AMENDED CLINICAL TRIAL PROTOCOL NO. 05

COMPOUND: GZ402673 (Alemtuzumab)

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

STUDY NUMBER: EFC13429

STUDY NAME: LemKids

VERSION DATE/STATUS: 15-Dec-2021/Approved

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PROTOCOL AMENDMENT CHANGES TABLE

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 05	All	15 December 2021, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 04	All	09 March 2020, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 03	All	21 June 2019, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	04 January 2019, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 03 (GB)	Great Britain only	21 May 2018, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02 (FR)	France only	21 May 2018, version 1 (electronic 1.0)
Protocol Amendment 06 (FR)	France only	21 May 2018, version 1 (electronic 1.0)
Protocol Amendment 05 (GB)	Great Britain only	21 May 2018, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 02 (IT)	Italy only	12 March 2018, version 1 (electronic 1.0)
Protocol Amendment 04 (IT)	Italy only	12 March 2018, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 02 (GB)	Great Britain only	08 November 2017, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02 (RU)	Russia only	08 November 2017, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01	All	08 November 2017, version 1 (electronic 1.0)
Protocol Amendment 03	All	08 November 2017, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01 (GB)	Great Britain only	05 May 2017, version 1 (electronic 2.0)
Protocol Amendment 02 (GB)	Great Britain only	05 May 2017, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01 (RU)	Russia only	23 January 2017, version 1 (electronic 2.0)
Protocol Amendment 01 (RU)	Russia only	23 January 2017, version 1 (electronic 1.0)
Clinical Trial Protocol	All	21 November 2016, version 1 (electronic 1.0)

Amended protocol 05 (13 December 2021)

This amended protocol (amendment 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

This amendment provides an updated list of adverse events of special interest based on the most recent update of the safety information from post marketing experience in adults with multiple sclerosis.

Protocol amendment summary of changes table

Section No. and name	Description of change	Brief rationale
Section 4 - Introduction	Added the following adverse events of special interest (AESIs) to 'Alemtuzumab Post-Marketing Updates in Adult': - Autoimmune encephalitis - Thrombotic thrombocytopenic purpura	Update of safety information based on post marketing experience in adults with multiple sclerosis (MS).
Section 10.4.1.3 – Adverse events of special interest	Added the following AESIs: - Autoimmune encephalitis - Thrombotic thrombocytopenic purpura	Update of the safety information based on post marketing experience in adults with MS.
Section 10.4.6 - Table 9 - Summary of adverse event reporting instructions	Added the following AESIs: - Autoimmune encephalitis - Thrombotic thrombocytopenic purpura	Update of the safety information based on post marketing experience in adults with MS.

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	Sanofi Genzyme 50 Binney St Cambridge, MA 02142 USA
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: GZ402673 (Alemtuzumab)	**STUDY No.: EFC13429**
TITLE	A multi-center, open-label, single-arm, before and after switch study to evaluate the efficacy, safety and tolerability of alemtuzumab in paediatric patients with relapsing remitting multiple sclerosis (RRMS) with disease activity on prior disease modifying therapy (DMT)
INVESTIGATOR/TRIAL LOCATION	Multinational
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVES	**Primary objective:** • To evaluate the efficacy, safety and tolerability of alemtuzumab intravenously (IV) in paediatric patients from 10 to <18 years of age with RRMS who have disease activity on prior DMT. **Secondary objective:** • To assess the pharmacokinetics (PK), pharmacodynamics (PD), antidrug antibody (ADA) formation, and potential effects of alemtuzumab on other multiple sclerosis (MS) disease characteristics such as cognition and quality of life (QoL).
STUDY DESIGN	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) - This phase consists of the screening assessments for study eligibility of patients on current DMT. • Prior DMT phase (approximately 4 months) - This phase consists of the efficacy measurements on current DMT, which will be used as comparator group in the study. Subjects will continue the use of their current DMT (limited to beta interferon therapy [IFNB] or glatiramer acetate [GA]) during this period until 7 days prior to administration of first dose of alemtuzumab at M0. • 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 the treatment phase compared to an equal period during the prior DMT phase. Note: EOTP refers to the end of the Alemtuzumab Treatment Phase. • 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: EOS refers to the end of the safety monitoring phase.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** • Patients with RRMS aged from 10 years (12 years in the Russian Federation) to less than 18 years at study entry are eligible. Patients must meet the criteria of diagnosis of MS as defined by the International Paediatric Multiple Sclerosis Study Group criteria for paediatric MS, and the criteria of MS based on McDonald criteria 2010. • Signed written informed consent/assent obtained from patient and patient's legal representative (parent or guardian) according to local regulations. • Expanded Disability Status Scale (EDSS) score 0.0 to 5.0 (inclusive) at screening. • At least 2 recorded MS attacks, and at least 1 MS attack (relapse) in the last year during treatment with a IFNB or GA after having been on that therapy for at least 6 months, and is currently still taking the same therapy. • At least 1 of the following: - ≥1 new or enlarging T2 hyperintense lesion or gadolinium enhancing lesion while on that same prior therapy (IFNB or GA), OR - 2 or more relapses in the prior year, OR - tried at least 2 MS DMTs. **Main exclusion criteria:** • Any prior exposure to alemtuzumab. • Any progressive or nonrelapsing form of MS. • Treatment with natalizumab, daclizumab, fingolimod, methotrexate, azathioprine, cyclosporine, or mycophenolate mofetil in the last 6 months, or as determined by the treating physician to have residual immune suppression from these or other MS treatments. • Treatment with teriflunomide in the last 12 months except if the patient underwent the accelerated elimination procedure as per local teriflunomide label. Previous treatment with mitoxantrone, cyclophosphamide, cladribine, rituximab, ocrelizumab, leflunomide or any cytotoxic therapy. • CD4+, CD8+, or CD19+ absolute cell count in blood at screening below lower limit of normal (LLN). • Prior documented history of thrombocytopenia, or platelet count at screening <LLN. In case of borderline results, one retest is allowed. • NOTE: Prior to initiation of any alemtuzumab treatment course, contraindications should be reviewed as pre-treatment verification of eligibility.
Total expected number of patients	At least 50 evaluable patients
Expected number of sites:	Approximately 50 sites

