be summarized as well.

2.4.4.1 Analysis of efficacy endpoint(s)

2.4.4.1.1 Annualized relapse rate (ARR)

The estimated annualized relapse rate using negative binomial model with robust variance estimation will be presented by year and in overall. The observed total number of relapses is the dependent variable, the log total amount of follow-up time in years for each patient will be the offset variable and analysis group indicator (IAT vs DAT) and geographic region will be the covariates in the model. Both IAT vs DAT comparison and ARR by alemtuzumab courses will be analyzed. The analysis period starts from prior studies (CAMMS323/324) until the end of TOPAZ study. The model will also be stratified by previous clinical study.

The observed annualized relapse rate will be reported as well, which is defined as the total number of relapses divided by the total years of follow-up for each patient.

The ARR will be presented separately for retreated population in overall group.

2.4.4.1.2 Proportion of Relapse free patients

The proportion of patients with relapse-free each year from prior studies (CAMMS323/324) until the end of TOPAZ study will be estimated based on Kaplan-Meier methods. The complementary log-log transformation will be used to construct 95% confidence intervals. A Kaplan-Meier graph summarizing the event probability over time will be presented by subgroups (IAT vs DAT) and by alemtuzumab courses. Hazard ratio and corresponding 95% confidence interval will be calculated using Cox proportional hazards (PH) regression with robust variance estimation (6). Covariates for the Cox PH model will include analysis groups and geographic region and prior clinical studies. Inference will be based on the Wald test of the log hazard ratio (estimated regression coefficient from the model). The analysis period starts from prior studies (CAMMS323/324) until the end of TOPAZ study.

The Kaplan-Meier (KM) estimates will be summarized for retreated population separately.

2.4.4.1.3 EDSS

The observed value, change from baseline as well as percentage change from baseline will be presented descriptively. The change from baseline in EDSS will be analyzed using a mixed model for repeated measures (MMRM) (7)(8)(9) with baseline EDSS score, analysis group indicator (IAT and DAT), geographic region, study visit and study visit by analysis group interaction as covariates. The TOPAZ study baseline at study entry is considered as post-baseline for efficacy analysis. The comparison of the change from baseline in EDSS with the MMRM will include the change from baseline to each consecutive year which can be constructed using the linear contrasts of the estimated regression parameters. All post-baseline EDSS scores will be included in the MMRM; patients without any post-baseline scores will not be included. For this model, imputation will not be used.

Similar analysis for change of EDSS by alemtuzumab courses and for retreated population will be analyzed as well.

2.4.4.1.4 MRI lesion count

The observed lesion count and change from baseline will be presented descriptively by analysis groups.

The cumulative count of lesions will be compared between IAT and DAT groups through a repeated negative binomial regression adjusted for the long-term baseline count, analysis groups and geographic region. The comparison of proportion of patients with lesion at any time post-baseline between IAT and DAT group will be analyzed using repeated measure generalized estimating equation (GEE) with logistic link. Covariates will include long-term baseline lesion count, geographic region, and analysis groups.

Similar analysis for MRI lesion count by alemtuzumab courses and for retreated population will be analyzed as well.

2.4.4.1.5 MRI volume and BPF

The observed value, change from baseline as well as percentage change from baseline will be presented descriptively.

The percent change in lesion volume / BPF from year to year and the percent change from long-term baseline will be calculated by analysis groups. To compare between IAT and DAT patients, the percent change from baseline in MRI lesion volume will be analyzed yearly using the ranked analysis of covariance (ANCOVA) model with adjustment for baseline lesion volume, analysis groups (IAT and DAT) and geographic region.

Similar analysis for MRI volume by alemtuzumab courses and for retreated population will be analyzed as well.

2.4.4.2 Multiplicity issues

Not applicable.

2.4.5 Analyses of safety data

The summary of safety results will be presented in overall group and by subgroups (IAT vs DAT).

Only data collected in TOPAZ study will be used for analysis in additional of baseline information from previous studies.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.1.1, unless otherwise specified, using the following common rules:

- The baseline value is defined as the available value assessed on or prior to the V01 Selection visit, unless otherwise specified. If laboratory, vital sign and physical examinations were performed in CAMMS03409 study within the pre-specified time-windows, then the last assessment within the time-window can be considered as baseline when the corresponding V01 assessments are missing.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs (PCSA version dated May 2014 [Appendix A])
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations.

