1.2 STUDY FLOW CHART

1.2.1 Schedule of events Part 1 (Year 1)

Table 1 - Schedule of events in Year 1

	DMT Phase			Alemtuzumab treatment phase													Unscheduled visits
Visit[a]	**Scrn. visit**[b]	**Period 1/ Prior DMT phase**		**M0/ D1**[u]	**M1**	**M2**	**M3**	**M4**	**Period 2**				**M9**	**M10**	**M11**	**M12**	**Relapse visit**[d]
		Eligibility confirmation on M-4	**D-14 to D-7**[c]						**M5**	**M6**	**M7**	**M8**					
Visit number	V1	V2	V3	V4v	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16v	
Entry procedures																	
Informed consent & assent	X																
Inclusion/exclusion criteria review	X																
Patient demography[e]	X																
Medical/Surgical history[f]	X																
Prior Medication history	X																
Eligibility confirmation		X															
Phone call[g]		X[g]															
Hepatitis B/C Serology testing	X																
Tuberculosis test (eg, Quanticore)[h]	X																
Other Serology tests as required[i]	X																
HPV[j](yearly)	X																
Treatment:																	
Confirm eligibility for alemtuzumab Rx			X													X	
Alemtuzumab administration				X												X	
Premedication administration				X[c]												X[c]	
Acyclovir administration[k]				X												X	
Compliance	X	X	X	X												X	
Concomitant medications	←															→	
Prior DMT	←		→														
Discontinue prior DMT			X														

	DMT Phase			Alemtuzumab treatment phase												Unscheduled visits
Visit[a]	**Scrn. visit**[b]	**Period 1/ Prior DMT phase**		**M0/ D1**[u]	**M1**	**M2**	**M3**	**M4**	**Period 2**				**M9**	**M10**	**M11**	**M12**	**Relapse visit**[d]
		Eligibility confirmation on M-4	**D-14 to D-7**[c]						**M5**	**M6**	**M7**	**M8**					
Visit number	V1	V2	V3	V4v	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16v	
Efficacy:																	
EDSS	X		X					X				X				X	X
Brain MRI[l]	X		X					X				X				X	
SDMT	X		X					X				X				X	
BVMT-R test	X		X					X				X				X	
PedsQL (QoL Questionnaire)/Ped. Neuro-QoL (sub-comp.)[m]	X		X					X				X				X	
Safety:																	
Physical examination[n]	X		X	X				X				X				X	X
Clinical chemistry laboratories[o]	X		X					X				X				X	
Hematology (Differential CBC)[o]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Thyroid Function Tests[p]	X		X				X			X			X			X	
Urinalysis[q]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	
Serum Creatinine and alanine aminotransferase				X	X	X	X		X	X	X		X	X	X		
Lymphocyte phenotyping	X		X		X			X				X				X	
Samples for antibodies to Study Drug				X	X		X									X	
Tanner Staging[r]	X															X	
AE/SAE recording (if any)	←																→
Vital Signs	X		X	X[s]				X				X				X[s]	X
Laboratory testing:																	
Pregnancy test (for female patients of childbearing potential[t]	X		X													X	
PK sampling[u]				X[u]	X[u]	X[u]										X[u]	
Immune Marker Sampling (optional)				X				X								X	

Abbreviations: AE: adverse event; BVMT-R: brief visuospatial memory test-revised, CBC: complete blood count; D: day; DMT: disease modifying therapy; EDSS: Expanded Disability Status Scale; M month(s); MRI: magnetic resonance imaging; Neuro-QoL: quality of life in neurological disorders; Ped: paediatric; PK: pharmacokinetics; QoL: quality of life; SAE: serious adverse event; Scrn: screening; SDMT: symbol digit modality test

a Recommended windows: The window for obtaining samples and performing assessments at any given visit will be ±7 days, except for the D-14 to D-7 day visit which should occur between -7 to -1 days prior to M0/D1and for Visit 16 (M12) which can occur within -7 days or +30 days of the scheduled visit. All post M0/D1 treatment period assessments should be completed within ±7 days of the scheduled visit date relative to the M0/D1 visit.

a Recommended windows: The window for obtaining samples and performing assessments at any given visit will be ±7 days, except for the D-14 to D-7 visit which should occur between -7 to -1 days prior to M0/D1. All post M0/D1 treatment period assessments should be completed within ±7 days of the scheduled visit date relative to the M0/D1 visit.

b This visit is only required for subjects that have a suspected relapse, and should occur within 7 days following the occurrence of the clinical event.

c The MRI assessments will be available to investigators to assess safety.

d PedsQL questionnaire (Paediatric Quality of Life Inventory) will be completed by patients/parents based on questionnaire recommendations. Peds NeuroQoL is a quality of life measurement developed for neurological disorders and consists of short form questions for multiple domains. Specific sub-domains will be utilized.

e The date of first menarche should be captured if applicable. 'A standard physical examination for clinical and neurological assessments which includes examination of major body systems, height and body weight.

f Hematology and differential panel (hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin, white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets) Complete chemistry panel (glucose, creatinine, blood urea nitrogen (BUN), sodium, potassium, chloride, bicarbonate, magnesium, calcium uric acid, aspartate aminotransferase (AST), ALT, gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total bilirubin, direct/indirect bilirubin, alkaline phosphatase, inorganic phosphorus, total protein, albumin, globulin, albumin/globulin ratio, triglycerides, cholesterol and creatine phosphokinase (CPK). It is preferred that CBCs with platelet count, and monitoring for any cytopenia as well as serum creatinine, and urinalysis with microscopy be analyzed at the central laboratory, but under special circumstances (eg, if patient is unable to visit the study center weekly or monthly, or results are needed urgently), the assay may be performed at a local laboratory provided that test results are entered into the e-CRF in a timely manner. However for study visits that only require laboratory sampling, home nursing or local laboratories may be used for sample collection and shipment to the central laboratory, as per local regulations. These visits are to be followed by telephone calls from the study site to assess AEs and concomitant medications.

g Thyroid stimulating hormone (TSH) & if abnormal T3 & T4 performed on the existing samples. However for study visits that only require laboratory sampling, home nursing or local laboratories may be used for sample collection and shipment to the central laboratory, as per local regulations. These visits are to be followed by telephone calls from the study site to assess AEs and concomitant medications.

h Urinalysis (pH, ketones, cells, protein, glucose, blood, urobilinogen, bilirubin, microscopic sediment, specific gravity).However for study visits that only require laboratory sampling, home nursing or local laboratories may be used for sample collection and shipment to the central laboratory, as per local regulations. These visits are to be followed by telephone calls from the study site to assess AEs and concomitant medications.

i Tanner stage to be assessed as noted until complete sexual maturity.

j Testing will be conducted for human papillomavirus (HPV) infection as and when recommended by local public health authorities. If the testing is positive, the patient may be eligible after the condition has resolved as per the Investigator opinion (eg, follow-up HPV test is negative or cervical abnormality has been effectively treated). An annual follow-up is recommended.

k For details on PK sampling, refer to Section 1.2.5.

c The MRI assessments will be available to investigators to assess safety.

d At these visits, in some countries, there is an option for the nurse to obtain samples for clinical chemistry laboratories, hematology, thyroid function tests, urinalysis and serum creatinine at the patient's home. This will therefore be considered a home visit. In this case, a phone call from the Investigator to review AE and concomitant medication is allowed. If home nursing cannot be implemented, local laboratories may be used for sample collection and shipment to the central laboratory, as per local regulations. These visits are to be followed by telephone calls from the study site to assess AEs and concomitant medications.