STUDY TREATMENT **Investigational medicinal product**	Alemtuzumab
Formulation:	Concentrate for solution for infusion (sterile concentrate). Each single-use vial contains 12 mg alemtuzumab (10 mg/mL; total extractable volume 1.2 mL).
Route(s) of administration: **Dose regimen:**	Intravenous (IV) infusion in a supervised medical setting Alemtuzumab administered as daily IV infusion for 5 consecutive days at Month 0 and for 3 consecutive days at Month 12. Calculation of the dose used will be determined based on patient weight: • 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).
Non Investigational medicinal product(s) **Formulation:**	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). • Day -1 (day before first IV infusion at each course) in the evening: - H1 antagonist according to the local label (eg, cetirizine), - H2 antagonist according to the local label (eg, ranitidine). • On days of IV infusions (1 hour prior to infusion): - H2 antagonist: eg, ranitidine or equivalent, - NSAID/antipyretic: Paracetamol or equivalent, - H1 antagonist IV diphenhydramine (25 mg or appropriate weight based dosing based on local health authority recommendation), immediately followed by: - IV methylprednisolone: administer 30 mg/kg or 1000 mg (whichever is lower) on infusion Days 1, 2, 3 (all courses) and ≥500 mg on infusion Days 4 and 5 (if 5 days of infusion). • Notes: a) If diphenhydramine IV is not available, an equivalent H1 antagonist can be used at an equivalent dosing, via IV route. b) If no H1 antagonist is available in IV formulation, an oral formulation of an equivalent compound can be used at an equivalent dosing, 2 hours prior to infusion. • Day 4 and Day 5 of the first course: - H1 antagonist, H2 antagonist, and antipyretics as needed, - Fluid intake will be encouraged. Concomitant medications: • Acyclovir 200 mg oral twice daily (or therapeutic equivalent) will also be provided at the beginning on the first day of each

	treatment course and continuing for a minimum of 1 month following treatment with alemtuzumab.
Route(s) of administration:	Methylprednisolone: IV Acyclovir: Oral Prednisone/Prednisolone: Oral Long-acting, nonsedating, nonselective antihistamine: Oral and/or IV H2-receptor antagonist: Oral
Dose regimen:	See above
ENDPOINTS	**Primary endpoint:** • The number of new or enlarging T2 lesions on brain MRI, during continuation of prior DMT (Period 1) compared to an equal period after the first course of alemtuzumab treatment (Period 2). **Secondary endpoints:** **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 statistics, eg, 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. **QoL:** • 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. **Safety endpoints:** • Safety and tolerability of alemtuzumab for up to 4 years after last dose of alemtuzumab. • Assessment of development of antialemtuzumab antibodies at baseline, and post dose Months 1, 3, 12 (prenext dose), 13, 15, and 24/at EOTP; and annually in the Safety Monitoring Phase. **Exploratory endpoint** • T1 weighted lesions and brain volume will be assessed on MRI as an exploratory endpoint throughout the study period.

ASSESSMENT SCHEDULE	**Efficacy** • EDSS: Screening, D-14 to D-7, M4, M8, M12, M15, M18, M21, M24/at end of treatment phase (EOTP); every 6 months in Safety Monitoring Phase, and at every relapse visit. • Brain MRI: Screening, D-14 to D-7, M4, M8, M12, M24/at EOTP; annually in Safety Monitoring Phase. • SDMT: Screening, D-14 to D-7, M4, M8, M12, M18, M24/at EOTP; annually in Safety Monitoring Phase. • BVMT-R: Screening, D-7, M4, M8, M12, M18, M24/at EOTP; annually in Safety Monitoring Phase. • QoL Questionnaires: Screening, D-7, M4, M8, M12, M18, M24/at EOTP; annually in Safety Monitoring Phase.
	Safety • Adverse event (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 safety monitoring phase, and at every relapse visit, if applicable. • Additionally, vital signs will be collected hourly during alemtuzumab infusion and post infusion observation for 2 hours. • Clinical chemistry laboratories: Screening, D-14 to D-7, M4, M8, M12, M15, M18, M21, M24/at EOTP; quarterly in safety monitoring phase. In addition, serum creatinine and alanine aminotransferase 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 safety monitoring phase. • Urinalysis: Screening, D-14 to D-7, monthly in alemtuzumab treatment phase (Year 1 and 2); EOTP and monthly in safety monitoring phase. • Thyroid function tests: Screening, D-14 to D-7, quarterly in both Alemtuzumab Treatment Phase (Year 1 and 2); EOTP, and in safety monitoring phase. • Tanner staging: Screening, M12, M24/at EOTP; annually in 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), M1, M3, M12 (prior to second course being administered), M13, M15, and M24/at EOTP; annually in safety monitoring phase. **Pharmacodynamics** • Lymphocyte phenotyping: Screening, D-14 to D-7, M1, M4, M8, M12, M13, M15, M18, M21, M24/at EOTP; annually in Safety Monitoring Phase. **Pharmacokinetics**

