NCT03368664

STATISTICAL ANALYSIS PLAN

A multi-center, open-label, single-arm, before and after switch study to evaluate the efficacy, safety and tolerability of alemtuzumab in paediatric patients with relapsing remitting multiple sclerosis (RRMS) with disease activity on prior disease modifying therapy (DMT)

GZ402673-EFC13429

STATISTICIAN: [redacted]

DATE OF ISSUE: 17-Jan-2018

Total number of pages: 52

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN **1**

TABLE OF CONTENTS **2**

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS **5**

1 OVERVIEW AND INVESTIGATIONAL PLAN **7**

1.1 STUDY DESIGN 7

1.2 OBJECTIVES 7

1.2.1 Primary objectives 7

1.2.2 Secondary objectives 7

1.3 DETERMINATION OF SAMPLE SIZE 7

1.4 STUDY PLAN 8

1.5 GRAPHIC STUDY DESIGN 8

1.6 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL 9

1.7 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN 9

2 STATISTICAL AND ANALYTICAL PROCEDURES **10**

2.1 ANALYSIS ENDPOINTS 10

2.1.1 Demographic and baseline characteristics 10

2.1.2 Prior and concomitant medications 11

2.1.3 Efficacy endpoints 11

2.1.3.1 Primary efficacy endpoint 11

2.1.3.2 Secondary efficacy endpoints 12

2.1.4 Safety endpoints 14

2.1.4.1 Adverse events variables 14

2.1.4.2 Deaths 16

2.1.4.3 Laboratory safety variables 16

2.1.4.4 ITP and antiGBM surveillance and monitoring 17

2.1.4.5 Physical examination and vital signs 17

2.1.4.6 Other safety endpoints 18

2.1.5 Pharmacokinetic variables 18

2.1.6 Pharmacodynamic variables 18

2.1.7 Quality-of-life endpoints 18

2.1.8 EXPLORATORY ENDPOINT 19

2.2 DISPOSITION OF PATIENTS 19
2.3 ANALYSIS POPULATIONS 20
2.3.1 Modified Intent-to-treat population 20
2.3.2 Safety population: 20
2.3.3 Population for pharmacokinetics/pharmacodynamics analyses 21
2.4 STATISTICAL METHODS 21
2.4.1 Demographics and baseline characteristics 21
2.4.2 Prior and Concomitant medications 21
2.4.3 Extent of study treatment exposure 22
2.4.4 Analyses of efficacy endpoints 22
2.4.4.1 Analysis of primary efficacy endpoint(s) 22
2.4.4.2 Analysis of secondary efficacy endpoint(s) 23
2.4.4.3 Multiplicity issues 24
2.4.5 Analyses of safety data 24
2.4.5.1 Analyses of adverse events 25
2.4.5.2 Deaths 27
2.4.5.3 Analyses of laboratory variables 28
2.4.5.4 Analyses of vital sign variables 28
2.4.5.5 Analyses of other safety endpoints 29
2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables 29
2.4.7 Analyses of quality of life (QoL) variables 30
2.4.8 Analyses of exploratory endpoints 30
2.5 DATA HANDLING CONVENTIONS 30
2.5.1 General conventions 30
2.5.2 Data handling conventions for secondary efficacy variables 31
2.5.3 Missing data 31
2.5.4 Windows for time points 32
2.5.4.1 Algorithm for Determining Analysis Visit Windows for Safety Observations 32
2.5.4.2 Algorithm for Determining Analysis Visit Windows for Efficacy Observations 33
2.5.5 Unscheduled visits 34
2.5.6 Pooling of centers for statistical analyses 34
2.5.7 Statistical technical issues 34
3 INTERIM ANALYSIS 35
4 DATABASE LOCK 36
5 SOFTWARE DOCUMENTATION 37
6 REFERENCES 38

7 LIST OF APPENDICES 39

APPENDIX A POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA 40

APPENDIX B SUMMARY OF STATISTICAL ANALYSIS 51

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	antidrug antibody
AE:	adverse event
AESI:	adverse events of special interest
ALT:	alanine aminotransferase
antiGBM:	AntiGlomerular Basement Membrane
ARR:	annualized relapse rate
AST:	aspartate aminotransferase
BMI:	Body Mass Index
BUN:	blood urea nitrogen
BVMT-R:	Brief Visuospatial Memory Test-Revised
CBC:	complete blood count
CRF:	case report form
CTCAE:	Common Terminology Criteria for Adverse Events
DMT:	disease modifying therapy
EOS:	end of study
EOTP:	end of treatment phase
GA:	glatiramer acetate
GEE:	generalized estimating equation
HLGT:	high level group term
HLT:	high level term
IAR:	infusion associated reaction
ICF:	informed consent form
IMP:	investigational medicinal product
ITP:	immune thrombocytopenic purpura
IV:	intravenous
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	modified intent to treat
MRI:	magnetic resonance imaging
MS:	multiple sclerosis
NIMP:	noninvestigational medicinal product
PD:	pharmacodynamics
PK:	pharmacokinetics
PT:	preferred term
QoL:	quality of life
RRMS:	relapsing-remitting multiple sclerosis
SAE:	serious adverse event
SD:	standard deviation
SDMT:	Symbol Digit Modality Test
SOC:	system organ class
TB:	tuberculosis

TEAE:	treatment emergent adverse event
TSH:	Thyroid Stimulating Hormone
ULN:	upper limit of normal
WBC:	white blood cell
WHO ATC:	World Health Organization Anatomical Therapeutic Chemical

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN

This is an open-label, rater-blinded, single-arm, before and after switch study of efficacy, safety and tolerability of alemtuzumab in paediatric patients from 10 to <18 years of age with relapsing-remitting multiple sclerosis (RRMS) with disease activity on prior disease modifying therapy (DMT).

This study has an open-label design. All enrolled patients will be on a DMT when entering into the study and up to approximately 4 months. After this period all patients will stop their prior DMT and will be treated with alemtuzumab during alemtuzumab treatment phase.

No randomization will be performed.

The study will be rater-blinded for magnetic resonance imaging (MRI). All brain scans will be reviewed and interpreted by one or more MRI experts at an independent, central facility with no access (ie, blinded) to treatment thereby avoiding bias.

At least 60 patients aged from 10 years to less than 18 years will be screened in this study from approximately 50 sites to account for screen failures, and to ensure at least 50 evaluable patients.

1.2 OBJECTIVES

1.2.1 Primary objectives

- To evaluate the efficacy, safety and tolerability of alemtuzumab (IV) in paediatric patients from 10 to <18 years of age with RRMS who have disease activity on prior DMT.

1.2.2 Secondary objectives

- To assess the pharmacokinetics (PK), pharmacodynamics (PD), antidrug antibody (ADA) formation, and potential effects of alemtuzumab on other multiple sclerosis (MS) disease characteristics such as cognition and quality of life.

1.3 DETERMINATION OF SAMPLE SIZE

The sample size calculation of the study was based on a 4 months period comparison of new or enlarged T2 lesions (Primary efficacy endpoint) on prior DMT versus on alemtuzumab.

At least 60 patients aged from 10 years to less than 18 years will be screened in this study to account for screen failures, and to ensure at least 50 evaluable patients. According to the means and variability reported in other paediatric MS studies (1), it was assumed that there is an average

of 9 new or enlarging T2 lesions during continuation of prior DMT and an overdispersion parameter of 0.7 for both study periods. Further assuming a conservative within-person correlation of 0.25 for the lesion counts, a 10% dropout rate, and a two-tailed significance level of 0.05, this sample size will provide at least 85% power to detect a 50% reduction in the number of new or enlarging T2 lesions after the first course of alemtuzumab compared to the equal-length prior DMT period. These sample size calculations were simulated using a correlated, repeated measures negative binomial regression model with GEE with robust variance estimation to account for the within-patient correlation in lesion counts between prior DMT period and the equal-length alemtuzumab treatment period.