e Complete chemistry panel (glucose, creatinine, blood urea nitrogen (BUN), sodium, potassium, chloride, bicarbonate, magnesium, calcium uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total bilirubin, direct/indirect bilirubin, alkaline phosphatase, inorganic phosphorus, total protein, albumin, globulin, albumin/globulin ratio, triglycerides, cholesterol and creatine phosphokinase (CPK). It is preferred that CBCs with platelet count, and monitoring for any cytopenia as well as serum creatinine, and urinalysis with microscopy be analyzed at the central laboratory, but under special circumstances (eg, if patient is unable to visit the study center weekly or monthly, or results are needed urgently), the assay may be performed at a local laboratory provided that test results are entered into the e-CRF in a timely manner.

f Hematology and differential panel (hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin, white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets). It is preferred that CBCs with platelet count, and monitoring for any cytopenia as well as serum creatinine, and urinalysis with microscopy be analyzed at the central laboratory, but under special circumstances (eg, if patient is unable to visit the study center weekly or monthly, or results are needed urgently), the assay may be performed at a local laboratory provided that test results are entered into the e-CRF in a timely manner.

g Urinalysis (pH, ketones, protein, glucose, blood, urobilinogen, bilirubin, microscopic sediment, specific gravity). However for study visits that only require laboratory sampling, home nursing or local laboratories may be used for sample collection and shipment to the central laboratory, as per local regulations. These visits are to be followed by telephone calls from the study site to assess AEs and concomitant medications.

h For alemtuzumab-treated patients, abnormal serum creatinine and/or urinalysis findings should be followed according to the guidelines provided in the protocol (guidelines will be based on current adult program guidelines)

i Testing will be conducted for human papillomavirus (HPV) infection as and when recommended by local public health authorities. If the testing is positive, the patient may be eligible after the condition has resolved as per the Investigator opinion (eg, follow-up HPV test is negative or cervical abnormality has been effectively treated). An annual follow-up is recommended.

2 TABLE OF CONTENTS

IWRS:	interactive web response system
LLN:	lower limit of normal
mITT:	modified intent to treat
MRI:	magnetic resonance imaging
MS:	multiple sclerosis
NCI:	National Cancer Institute
NIMP:	noninvestigational medicinal product
NSAID:	nonsteroidal anti-inflammatory drug
PD:	pharmacodynamic(s)
PDCO:	Paediatric Committee
PI:	Principal Investigator
PIP:	Paediatric Investigation Plan
PK:	pharmacokinetic(s)
PV:	pharmacovigilance
QoL:	quality of life
RRMS:	relapsing remitting multiple sclerosis
SAC:	Scientific Advisory Committee
SC:	subcutaneous(ly)
SD:	standard deviation
SDMT:	Symbol Digit Modality Test
$T_{1/2z}$:	terminal half-life associated with the terminal slope
TB:	tuberculosis
TEAEs:	treatment emergent adverse events
T_{max}:	time to reach C_{max}
uRTI:	upper respiratory tract infection
UTI:	urinary tract infection
WBC:	white blood cell

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

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 RRMS with disease activity on prior DMT.

The study will consist of:

- **Screening period** (0-28 days prior to M-4) **-** Patients and parents will receive information on the study and on alemtuzumab. Inclusion/exclusion criteria will be reviewed. After informed consent signature, screening assessments for eligibility will be performed. Screening assessments may require more than one visit within the screening period which may last a maximum of 28 days.
- **Prior DMT phase (approximately 4 months): M-4 to M0**
  - **Eligibility confirmation visit:** At the end of the screening period (at M-4) patients/parents will come to the site to confirm patient is eligible for the study. Investigator will check that all assessment allow patient inclusion. During this visit patients will be reminded to continue their prior DMT (limited to interferon or GA only).
  - **From M-4 visit to D-14 to D-7:** Phone calls (approximately every month) will be done, to remind patients to continue on their DMT and check patient status.
  - **Day -14 to D-7 visit**: Investigator will confirm patient is eligible for alemtuzumab administration and will tell the patient to discontinue current DMT 7 days prior to administration of first dose of alemtuzumab at Month 0.
- **Alemtuzumab treatment phase** (approximately 2 years) – This phase starts with administration of first dose of alemtuzumab at M0, after discontinuation of current DMT, and ends at M24. The second dose of alemtuzumab will be administered at M12. The MRI based primary efficacy endpoint will be assessed over a 4 month period during this 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 (see graphic study design [Section 1.1]).
- **Safety monitoring phase** (approximately 3 years) – 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: end of study (EOS) refers to the end of the safety monitoring phase (see graphic study design [Section 1.1]).

In addition, and for the primary endpoint assessment, two periods have been defined:

- **Period 1**: will occur from M-4 up to M0. A baseline MRI will be performed close to M-4 during the screening period and another at Visit 3. Both MRI will be taken while patients are on their prior DMT. 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. It is important to ensure that these 2 MRI assessments are performed 4 months (±7 days) apart.

  These two periods will be compared for the primary endpoint analysis.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The maximum study duration per patient will be approximately 5 years and 5 months:

- **Screening period:** 0-28 days prior to M-4 from signed informed consent to eligibility confirmation.
- **Prior DMT phase**: approximately 4 months from signed informed consent and screening qualification to prior DMT discontinuation. **Alemtuzumab treatment phase**: approximately 2 years, from first dose alemtuzumab administration to one year after last dose of alemtuzumab administration.
- **Safety monitoring phase:** approximately 3 years to complete the 48 months safety follow-up post last treatment with alemtuzumab.

6.2.2 Determination of end of clinical trial (all patients)

The EOS is defined as being the “last patient last visit” planned with the protocol. The last patient visit will be considered when the last patient has completed safety monitoring phase (M60).
The Sponsor reserves the right to discontinue the study at any time.

6.3 INTERIM ANALYSIS

A partial database lock will be done after the last patient has completed efficacy assessments including MRI at the end of Period 2. This database lock will allow comparing lesion counts between Period 1 (M-4 to M0) and Period 2 (M4-M8). No formal interim analysis will be performed.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Name of the Investigational Medicinal Product (IMP):

Alemtuzumab.

Pharmaceutical form:

Concentrate for solution for infusion (sterile concentrate). Each vial contains 12 mg/1.2 mL of solution.

Dose of drug per administration:

First course: at Month 0 for 5 consecutive days

Calculation of the dose used will be determined based on patient weight taken at the first infusion visit, of the first course, during the physical examination:

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

Second course: at Month 12 for 3 consecutive days

Calculation of the dose used will be determined based on patient weight taken at the first infusion visit, of the second course, during the physical examination:

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

Route of administration:

IV infusion.

8.1.1 Administration

Alemtuzumab will be administered only after a decision from the Study Investigator.

First course: Alemtuzumab will be administered by IV infusions for 5 consecutive days at Month 0 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.

MRI should not be conducted within 2 weeks of steroid administration due to potential interference with MRI assessment.

9.2 SECONDARY ENDPOINTS

Secondary endpoints include the efficacy, quality of life and pharmacokinetic/Pharmacodynamic endpoints are listed below, and will be assessed as shown in Section 9.2.1 and Section 9.2.2:

Efficacy:

- 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).
- EDSS (descriptive analysis, ie percentages of stable/improved/worsened since the end of Period 1).
- Annualized relapse rate (ARR) at Year 2.
- Cognition test scores: Brief Visuospatial Memory Test – Revised (BVMT-R) and Symbol Digit Modality Test (SDMT); administered at least every 6 months over 2 years.