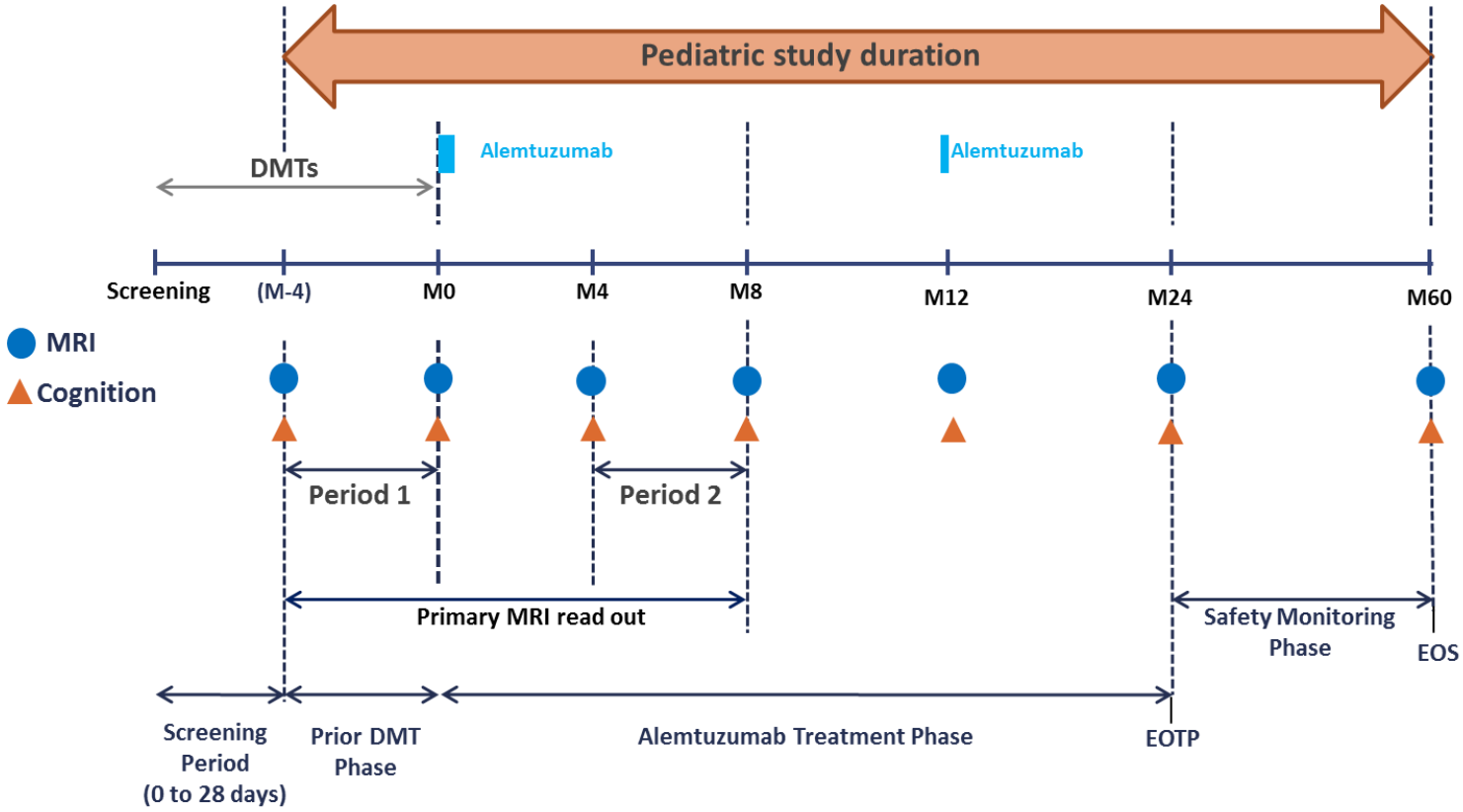
	• For patients receiving alemtuzumab, serum concentrations and PK parameters will be studied. **Immune Markers (optional)** • Immune Markers (optional): M0/D1 (baseline), M4, M12, M18 and M24/at EOTP.
STATISTICAL CONSIDERATIONS	**Sample size determination:** At least 60 patients will be screened in this study to ensure 50 evaluable patients to receive alemtuzumab treatment. This sample size will provide at least 85% power to detect a 50% reduction in the number of new or enlarging T2 lesions during continuation of prior DMT (Period 1) with their number in an equal period after the first course of alemtuzumab (Period 2), assuming 10% dropout and a two-tailed significance level of 0.05. These sample size calculations were simulated using a correlated repeated measures negative binomial regression model with generalized estimating equations (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). The sample size calculations also assume an overdispersion parameter of 0.7 for both study periods, which is consistent with the variability reported in other paediatric MS studies. **Analysis population:** Modified ITT (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. Safety: Safety and tolerability analyses will be conducted on all patients. **Primary analysis:** The number of new or enlarging T2 lesions during continuation of prior DMT (Period 1) and in an equal length period after the first course of alemtuzumab treatment (Period 2) will be analyzed and compared using a repeated measures negative binomial regression model with GEE. **Analysis of secondary endpoints:** • Safety and tolerability will be assessed using descriptive statistics and evaluated in comparison to the adult data for the treatment of MS using alemtuzumab. • EDSS (descriptive statistics, eg, percentages of stable/improved/worsened since the end of Period 1). • The ARR at Year 2 will be estimated using a negative binomial model with robust variance estimation. • The change from baseline in cognitive outcomes will be analyzed descriptively.