1.4 STUDY PLAN

The study will consist of

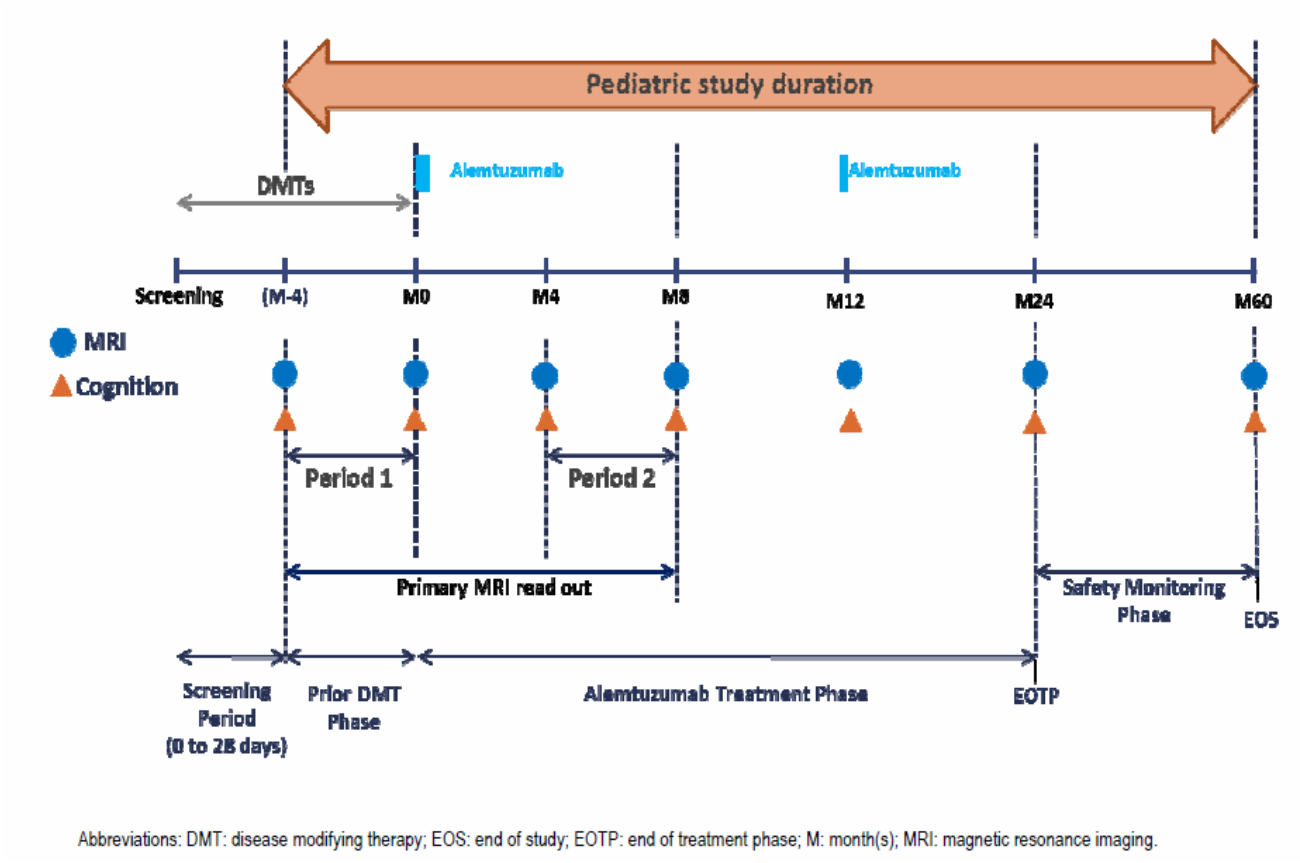
- Screening period (0-28 days prior to M-4): This phase consists of the screening assessments for study eligibility of patients on current DMT.
- Prior DMT phase (approximately 4 months from M-4 to M0): This phase consists of the efficacy measurements on current DMT, which will be used as comparator group in the study. Subjects will continue the use of their current DMT during this period until 7 days prior to administration of first dose of alemtuzumab at M0.
- Alemtuzumab treatment phase (approximately 2 years from M0 to M24): This phase starts with administration of first course of 5 infusions of alemtuzumab at M0, after discontinuation of current DMT, and ends at M24. The second course of 3 infusions of alemtuzumab will be administered at M12. The MRI based primary efficacy endpoint will be assessed over a 4 month period during the treatment phase compared to an equal period during the prior DMT phase.

  Note: End of treatment phase (EOTP) refers to the end of the Alemtuzumab Treatment Phase.
- Safety monitoring phase (approximately 3 years from M24 to M60): Additional safety follow-up and monitoring for all patients treated with alemtuzumab will be conducted during this phase to yield a total of 5 years of follow-up since first alemtuzumab treatment, including 4 years post last treatment with alemtuzumab.

  Note: EOS refers to the end of the safety monitoring phase.

1.5 GRAPHIC STUDY DESIGN

Please refer of section 1.2 of the study protocol for the detailed study flow chart.



Abbreviations: DMT: disease modifying therapy; EOS: end of study; EOTP: end of treatment phase; M: month(s); MRI: magnetic resonance imaging.

1.6 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

NA

1.7 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

NA

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

Unless otherwise specified, all baseline values will be defined as the last non-missing value prior to the first course of alemtuzumab.

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

Demographic characteristics

Demographic variables are:

- Age in years (quantitative and qualitative variable : <13, 13-18 years)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Weight in kg
- Height in cm
- Body Mass Index (BMI) in kg/m^2
- Geographic Region (EU, Non-EU Europe and Israel)

Medical or surgical history

Medical (or surgical) history includes all the relevant medical (or surgical) history during the lifetime of the patient.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics at baseline

The following disease characteristics (assessed at both screening visit and baseline) will be summarized

- EDSS

- Time (years) since first MS diagnosis
- Total number of relapse since the first MS diagnosis/ Number of relapse within past year
- Brain imaging characteristics (eg, T1-Hyperintense Lesion Volumes and T2-Hyperintense Lesion Volumes)

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

2.1.2 Prior and concomitant medications

All medications taken from the first visit of the study until the end of the study, including alternative medications (eg, herbal treatments, botanicals, etc.) for treatment of MS and systemic corticosteroids are to be reported in the case report form (CRF) pages.

All medications will be coded using the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used prior to screening visit of the study
- Concomitant medications are any treatments received by the patient concomitantly to alemtuzumab from the first visit of the study until the end of the study. Concomitant treatments have been detailed for all phases of the study in section 8.8 of the study protocol and are not limited to the treatment received with alemtuzumab (treatment phase).
  - Prior DMTs (ie, limited to interferons and glatiramer acetate [GA] only) and systemic corticosteroids administrated in Screening and Prior DMT phase are treated as concomitant medications.
  - Pre-medications (please refer to section 8.2 of the study protocol) prior to alemtuzumab administration are treated as concomitant medications as well.

  A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the posttreatment period (as defined in the observation period in Section 2.1.3).

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

2.1.3 Efficacy endpoints

Baseline for efficacy endpoints is defined as the last non-missing value prior to the first course of alemtuzumab, unless otherwise specified.

2.1.3.1 Primary efficacy endpoint

The primary efficacy endpoint of the study is the number of new or enlarging T2 lesions on brain MRI, during continuation of prior DMT (Period 1) compared to an equal period after the first course of alemtuzumab treatment (Period 2).

For primary endpoint assessment, two periods have been defined

- Period 1: will occur from M-4 up to M0. A baseline MRI will be performed during the screening period and another at D-7 visit (7 days before M0). Both MRI will be taken while patients are on their prior DMT. The two MRIs will be compared by a central assessor to count the number of new or enlarging T2 lesions. It is important to ensure that these 2 MRI assessments are performed 4 months (±7 days) apart.
- Period 2: will occur from M4 to M8: The MRI performed at the M4 visit will be the baseline MRI for Period 2. A second MRI will be performed after alemtuzumab first course of treatment at M8. The two MRIs will be compared by a central assessor to count the number of new or enlarging T2 lesions. It is important to ensure that these 2 MRI assessments are performed 4 months (±7 days) apart.

"Baseline" MRI will be collected during the screening visit (baseline for Period 1) and the M4 visit (baseline for Period 2). The "baseline" lesion volume for the corresponding period will be adjusted in the generalized estimating equation (GEE) model.

In addition to primary endpoint MRIs (Screening, D-7, M4, M8) other MRIs will be performed at M12, M24/at EOTP, and then annually in the Safety Monitoring Phase.

All brain MRIs will be reviewed and interpreted by one or more MRI experts at an independent, central facility with no access (ie, blinded) to patients' treatment thereby avoiding bias.

Besides the number of new and enlarging T2 lesions, the number of patients with new and enlarging T2 lesions on brain MRI comparing period 1 and period 2 is also of interest and will be considered as one of the secondary efficacy endpoints.

2.1.3.2 Secondary efficacy endpoints

The secondary efficacy endpoints are:

- The number of patients with new or enlarging T2 lesions during continuation of prior DMT (Period 1) compared to an equal period after the first course of alemtuzumab treatment (Period 2) (introduction refer to Section 2.1.3.1) .
- EDSS
- Annualized relapse rate (ARR) at Year 2
- Cognition test scores: Brief Visuospatial Memory Test – Revised (BVMT-R) and Symbol Digit Modality Test

2.1.3.2.1 EDSS (Expanded disability status scale)

Patient disability will be evaluated using the EDSS (see Appendix D in the protocol), which has long been considered the standard for assessing disability in patients with MS.

The EDSS is an ordinal clinical rating scale which ranges from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments. Briefly, the assessing neurologist rates

7 functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual ratings) in conjunction with observations and information concerning the patient's mobility, gait, and use of assistive devices to assign an EDSS score.

EDSS steps 1.0 to 4.5 refer to people with MS who are fully ambulatory, while EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation.

The EDSS will be performed by the neurologist at the following visits: Screening, D-7, M4, M8, M12, M15, M18, M21, M24/at EOTP; every 6 months in Safety Monitoring Phase, and at every relapse visit.