Quality of life:

- Established generic paediatric QoL measures administered every 6 months over 2 years.

Pharmacokinetics/Pharmacodynamics:

- PK serum concentration and PK parameters (C_{max}, T_{max}, AUC, AUC_{last}, $T_{1/2z}$) calculated where possible.
- PD assessment including lymphocyte subsets.

9.2.1 Secondary efficacy endpoints

9.2.1.1 Expanded disability status scale

Patient disability will be evaluated using the EDSS (Appendix D), which has long been considered the standard for assessing disability in patients with MS (19).

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.

9.2.1.2 Annualized relapse rate at Year 2

Subjects/parents/guardians will be instructed to contact their Investigator immediately should any symptoms suggestive of an MS relapse appear. The subject must be examined as soon as possible, within 7 days from the onset date of the relapse.

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 (see AE Section 10.4.3).

9.2.1.3 Cognition test scores

9.2.1.3.1 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 patients 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. Central scoring will be performed by an independent rater who is blinded to treatments (ie, current DMT or alemtuzumab).

Table 8 - List of pharmacokinetic parameters and definitions

Parameters	Drug/Analyte	Matrix	Definition/Calculation
C_{max}	Alemtuzumab	Serum	Maximum serum concentration observed
T_{max}	Alemtuzumab	Serum	Time to reach C_{max}
AUC_{last}	Alemtuzumab	Serum	Area under the cumulative serum concentration versus time curve calculated using the trapezoidal method from time zero to the real time t_{last}
AUC	Alemtuzumab	Serum	Area under the cumulative serum concentration versus time curve extrapolated to infinity according to the following equation: $AUC = AUC_{last} + \frac{C_{last}}{\lambda_Z}$ Values with percentage of extrapolation >30% will not be reported
$t_{1/2z}$	Alemtuzumab	Serum	Terminal half-life associated with the terminal slope (λz) determined according to the following equation: $t_{1/2Z} = \frac{0.693}{\lambda_z}$ where λz is the slope of the regression line of the terminal phase of the cumulative serum concentration versus time curve, in semi-logarithmic scale. Half-life is calculated by taking the regression of at least 3 points.

9.2.2.2 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.

9.2.2.2.1 Assessment methods

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 screening, D-14 to D-7, M1, M4, M8, M12, M13, M15, M18, M21, M24/at EOTP; annually in Safety Monitoring Phase.

9.2.2.3 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. The PedsQL Measurement Model integrates seamlessly both generic core scales and disease-specific modules into one measurement system.

The 23-item PedsQL Generic Core Scales (Appendix F) were designed to measure the core dimensions of health as delineated by the World Health Organization, as well as role (school) functioning.

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).

PedsQL and paediatric NeuroQoL questionnaire will be assessed at Screening, D-14 to D-7, M4, M8, M12, M18, M24/at EOTP; and annually in Safety Monitoring Phase.

9.3 SAFETY ENDPOINTS

Safety endpoints will be assessed by:

- AE reporting at each visit.
- Physical examination and vital signs: Screening, D-14 to D-7, M0/D1, M4, M8, M12, M15, M18, M21, M24/at EOTP; every 6 months in the safety monitoring phase, and at every relapse visit.
- Additionally, vital signs will be collected hourly during alemtuzumab infusion and post infusion observation period.
- Clinical chemistry laboratories: Screening, D-14 to 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-14 to 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-14 to D -7, monthly in alemtuzumab treatment phase (Year 1 and 2); EOTP, and monthly in the safety monitoring phase.
- Thyroid Function tests: Screening, D-14 to D -7, quarterly in alemtuzumab treatment phase (Year 1 and 2); EOTP, and quarterly in the safety monitoring phase.
- Tanner staging: Screening, M12, M24/at EOTP; annually in the safety monitoring phase.
- Pregnancy testing (females only): Screening (blood test), D-14 to 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.

9.3.1 Adverse events

Adverse events reported by the patient or observed by the Investigator will be monitored, and include:

- Occurrence, seriousness, grade/intensity, relationship to study drug, resolution, and outcome of serious adverse event (SAE), adverse event of special interest (AESI) , and AEs.
- Assessment of IARs: An IAR is defined as any AE occurring during alemtuzumab infusion or within the 24 hour post-infusion period. However, some IARs may occur beyond 24 hours (such as pulmonary alveolar hemorrhage, stroke, cervicocephalic arterial dissection, myocardial ischemia, thrombocytopenia and myocardial infarction). Toxicity grade (severity) of IAR is based on CTCAE. The timing of IAR in relation to alemtuzumab administration and distribution of IARs based on toxicity grade (severity) observed in the study for both study periods will be assessed.

Refer to Section 10.4.1 for details.

9.3.2 Laboratory safety variables

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

All laboratory data listed in this section will be measured at a central laboratory. The laboratory data will be collected at designated visits as shown in study flow chart Section 1.2.

It is preferred that CBCs with platelet count (for monitoring for any cytopenia as well as), serum creatinine, and urinalysis with microscopy be analyzed at the central laboratory, but under special circumstances (eg, if patient is unable to visit the study center weekly or monthly, or results are needed urgently), the assay may be performed at a local laboratory provided that test results are entered into the e-CRF in a timely manner. In addition, at some visits during the safety monitoring phase, there is an option for the nurse to obtain samples for clinical chemistry laboratories, hematology, thyroid function tests, urinalysis and serum creatinine at the patient's home if needed (refer to study flow chart Section 1.2).

The following laboratory safety variables will be analyzed:

- Hematology and differential panel: red blood cell count, hematocrit, hemoglobin, mean corpuscular hemoglobin, white blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) and platelets.
- Complete Chemistry panel: glucose, serum creatinine, blood urea nitrogen (BUN), sodium, potassium, chloride, bicarbonate, magnesium, calcium, uric acid, aspartate aminotransferase, alanine aminotransferase (ALT), gamma-glutamyl transferase, lactate dehydrogenase, total bilirubin, direct/indirect bilirubin, alkaline phosphatase, inorganic phosphorus, total protein, albumin, globulin, albumin/globulin ratio, triglycerides, total cholesterol and creatinine phosphokinase.

- Urinanalysis: pH, ketones, protein, glucose, blood, urobilinogen, bilirubin, microscopic sediment, specific gravity.
- Thyroid function testing: thyroid stimulating hormone and if abnormal T3 and T4.
- Hepatitis B and C serology testing.
- HPV serology testing: Testing will be conducted for human papillomavirus (HPV) infection as and when recommended by local public health authorities. If the testing is positive, the patient may be eligible after the condition has resolved as per the Investigator opinion (eg, follow-up HPV test is negative or cervical abnormality has been effectively treated). An annual follow-up is recommended.
- Tuberculosis test screening. It should be performed as per local health care authority recommendations.

Pregnancy testing: β-Human chorionic gonadotropin.

In accordance with international recommendations (20), sampling blood volume will be minimized to approximately 1% of total blood volume at each visit and approximately 3% of total blood volume over a 4 week period.

Blood sample volume will range from 9 to 57 ml, depending on tests required at study visits (ie, an average blood sample amount of 23 ml per visit). The total amount of blood withdrawn will be approximately 350 ml in Year 1 and 200 ml in Year 2. During the safety monitoring phase, approximately 120 ml will be drawn each year. However, additional blood samples may be collected at the Investigator's discretion for patient safety monitoring.