	• The change from baseline in QoL measures will be analyzed descriptively. • PK serum concentrations and PK parameters will be analyzed descriptively. • PD parameters including lymphocyte subsets will be analyzed descriptively. • Antialemtuzumab antibody results will be analyzed descriptively. • The number and proportion of patients with new or enlarging T2 lesions during Period 1 and Period 2 will be analyzed and compared using a repeated measures logistic regression model. **Planned Database lock date:** 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. The second database lock will be after the last patient has completed the safety monitoring phase (M60).
DURATION OF STUDY PERIOD (per patient)	Approximately 5 years 5 months: • Screening period: maximum 28 days prior to M 4. • Prior DMT phase: approximately 4 months. • Alemtuzumab treatment phase: approximately 2 years. • Safety follow-up period: approximately 3 years.
STUDY COMMITTEES	**Scientific Advisory Committee:** ☒ Yes ☐ No 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 SAC members. Detailed activities and responsibilities of the SAC are provided in the SAC charter. **Data Monitoring Committee:** ☒ Yes ☐ No 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 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. **Adjudication Committee:** ☐ Yes ☒ No

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



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

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.

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.

v Contraindications, including the following must be checked before infusion: severe active infection, uncontrolled hypertension, history of arterial dissection of the cervicocephalic arteries, history of stroke, history of angina pectoris or myocardial infarction, known coagulopathy or on concomitant anti-coagulant therapy

1.2.2 Schedule of events Part 2 (Year 2)

Table 2 - Schedule of events in Year 2

Visit Day[a]	**M13**	**M14**	**M15**	**M16**	**M17**	**M18**	**M19**	**M20**	**M21**	**M22**	**M23**	**M24 (EOTP)**	**Relapse Visit**[b]
Visit number	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28	
Treatment:													
Efficacy:													
EDSS			X			X			X			X	X
Brain MRI[c]												X	
SDMT						X						X	
BVMT-R Test						X						X	
PedsQL (QoL Questionnaire)/ Ped. NeuroQoL (subcomp.)[d]						X						X	
Safety:													
Physical examination[e]			X			X			X			X	X
Clinical chemistry laboratories[f]			X			X			X			X	
Hematology (Differential CBC[f])	X	X	X	X	X	X	X	X	X	X	X	X	
Thyroid Function Tests[g]			X			X			X			X	
Urinalysis[h]	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		
Lymphocyte phenotyping	X		X			X			X			X	
Samples for antibodies to Study Drug	X		X									X	
Tanner Staging[i]												X	
Concommitant medications	◄	─	─	─	─	─	─	─	─	─	─	─►	
AE/SAE recording (if any)	◄	─	─	─	─	─	─	─	─	─	─	─►	
Vital Signs			X			X			X			X	X
HPV[j] (yearly)	◄	─	─	─	─	─	─	─	─	─	─	─►	
Laboratory testing:													
PK sampling[k]	X[k]	X[k]											
Immune Marker Sampling (optional)						X						X	

Abbreviations: AE: adverse event; BVMT-R: brief visuospatial memory test-revised, CBC: complete blood count; EDSS: Expanded Disability Status Scale; EOTP: end of treatment phase; M: month(s); MRI: magnetic resonance imaging; Neuro-QoL: quality of life in neurological disorders; Ped: pediatric; PK: pharmacokinetics; QoL: quality of life; SAE: serious adverse event; 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 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.

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.

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.

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.

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3 LIST OF ABBREVIATIONS

ADA: antidrug antibody
AE: adverse event
ALT: alanine aminotransferase
ARR: annualized relapse rate
AUC: area under the cumulative serum concentration versus time curve
AUC_{last}: area under the cumulative serum concentration versus time curve extrapolated to infinity
BVMT-R: Brief Visuospatial Memory Test-Revised
CBC: complete blood count
C_{max}: maximum serum concentration observed
CMV: cytomegalovirus
CTCAE: Common Terminology Criteria for Adverse Events
DMC: Data Monitoring Committee
DMT: disease modifying therapy
e-CRF: electronic-case report form
EDSS: Expanded Disability Status Scale
EMA: European Medicines Agency
EOS: end of safety monitoring phase
EOTP: end of treatment phase
EU: European Union
GA: glatiramer acetate
GBM: glomerular basement membrane
GCP: Good Clinical Practice
Gd: gadolinium
GEE: generalized estimating equations
H1: histamine receptor H1
H2: histamine receptor H2
HLGT: high level group term
HLH: hemophagocytic lymphohistiocytosis
HLT: high level term
HPV: human papillomavirus
HSV: herpes simplex virus
IAR: infusion-associated reaction
ICF: informed consent form
IEC: independent ethics committee
IFNB: interferon beta
IFNB-1a: interferon beta 1-alpha
IMP: Investigational Medicinal Product
IRB: institutional review board
ITP: immune thrombocytopenia
IV: intravenous(ly)
IVRS: interactive voice response system

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

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).

Alemtuzumab Clinical Data in Adults

Alemtuzumab is a humanized monoclonal antibody that targets CD52, a cell surface antigen present at high levels on B and T lymphocytes and at lower levels on natural killer cells, monocytes and macrophages. There is little or no CD52 detected on neutrophils, plasma cells, or bone marrow stem cells. Alemtuzumab acts through antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity following cell surface binding to T and B lymphocytes. It effects rapid and sustained lymphocyte depletion and has shown potent efficacy in treatment-naïve as well as treatment-refractory patients with relapsing remitting multiple sclerosis (RRMS). Treatment with alemtuzumab 12 mg/day is efficacious in patients with RRMS and was associated with clinically meaningful and statistically significant improvements in clinical endpoints, imaging endpoints and composite disease measures, compared with subcutaneous (SC), high-dose, high-frequency interferon-beta-1alpha (IFNB-1a).