The number of all such patients will be the numerator for the on-treatment PCSA percentage

- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period in overall group and by subgroups (IAT vs DAT) on the safety population.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and analysis group.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

2.4.5.1 Analyses of adverse events

Generalities

All the reported AE will be considered as treatment emergent adverse event (TEAE).

Adverse event incidence tables will present by SOC, HLGT, HLT, and PT, sorted in alphabetical order in overall group and by subgroups (IAT vs DAT), the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables. The denominator for computation of percentages is the safety population in overall group and by subgroups (IAT vs DAT).

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period. For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs in overall group within SOCs will define the presentation order for all other tables unless otherwise specified.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - Treatment-emergent adverse event
  - Serious treatment-emergent adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC

internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order

- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified
- All treatment-emergent adverse events regardless of relationship and related by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order

  All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- The event rate per patient-year (the number of events in question divided by total treatment exposure in patient years) will be provided for SAEs by SOC and PT
- By-patient listing of treatment-emergent SAEs showing analysis group (IAT vs DAT), patient ID, time since first dose of Alemtuzumab infusion in years, age, gender, race, primary SOC decode, PT decode, verbatim (diagnosis), onset date and study day, date of death (if relevant), recovery date/time, event duration, outcome, intensity/grade, relationship to study treatment, action taken with study treatment AE serious criteria.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All treatment-emergent adverse events leading to treatment discontinuation by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order

- All treatment-emergent adverse events leading to treatment discontinuation by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified
- By-patient listing of treatment-emergent adverse events leading to treatment discontinuation showing analysis group (IAT vs DAT), patient ID, time since first dose of Alemtuzumab infusion in years, age, gender, race, primary SOC decode, PT decode, verbatim (diagnosis), onset date and study day, date of death (if relevant), recovery date/time, event duration, outcome, intensity/grade, relationship to study treatment, action taken with study treatment AE serious criteria.

Analysis of adverse events of special interest (AESI)

- All treatment-emergent adverse events of special interest by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events of special interest by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified
- All treatment emergent adverse events of special interest by PT, showing the number (%) of patients, sorted by decreasing incidence of PT
- The event rate per patient-year (the number of events in question divided by total treatment exposure in patient years) for non-temporary AESI(s) will be provided by SOC and PT
- The frequency of treatment-emergent adverse events over time will be provided for the non-temporary treatment-emergent AESIs, where the time intervals will be defined as: <2 courses, 2 – 4 courses, 4 – 6 courses, 6 – 8 courses, etc. In each time interval, the denominator for calculation of percentage will be the number of patients who entered the time interval and the numerator will be the number of patients with at least 1 treatment emergent AESI occurring in this time interval. Note that only the first event will be counted and all recurrent events will not be included
- For retreated population, the frequency of treatment-emergent temporary adverse events over time will be provided for the temporally associated AESIs (pulmonary alveolar hemorrhage, myocardial ischemia, myocardial infarction, stroke, cervicocephalic arterial dissection), where the time intervals will be defined as: during alemtuzumab infusion day 1, during alemtuzumab infusion day 2, during alemtuzumab infusion day 3, 1 day after alemtuzumab infusion, 2 days after alemtuzumab infusion and 3 days after alemtuzumab infusion. In each time interval, the denominator for calculation of percentage will be the number of patients who entered the time interval and the numerator will be the number of patients with at least 1 treatment emergent AESI occurring in this time interval. Note that only the first event will be counted and all recurrent events will not be included

- By-patient listing of treatment-emergent adverse events of special interest showing analysis group (IAT vs DAT), patient ID, number of alemtuzumab courses age, gender, race, AESI group, primary SOC decode, PT decode, verbatim (diagnosis), onset date and study day, date of death (if relevant), recovery date/time, event duration, outcome, intensity/grade, relationship to study treatment, action taken with study treatment AE serious criteria.

Analysis of infusion associated reaction (IAR)

- All infusion associated reaction by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All infusion associated reaction by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified
- By-patient listing of treatment-emergent adverse events of special interest showing analysis group (IAT vs DAT), patient ID, age, gender, race, primary SOC decode, PT decode, verbatim (diagnosis), onset date and study day, date of death (if relevant), recovery date/time, event duration, outcome, intensity/grade, relationship to study treatment, action taken with study treatment AE serious criteria.

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-study, poststudy)
- Deaths in nonrandomized patients or randomized but not treated patients
- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC .

2.4.5.3 Analyses of laboratory variables

Laboratory analysis will be conducted for retreated population and 48 months follow-up population. The baselines for each population are defined as below.