2.1.3.2.2 Annualized relapse rate (ARR) at year 2

Annualized Relapse Rate (ARR) at year 2 is defined as the total number of relapses happened in the alemtuzumab treatment phase divided by the time of follow up in alemtuzumab treatment phase for each patient. Relapses are defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the neurologist and documented by the functional system scores. The subject must have objective signs on the neurologist's examination confirming the event.

New or recurrent symptoms that occur less than 30 days following the onset of a relapse should be considered part of the same relapse. The Investigator can, at his/her discretion, treat the patient with corticosteroids.

Relapses will not be considered as AEs.

2.1.3.2.3 Cognition test scores

2.1.3.2.3.1 Brief Visuospatial Memory Test – Revised

The Brief Visuospatial Memory Test - Revised (BVMT-R) is a commonly used, commercialized, assessment tool to measure visuospatial learning and memory abilities across research and clinical settings.

A visual display of six simple figures arranged in a 2 × 3 matrix on separate pages is shown to participants for three consecutive 10-second trials. After each trial, participants are to draw as many designs as accurately as they can and in the correct location. They are again asked to reproduce the designs in the exact layout after a 25-minute delay filled with other distractor tasks. A forced-choice recognition trial is administered immediately following the delayed memory trial. An optional copy trial is included at the end of the test where the participants are asked to copy the figure display as accurately as they can. Scoring of the immediate and delayed recall as well as copy trials are based on the accuracy of the drawings and the location of the figures. For each figure, one point is awarded to each satisfactory domain resulting in a maximum of 12-points per trial.

Brief Visuospatial Memory Test-Revised will be assessed at Screening, D-7, M4, M8, M12, M18, M24/at EOTP; annually in Safety Monitoring Phase.

2.1.3.2.3.2 Symbol digit modality test

Cognitive impairment will be assessed using the Symbol Digit Modality Test (SDMT) Brief and easy to administer, the SDMT has demonstrated remarkable sensitivity in detecting not only the presence of brain damage, but also changes in cognitive functioning over time and in response to treatment. The SDMT involves a simple substitution task that normal children and adults can easily perform. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. Responses can be written or oral, and for either response mode, administration time is just 5 minutes. For this study, only ORAL form of response is desired (ie, patient does NOT write down the responses, instead, patient is instructed to verbally call out the numbers that correspond to the symbols and the administer writes down his/her responses.

Symbol Digit Modality Test will be assessed at Screening, D-7, M4, M8, M12, M18, M24/at EOTP; annually in Safety Monitoring Phase.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data, vital signs, physical examination, thyroid function tests, Tanner staging, pregnancy test when applicable, and ADA detection/assessment.

Observation period:

- Pretreatment period is defined as the time from the signed informed consent date up to the 1st alemtuzumab dose
- On-treatment period is defined as the time from the 1st alemtuzumab dose to the end of the study (EOS)
- Posttreatment period is defined as the time after EOS.

2.1.4.1 Adverse events variables

AE observation period:

- Pretreatment AEs are defined as those AEs that developed or worsened during the pretreatment period.
- On-treatment AEs are defined as those AEs that developed or worsened during the on-treatment period.
- Posttreatment AEs are defined as those AEs that developed or worsened during the posttreatment period.

On-study period will include pretreatment and on-treatment period. Treatment emergent adverse events (TEAEs) for analysis purpose will include all on-treatment AEs, then treatment emergent adverse event period equals on-treatment period.

The primary analysis of adverse event reporting will be on TEAEs. Pretreatment AEs will be summarized separately.

All adverse events (including serious adverse events [SAEs], infusion associated reactions [IARs] and adverse events of special interests [AESI]) 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.

Adverse events with special interest include the following terms:

AESIs reported by the investigator in CRF based on the protocol instruction

- Hypersensitivity or anaphylaxis.
- Pregnancy occurring in a female 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 female participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or nonserious) with investigational medicinal product (IMP)/noninvestigational medicinal product (NIMP).
  - An overdose (accidental or intentional) with the IMP is an event caused by the Investigator or a nurse and defined as an 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.
  - An overdose with the NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.
  - Of note, asymptomatic overdose has to be reported as a standard AE.
- Increase in alanine aminotransferase (ALT) (see the “Increase in ALT” flow diagram in Appendix B of the study protocol).
- Other project specific AESI(s):
  - Autoimmune mediated conditions including but not limited to: cytopenias, immune thrombocytopenic purpura (ITP) (see Appendix B of the study protocol), autoimmune hemolytic anemia, autoimmune neutropenia, autoimmune pancytopenia.
  - Nephropathies including AntiGlomerular Basement Membrane (antiGBM) disease (See Appendix B of the study protocol)
  - Thyroid disorder
  - Pneumonitis.
  - Serious infections (including serious opportunistic infections).
  - Disseminated Infections.
  - Malignancy (including cervical dysplasia, thyroid malignancy).

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 period
- Death on-TEAE: deaths occurring during the treatment emergent adverse event period
- Death post-study: 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 in standard international units and international units will be used in listings and tables.

Blood samples for clinical laboratories will be taken at Visit 1 (Screening), Visit 3 (D-7), every visit (visit 4 to visit 28, monthly) in the alemtuzumab treatment phase, every visit (visit 29 to visit 64, monthly) in the safety monitoring phase and early termination unless otherwise specified. The laboratory parameters will be classified as follows:

- Hematology
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, mean corpuscular hemoglobin, red blood cell count, platelet count
  - White blood cells: white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry (Blood samples for clinical chemistry will be taken at Visit 1 (Screening), Visit 3 (D-7), Visit 8 (M4), Visit 12 (M8), Visit 16 (M12), Visit 19 (M15), Visit 22 (M18), Visit 25 (M21), Visit 28 (M24/EOTP), Visit 31, Visit 34, Visit 37, Visit 40, Visit 43, Visit 46, Visit 49, Visit 52, Visit 55, Visit 58, Visit 61, Visit 64 (quarterly) in the safety monitoring phase and early termination unless otherwise specified)
  - Metabolism: glucose, cholesterol, protein, albumin, triglycerides, creatinine kinase, globulin, albumin/globulin
  - Electrolytes: sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphate
  - Renal function: serum creatinine, blood urea nitrogen (BUN), uric acid (only serum creatinine will be assessed at every visit (Visit 4 to Visit 28, monthly) in the alemtuzumab treatment phase and every visit (Visit 29 to Visit 64, monthly) in the safety monitoring phase)
  - Liver function: aspartate aminotransferase (AST), ALT, alkaline phosphatase, gamma glutamyl transferase, bilirubin, direct bilirubin, indirect bilirubin, LDH
- Pregnancy test: serum β-human chorionic gonadotropin (only female patients) will be performed at Visit 1 (Screening) in women of childbearing potential
- Serology tests: hepatitis B/C (includes hepatitis B surface antigen, hepatitis B Surface antibody, hepatitis B core antibody, hepatitis C virus antibody, hepatitis C virus antigen)

will be performed at Visit 1 (Screening). Other serology test may be required according the patient vaccination status.

- Tuberculosis (TB) test screening. It should be performed at Visit 1 (Screening) as per local health care authority recommendations.
- Thyroid Function tests: thyroid stimulating hormone (TSH) and if abnormal T3 and T4. (will be assessed at Visit 1 (Screening), Visit 3 (D-7), Visit 7, Visit 10, Visit 13, Visit 16, Visit 19, Visit 22, Visit 25, Visit 28 (quarterly) in alemtuzumab treatment phase (Year 1 and 2); and Visit 31, Visit 34, Visit 37, Visit 40, Visit 43, Visit 46, Visit 49, Visit 52, Visit 55, Visit 58, Visit 61, Visit 64 (quarterly) in the safety monitoring phase.)

Urine samples will be collected as follows:

- Urinalysis: pH, ketones, protein, glucose, blood, urobilinogen, bilirubin, microscopic sediment, specific gravity (will be taken at Visit 1 (Screening), Visit 3 (D-7), every visit (Visit 4 to Visit 28, monthly) in the alemtuzumab treatment phase, every visit (Visit 29 to Visit 64, monthly) in the safety monitoring phase and early termination unless otherwise specified).
- A urine dipstick pregnancy test will be performed at Visit 3 (D-7) and Visit 16 (M12).

2.1.4.4 ITP and antiGBM surveillance and monitoring

In an effort to identify ITP early and minimize the risk of bleeding due to low platelet counts, this study requires safety measures including monthly blood testing to monitor complete blood count (CBCs) with platelets. Patients with certain abnormalities may be required to have more frequent blood tests. See Appendix B of the study protocol (Immune thrombocytopenia).

2.1.4.5 Physical examination and vital signs

A standard physical examination for clinical and neurological assessments which includes examination of major body systems, height and body weight will be performed at Visit 1 (screening), Visit 3 (D-7), Visit 4 (M0/D1), Visit 8 (M4), Visit 12 (M8), Visit 16 (M12), Visit 19 (M15), Visit 22 (M18), Visit 25 (M21), Visit 28 (M24/at EOTP); Visit 34, Visit 40, Visit 46, Visit 52, Visit 58, Visit 64 (every 6 months) at safety monitoring phase, and at every relapse visit.