MS relapses are caused by focal inflammatory lesions, which are detected by magnetic resonance imaging (MRI) as new or enlarging T2-hyperintense and Gd (Gadolinium)-enhancing lesions, in brain or spinal cord. Prior studies have established a strong correlation between relapse outcomes and the occurrence of such lesions (13). A correlation between effects on MRI measures and relapses is also seen in alemtuzumab studies. Table 6 shows the odds ratio for the occurrence of at least one relapse (versus no relapses) for patients who developed at least one new or enlarging T2 lesion (versus no new/enlarging lesions) over the course of the 2-year study period in studies CAMMS323 or CAMMS324. In both studies, a strong and statistically significant relationship is seen between risk of T2 lesions and relapse, with patients being at least 50% more likely to experience relapse if they have MRI lesion activity. These findings demonstrate that the conclusion from prior studies (13) of a strong correlation between this objective MRI outcome and relapse rate applies also to alemtuzumab clinical studies of adult MS patients, and support the use of new/enlarging T2 lesions as a primary efficacy endpoint in the proposed paediatric MS study.

Table 6 - MRI correlative analyses with relapse in adult Phase 3 studies (CAMMS323 and CAMMS324)

	Study CAMMS323		Study CAMMS324	
Endpoint	OR	p-value	OR	p-value
Gadolinium enhancing lesions at Month 24	1.58	0.1217	2.31	0.0012
New/enlarging T2 lesions over 24 months	1.54	0.0312	1.52	0.0200
New T1 lesions over 24 months	1.59	0.0347	1.69	0.0078
MRI activity over 24 months	1.53	0.0384	1.48	0.0296

Abbreviation: MRI: magnetic resonance imaging; OR: odds ratio

Clinical trials with alemtuzumab in adult MS patients have provided a consistent pattern of safety observations that include infusion associated reactions (IARs), autoimmune disorders (thyroid disorders, immune thrombocytopenia [ITP], nephropathies such as antiglomerular basement membrane [antiGBM disease and other cytopenias), and infections. Measures to detect and manage these effects were implemented early and refined throughout the clinical program. These measures enabled the management of patients within the studies and have laid a foundation for the care of patients outside of the clinical trial setting.

Most patients treated with alemtuzumab in controlled clinical trials in MS experienced mild to moderate IARs during or soon after alemtuzumab 12 mg administration. Common IARs include headache, rash, pyrexia, nausea, urticaria, pruritus, insomnia, chills, flushing, fatigue, dyspnea, dysgeusia, chest discomfort, generalized rash, tachycardia, dyspepsia, dizziness, and pain. Serious reactions occurred in 3% of patients including cases of pyrexia, urticaria, atrial fibrillation, nausea, chest discomfort, and hypotension. In addition, anaphylaxis has been reported rarely. Prophylactic use of corticosteroids was useful in alleviating IARs and is part of the recommended prescribing information for alemtuzumab use in MS patients. In addition, modification of the duration of infusion is permitted to help patients tolerate infusions if needed and symptomatic medications such as antihistamines and/or antipyretics were administered often in the studies.

Alemtuzumab treatment increases the risk of autoimmune-mediated conditions. Autoimmune thyroid disorders occurred in 36 % of patients in clinical trials in MS through 4 years following first exposure. Observed autoimmune thyroid disorders included hyperthyroidism and hypothyroidism, which occurred at similar rates. Serious thyroid related events occurred in <1% patients. No consistent pattern was observed with regards to time of onset after treatment initiation, although the highest incidence of thyroid adverse events (AEs) was observed in Year 3 after the first treatment course. Therefore, as part of the risk minimization strategy for autoimmune disorders, thyroid function tests must be obtained prior to the initiation of alemtuzumab treatment and every 3 months thereafter until 48 months following the last infusion. This will allow the timely detection and treatment of thyroid disorders for patients treated with alemtuzumab.

Immune thrombocytopenia and nephropathies, including antiGBM disease, although potentially more serious than thyroid disorders, were observed infrequently. Serious events of ITP have been observed in approximately 1% of patients treated with alemtuzumab in clinical trials in MS. Fatality in the index case of ITP, which was reported in the Phase 2 study, highlights the seriousness of the risks associated with the disorder. However, risk minimization measures including patient education and monthly complete blood counts (CBCs) introduced to monitor for ITP and other potential autoimmune cytopenias in the clinical studies allowed the prompt diagnosis and treatment of patients who subsequently developed these conditions. AntiGBM disease was reported rarely in the clinical program. Nephropathies including antiGBM disease have been observed in controlled clinical trials in MS. Patient education and monthly testing of serum creatinine were effective in identifying cases early to allow prompt treatment. Similarly, urinalysis testing was also effective in identifying nephropathies during the clinical studies. Accordingly, monthly testing including CBC with differential, platelet count and monitoring for any cytopenia as well as serum creatinine testing and urinalysis with microcopy, must be obtained prior to treatment with alemtuzumab and every month thereafter until 48 months following the last infusion. This will facilitate the early detection and treatment of these disorders, should they occur.

Infections occurred in 71% of patients treated with Lemtrada® 12 mg as compared to 53% of patients treated with Rebif® (IFNB-1a) in controlled clinical trials in MS up to 2 years in duration and were predominantly mild to moderate in severity. Serious infections occurred in 2.7% of patients treated with alemtuzumab as compared to 1.0% of patients treated with IFNB-1a in controlled clinical trials in MS. The most frequent infections reported in alemtuzumab-treated

patients were nasopharyngitis, urinary tract infections (UTI), upper respiratory tract infections (uRTI), sinusitis, influenza, bronchitis, oral herpes and herpes zoster. Prophylactic acyclovir treatment was used effectively in the clinical studies to reduce risk of Herpes Simplex virus infection (HSV) and therefore patients should receive concomitant acyclovir starting on the first day of any alemtuzumab course and continuing for at least 1 month after the last day of the course. Preservation of innate immunity and relative sparing of memory lymphocytes, together with the preservation of serum immunoglobulins (14), may contribute to the relatively low rate of serious infections following alemtuzumab treatment in MS patients.