- Retreated population baseline: The last non-missing assessment prior to first dose of alemtuzumab in TOPAZ study. The baseline should be taken within 2 weeks prior to the treatment for laboratory assessment except for HPV and pregnancy test. For HPV and pregnancy test, it can be taken in 12 months before the treatment.
- 48 months follow-up population baseline: The last non-missing assessment prior to the last dose of alemtuzumab in previous studies. The baseline should be taken within 2 weeks

prior to the treatment for laboratory assessment except for HPV and pregnancy test. For HPV and pregnancy test, it can be taken in 12 months before the treatment.

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or worst on-treatment value and/or other specific assessment) in overall group and by subgroups (IAT vs DAT). This section will be organized by biological function Section 2.1.4.3.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period will be summarized by biological function and in overall group and by subgroups (IAT vs DAT) whatever the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

Drug-induced liver injury

The liver function tests, namely AST, ALT, alkaline phosphatase, direct bilirubin and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any postbaseline visit by baseline status will be displayed in overall group and by subgroups (IAT vs DAT) for each parameter.

Time to onset of the initial ALT and AST elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) (time to first observation of ALT > 3 x ULN or total bilirubin > 2 x ULN, whichever comes first) will be analyzed using Kaplan-Meier estimates, using the midpoint of the time interval between the first assessment showing the elevation and the previous assessment, presented in overall group and by subgroups (IAT vs DAT).

Listing of possible Hy's law cases identified (eg, patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin ≥2 x ULN) with ALT, AST, alkaline phosphatase and total bilirubin.

Summarize the incidence of liver-related adverse events in overall group and by subgroups (IAT vs DAT). The selection of preferred terms will be based on the hepatic disorder SMQ.

2.4.5.4 Analyses of vital sign variables

Vital sign analysis will be done for all safety population and for retreated population.

The infusion related vital sign analysis will be done separately for retreated population. The baseline for infusion related analysis is the assessment taken before steroid administration.

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all vital signs variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or worst on-treatment value and/or other specific assessment) in overall group and by subgroups (IAT vs DAT). For parameters provide a list of parameters for which plots will be displayed; mean changes from baseline with the corresponding standard error will be plotted over time (at same time points) in overall group and by subgroups (IAT vs DAT).

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized in overall group and by subgroups (IAT vs DAT) irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

2.4.5.5 Analyses of electrocardiogram variables

By-patient listing will be provided for retreated patients as needed.

2.4.6 Analyses of quality of life/health economics variables

Descriptive statistics for observe value, change from baseline as well as percentage change from baseline will be presented in reference of long-term baseline from prior studies by subgroups (IAT vs DAT). MMRM model may be applied if necessary as supportive.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General convention

For long-term analysis, the reference date is the date of first alemtuzumab or SC IFNB-1a treatment in prior studies.

2.5.2 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a concomitant medication.

Handling of adverse events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity/grades of adverse events

If the severity/grade is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category “normal/missing at baseline.”

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

2.5.3 Windows for time points

This D1 selection visit must be conducted within 3 months (6 months for US) after completion of the Extension Study CAMMS03409. When possible, the visit will be performed at the same time as the last visit of the Extension Study CAMMS03409. For the follow-up visits, the protocol specified time window is ± 14 days of target dates for the post-baseline scheduled visits. The target dates for the scheduled visits are based on the calendar date of the D1 selection. All scheduled visits including those that occurred outside the specified windows will be included in the efficacy analysis.

2.5.3.1 Algorithm for Determining Analysis Visit Windows for Safety Observations

For the safety assessment, the reference date for the derivation of relative days of events or findings will be corresponding to TOPAZ baseline definition specified in Section 2.4.5.

Selected safety variables will be summarized by the following analysis window:

- CBC with differential (including platelet count), Serum Creatinine, liver function and Urinalysis (assessed monthly for all the patients re-treated with alemtuzumab and for 48 months after last infusion)
- TSH (assessed every 3 months for all the patients re-treated with alemtuzumab and for 48 months after last infusion)
- Vital signs variable (assessed every 6 months from TOPAZ Day 1 to TOPAZ Month 60, at End of Study (EOS) visit, and at unscheduled visits.)