9.3.3 ITP, cytopenia, and antiGBM surveillance and monitoring

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

If a cytopenia is suspected, appropriate medical intervention should be promptly initiated, including referral to specialist.

Alemtuzumab has also been associated with antiGBM disease, which can cause a pulmonaryrenal syndrome known as Goodpasture's disease (21, 22). AntiGBM disease is a rare autoimmune disorder in which circulating antibodies are directed against an antigen normally present in the basement membranes of renal glomeruli and pulmonary alveoli. The target antigen is the alpha-3 chain of type IV collagen. The resultant clinical syndrome encompasses a spectrum ranging from mild or no renal involvement to rapidly progressive glomerulonephritis. Patients may develop pulmonary hemorrhage.

In an effort to identify potential cases of antiGBM disease early, all patients in the study will undergo monthly evaluation of serum creatinine levels alone or as part of a full chemistry panel and laboratory urinalysis (minimally including examination of protein and hemoglobin) with

an imaging biomarker for comparative purposes. The number of new or enlarging hyperintense lesions as detected by T2-weighted MRI has been used as a surrogate marker of efficacy in MS studies (25, 26). Cranial MRI will be performed at the times specified in Section 1.2.

In the analysis of secondary endpoints, 4 primary areas will be prioritized. Safety and tolerability for up to 4 years after last dose of alemtuzumab will be assessed using descriptive statistics and evaluated in comparison to the adult data for the treatment of MS using alemtuzumab. Adverse events of special interest will be examined including the subsequent development of infusion-related reactions, events of autoimmunity particularly thyroid, ITP and nephropathies; serious infections. Certain exclusion criteria related to prior disease states associated with such reactions will be emphasized during screening. Routine lab monitoring during the course of the study and followup over 4 years following last infusion is planned.

EDSS score changes occurring following Period 1 will be analyzed. The EDSS will be performed by the neurologist at the following visits: Screening, Day-14 to Day -7, Months 4, 8, 12, 15, 18, 21, and 24/at EOTP, every 6 months in the safety monitoring phase, and at every relapse visit. The EDSS has long been considered the standard for assessing disability in patients with MS (27, 28).

The annualized relapse rate (ARR) will be assessed at Year 2. The annualized relapse rate is widely used and generally accepted as an indicator of the efficacy of drugs to reduce cerebral inflammation in MS studies (27, 28).

Cognition test scores (BVMT-R and SDMT) will be tested over 2 years. Cognitive decline is recognized as a prevalent and debilitating symptom of multiple sclerosis (MS), especially deficits in episodic memory and processing speed. The change from baseline in cognitive outcomes are to be analysed descriptively. The SDMT is a test of speed that screens for organic cerebral dysfunction and has been validated and used in numerous MS clinical trials (29, 30).
The BVMT-R is a test of memory that has been validated in MS and has been used in clinical trials (31). Quality of life measures will be assessed using the validated pediatric Neuro-QOL which will be measured at least every 6 months over 2 years. This measure assesses how disease and health factors affects children's lives (32).

- Serology tests: hepatitis B/C and HPV. Other serology test may be required according the patient vaccination status,
- Urinalysis (pH, ketones, cells, protein, glucose, blood, urobilinogen, bilirubin, microscopic sediment, specific gravity),
- TB testing (as per local practice),
- For women: Beta human chorionic gonadotropin pregnancy test for women of childbearing potential, who have commenced menstruating.

- Blood sample collection for lymphocyte phenotyping.
- Perform MRI scan without contrast. It is important to ensure that this MRI assessment is performed 4 months (±7 days) apart to the MRI assessment on D-7 visit. The MRI assessments will be available to investigators to assess safety.
- Perform EDSS assessment.
- Perform SDMT and BVMT-R test.
- Recording of PedsQL/Ped NeuroQoL.
- Remind patient to continue on their DMT.
- Commence AE/SAE reporting.

Note: The above investigations may be performed on separate visits as long as all are completed within the 28 days prior to inclusion (V2, M-4). If any of the examinations/measurements does not fulfill the inclusion/exclusion criteria at the screening visit, they may be repeated before Visit 2.

10.1.2 Visit 2/(M-4) study eligibility confirmation visit

The following items will be checked/performed and recorded for all patients:

- Review any potential AEs/SAEs and concomitant mediation used since Visit 1.
- Review/confirm eligibility criteria based on review of inclusion/exclusion criteria.

Only patients who meet all the inclusion criteria and none of the exclusion criteria will be included in the study. Each patient will receive an incremental identification number corresponding to his/her order of enrollment in the study.

- If the patients do not meet eligibility criteria, they will be considered screen failures. These patients may be re-assessed and included in the study if they meet all eligibility criteria,
- After this visit, during DMT phase until Day -7 visit, Investigator or designee will perform monthly phone calls to remind patients and parents about continuation of DMT and check patient status.

- Is life-threatening, or,
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or,
- Results in persistent or significant disability/incapacity, or,
- Is a congenital anomaly/birth defect.
- Is a medically important event.
  Medical and scientific judgment must be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm,
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse.
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN.
- Suicide attempt or any event suggestive of suicidality.
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
- Bullous cutaneous eruptions.
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies).
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).
- Suspected transmission of an infectious agent: if any suspected transmission of an infectious agent via a medicinal product (eg, product contamination).

Hospitalization for the scheduled alemtuzumab infusions, not related with any AE, due to Investigator decision or local requirement, will not be considered as an SAE.

10.4.1.3 Adverse event of special interest

Any AESI will be reported to the Sponsor in the same timeframe as SAEs, ie, within 24 hours, as detailed in Section 10.4.4.

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

The following AE will be considered as an AESI:

- 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 (see Section 10.4.1.2). Follow-up of the pregnancy in a female participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or nonserious) with IMP/non-investigational medicinal product (NIMP).
  - An overdose (accidental or intentional) with the IMP is an event suspected 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 ALT (see the "Increase in ALT" flow diagram in Appendix B of the protocol).
- Other product specific AESI(s):
  - Autoimmune mediated conditions including but not limited to autoimmune encephalitis, cytopenias, ITP, autoimmune hepatitis, nephropathies including anti-glomerular basement membrane (GBM) disease, thyroid disorders and acquired Hemophilia A (see Appendix B)
  - 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)
  - HLH,
  - Progressive multifocal leukoencephalopathy (PML)
  - Pneumonitis,
  - Serious infections including serious opportunistic infections (eg, Listeria infections, CMV, EBV), HPV associated with cervical dysplasia
  - Malignancy
  - Thrombotic thrombocytopenic purpura

10.4.4 Instructions for reporting serious adverse events

In the case of occurrence of an SAE or AESI, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE or AESI in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In such case, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the study are properly mentioned on any copy of a source document provided to the Company. For laboratory results, include the laboratory normal ranges
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE or AESI. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.5 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.4 even if not fulfilling a seriousness criterion, using the screens in the e-CRF.

Instructions for AE reporting are summarized in Table 9.

10.4.6 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by sanofi are provided in Appendix B.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia.
- Thrombocytopenia.
- ALT increase.
- Acute renal insufficiency.
- Suspicion of rhabdomyolysis.