The following vital signs: including respiratory rate, heart rate, systolic and diastolic blood pressure and body temperature, will be measured during each physical examination and at the following timepoints during alemtuzumab treatment infusions:

- before methylprednisolone infusion,
- at a time after methylprednisolone infusion and prior to alemtuzumab infusion,
- 1 hour after the start of alemtuzumab infusion and hourly during and after infusion, until observation postinfusion has ended.

The date of the first menarche should be captured if applicable.

The Tanner stage (Appendix E of the study protocol) should be assessed until complete sexual maturity at the specified time points: Visit 1 (Screening), and then Visit 16, Visit 28, Visit 40, Visit 52, Visit 64 (annually) during the whole study period.

The Tanner scale (also known as the Tanner stages I-V) is a scale of physical development in children, adolescents and adults (2, 3). The scale defines physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitalia, and development of pubic hair.

2.1.4.6 Other safety endpoints

The other safety endpoints will be assessed by:

- Antidrug antibody formation (ADA).

Assessment of ADA formation will be performed at Visit 4 (M0/D1, baseline), Visit 5 (M1), Visit 7 (M3), Visit 16 (M12), Visit 17 (M13), Visit 19 (M15), Visit 28 (M24/at EOTP); and Visit 40, Visit 52, Visit 64 (annually) in the safety monitoring phase.

2.1.5 Pharmacokinetic variables

For patients receiving alemtuzumab, serum concentrations and PK parameters will be studied. Please refer to section 9.2.2.1 of the study protocol for the detailed introduction.

2.1.6 Pharmacodynamic variables

Pharmacodynamic assessments of lymphocyte subsets will be performed in order to characterize the PD profile of 2 treatment courses of alemtuzumab in paediatric patients.

Lymphocyte phenotyping

To monitor the extent of lymphocyte depletion and repopulation, lymphocyte phenotyping, including a standard, 6-color TBNK (T cells, B cells, and natural killer cells) panel (CD3+, CD4+, CD8+, CD19+, CD16+, CD56+, total lymphocytes, and helper/suppressor ratio [CD4+/CD8+]), will be performed. Lymphocyte phenotyping will be assessed at Visit 1 (screening), Visit 3 (D-7), Visit 4 (M1), Visit 8 (M4), Visit 12 (M8), Visit 16 (M12), Visit 17 (M13), Visit 19 (M15), Visit 22 (M18), Visit 25 (M21), Visit 28 (M24/at EOTP); Visit 40, Visit 52, Visit 64 (annually) in Safety Monitoring Phase.

2.1.7 Quality-of-life endpoints

Quality of Life (QoL) will be assessed by established generic paediatric QoL measures.

PedsQL questionnaire

The PedsQL™ Measurement Model is a modular approach to measuring health-related quality of life (HRQOL) in healthy children and adolescents and those with acute and chronic health conditions. It consists of 23 items, rates from 0 to 4, and four scales (physical, emotional, social and school functioning) (details please refer to Appendix F of the study protocol).

Paediatric NeuroQoL questionnaire

Paediatric NeuroQoL (Quality of Life in Neurological Disorders) is a measurement system that evaluates and monitors the physical, mental, and social effects experienced by children living with neurological conditions. Physical effects (fatigue and pain) and mental effects (cognitive function, anxiety, and depression) experienced by patients will be assessed (Appendix G of the study protocol).

PedsQL and paediatric NeuroQoL questionnaire will be assessed at Visit 1 (screening), Visit 3 (D-7), Visit 8 (M4), Visit 12 (M8), Visit 16 (M12), Visit 22 (M18), Visit 28 (M24/at EOTP); Visit 40, Visit 52, Visit 64 (annually) in Safety Monitoring Phase.

2.1.8 EXPLORATORY ENDPOINT

T1 weighted lesions and brain volume will be assessed on MRI as an exploratory endpoint MRI throughout the study period.

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 patient who met the inclusion criteria and signed the informed consent.

Enrolled patients are defined as any patient with a signed informed consent form (ICF) who met all the inclusion criteria and none of the exclusion criteria.

This is an open-label, single-arm, before and after switch study without randomization.

Patients who were screened but did not receive any dose of alemtuzumab will be reported separately, but will not be included in any efficacy or safety population.

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:

- Screened patients
- Screened failure patients and reasons for screen failure (if data is available)

- Number and percentage of patients who did not complete prior DMT phase, with corresponding reasons
- Number and percentage of patients who did not complete Period 2 with alemtuzumab, with corresponding reasons
- Number and percentage of patients who did not complete safety monitoring phase (will be included in final study report only), with corresponding reasons.
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation
- Status at last study contact

For all categories of patients (except for the screened categories), percentages will be calculated using the number of enrolled patients as the denominator divided by the number of exposed patients. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages.

All critical or major deviations potentially impacting efficacy analyses, and other major or critical deviations will be summarized in tables giving numbers and percentages.

Additionally, the analysis populations for safety, efficacy, and pharmacokinetics (PK), pharmacodynamics (PD) will be summarized in a table.

- Efficacy population: modified intent-to-treat (mITT) population
- Safety population
- PK population
- PD population

2.3 ANALYSIS POPULATIONS

2.3.1 Modified Intent-to-treat population

Modified Intent-to-treat (mITT): The primary analysis will be conducted on the population of patients who have received at least 1 dose of alemtuzumab and also have evaluable data (at least one measurement of primary efficacy endpoints) for both Period 1 and Period 2. The mITT population will be used for the analyses of the primary and secondary efficacy endpoints.

2.3.2 Safety population:

The safety population consists of patients who have received at least 1 dose of alemtuzumab. Safety and tolerability analyses will be conducted on all the patients from safety population. At the first database lock after the last patient has completed efficacy assessments including MRI at end of Period 2, some patients will have follow-up beyond the end of Period 2, all available information will be used for safety and tolerability analyses.

2.3.3 Population for pharmacokinetics/pharmacodynamics analyses

PK: the PK population consists of patients who have received at least 1 dose of alemtuzumab and also have evaluable PK data (at least one measurement of PK endpoints).

PD: the PD population consists of patients who have received at least 1 dose of alemtuzumab and also have evaluable PD data (at least one measurement of PD endpoints).

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, Q1, Q3, and maximum. Categorical and ordinal data will be summarized using the number and percentage of patients.

Parameters will be summarized on the enrolled patients. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the primary analysis population.

Medical and surgical history will be summarized by system organ class (SOC) and preferred term (PT) sorted by internationally agreed order of SOC and by the decreasing frequency of PT within SOC.

No statistical testing on demographic and baseline characteristic data will be performed.

No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

2.4.2 Prior and Concomitant medications

The prior and concomitant medications will be summarized for the enrolled patients. DMTs and system corticosteroids in period 1 will be summarized separately.

Medications will be summarized based on the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) Level 4 Class code and generic name. In addition, commonly used medications, defined as those used by more than 5% patients, will be presented.

The tables for prior and concomitant medications will be sorted by alphabetical order of ATC level 4, and within ATC Level 4 the Generic Names are presented by decreasing incidence. Multiple records of the same generic drug used by a patient are counted once within an ATC level and within a generic name. If a medication of the same generic drug is associated with multiple ATC Level 4 values, it will be counted under each ATC Level 4.

2.4.3 Extent of study treatment exposure

Alemtuzumab will be administered by IV infusions in a supervised medical setting at a dose of:

- For patients ≥50 kg: 12 mg/day
- For patients <50 kg: 0.24 mg/kg/day.

There are two courses. The first treatment course includes 5 consecutive days of infusion, and the second treatment course is administered 12 months after the first treatment course and includes 3 consecutive days of infusion.

Total dose taken and total dose taken over total dose expected in each course will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum).

The number and percentage of patients who complete or partially (partially refers to <5 infusions in first alemtuzumab course or <3 infusions in the second alemtuzumab course) complete all infusions in each course will also be summarized.

2.4.4 Analyses of efficacy endpoints

Analyses for all the primary and secondary efficacy endpoints will be conducted using the mITT population.

2.4.4.1 Analysis of primary efficacy endpoint(s)

The number of new or enlarging T2 lesions during continuation of prior DMT (Period 1) and in an equal-length period after the first course of alemtuzumab treatment (Period 2) will be analyzed and compared using a repeated measures negative binomial regression model with GEE. The default log link function will be used to model the expected number of T2 lesions. The robust, sandwich covariance matrix will be constructed assuming an unstructured/exchangeable working correlation matrix. Baseline T2 lesion count, geographic region and treatment status (DMT or alemtuzumab treatment) will be used as covariates for the model. Geographic region will be removed from the model if the model does not converge.

The primary statistical objective is to test superiority of alemtuzumab versus prior DMT at 5% level of significance. No missing data is expected as the mITT population is restricted to the patients with evaluable data for both Period 1 and Period 2.