During the course of the clinical studies, malignancies were observed in both alemtuzumab- and IFNB-1a-treated patients. However, the annualized rates of malignancy were similar across all treatment groups, and moreover, the malignancy risk was similar to the background incidence in the general population. The risk of malignancy will be further investigated in a long-term observational study.

As previously mentioned, the identified risks of alemtuzumab in patients with RRMS include:

- IARs (including cerebrovascular, cardiovascular, and pulmonary alveolar hemorrhage events).
- Serious infections.
- Autoimmunity (notably, ITP, thyroid disorders, or rarely nephropathies and autoimmune hepatitis, and hepatic injury).

Alemtuzumab Post-Marketing Updates in Adult

In post-marketing pharmacovigilance (PV) monitoring, infrequent cases of temporally associated pulmonary alveolar haemorrhage, myocardial ischemia, stroke (including ischemic and hemorrhagic stroke) and cervicocephalic (eg, vertebral, carotid) arterial dissection have been reported. Reactions may occur following any of the infusions during the treatment course. In the majority of cases time to onset was within 1-3 days of alemtuzumab infusion. Patients should be informed about the signs and symptoms, and advised to seek immediate medical attention if any of these symptoms occur.

Post marketing PV monitoring has also identified events reported as autoimmune encephalitis, autoimmune hepatitis, acquired hemophilia A, thrombotic thrombocytopenic pupura (TTP) and hepatic injury. Infrequent events reported as hemophagocytic lymphohistiocytosis (HLH) and PML have been noted. The emergence of these events during the clinical development program and post-marketing PV reporting prompted the initiation and ongoing modification of risk minimization measures. In conclusion, there are recently identified serious but rare risks associated with alemtuzumab administration. Risk minimization measures for clinical studies are in place, and they have been modified based upon post-marketing PV reporting.

Alemtuzumab has been approved in the European Union, United States, Canada, Australia, Brazil and several other countries as Lemtrada for the treatment of active RRMS in adults with RRMS; the specific indicated population varies by country.

Study design rationale

The proposed design will investigate efficacy, safety, and tolerability of alemtuzumab compared to other DMTs, (ie, IFNB and glatiramer acetate [GA]) in an open-label, rater-blinded, single-arm, before and after switch study, in paediatric patients with RRMS aged from 10 years to less than 18 years with disease activity on prior DMT, with a rater-blinded MRI endpoint.

This study is based on the paediatric investigational plan (PIP) agreed with the European Medicines Agency (EMA) and its Paediatric Committees (PDCO).

Patient population

- The patient population intended for this paediatric study will be narrower than the population described in the adult indication to expose only these paediatric patients with high medical need, having MS disease activity while on treatment with prior DMT. The MS disease activity criteria include having at least 2 recorded MS attacks; at least 1 MS relapse in the last year during treatment with an IFNB or GA after having been on that therapy for at least 6 months, and is currently still taking the same therapy; and having either ≥1 new or enlarging T2 hyperintense lesion or gadolinium enhancing lesion while on that same prior therapy (IFNB or GA), or 2 or more relapses in the prior year, or tried at least 2 MS DMTs.

The age group eligible to enroll (from 10 years to less than 18 years) has higher MS prevalence than younger age groups.

Interferon-beta (IFNB) and GA have not been formally tested in paediatric MS patients with a relapsing-remitting course during placebo-controlled trials. However, class III and IV evidence of effectiveness resulting from observational open-label studies have prompted their current use and recommendation. Nonetheless, in about 30% of paediatric MS patients, the disease continues to be active despite immunomodulatory treatment, supporting the need to explore other therapeutic options (15). There are few data to support the use of other DMTs in paediatric populations. Considering the high frequency of inadequate response to first-line DMT and the lack of clinical trial data regarding the efficacy of switching to other DMTs, this paediatric population has a high unmet need.

Alemtuzumab dose selection

Alemtuzumab will be administered as a daily intravenous (IV) infusion, similar to adult treatment regimen (course 1 at Month 0, 12 mg on 5 consecutive days, and course 2 at Month 12, 12 mg on 3 consecutive days), giving a cumulative dosage of 60 mg at first course, and 36 mg at second course. The adult dose will be adjusted (reduced) proportionately for paediatric patients <50 kg based on the patient's weight. Calculation of a paediatric patient's dose will be based on patient's last visit weight taken during the physical examination:

- 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).

The 0.24 mg/kg/day dose is based on experience using alemtuzumab in the treatment of children undergoing bone marrow or solid organ transplantation, and is similar to or lower than doses previously used (16). This corresponds to a cumulative dose over 5 days of 1.2 mg/kg at Month 0, with a smaller dose of 0.72 mg/kg at Month 12.

Prophylactic administration of methylprednisolone, antiH1 and antiH2 medications will be a part of the alemtuzumab treatment regimen, to minimize infusion associated reactions.

MRI

The proposed study will have an MRI-based primary endpoint. Recent publications have demonstrated a correlation between the MRI lesions and clinical relapse for IFNB or GA based on meta-analysis of data collected in randomized controlled trials (17), and for alemtuzumab (13). MRI assessments will be available to investigators to assess safety.