Table 9 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
AE (nonSAE, nonAESI)	Routine	Any AE that is not an SAE or AESI	Yes	No	No
SAE (nonAESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.3	Yes	Yes	No
AESI	Expedited (within 24 hours)	Acute hypersensitivity/ anaphylaxis	Yes	Yes	No
		Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	No
		ALT>=3ULN or >= 2 baseline	Yes	Yes	Yes
		Autoimmune mediated conditions including but not limited to autoimmune encephalitis, cytopenias, ITP, autoimmune hepatitis, nephropathies including anti-glomerular basement membrane (GBM) disease, thyroid disorders and acquired Hemophilia A	Yes	Yes	No
		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)			
		HLH,			
		Progressive multifocal leukoencephalopathy (PML)			
		Pneumonitis,			
		Serious infections including serious opportunistic infections (eg, Listeria infections, CMV, EBV), HPV associated with cervical dysplasia			
		Malignancy			
		Thrombotic thrombocytopenic purpura			

Abbreviations: AE: adverse events; AESI: adverse event of special interest; ALT: alanine aminotransferase; IMP: investigational medicinal product; ITP: immune thrombocytopenia; nonSAE: nonserious adverse events.

10.4.7 Guidelines for reporting product complaints (IMP/NIMP/device)

Any defect in the IMP/NIMP/device (alemtuzumab/oral prednisone/prednisolone 1 mg/kg or 50 mg, and H2 antagonist) must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

10.5 OBLIGATIONS OF THE SPONSOR

Adverse events that are considered expected will be specified by the reference safety information (label).

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, independent ethics committee (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 SAFETY INSTRUCTIONS

For more information about alemtuzumab, please refer to label.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

A SAP will be written and finalized prior to database lock to give guidance to the statistical analysis. It will be in compliance with the International Council for Harmonization (ICH) and Food and Drug Administration's Guidance for Industry: Statistical Principles for Clinical Trials.

The Sponsor or its designee will perform the statistical analysis of the data from this study. The analysis will be performed using the SAS® statistical software system Version 9.1 or higher.

11.1 DETERMINATION OF SAMPLE SIZE

At least 60 patients aged from 10 years to less than 18 years will be screened in this study to account for screen failures, to ensure that at least 50 patients are evaluable. According to the means and variability reported in other paediatric MS studies (17), it was assumed that there is an average of 9 new or enlarging T2 lesions during continuation of prior DMT (Period 1) 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 (Period 2) compared to the equal-length Period 1. 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 treatment Period 1 (prior DMT) and Period 2 (alemtuzumab).

11.2 DISPOSITION OF PATIENTS

Appropriate tracking documents for screening, enrollment and follow-up of patients will be established in each center, as needed and in accordance with local regulations.

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

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.

11.3 ANALYSIS POPULATIONS

11.3.1 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 for both Period 1 and Period 2. The mITT population will be used for the analyses of the primary and secondary efficacy endpoints.

11.4.3 Analyses of safety data

11.4.3.1 Adverse events

AE observation period:

- Pretreatment AEs are defined as those AEs that developed or worsened prior to the 1st alemtuzumab dose.
- On treatment AEs are defined as those AEs that developed or worsened after the 1st alemtuzumab dose and until the end of the study (Month 60).
- Posttreatment AEs are defined as those AEs that developed or worsened after the ontreatment period.

On-study period will include pretreatment and ontreatment period. Treatment emergent adverse events (TEAEs) for analysis purpose will include all ontreatment AEs.

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

The incidence of TEAEs (including IARs), AESI, will also be tabulated (frequencies and percentages) by severity, grade/intensity, and relationship to study drug. 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 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. Actions taken regarding treatment and patient outcome will also be listed.

In addition to IARs analysis above, TEAEs that occurs from start of infusion up to 72 hours postinfusion will be summarized if applicable.

The incidence of AEs leading to study discontinuations will also be summarized by treatment group, with details provided in the listing.

Death: The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population.
- TEAE leading to death (death as an outcome on the AE e-CRF 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.

11.4.3.2 Laboratory safety variables

Observed measurements and changes from baseline to scheduled study visits in biochemistry, hematology, and urinalysis will be descriptively summarized. All laboratory values will be

classified as normal, above normal, or below normal based on normal ranges provided by the laboratory. Patients who have at least one incidence of potentially clinically significant abnormalities (PCSA) during the TEAE period will be summarized. Individual listings of patients with PCSA will be presented.

The liver function test, alanine aminotransferase (ALT) will be used to assess possible liver function injure. Time to onset of the initial ALT elevation (>3ULN) will be analyzed using Kaplan-Meier estimate. The normalization (to ≤1 ULN) of ALT will be summarized by categories of elevation (3 x, 5 x, 10 x, 20 x ULN) with the following categories of normalization: never normalized, normalized before permanent discontinuation of study drug, and normalized after permanent discontinuation of study drug. Note that a patient will be counted only under the maximum elevation category.

11.4.3.3 Physical examination and vital signs

Potentially clinically significant findings observed during the TEAE observation period for vital signs (including but not limited to blood pressure, heart rate, respiratory rate, etc.) will be summarized by study visit. 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 paediatric patients, will be presented. Change in vital signs during and immediately following IV administration from preinfusion will also be summarized.

11.4.3.4 Other safety endpoints

Observed measurements and changes from baseline to study time points in antialemtuzumab antibody titers will be summarized using descriptive statistics.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

The list of pharmacokinetics parameters is listed in Section 9.2.2.1.4.

PK exposures (C_{max} and AUC_{last}) for alemtuzumab will be determined using noncompartmental analysis. Values will be reported for individual subjects and summarized using descriptive statistics by study week as appropriate.

Pharmacodynamic endpoints as described in Section 9.2.2.2 will be summarized using descriptive statistics at each scheduled study visit. Observed measurements as well as change from baseline will be summarized. If a linear trend in the change of a PD endpoint is observed, longitudinal model may be employed to model change from baseline over time. In addition, 95% confidence interval of changes will be presented.

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

11.4.5 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.

11.5 INTERIM ANALYSIS

A partial database lock will be done after the last patient has completed efficacy assessments including MRI at the end of Period 2. This database lock will allow comparing brain lesion counts between Period 1 (M-4 to M0) and Period 2 (M4-M8). No formal interim analysis will be performed.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Subinvestigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules, and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient and parents of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the IRB/IEC. All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the written ICF should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written ICF will be provided to the patient.

In addition, participants will assent as detailed below or will follow the ethics committee (IRB/IEC) approved standard practice for paediatric participants at each participating center (age of assent to be determined by the IRB’s/IEC’s or be consistent with the local requirements).

Participants who can read the assent form and who can write will do so before writing their name and dating or signing and dating the form.

Participants who can write but cannot read will have the assent form read to them before writing their name on the form.

Participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

Prior to collection of blood for PK and immune markers, the optional PK/immune markers ICF (written) must be signed, name filled in, and personally dated by the patient or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional ICF will be provided to the patient.

b Screening visit should be a maximum of 28 days prior to eligibility confirmation (M-4). If needed, the assessments can be performed over multiple days as long as the window is observed.

c Some premedications should have been taken prior to Day 1. All lab results/assessments should be available prior to D-7 to confirm patient eligibility. If patient is eligible to receive alemtuzumab a follow-up call should be performed and INF/copaxone should be stopped at D-7.

d This visit is only required for subjects who have a suspected relapse, and should occur within 7 days following the occurrence of the clinical event.

e Subject race will be collected in this study because these data are required by several regulatory authorities.

f Information on alcohol habits will be collected along with medical history at Visit 1 and in case of alanine aminotransferase (ALT) increase.

g Phone calls to remind patients and parents about continuation of DMT and participation in study will be utilized at monthly intervals (between V2 and V3) in prior DMT period (Period 1). The phone calls will be captured in the e-CRF.

h Screening tuberculosis test should be performed as per local health care authority recommendations and during the study if deemed clinically indicated. Blood testing (QuantiFERON®-TB Gold test) or skin testing on site (purified protein derivative [PPD] skin test) will be allowed only if the Quantiferon TB Gold test is used. Blood testing is preferred where available. . If Quantiferon test results are indeterminate, confirmation via skin testing is required.

i Serological testing for Herpes zoster is recommended, in accordance with local public health authority recommendations. Herpes zoster (varicella zoster) vaccination (VZV) of antibody-negative patients should be considered prior to treatment with alemtuzumab. In addition if patient receives any vaccination during screening or Alemtuzumab Treatment Phase, relevant antibody titers will be assessed before and approximately 6 weeks after completing vaccination course (inactivated vaccines only).

j Testing will be conducted for human papillomavirus (HPV) infection as and when recommended by local public health authorities. If the testing is positive, the patient may be eligible after the condition has resolved as per the Investigator opinion (eg, follow-up HPV test is negative or cervical abnormality has been effectively treated). An annual follow-up is recommended.

k Acyclovir 200 mg twice daily (or a therapeutic equivalent) starting on the first day of each alemtuzumab course and continuing for a minimum of 1 month following treatment with alemtuzumab.

l The MRI assessment will be 4 months (±7 days) apart in Year 1. The MRI assessments will be available to investigators to assess safety.

m PedsQL questionnaire (Paediatric Quality of Life Inventory) will be completed by patients/parents based on recommendations. Peds NeuroQoL is a quality of life measurement developed for neurological disorders and consists of short form questions for multiple domains. Specific subdomains will be utilized.

n The date of first menarche should be captured if applicable. 'A standard physical examination for clinical and neurological assessments includes examination of major body systems, height and body weight.

o Hematology and differential panel (hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin, white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets) Complete chemistry panel (glucose, creatinine, blood urea nitrogen (BUN), sodium, potassium, chloride, bicarbonate, magnesium, calcium uric acid, aspartate aminotransferase (AST), ALT, gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total bilirubin, direct/indirect bilirubin, alkaline phosphatase, inorganic phosphorus, total protein, albumin, globulin, albumin/globulin ratio, triglycerides, cholesterol and creatine phosphokinase (CPK). It is preferred that CBCs with platelet count, and monitoring for any cytopenia as well as serum creatinine, and urinalysis with microscopy be analyzed at the central laboratory, but under special circumstances (eg, if patient is unable to visit the study center weekly or monthly, or results are needed urgently), the assay may be performed at a local laboratory provided that test results are entered into the e-CRF in a timely manner. However for study visits that only require laboratory sampling, home nursing or local laboratories may be used for sample collection and shipment to the central laboratory, as per local regulations. These visits are to be followed by telephone calls from the study site to assess AEs.

p Thyroid stimulating hormone (TSH) & if abnormal T3 & T4 performed on the existing samples. However for study visits that only require laboratory sampling, home nursing or local laboratories may be used for sample collection and shipment to the central laboratory, as per local regulations. These visits are to be followed by telephone calls from the study site to assess AEs and concomitant medications.

q Urinalysis (pH, ketones, cells, protein, glucose, blood, urobilinogen, bilirubin, microscopic sediment, specific gravity). However for study visits that only require laboratory sampling, home nursing or local laboratories may be used for sample collection and shipment to the central laboratory, as per local regulations. These visits are to be followed by telephone calls from the study site to assess AEs and concomitant medications.

r Tanner stage to be assessed as noted until complete sexual maturity.

s The following vital signs will be recorded before methylprednisolone infusion, at a time after methylprednisolone infusion and prior to alemtuzumab infusion; and 1 hour after the start of alemtuzumab infusion and hourly during and after infusion, until 2 hours after infusion has ended or longer until stabilization: systolic and diastolic blood pressure (millimeters of mercury [mm Hg]), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]).

t β-human chorionic gonadotropin test will be performed at Screening. Pregnancy test after Screening will be done by urine dipstick and must be conducted prior to methylprednisolone administration; pregnancy testing is required for all female patients capable of bearing children and who have commenced menstruating. Those female patients who commence initial menstruation during the study will be similarly monitored with urine dipstick pregnancy tests for the duration of the study. Pregnancy testing to be repeated as permitted by national law.

u For details on PK sampling, refer Section 1.2.4.

1.2.3 Schedule of events Part 3 (Safety monitoring phase Year 3 - Year 5)

Table 3 - Safety monitoring phase Year 3-5

	Safety monitoring phase												
Visit Day[a]	**M25**	**M26**	**M27**	**M28**	**M29**	**M30**	**M31**	**M32**	**M33**	**M34**	**M35**	**M36**[b]	**Relapse Visit**
	M37	**M38**	**M39**	**M40**	**M41**	**M42**	**M43**	**M44**	**M45**	**M46**	**M47**	**M48**[b]	
	M49	**M50**	**M51**	**M52**	**M53**	**M54**	**M55**	**M56**	**M57**	**M58**	**M59**	**M60**[b]	
Visit number	V29	V30	V31	V32	V33	V34	V35	V36	V37	V38	V39	V40	
	V41	V42	V43	V44	V45	V46	V47	V48	V49	V50	V51	V52	
	V53	V54	V55	V56	V57	V58	V59	V60	V61	V62	V63	V64	
Efficacy:													
EDSS						X						X	X
Brain MRI[c]												X	
SDMT												X	
BVMT-R Test												X	
PedsQL (QoL Questionnaire)/ Ped. NeuroQoL (sub-comp.)												X	
Safety:													
Physical examination						X						X	X
Clinical chemistry laboratories[d,e]			X			X			X			X	
Hematology (Differential CBC)[d,f]	X	X	X	X	X	X	X	X	X	X	X	X	
Thyroid Function Tests[d]			X			X			X			X	
Urinalysis[g]	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Creatinine[h] and alanine aminotransferase[d]	X	X		X	X		X	X		X	X		
Lymphocyte phenotyping												X	
Samples for antibodies to Study Drug												X	
Tanner Staging												X	
AE/SAE recording (if any)	◄	———	———	———	———	———	———	———	———	———	———	———	►
Concommitant medications	◄	———	———	———	———	———	———	———	———	———	———	———	►
Vital Signs						X						X	X
HPV[i] (yearly)	◄	·····	·····	·····	·····	·····	·····	·····	·····	·····	·····	·····	►

Abbreviations: AE: adverse event; BVMT-R: brief visuospatial memory test-revised, CBC: complete blood count; EDSS: Expanded Disability Status Scale; M: month(s); MRI: magnetic resonance imaging; Neuro-QoL: quality of life in neurological disorders; Ped: paediatric; QoL: quality of life; SAE: serious adverse event; SDMT: symbol digit modality test.

a All study visits during safety monitoring phase except the M36,M48 and M60 visits can be performed within ±7 days.

b M36, M48 and M60 Study visits can be performed within ±4 weeks for these visits, to allow for scheduling of assessments.