Sample SAS code can be found below:

```
proc genmod data= t2_count;
   class usubjid treatment region;
   model aval = baseline treatment  region / dist = negbin link = log;
   repeated subject = usubjid / type=un;
   contrast 'period 1 vs period 2'  treatment 1 -1/ wald;
   run;
```

2.4.4.2 Analysis of secondary efficacy endpoint(s)

2.4.4.2.1 The number of patients with new or enlarging T2 lesions during Period 1 and Period 2

The proportion of patients with new or enlarging T2 lesions during Period 1 and Period 2 will be analyzed and compared using repeated measures logistic regression model with GEE and robust variance estimation adjusted by baseline T2 lesions count, treatment status and geographic region. Geographic region will be removed from the model if the model does not converge.

The analyses will be similar to the primary endpoint analyses with the exception of the use of the logit link function and the Bernoulli distribution. Odds ratio with the corresponding 95% confidence interval and the p-value will be provided for comparisons of alemtuzumab treatment against DMT along with descriptive statistics.

Sample SAS code can be found below:

```
proc genmod data= t2_act descend;
  class usubjid treatment region;
  model act = baseline treatment region / link=logit dist=bin;
  repeated subject=usubjid / corr=unstr;
  estimate "O.R. period 1 vs period 2 " treatment 1 -1/ exp;
  run;
```

2.4.4.2.2 EDSS

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of observed EDSS scores (values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point). Baseline for EDSS is defined as the last non-missing value prior to the first course of alemtuzumab.

2.4.4.2.3 Annualized relapse rate (ARR) at Year 2

If a patient completed the alemtuzumab treatment phase, all relapse events that happened during the alemtuzumab treatment phase will be included in this efficacy analysis, regardless if the patient is on-treatment or not, and the observation period is defined as the time from Visit 4 (M0/D1) to Visit 28 (M24/EOTP). If a patient withdraws from study prior to the end of alemtuzumab treatment period, all relapse events up to the last contact date will be included in the analysis, and the observation period is defined as the time from Visit 4 (M0/D1) to the last contact date. No imputation will be performed for the unobserved events that may happen after study discontinuation and up to Visit 28 (M24/EOTP).

The annualized relapse rate at Year 2 will be estimated using a negative binomial model with robust variance estimation. The model will include the total number of relapses occurred during the observation period defined above as the response variable. Log transformed duration time of observation period will be the offset variable.

The estimated annualized relapse rate and its corresponding 95% confidence interval will be provided.

Sample SAS code can be found below:

```
proc genmod data= arr2;
    class usubjid;
    model aval = / dist=negbin link=log offset=lreflyr MAXITER=1000 ITPRINT;
    repeated subject = usubjid / type = un sorted;
    estimate "ARR" intercept 1  / exp ;
 run;
```

2.4.4.2.4 Cognition test scores

2.4.4.2.4.1 Brief Visuospatial Memory Test – Revised

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) and 95% confidence interval of the means of the total score of BVMT-R (values and changes from baseline) , when appropriate, will be calculated for each visit or study assessment (baseline, each postbaseline time point).

2.4.4.2.4.2 Symbol digit modality test

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) and 95% confidence interval of the means of the total score of SDMT (values and changes from baseline) , when appropriate, will be calculated for each visit or study assessment (baseline, each postbaseline time point).

2.4.4.3 Multiplicity issues

There is no formal hypothesis testing for the secondary efficacy endpoints, therefore the study overall type I error will not need to be adjusted for multiplicity.

2.4.5 Analyses of safety data

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- The baseline value is defined as the last non-missing value prior to the first course of alemtuzumab.
- 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 treatment-emergent PCSA percentage.
- The treatment-emergent PCSA denominator for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period on the safety population. Number (%) of patients with at least 1 PCSA will be summarized regardless of baseline PCSA status and also by baseline PCSA status.
- 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.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.
- All safety values including unscheduled measurements will be assigned to the appropriate safety analysis visit window defined in Section 2.5.4.1.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pretreatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment, treatment-emergent, or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment or posttreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.

Adverse event incidence tables will present by SOC and PT, sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs, using 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 any given category (eg, SOC or preferred term). The denominator for computation of percentages is the safety population for the treatment emergent adverse events or screened population for the pretreatment adverse events.

In tabulating severity of AEs on a per patient basis, the greatest severity will be assigned to a patient when there is more than one occurrence of the same AE with different reported severities. Relationships of the AE to alemtuzumab treatment will be categorized as not related, or related. The highest level of association will be reported in patients with differing relationships for the same AE.

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
  - Treatment-emergent serious adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation
- 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 by primary SOC and PT by relationship, 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.
- All treatment-emergent adverse events by primary SOC and PT by grade/intensity, 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.

Analysis of all treatment emergent serious adverse event(s)

- 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.
- All treatment-emergent serious adverse events by primary SOC and PT by relationship, 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.

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

- All treatment-emergent adverse events leading to permanent treatment discontinuation, by primary SOC and PT, showing number (%) of patients with at least one TEAE, will be presented by SOC internationally agreed order and by decreasing incidence of PTs within each SOC.

Analysis of all treatment-emergent infusion associated reactions (IARs)

- Overview of treatment-emergent IARs, summarizing number (%) of patients with any
  - Treatment-emergent IARs
  - Treatment-emergent serious IARs

  - Treatment-emergent IARs leading to death
  - Treatment-emergent IARs leading to permanent treatment discontinuation
- All treatment-emergent IARs 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.
- All treatment-emergent IARs by primary SOC and PT by grade/intensity, 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.
- Distribution of treatment-emergent IARs by grade/intensity, showing average number of treatment-emergent IARs by grade/intensity in the figure.
- Distribution of treatment-emergent IARs in relation to alemtuzumab administration, showing average number of treatment-emergent IARs by alemtuzumab course and infusion day in the figure.

Analysis of all treatment-emergent adverse events of special interest (AESI)

- Overview of treatment-emergent AESI, summary number (%) of patients with any
  - Treatment emergent AESI
  - Treatment emergent serious AESI
  - Treatment emergent AESI leading to death
  - Treatment emergent AESI leading to permanent study drug discontinuation
- All treatment-emergent AESI by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent AESI, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All treatment-emergent AESI by primary SOC and PT by relationship, showing the number (%) of patients with at least 1 treatment-emergent AESI, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All treatment-emergent AESI by primary SOC and PT by grade/intensity, showing the number (%) of patients with at least 1 treatment-emergent AESI, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

Analysis of pretreatment adverse events

The analyses of pretreatment adverse events are similar to those of treatment emergent adverse events described above.

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, on-treatment)
- 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 system organ class (SOC), high level group term (HLGT), high level term (HLT) and preferred term (PT)

showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

- All pretreatment adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary system organ class (SOC), high level group term (HLGT), high level term (HLT) and preferred term (PT) showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

2.4.5.3 Analyses of laboratory variables

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). For each continuous parameters listed in Section 2.1.4.3, mean changes from baseline with the corresponding standard error will be plotted over time. This section will be organized by biological function as specified in Section 2.1.4.3.

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

1. Normal/missing
2. 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.

For PCSA analyses, the laboratory measurements obtained at either scheduled or unscheduled visits should be used; and, both the centralized and local test results should be used, as long as their available dates/time is different from each other's. Centralized data will be used preferentially to the local measures in the PCSA analyses when measurements are performed on the same date and at the same time for a given laboratory test.

A listing of PCSAs will be provided.

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all vital signs variables (values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point). Change in vital signs during and immediately following intravenous (IV) administration from preinfusion will also be summarized.

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

1. Normal/missing
2. Abnormal according to PCSA criterion or criteria

Listings of abnormal findings/values from these data as well as from physical examination inclusive of body weight and height, as well as Tanner stage in pediatric patients, will be presented.

2.4.5.5 Analyses of other safety endpoints

Observed measurements and changes from baseline to study time points in antialemtuzumab antibody titers will be summarized using descriptive statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum).

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

The list of pharmacokinetics parameters is listed in Section 2.1.5.

PK exposures (Cmax and AUClast) for alemtuzumab will be determined using noncompartmental analysis. Values will be reported for individual subjects and summarized using descriptive statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) by study week as appropriate.

Pharmacodynamic endpoints (ie, lymphocyte phenotyping) as described in Section 2.1.6 will be summarized using descriptive statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) at each scheduled study visit. Observed measurements as well as change from baseline will be summarized.

If a linear trend in the values and change from baseline of lymphocyte phenotyping is observed, a mixed model with repeated measures (MMRM) with robust variance estimation will be used to model change from baseline value of lymphocyte phenotyping over time. Baseline lymphocyte phenotyping and analysis study visit will be used as covariates of the model. The estimated changes at each post baseline scheduled visit with its 95% confidence interval will be presented.

Sample SAS code can be found below:

```
proc mixed data=LYM  method=reml;
    class usubjid avisitn;
    model chg  = baseline avisitn/ s;
    repeated avisitn / type=un subject=usubjid r;
    lsmeans avisitn / cl at baseline = &mean;
  run;
```

Correlation between PD endpoints, biomarkers, efficacy assessments, and exploratory endpoints may be explored as appropriate.