The period of 4 months for comparison of new or enlarged T2 lesions on prior DMT versus on alemtuzumab was selected on advice of paediatric MS experts as representing the optimum interval to achieve the scientific aims of the study consistent with current patient care practice for children experiencing disease activity while using IFNB or GA.

5 STUDY OBJECTIVES

5.1 PRIMARY

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

5.2 SECONDARY

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

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.

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.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Patients with RRMS aged from 10 years to less than 18 years at study entry are eligible. Patients must meet the criteria of diagnosis of MS as defined by the International Paediatric Multiple Sclerosis Study Group criteria for paediatric MS (12) and the criteria of MS based on McDonald criteria 2010 (18) (Appendix C).

Specific to the Russian Federation:
In the Russian Federation: Patients with RRMS aged ≥12 years to <18 years are eligible at study entry (Appendix H).

I 02. Signed written informed consent/assent obtained from patient and patient's legal representative (parent or guardian) according to local regulations.

I 03. Expanded Disability Status Scale (EDSS) score of 0.0 to 5.0 (inclusive) at screening (Appendix D).

I 04. At least 2 recorded MS attacks, and at least 1 MS attack (relapse) in the last year during treatment with an IFNB or GA after having been on that therapy for at least 6 months, and is currently still taking the same therapy.

I 05. At least 1 of the following:

- ≥1 new or enlarging T2 hyperintense lesion or gadolinium enhancing lesion while on that same prior therapy (IFNB or GA), OR
- 2 or more relapses in the prior year, OR
- tried at least 2 MS DMTs.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 3 subsections:

NOTE: Prior to initiation of any alemtuzumab treatment course, contraindications should be reviewed as pre-treatment verification of eligibility.

7.2.1 Exclusion criteria related to study methodology

E 01. Any progressive or nonrelapsing forms of MS.

E 02. Conditions/situations such as:

- Impossibility to meet specific protocol requirements,
- Current participation in another interventional clinical study. If a patient has been enrolled in a clinical trial and treated with a comparator agent that is an approved agent

for screening inclusion (INF or GA), they may be considered for this trial if they meet all inclusion and exclusion criteria otherwise,

- Patient is the Investigator or any SubInvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol,
- Uncooperative patient or any condition that could make the patient potentially noncompliant to the study procedures in the opinion of the Investigator.

E 03. Mental condition rendering the patient or parent/guardian unable to understand the nature, scope, and possible consequences of the study.

E 04. Clinically relevant cardiovascular, hepatic, neurological, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult or that would put the patient at risk by participating in the study in the opinion of the Investigator.

E 05. History of drug or alcohol abuse.

E 06. History of known HIV positivity.

7.2.2 Exclusion criteria related to alemtuzumab and/or mandatory background therapies

E 07. Pregnant or breast-feeding female patients or those who plan to become pregnant during the study.

E 08. Unwilling to agree to use a highly effective contraceptive method as defined (Appendix A) when receiving a course of alemtuzumab treatment and for 4 months following that course of treatment (fertile patients only).

E 09. Female patients who have commenced menstruating (ie, are of childbearing potential) and are unwilling or unable to be tested for pregnancy.

E 10. Previous treatment with alemtuzumab.

E 11. Treatment with natalizumab, daclizumab, fingolimod, methotrexate, azathioprine, cyclosporine, or mycophenolate mofetil in the last 6 months prior to screening, or as determined by the treating physician to have residual immune suppression from these or other MS treatments.

E 12. Treatment with teriflunomide in the last 12 months except if the patient underwent the accelerated elimination procedure as per local teriflunomide label.

E 13. Previous treatment with mitoxantrone, cyclophosphamide, cladribine, rituximab, ocrelizumab, leflunomide, or any cytotoxic therapy.

E 14. Previous treatment with any investigational medication (drug that has not been approved at any dose or for any indication). Use of an investigational medication that was subsequently licensed and nonstandard use of a licensed medication (eg, using a dose other than the dose

that is stated in the licensed product labeling or using a licensed therapy for an alternative indication) is not exclusionary. Prior treatment with herbal medications or nutritional supplements is also permitted.

E 15. Intolerance of pulsed corticosteroids, especially a history of steroid psychosis.

7.2.3 Exclusion criteria related to the current knowledge of alemtuzumab and study methodology

If a patient was deemed a screen failure, he or she may be re-screened for this study up to 2 times. If a patient who previously failed screening for any reason is re-screened, the patient must sign a new informed consent form and be assigned a new patient number by IWRS/IVRS (the next sequential patient number at the site). All screening assessments need to be repeated to confirm eligibility for the study. Rescreening assessments may be discussed with the Sponsor on a case-by-case basis.

Medical History

E 16. History of malignancy.

E 17. Prior documented history of thrombocytopenia, or platelet count at screening < lower limit of normal (LLN).

E 18. Any disability acquired from trauma or another illness that, in the opinion of the Investigator, could interfere with evaluation of disability due to MS.

E 19. Patients with known Type 1 hypersensitivity or anaphylactic reactions to the active substances or any of the excipients, or intolerance of acyclovir or its therapeutic equivalent.

Medical Conditions

E 20. Major systemic disease or other illness that would, in the opinion of the Investigator, compromise patient safety or interfere with the interpretation of study results, eg, current peptic ulcer disease, or other conditions that may predispose to hemorrhage, immune cytopenias, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue disorders, vasculitis, inflammatory bowel disease, severe psoriasis.

E 21. Medical, psychiatric, cognitive, or other conditions that, in the Investigator's opinion, compromise the patient's ability to understand the patient information, to give informed consent, to comply with the trial protocol, or to complete the study.