1.2.4 Schedule of events Part 4: Table for PK sampling (Year 1)

Table 4 - PK Sampling schedule (Year 1)

PK sampling time	Day 1 predose	Day 5 End of Infusion	Day 14[a,b]	M1[a]	M2[a]
Schedule	X	X	X	X	X
Sample ID	S1	S2	S3	S4	S5

a A window of ±2 days for sample collection is permitted to ensure that sample collection does not fall on a weekend and allow for patient flexibility.

b The sample will be drawn at local lab, if feasible per country regulation (no site visit).

Note: "End" refers to the end of the infusion period; these samples should be collected within 15 minutes prior to the end of the infusion from the side of the body opposite the alemtuzumab infusion site.

1.2.5 Schedule of events Part 5: Table for PK sampling (Year 2)

Table 5 - PK sampling schedule (Year 2)

PK sampling time	M12 Day 1 predose	M12 Day 3 EOI	M12 Day 12[a,b]	M13[a]	M14[a]
Schedule	X	X	X	X	X
Sample ID	S1	S2	S3	S4	S5

a A window of ±2 days for sample collection is permitted to ensure that sample collection does not fall on a weekend.

b The sample will be drawn at local lab, if feasible per country regulation (no site visit).

Note: "EOI" refers to the end of the infusion period; these samples should be collected within 15 minutes prior to the end of the infusion from the side of the body opposite the alemtuzumab infusion site.

4 INTRODUCTION AND RATIONALE

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that affects approximately 2.3 million people worldwide (1). Its clinical course is typically characterized by initial episodes of transient neurological compromise with full recovery, followed by a phase of cumulative deficits that may increase with each new episode. Most patients eventually develop secondary progression leading to a constellation of chronic sequelae including profound muscle weakness, impaired gait and mobility, bladder and bowel dysfunction, and cognitive and visual impairments.

MS is typically considered to be a disease of young adults. However, paediatric MS is increasingly recognized and accounts for approximately 5 percent of cases (2, 3, 4). Differential diagnosis includes leukodystrophies, vasculopathies, sarcoidosis, lymphoma, mitochondrial defects, and other metabolic disorders.

The estimated prevalence of paediatric patients among all patients with MS ranges between 2.7% to 10.5% (3), and it is estimated that approximately 20% to 25% of children with MS experience breakthrough disease activity that may trigger a switch to another therapy (2, 4).

The onset of MS in childhood typically occurs during the key formative years. It can restrict school attendance and has the potential to negatively affect the developing neural connections implicated in learning and higher-order information processing. Fatigue may also have a great impact on activities and development.

Paediatric MS patients develop disability, as well as shift to the secondary progressive phase of MS, after a longer disease interval but at a younger age, compared with adult MS patients (5, 6, 7).

With increased recognition of paediatric MS worldwide, children are now being treated earlier in their disease course with the goal of limiting long-term disability (8). There is no approved disease modifying therapy (DMT) indicated for paediatric MS and the effects of DMTs in children have not been formally evaluated in controlled clinical trials. The current treatment and prognosis of paediatric MS are based on that of adult patients, because data are limited in paediatric MS and it is assumed that the disease response in children is likely to be similar (9, 10, 11, 12).

Off label use of medicinal products in children without proper evidence poses an ethical problem. That is why the need for clinical trials with children has now been widely recognised and is stimulated by European Union legislation (EU regulation). Trials of alemtuzumab are therefore necessary in the paediatric population to develop a better knowledge of the drug’s effects in children (safety and efficacy).

6.4 STUDY COMMITTEE

6.4.1 Scientific advisory committee:

The scientific advisory committee (SAC) is composed of field experts and Sponsor-based scientists with clinical and methodological expertise. This Committee, led by a Chairperson, is selected by the Sponsor for advice regarding scientific issues and operational conduct of the study. The SAC will also review any amendments, and provide input regarding interpretation of study results.

Among its responsibilities, the SAC will receive study status reports from the Sponsor, and will review the recommendations from the data monitoring committee (DMC) throughout the study.

Moreover, the SAC will be responsible for the primary publication(s) emanating from the study. The Principal Investigator (PI) of the study will be selected by the Sponsor and will be the first author for the primary publication(s). PIs at the 3 sites enrolling the most patients will also be included as authors for the primary publication, in addition to the other SAC members.

Detailed activities and responsibilities of the SAC are provided in the SAC charter.

6.4.2 Data monitoring committee

A DMC, operating independently from the Sponsor and Clinical Investigators, will be responsible for overseeing the safety of patients and the risk/benefit ratio throughout the study.
This committee is composed of externally-based individuals with expertise in the disease under study, biostatistics and/or clinical research. The primary responsibilities of the DMC are to ensure the patients welfare as well as to evaluate and review the safety and other applicable data throughout the course of the study and make appropriate recommendations to the Sponsor regarding the conduct of the clinical trial. The specific responsibilities of the DMC will be described in the DMC charter.

Second Course will occur 12 months after the first course.

Second Course: Alemtuzumab will be administered by IV infusion for 3 consecutive days at Month 12 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 (this equates to 12 mg/day for a 50 kg patient).

8.1.1.1 Method of preparation at the clinical site

Alemtuzumab must be diluted before infusion. The diluted solution must be administered by IV infusion. The infusion duration will be approximately 4 hours starting within 8 hours after dilution. Extend the duration of the infusion if clinically indicated.

Additional requirements for alemtuzumab infusion and monitoring during and post infusion are specified in Section 10.1.4 Visit 4/M0/D1 (first course of alemtuzumab) and Section 10.1.10 Visit 16/M12 (second course of alemtuzumab).

8.1.1.2 Special precautions for disposal and other handling

The vial contents must be inspected for particulate matter and discoloration prior to administration. Do not use if particulate matter is present or the concentrate is discolored. Do not shake the vials prior to use.

For IV administration, withdraw the prescribed amount of alemtuzumab from the vial into a syringe using aseptic technique. Inject into 100 mL of sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose (5%) solution for infusion. This medicinal product must not be diluted with other solvents. The bag must be inverted gently to mix the solution.

Alemtuzumab contains no antimicrobial preservatives and, therefore, care must be taken to ensure the sterility of the prepared solution. It is recommended that the diluted product be administered immediately. Each vial is intended for single use only.

Any partially used, unused, or damaged drug vials should be disposed of in accordance with local requirements.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCTS

A) Premedications:

- Day -1 (day before first IV infusion at each course) in the morning:
  - Oral prednisone/prednisolone 1 mg/kg or 50 mg one dose, whichever is lower, or equivalent,
  - H2 antagonist according to the local label (eg, ranitidine).

9.2.1.3.2 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.

9.2.2 Other secondary endpoints

9.2.2.1 Pharmacokinetics

For patients receiving alemtuzumab, serum concentrations and PK parameters will be studied

9.2.2.1.1 Sampling time

The sampling times for blood collection can be found in the Study Flow Chart Section 1.2.4 and Section 1.2.5.

9.2.2.1.2 Pharmacokinetics handling procedure

Special procedures for collection, storage, and shipment of plasma samples collected for EFC13429 concentrations will be provided in a separate laboratory manual.

9.2.2.1.3 Bioanalytical method

Details of the bioanalytical methods are described in Appendix B and detailed in a separate laboratory manual.

9.2.2.1.4 Pharmacokinetics parameters

The following PK parameters will be calculated, using noncompartmental methods from the cumulative serum alemtuzumab concentrations. The parameters will include, but may not be limited to the following Table 8:

microscopy. Follow up of abnormal results will be guided by the algorithm below in Appendix B (Anti-Glomerular Basement Membrane Disease).