2.4.7 Analyses of quality of life (QoL) variables

PedsQL questionnaire

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) and the 95% confidence interval of the means of the total score of PedsQL questionnaire (values and changes from baseline) , when appropriate, will be calculated for each visit or study assessment (baseline, each postbaseline time point). The total score of child report and parent report for children will be analyzed separately.

Paediatric NeuroQoL questionnaire

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) and 95% confidence interval of the means of the physical effects scores (fatigue and pain) and mental effects scores (cognitive function, anxiety, and depression) of Paediatric NeuroQoL questionnaire (values and changes from baseline), when appropriate, will be calculated for each visit or study assessment (baseline, each postbaseline time point).

2.4.8 Analyses of exploratory endpoints

For the exploratory endpoint of T1 weighted lesion counts, observed measurements will be summarized by visit using descriptive statistics including the number of available observations, mean, SD, median, minimum, and maximum. It may be categorized into different levels and summarized using the number and percentage of patients among the safety population.

For the exploratory endpoint of brain volume, observed measurements and change over time from baseline to each postbaseline visit with MRI will be summarized using descriptive statistics including the number of available observations, mean, SD, median, minimum, and maximum.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

Time since first MS diagnosis (years) is calculated as:

(Year of screening -Year of first MS diagnosis) + (month of screening - month of first MS diagnosis)/12

BMI is calculated as:

Weight in kg / (height^2 in meters)

2.5.2 Data handling conventions for secondary efficacy variables

NA

2.5.3 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 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 alemtuzumab administration is missing, all adverse events that occurred on or after the first day of alemtuzumab treatment phase (M0/D1) should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

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

If the assessment of the relationship to alemtuzumab is missing, then the relationship to alemtuzumab 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 > upper limit of normal (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.

2.5.4 Windows for time points

2.5.4.1 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 the date of first alemtuzumab treatment. Selected safety variables will be summarized by the following analysis visits:

- Physical examination and vital signs: Screening, D-7, M0/D1, M4, M8, M12, M15, M18, M21, M24/at EOTP; every 6 months in the safety monitoring phase.
- Clinical chemistry laboratories: Screening, D-7, M4, M8, M12, M15, M18, M21, M24/at EOTP; quarterly in the safety monitoring phase. In addition, only serum creatinine will be assessed at M0/D1, monthly in alemtuzumab treatment phase (Year 1 and 2); monthly in the safety monitoring phase (inclusive of chemistry panel).
- Hematology: Screening, D-7, M0/D1, and monthly in alemtuzumab treatment phase (Year 1 and 2); EOTP, and monthly in the safety monitoring phase.
- Urinalysis: Screening, D-7, monthly in alemtuzumab treatment phase (Year 1 and 2); EOTP, and monthly in the safety monitoring phase.
- Thyroid Function tests: Screening, D-7, quarterly in alemtuzumab treatment phase (Year 1 and 2); EOTP, and quarterly in the safety monitoring phase.
- Pregnancy testing (females only): Screening (blood test), D-7 and M12 (urine test).
- Assessment of ADA: M0/D1 (baseline), post dose M1, M3, M12 (prenext dose), M13, M15, M24/at EOTP; and annually in the safety monitoring phase.

Protocol specified that the time windows for the evaluation of the above clinical safety assessments will be ±7 days, except for the D-7 day visit which should occur between -7 to -1 days prior to M0/D1. All post alemtuzumab treatment period assessments should be completed within ±7 days of the target date. The target dates for the scheduled visits are based on the calendar date of the first day's dosing or the day of enrollment for those patients who receive no treatment. All scheduled visits including those that occurred outside the specified windows will be included in the safety analysis.

A post-baseline scheduled visit will be assigned to the same analysis visit equivalent to it. Data from early withdrawal and unscheduled visits will be assigned to an appropriate analysis visit by using the following windowing scheme.

For D-7 visit, the analysis visit window is between -7 to -1 days. For the first scheduled visit after alemtuzumab treatment, the analysis visit window is between Day 1 to the midpoint of the target dates of the next scheduled visit and itself. For all other post-baseline scheduled visits, the lower bound and the upper bound for the analysis visit windows are defined as the midpoints of the target dates of its adjacent scheduled visits and itself.

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 8 analysis visit will be Month 6 and Month 10 respectively, ie, Month 8 ±2 months. If the early withdrawal visit date for the vital sign assessment falls at Month 9 (ie, between Month 6 and Month 10), then this early withdrawal visit will be assigned to the Month 8 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 target date of analysis visit window will be used in the summary statistics and by visit analyses. If two visits are “tied” before and after the target date, 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.

For safety analyses, all visits up to the end of the study, including those outside the protocol specified windows will be included.

2.5.4.2 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 the date of first alemtuzumab treatment.

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

- MRIs: Screening, D-7, M4, M8, M12, M24/at EOTP, and then annually in the Safety Monitoring Phase.
- EDSS: Screening, D-7, M4, M8, M12, M15, M18, M21, M24/at EOTP; every 6 months in Safety Monitoring Phase.
- Brief Visuospatial Memory Test-Revised (BVMT-R): Screening, D-7, M4, M8, M12, M18, M24/at EOTP; annually in Safety Monitoring Phase.

- Symbol Digit Modality Test (SDMT): Screening, D-7, M4, M8, M12, M18, M24/at EOTP; annually in Safety Monitoring Phase.
- PedsQL and paediatric NeuroQoL questionnaire: Screening, D-7, M4, M8, M12, M18, M24/at EOTP; and annually in Safety Monitoring Phase.

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.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data and vital signs will be included in the by-visit summaries, computation of baseline, and PCSAs.

Unscheduled visit measurements of efficacy endpoints will be included in the efficacy analysis and computation of baseline.

2.5.6 Pooling of centers for statistical analyses

NA

2.5.7 Statistical technical issues

NA

3 INTERIM ANALYSIS

No interim analysis planned.

4 DATABASE LOCK

There will be two database locks in this study. The first database lock will be after the last patient has completed efficacy assessments including MRI at the end of Period 2. The second database lock will be after the last patient has completed the safety monitoring phase (M60).

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

1. Verhey L, Signori A, Arnold D, Amit B, Sadovnick A, Marrie R, et al. Clinical and MRI activity as determinants of sample size for pediatric multiple sclerosis trials; Neurology. 2013 Oct;81(14):1215-21.

2. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44:235:291-303.

3. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45:13-23.

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix B: Summary of statistical analysis

Appendix A Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
ECG parameters			Ref. : Rijnbeek P.R. et al., Eur Heart J 2001; Davignon A. et al., Ped Cardiol 1979/1980; Semizel E.et al., Cardiol Young 2008; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009
HR	Birth/0 to 27 days old (Neonates)	≤90 bpm and decrease from baseline ≥20 bpm ≥190 bpm and increase from baseline ≥20 bpm	
	28 days/1 month to 23 months old (Infants)	≤80 bpm and decrease from baseline ≥20 bpm ≥175 bpm and increase from baseline ≥20 bpm	
	24 months/2 years to <6 years old (Children)	≤75 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm	
	6 to <12 years old (Children)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
	12 to 16/18 years old (Adolescents)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	Birth/0 to 27 days old (Neonates)	≥120 ms	
	28 days/1 month to 23 months old (Infants)	≥140 ms	
	24 months/2 years to <6 years old (Children)	≥160 ms	
	6 to <12 years old (Children)	≥170 ms	
	12 to 16/18 years old (Adolescents)	≥180 ms	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
QRS	Birth/0 to 27 days old (Neonates)	≥85 ms	
	28 days/1 month to 23 months old (Infants)	≥85 ms	
	2 to <6 years old (Children)	≥95 ms	
	6 to <12 years old (Children)	≥100 ms	
	12 to 16/18 years old (Adolescents)	≥110 ms	
QTc	Birth/0 to <12 years old (Neonates, Infants, Children)	Absolute values (ms) Borderline: 431-450 ms Prolonged*: >450 ms Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms	**To be applied to QTcF** *QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings.
	12 to 16/18 years old (Adolescents)	Borderline: 431-450 ms (Boys); 451-470 ms (Girls) Prolonged*: >450 ms (Boys); >470 ms (Girls) Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Vital Signs			Ref. : Kidney Disease Outcomes Quality Initiatives (KDOQI) Guideline 13; 1996; The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, Pediatrics 2004; Bowman E & Fraser S Neonatal Handbook 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Pediatric respiratory rates http://www.health.ny.gov/
SBP	Birth/0 to 27 days old (Neonates)	≤60 mmHg and decrease from baseline ≥20 mmHg ≥85mHg and increase from baseline ≥20 mmHg	Based on definition of Hypertension as average SBP or DBP ≥95th percentile for gender, age, and height on ≥3 occasions
	28 days/1 month to 23 months old (Infants)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥98 mmHg and increase from baseline ≥20 mmHg	
	24 months/2 years to <6 years old (Children)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥101mHg and increase from baseline ≥20 mmHg	
	6 to <12 years old (Children)	≤80 mmHg and decrease from baseline ≥20 mmHg ≥108 mmHg and increase from baseline ≥20 mmHg	
	12 to 16/18 years old (Adolescents)	≤90 mmHg and decrease from baseline ≥20 mmHg ≥119mmHg and increase from baseline ≥20 mmHg	
DBP	Birth/0 to 27 days old (Neonates)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥50mHg and increase from baseline ≥10 mmHg	
	28 days/1 month to 23 months old (Infants)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥54mHg and increase from baseline ≥10 mmHg	
	24 months/2 years to <6 years old (Children)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥59mHg and increase from baseline ≥10 mmHg	
	6 to <12 years old (Children)	≤48 mmHg and decrease from baseline ≥10 mmHg	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
		≥72mHg and increase from baseline ≥10 mmHg	
	12 to 16/18 years old (Adolescents)	≤54 mmHg and decrease from baseline ≥10 mmHg ≥78mHg and increase from baseline ≥10 mmHg	
Orthostatic hypotension	All age ranges	SBP : St — Su ≤ - 20 mmHg DBP : St — Su ≤ - 10 mmHg	
Temperature	All age ranges	Rectal, ear or temporal artery: ≥100.4 °F/38.0 °C Oral or pacifier: ≥99.5 °F/37.5 °C Axillary or skin infrared: ≥99 °F/37.2 °C	Ear temperature not accurate below 6 months of age
Respiratory rate	Birth/0 to 27 days old (Neonates)	<30 per minutes >60 per minutes	Based on normal range
	28 days/1 month to 23 months old (Infants)	<24 per minutes >40 per minutes	
	24 months/2 years to <6 years old (Children)	<22 per minutes >34 per minutes	
	6 to <12 years old (Children)	<18 per minutes >30 per minutes	
	12 to 16/18 years old (Adolescents)	<12 per minutes >20 per minutes	
Sa02	All age ranges	≤95%	
Weight	All ranges	≥5% weight loss from baseline	Based on identification of trends in the child's growth with a series of visits WHO Multicentre Reference Study Group, 2006; Center for Disease Control. Growth chart 2007