If a patient withdraws after the date of first study treatment, but prior to the first scheduled visit, data from the early withdrawal visit will be assigned to the analysis visit corresponding to the first scheduled visit. For all other visits, the lower bound and the upper bound for the analysis visit windows are defined as the midpoints of the target date of scheduled visits. If the date of the early withdrawal or an unscheduled visit falls in between the lower bound and the upper bound for a scheduled visit, then it will be assigned to that visit. For example, for the vital sign data, the lower and upper bound for the Month 18 analysis visit in a 6 month visit schedule will be Month 15 and Month 21 respectively, i.e. Month 18 ±3 months. If the early withdrawal visit date for the vital

sign assessment falls at Month 20 (i.e., between Month 15 and Month 21), then this early withdrawal visit will be assigned to the Month 18 analysis visit.

If only one record is within an analysis visit window, the data from that record will be used in the summary statistics and by visit analyses. If more than one record is within the same analysis visit window, the record from the regularly scheduled visit will be used in the summary statistics and by visit analyses. If more than one record is from a regularly scheduled visit, or more than one record is from unscheduled visits within the same analysis visit window, the record from the visit nearest to the middle of the interval will be used in the summary statistics and by visit analyses. If two visits are "tied" before and after the middle of the interval, the later record will be used in the summary statistics and by visit analyses. If the scheduled visit does not have any record but the windowed unscheduled visit is in an analysis visit window, data from the unscheduled visit will be used for the summary statistics and by visit analyses.

2.5.3.2 Algorithm for Determining Analysis Visit Windows for Efficacy Observations

For the efficacy assessment, the reference date for the derivation of relative days of events or findings will be D1 selection visit.

Selected efficacy variables will be summarized by the following analysis window:

- EDSS (assessed every 6 months from TOPAZ Day 1 to TOPAZ Month 60, at End of Study (EOS) visit, and at unscheduled visits.)
- SF-36, FAMS and EQ-5D (assessed yearly from TOPAZ Day 1 to TOPAZ Month 60, and at End of Study (EOS) visit.)
- MRI assessments (assessed yearly from TOPAZ Day 1 to TOPAZ Month 60, and at End of Study (EOS) visit.)

The algorithm for determining analysis visit windows and the observations to be used in the safety analyses will be applied to the above efficacy assessments in a similar manner. For efficacy analyses, all visits up to the end of the study, including those outside the protocol specified windows will be included.

2.5.4 Unscheduled visits

Unscheduled MRI scans EDSS and questionnaires will be assigned to the appropriate analysis window. Otherwise, only scheduled visit efficacy measurements will be used for by visit analysis to exclude the temporary fluctuations in the clinical status that may occur with a relapse.

Laboratory and vital sign data from unscheduled visits will be used in PCSA and descriptive analysis. The unscheduled visits will also be assigned to the appropriate analysis time for the summary of change from baseline by visit. The one closest to the targeted visit date will be used in the presence of multiple measurements within the same time window.

2.5.5 Pooling of centers for statistical analyses

Not applicable.

2.5.6 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

A yearly interim analysis is planned for this study. Only data collected in TOPAZ study will be used for this interim analysis. Generally, demographic and disposition of patients, summary of safety results, and summary of efficacy results will be provided.

For safety, key safety results including TEAE, SAE, AESI, death, AEs leading to treatment discontinuation along with related laboratory values and vital sign values in which details are provided in Section 2.4.5 will be provided in the interim analysis report. For efficacy, the interim analysis is performed for EDSS, relapse and MRI related efficacy endpoints and Quality of life outcomes in which details are provided in Section 2.4.4. Summary of demographics and disposition of patients will also be provided.

4 DATABASE LOCK

The database is planned to be locked approximately at 6 months after first patient completed 5 years of follow-up.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.0 or higher.

6 REFERENCES

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7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix A Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for Phase 2/3 studies (oncology excepted)
(Version 3.0 May 2014)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI - FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI - FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI - FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurements.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for Phase 2/3 studies (oncology excepted)
(Version 3.0 May 2014)

Parameter	PCSA	Comments
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CrCl (mL/min) (Estimated creatinine clearance based on the Cockcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for Phase 2/3 studies (oncology excepted)
(Version 3.0 May 2014)

Parameter	PCSA	Comments
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 GIGA/L (Non-Black); <2.0 GIGA/L (Black) ≥16.0 GIGA/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 GIGA/L	
Neutrophils	<1.5 GIGA/L (Non-Black);<1.0 GIGA/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 GIGA/L	
Basophils	>0.1 GIGA/L	
Eosinophils	>0.5 GIGA/L or >ULN (if ULN≥0.5 GIGA/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 GIGA/L ≥700 GIGA/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
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Parameter	PCSA	Comments
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SDB Orthostatic DBP	 ≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

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