9.3.4 *Hemophagocytic lymphohistiocytosis*

During postmarketing use, HLH has been reported in patients treated with alemtuzumab. Hemophagocytic lymphohistiocytosis is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation, including fever, swollen lymph nodes, bruising or skin rash. It is associated with high mortality rates if not recognized early and treated. Symptoms have been reported to occur within a few months to four years following the initiation of treatment. Patients who develop disease manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH as well as referral of the patient to a specialist should be considered.

9.3.5 Physical examination and vital signs

Whenever possible, the same physician should perform the physical examination at all study visits. The findings of each examination will be recorded.

A standard physical examination for clinical and neurological assessments which includes examination of major body systems, height and body weight will be performed.

Physical examination and vital signs will be performed at screening, D-14 to D-7, M0/D1, M4, M8, M12, M15, M18, M21, M24/at EOTP; every 6 months safety monitoring phase, and at every relapse visit.

The following vital signs: 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:

- 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 2 hours after infusion has ended or longer until stabilization.

Body temperature will be collected using the same method at each assessment for a given patient.

Blood pressure will be measured under standardized conditions using the same method at each assessment for a given patient. It will be determined at each study visit using a well calibrated apparatus. Both systolic and diastolic blood pressure must be recorded.

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

The Tanner stage (Appendix E) should be assessed until complete sexual maturity at the specified time points, see Study flowchart Section 1.2 for further details.

10 STUDY PROCEDURES

All the study procedures will be performed following the standard clinical practice of each study center. Refer to the Section 1.2 for more details.

10.1 VISIT SCHEDULE

The visit schedule consists of the following visits:

10.1.1 Visit 1 Screening visit

This visit has to be conducted maximum 28 days prior to M-4 visit.

Prior to any assessments, information for the parents/patient regarding the aims and methods of the study, its constraints and risks, and educational material consistent with the risk management plan for alemtuzumab will be reviewed with the parents/patient and a written summary in the form of an informed consent will be given to the parents/patient.

The patient/patient's legal guardian must sign the informed consent/assent prior to any action related to the study.

The screening visit will include the following investigations (refer to Section 1.2.1):

- Recording of medical/surgical history.
- **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. Tanner stage will be assessed as well.
- The following vital signs will be recorded: systolic and diastolic blood pressure (millimeters of mercury [mm Hg]), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]).
- **Demographics** (gender, age, and race).
- Recording of prior MS medications and concomitant medications.
- **Laboratory screening:**
  - Hematology (CBC with differential, including platelet count for monitoring for any cytopenia),
  - Chemistry panel: Glucose, creatinine, blood urea nitrogen (BUN), sodium, potassium, chloride, bicarbonate, magnesium, calcium uric acid, aspartate aminotransferase, ALT, gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase, total bilirubin, direct/indirect bilirubin, alkaline phosphatase, inorganic phosphorus, total protein, albumin, globulin, albumin/globulin ratio, triglycerides, cholesterol and creatinine phosphokinase will be assessed,
  - Thyroid function testing (thyroid stimulating hormone),

10.1.3 Visit 3/Days -14 to -7

Visit 3 assessments can be performed over multiple days as long the time windows below are respected.

The following items will be checked/performed and recorded for all patients:

- Perform MRI scan without contrast. It is important to ensure that this MRI assessment is performed 4 months (±7 days) from the MRI assessment done at screening.
- Physical examination including vital signs.
- AEs/SAEs (if any) will be monitored.
- Concomitant medication (if any) will be checked and reported.
- Blood and urine sample for laboratory assessments (hematology and chemistry) including thyroid function test; pregnancy test (for females of childbearing potential), and urinalysis will be collected at Day -14 in order that results can be available at the latest on Day -7.
- Check for prior DMT compliance.
- Perform EDSS assessment.
- Perform SDMT and BVMT-R test.
- Recording of PedsQL/Ped NeuroQoL.
- Day -7 (phone call or visit): The Investigator will assess and confirm eligibility for alemtuzumab administration. If the patient is eligible for alemtuzumab administration, the prior DMT will be discontinued.

Premedication will be given to the patient and patient will be instructed to take premedication the day prior to the alemtuzumab administration in the morning and in the evening according to the schedule. Refer to Section 8.2 for further details.

10.1.4 Visit 4/M0/D1 (first course of alemtuzumab)

Alemtuzumab treatment must be initiated and supervised by a neurologist experienced in the treatment of patients with MS. Specialists and equipment required for the timely diagnosis and management of the most frequent adverse reactions, especially autoimmune conditions and infections, must be available.

During the alemtuzumab infusion days, patients are not required to stay hospitalized overnight; however it remains at Investigator's discretion to decide if patient needs to be hospitalized during infusion periods.

Observation for infusion reactions is recommended during and for at least 2 hours (based on local requirements) after alemtuzumab infusion.

The day prior to first alemtuzumab administration patient should take the premedication as specified in Section 1.2.1 and Section 8.2.

10.4.2 Serious adverse events waived from expedited regulatory reporting to regulatory authorities

Not applicable.

10.4.3 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the ICF form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the e-CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor in the protocol and informed consent. At the prespecified study end date, patients who experience an ongoing SAE or an AESI should be followed until resolution, stabilization, or death and related data will be collected.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs are to be recorded as AEs only if:
  - Symptomatic and/or,
  - Requiring either corrective treatment or consultation, and/or,
  - Leading to IMP discontinuation or modification of dosing, and/or,
  - Fulfilling a seriousness criterion, and/or,
  - Defined as an AESI.

In this protocol, symptoms and signs of exacerbation or worsening of the disease under trial will usually be captured in the context of efficacy assessment, and recorded on the relapse module of the e-CRF. Therefore, symptoms, relapses or worsening of MS will not be considered as AEs nor captured on the AE module of the e-CRF unless this event is considered possibly or probably related to the IMP (ie, worsening is not consistent with the anticipated natural progression of the disease) and/or the MS relapse meets the criteria for a serious AE (eg, requires hospitalization). However, for all associated symptoms or events or if an event that was initially considered a possible MS relapse but upon evaluation is found to be any other type of event (some example but not limited to: fever, injury, musculoskeletal event, systemic illness, mood disorder, etc) the event must be captured as an AE/SAE.

Instructions for AE reporting are summarized in Table 9.

11.3.2 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 patients in the 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.

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

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

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.

11.4 STATISTICAL METHODS

Analyses for the primary and secondary efficacy endpoints will be conducted using the mITT population. Analyses for the safety endpoints will be conducted using the safety population. Analyses for the PD endpoints will be conducted using the PD populations. Analyses for the PK endpoints will be conducted using the PK populations. Analyses for the exploratory endpoints will be conducted using the safety population.

In the descriptive analyses, summary statistics for continuous variables will minimally include n, mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

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

11.4.1 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.

The ICF and the assent form, used by the Investigator for obtaining the Patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

In relation with the population of patients exposed in the trial ie, paediatric/minor patients, the IRB/IEC must ensure proper advice from specialist with paediatrics expertise (competent in the area of clinical, ethical and psychosocial problems in the field of paediatrics) according to national regulations. This must be documented.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, ICF, Investigator's Brochure with any addenda or labeling documents, summary of product characteristics, package insert, Investigator's curriculum vitae, etc) and the date of the review must be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol must be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC must be informed as soon as possible. They must also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure or labeling information, will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.