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Clinical Chemistry			Ref Molleston JP et al. JPGN 2011; Moritz et al., Pediatrics 1999; Moritz et al., Pediatr Nephrol 2005 ; Sedlacek et al., Seminars in Dialysis 2006) Gong G et al. Clinical Biochemistry 2009; Masilamani et al. Arch Dis Children 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009
ALT/SGPT	All age ranges	≥3 ULN By distribution analysis: ≥3 ULN ≥5 ULN ≥10 ULN ≥20 ULN	Based on normal ranges: 6 to 50 U/L (0-5 days), 5 to 45 U/L (1-19 years)
AST/SGOT	All age ranges	≥3 ULN By distribution analysis: ≥3 ULN ≥5 ULN ≥10 ULN ≥20 ULN	Based on normal ranges: 35 to 140 U/L (0-5 days), 15 to 55 U/L (1-9 years), 5 to 45 U/L (10-19 years)
Alkaline Phosphatase	All age ranges	≥1.5 ULN	Based on normal ranges: 145 to 420 U/L (1-9 years), 130 to 560 U/L (10-11 years), 200 to 495 U/L (Boys 12-13 years), 105 to 420 U/L (Girls 12-13 years), 130 to 525 U/L (Boys 14-15 years), 70 to 130 U/L (Girls 14-15 years), 65 to 260 U/L (Boys 16-19 years), 50 to 130 U/L (Girls 16-19 years)
Total Bilirubin	All age ranges	≥1.3 ULN	CF = mg x 1.7 = µmol Based on normal ranges: <6 mg/dL (Term 0-1 day), <8 mg/dL (Term 1-2 days), <12 mg/dL (Term 3-5 days), <1 mg/dL (Term >5 days)

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Conjugated Bilirubin	All age ranges	>35% Total Bilirubin and TBILI≥1.3 ULN	CF = mg x 1.7 = µmol Based on normal range: 0 to 0.4 mg/dL
ALT and Total Bilirubin	All age ranges	ALT ≥3 ULN and Total Bilirubin ≥2 ULN	
CPK	All age ranges	≥3 ULN	
Creatinine	Birth/0 to <6 years old (Neonates, Infants, Children)	>53 µmol/L or 0.6 mg/dL	CF = mg x 8.8 = µmol Based on normal ranges: ≤0.6 mg/dL (0-1 year), 0.5 to 1.5 mg/dL (1 to 16/18 years)
	6 years to <12 years old (Children)	≥90 µmol/L or 1.1mg/dL	
	12 years to 16/18 years old (Adolsecents)	≥132µmol/L or 1.5mg/dL	
Creatinine Clearance	All age ranges	50 % of normal <60 mL/min/1.73m^2 (After 1 year old)	Based on GFR Bedside Schwartz Formula Based on normal ranges: 20 to 50 (<8 days), 25 to 80 (8 days to 1 month), 30 to 90 (1-6 months), 40 to 115 (6-12 months), 60 to 190 (12-23 months), 90 to 165 (2-12 years), 80-120 (After 12 years)
Uric Acid	All age ranges	≤2.0 mg/dL or 119 µmol/L ≥8.0 mg/dL or 476 µmol/L	CF = mg x 5.95 = µmol Based on normal ranges: 2.4 to 6.4 mg/dL
Blood Urea Nitrogen (BUN)	Birth/0 to 27 days old (Neonates)	≥4.3 mmol/L or 12 mg/dL	CF = g x 16.66 = mmol Based on normal ranges: 3 to 12 mg/dL (NN; 5 to 18 mg/dL (other classes of age)
	28 days/1 month to 16/18 years old (Infants, Children, Adolescents)	≥6.4 mmol/L or 18 mg/dL	
Chloride	All age ranges	≤80 mmol/L or 80 mEq/L ≥115 mmol/L or 115 mEq/L	CF = 1 Based on normal range: 98 to 106
Sodium	All age ranges	≤129 mmol/L or 129 mEq/L ≥150 mmol/L or 150 mEq/L	CF = 1 Based on normal range : 134 to 146

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Potassium	Birth/0 to 27 days old (Neonates)	≤3.0 mmol/L or 3.0 mEq/L ≥7.0 mmol/L or 7.0 mEq/L	CF = 1 Based on normal ranges: 3.0 to 7.0 (NN); 3.5 to 6.0 (Infants); 3.5 to 5.0 (>Infants)
	28 days/1 month to 23 months old (Infants)	≤3.5 mmol/L or 3.5 mEq/L ≥6.0 mmol/L or 6.0 mEq/L	
	24 months/2 years to 16/18 years old (Children, Adolescents)	≤3.5 mmol/L or 3.5 mEq/L ≥5.5 mmol/L or 5.5 mEq/L	
Bicarbonate	All age ranges	≤16 mmol/L or 16 mEq/L ≥30 mmol/L or 30 mEq/L	CF = 1 Based on normal range: 18 to 26
Calcium total	All age ranges	≤2.0 mmol/L or 8.0 mg/dL ≥2.9 mmol/L or 11.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 8.4 to 10.9 mg/dL
Calcium ionized	All age ranges	≤1.0 mmol/L or 4.0 mg/dL ≥1.4 mmol/L or 5.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 4.0 to 5.1 mg/dL
Total Cholesterol	All age ranges	≥6.20 mmol/L or 240 mg/dL	CF = g x 2.58 = mmol Based on normal ranges: 45 to 182 mg/dL (1-3 years), 109 to 189 mg/dL (4-6 years), 126 to 191 mg/dL (Boys 6-9 years), 122 to 209 mg/dL (Girls 6-9 years), 130 to 204 mg/dL (Boys 10-14 years), 124-217 mg/dL (Girls 10-14 years), 114 to 198 mg/dL (Boys 15-19 years), 125 to 212 mg/dL (Girls 14-19 years)
Triglycerides	All age ranges	≥4.0 mmol/L or 350 mg/dL	After >12 hours of fast) CF = g x 1.14 = mmol Based on normal ranges: 30 to 86 mg/dL (Boys 0-5 years), 32 to 99 mg/dL (Girls 0-5 years), 31-108 mg/dL (Boys 6-11 years), 35 to 114 mg/dL (Girls 6-11 years), 36 to 138 mg/dL (Boys 12-15 years), 43 to 138 mg/dL (Girls 12-15 years), 40 to 163 mg/dL (Boys 16-19 years), 40-

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
			128 mg/dL (Girls 16-19 years)
Lipasemia	All age ranges	≥2 ULN	Based on normal ranges: 3 to32 U/L (1-18 years)
Amylasemia	All age ranges	≥2 ULN	Based on normal ranges: 10 to 30 U/L (NN), 10 to 45 U/L (1-18 years)
Glucose	All age ranges	Hypoglycaemia <2.7 mmol/L or 50 mg/dL Hyperglycaemia ≥7 mmol/L or 120 mg/dL (fasted after >12 hours of fast); ≥10.0 mmol/L or 180 mg/dL (unfasted)	CF = g x 5.55 = mmol Based on normal ranges: 50 to 90 mg/dL (NN), 60 to 100 mg/dL (Child)
CRP	All age ranges	>2 ULN or >10 mg/L (if ULN not provided)	Based on normal ranges: <6 mg/L

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Hematology			Common Terminology Criteria for Adverse Events (CTCAE) v3.0, 2006 ; Division of Microbiology and Infections Diseases Pediatric Toxicity Tables, 2007 ; Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2004; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Family Practice Notebook, LLC, 2012; Tietz NW et al. Clinical Guide to Laboratory Testing, 3rd edition 1995
WBC	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4,000 /mm^3 >25.0 GIGA/L or 25,000 /mm^3	To be used if no differential count available Based on normal ranges: 9,000 to 30,000 /mm^3 (birth), 9,400 to 38,000 /mm^3 (0-1 day), 5,000 to 21,000 /mm^3 (1 day-1 month), 6,000 to 17,500 /mm^3 (1 month-2 years), 5,000 to 17,000 /mm^3 (2-6 years), 4,500 to 15,500 /mm^3 (6-11 years), 4,500 to 13,500 /mm^3 (11-18 years)
	28 days/1 month to 23 months old (Infants)	<4.0 GIGA/L or 4,000 /mm^3 >20.0 GIGA/L or 20,000 /mm^3	
	24 months/2 years to <6 years old (Children)	<3.0 GIGA/L or 3,000 /mm^3 >16.0 GIGA/L or 16,000 /mm^3	
	6 to <12 years old (Children)	<5.0 GIGA/L or 5,000 /mm^3 >17.0 GIGA/L or 17,000 /mm^3	
	12 to 16/18 years old (Adolescents)	<4,5 GIGA/L or 5,000 /mm^3 >13.5 GIGA/L or 17,000 /mm^3	
Lymphocytes (ALC)	Birth/0 to 27 days old (Neonates)	<1.2 GIGA/L or 1,200 /mm^3 >17.0 GIGA/L or 17,000 /mm^3	Based on normal ranges: 2,000 to 11,500 /mm^3 (0-1 days), 2,000 to 17,000 /mm^3 (2 days-1 month), 3,000 to 13,500 /mm^3 (1 month-2 years), 1,500 to 9,500 /mm^3 (2-6 years), 1,500 to 8,000 /mm^3 (6-10 years), 1,200 to 5,200 /mm^3 (10-18 years)
	28 days/1 month to 23 months old (Infants)	<2.0 GIGA/L or 2,000 /mm^3 >13.5 GIGA/L or 13,500 /mm^3	
	24 months/2 years to <6 years old (Children)	<1.0 GIGA/L or 1,000 /mm^3 >9.5 GIGA/L or 9,500 /mm^3	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
	6 to <12 years old (Children)	<1.0 GIGA/L or 1,000 /mm^3 >8.0 GIGA/L or 8,000 /mm^3	
	12 to 16/18 years old (Adolescents)	<0.6 GIGA/L or 600 /mm^3 >6.0 GIGA/L or 6,000 /mm^3	
Absolute Neutrophil Count (ANC)	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4,000 /mm^3 (1 day old) <1.5 GIGA/L or 1,500 /mm^3 (2-7 days old) <1.25 GIGA/L or 1,250 /mm^3 (>7 day-1 month old) >1 ULN	Based on normal ranges: 5,000 to 28,000 /mm^3 (0-1 day), 1,000 to 10,000 (1 day-1 month), 1,000 to 8,500 (1-12 months), 1,500 to 8,500 (1 to 6 years), 1,500 to 8,000 (6 to 10 years), 1;800 to 8,000 (10 to 18 years)
	28 days/1 month to 23 months old (Infants)	<1.0 GIGA/L or 1,000/mm^3 (1-3 months) <1.2 GIGA/L or 1,200 /mm^3 (3-24 months) >1 ULN	
	24 months/2 years to <6 years old (Children)	<1.2 GIGA/L or 1,200 /mm^3 >1 ULN	
	6 to <12 years old (Children)	<1.2 GIGA/L or 1,200 /mm^3 >1 ULN	
	12 to 16/18 years old (Adolescents)	<1.2 GIGA/L or 1,200 /mm^3 >1 ULN	
Eosinophils	All age ranges	>0.5 GIGA/L or 500 /mm^3 Or >ULN if ULN >0.5 GIGA/L or 500 /mm^3	Based on normal ranges: 0 to 500 /mm^3 (0-1 month), 0 to 300 /mm^3 (1 month-18 years)
Hemoglobin	Birth/0 to 27 days old (Neonates)	<86 mmol/L or 12.0 g/dL or any decrease $\geq$0.31 mmol/L or 2 g/dL	CF = g x 1.55 = mmol Based on normal ranges: 15 to 20 g/dL (0-3 days), 12.5 to 18.5 g/dL (1-2 weeks), 10.0 to 13.0 g/dL (1-6 months), 10.5 to 13.0 g/dL (7 months-2 years), 11.5 to 13.0 g/dL (2-5 years), 11.5 to 14.5 (5-8 years), 12.0 to 15.2 g/dL (13-18 years)
	28 days/1 month to 23 months old (Infants)	<1.40 mmol/L or 9.0 g/dL or any decrease $\geq$0.31 mmol/L or 2 g/dL	
	24 months/2 years to <16/18 years old	<1.55 mmol/L or10.0 g/dL or any decrease $\geq$0.31 mmol/L	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
	(Children, Adolescents)	or 2 g/dL	
Hematocrit	Birth/0 to 27 days old (Neonates)	<0.39 l/l or 40% >0.61 l/l or 47%	CF = % x 0.01 = l/l Based on normal ranges: 45 to 61% (0-3 days), 39 to 57% (1-2 weeks), 29 to 42% (1-6 months), 33 to 38% (7 months-2 years), 34 to 39 % (2-5 years), 35 to 42 % (5-8 years); 36 to 47 % (13-18 years)
	28 days/1 month to 23 months old (Infants)	<0.29 l/l or 29% >0.42 l/l or 42%	
	24 months/2 years to <16/18 years old (Adolescents)	<0.32 l/l or 32% >0.47 l/l or 47%	
Platelets	All age ranges	<100 GIGA/L or 100,000 /mm^3 >700 GIGA/L or 700,000 /mm^3	Based on normal ranges: 250,000 to 450,000 /mm^3 (NN); 300,000 to 700,000 /mm^3 (1-6 months), 250,000 to 600,00 /mm^3 (7 months-2 years), 250,000 to 550,000 /mm^3 (2-12 years), 150,000 to 450,000 /mm^3 (13-18 years)
Urinalysis			Patel HP, Pediatr Clin N Am, 2006
Ketonuria	All age ranges	Presence	Semi-quantitative methods
Glycosuria	All age ranges	Presence	Semi-quantitative methods
Hematuria	All age ranges	$\geq$1+	Semi-quantitative methods
Proteinuria	All age ranges	$\geq$1+	Semi-quantitative methods

Appendix B Summary of statistical analysis

EFFICACY ANALYSIS

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoint					
The number of new or enlarging T2 lesions during continuation of prior DMT (Period 1) and in an equal-length period after the first course of alemtuzumab treatment (Period 2)	mITT	Repeated measures negative binomial regression model with GEE with baseline T2 lesion count, geographic region and treatment status as covariates	No	No	No
Secondary endpoints					
The number of patients with new or enlarging T2 lesions during period 1 and period 2	mITT	Repeated measures logistic regression model with GEE with baseline T2 lesions count, treatment status and geographic region as covariates	No	No	No
EDSS	mITT	Descriptive statistics for the change from baseline in observed EDSS scores	No	No	No
Annualized relapse rate (ARR) at year 2	mITT	Negative binomial regression model	No	No	No
Cognition test scores: Brief Visuospatial Memory Test – Revised (BVMT-R) and Symbol Digit Modality Test	mITT	Descriptive statistics and 95% CI for the change from baseline in cognitive outcomes	No	No	No
Other Secondary endpoints					
pharmacokinetic variables	mITT	Descriptive statistics	No	No	No
pharmacodynamic variables	mITT	Descriptive statistics for the change from baseline in pharmacodynamics variables	No	No	Mixed model with repeated measures (MMRM) will be used to model change from baseline value of lymphocyte phenotyping over time.
Quality of life (QoL)	mITT	Descriptive statistics and 95% CI for the change from baseline in QoL outcomes	No	No	No

SAFETY ANALYSIS

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Adverse events	Safety	Follow safety guidelines	No	No	No
Laboratory variables	Safety	Descriptive statistics and plots for the change from baseline in laboratory variables Incidence of PCSAs	No	No	Listings of PCSAs
Vital sign variables	Safety	Descriptive statistics for the change from baseline in vital sign variables and vital signs during and immediately following IV administration from preinfusion Incidence of PCSAs	No	No	Listings of abnormal findings/values from vital signs as well as from physical examination inclusive of body weight and height, as well as Tanner stage in pediatric patients
Antidrug antibody formation (ADA)	Safety	Descriptive statistics for the change from baseline in ADA	No	No	No

EFC13429 16.1.9 Statistical analysis plan

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval Clinical Approval	[redacted]