E 22. Major psychiatric disorder that is not adequately controlled by treatment in the opinion of the Investigator.

E 23. Epileptic seizures that are not adequately controlled by treatment.

E 24. MRI-related conditions: conditions that could interfere with MRI acquisition and/or interpretation of MRI results (eg, claustrophobia, orthopedic implants/treatments, orthodontic treatments etc).

E 25. Known bleeding disorder (eg, dysfibrinogenemia, factor IX deficiency, hemophilia, Von Willebrand's disease, disseminated intravascular coagulation, fibrinogen deficiency, clotting factor deficiency).

Infections

E 26. Prior history of invasive fungal infections.

E 27. Active infection, eg, deep-tissue infection, that the Investigator considers sufficiently serious to preclude study participation.

E 28. In the Investigator's opinion, patient is at high risk for infection (eg, indwelling catheter, dysphagia with aspiration, decubitus ulcer, history of prior aspiration pneumonia or recurrent urinary tract infection).

E 29. Infection with hepatitis B, C viruses (positive serology, but not due to hepatitis immunization).

E 30. History of tuberculosis (TB)/latent TB (unless it is documented by a specialist that the patient has been adequately treated and can now start treatment with a biologic agent).

E 31. 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).

E 32. Any other illness or infection (latent or active) that, in the Investigator's opinion, could be exacerbated by study medication.

Laboratory Parameters

E 33. Confirmed platelet count <LLN of the evaluating laboratory at Screening or documented at <100 000/μL within the past year on a sample without platelet clumping.

E 34. CD4+, CD8+, or CD19+ (ie, absolute CD3+CD4+, CD3+CD8+, or CD19+/mm^3) count <LLN at Screening; if abnormal cell count(s) return to within normal limits, eligibility may be reassessed.

E 35. Absolute neutrophil count <LLN at Screening; if abnormal cell count returns to within normal limits, eligibility may be reassessed.

Note: If the treating physician suspects out-of-range cell count results are based upon issues of sample transportation or environmental conditions, the treating physician may request a repeat sample to be evaluated locally to confirm the patient is not excluded from the trial. If out-of-range cell counts are not confirmed through evaluations performed locally, the treating physician should

document (in source data and in a CRF comment) that the central laboratory results are considered falsely exclusive, and proceed to enroll the patient.

E 36. Any hepatic or renal function value Grade 2 or higher at Screening, with the exception of hyperbilirubinemia due to Gilbert's syndrome, unless, in the Investigator's opinion, the abnormality is due to a condition that has resolved (eg, recent interferon treatment subsequently discontinued) and levels return to within normal limits. See Table 7 below, drawn from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE), published 09 August 2006.

Table 7 - Common terminology criteria for adverse events v3.0, published 09 August 2006.

Hepatic	
Bilirubin	>1.5 x ULN
SGOT/AST	>2.5 x ULN
SGPT/ALT	>2.5 x ULN
Alkaline phosphatase	>2.5 x ULN
Renal	
Creatinine	>1.5 x ULN

Abbreviations: AST: aspartate aminotransferase; ALT: alanine aminotransferase; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; ULN: upper limit of normal.

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.

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).

- Day -1 (day before first IV infusion at each course) in the evening:
  - H1 antagonist according to the local label (eg, cetirizine),
  - H2 antagonist according to the local label (eg, ranitidine).
- On days of IV infusions (1 hour prior to infusion):
  - H2 antagonist: eg, ranitidine or equivalent,
  - NSAID/antipyretic: paracetamol or equivalent,
  - H1 antagonist IV diphenhydramine (25 mg or appropriate weight based dosing based on local health authority recommendations [Appendix H]), immediately followed by:
  - IV methylprednisolone: administer 1000 mg on infusion Days 1, 2, 3 (all courses) and ≥500 mg on infusion Days 4 and 5 (if 5 days of infusion).

    Notes:
- a) If diphenhydramine IV is not available, an equivalent H1 antagonist can be used at an equivalent dosing, via IV route,

  b) If no H1 antagonist is available in IV formulation, an oral formulation of an equivalent compound can be used at an equivalent dosing, 2 hours prior to infusion.
- Day 4 and Day 5 of the first course:
  - H1 antagonist, H2 antagonist, and antipyretics as needed,
  - Fluid intake will be encouraged.

B) Concomitant medications:

- Acyclovir 200 mg oral twice daily (or therapeutic equivalent) will also be provided/given at the beginning on the first day of each treatment course and continuing for a minimum of 1 month following treatment with alemtuzumab.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

This study has an open-label design. All enrolled patients will be on prior DMT when entering into the study and will be treated with alemtuzumab during alemtuzumab treatment phase. No randomization will be done.

The study will be rater-blinded for MRI. All brain scans will be reviewed and interpreted by one or more MRI experts at an independent, central facility with no access (ie, blinded) to treatment thereby avoiding bias. Refer to Section 9.1.1.1 and Section 9.2.1.1.

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

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

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

No randomization will be performed.

An interactive voice response system (IVRS)/interactive web response system (IWRS) will be used for this study to manage and control alemtuzumab dispensation. The treatment kit number list is generated centrally by Sanofi. Alemtuzumab will be packaged in accordance with this list.

8.5 PACKAGING AND LABELING

Packaging will be in accordance with the administration schedule. The content of the labeling will be in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing alemtuzumab in a secure and safe place in accordance with local regulations, labeling specifications, policies and procedures.

Control of storage conditions for alemtuzumab will be provided by the Sponsor, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling alemtuzumab.

Alemtuzumab, in vials, must be stored between +2°C to + 8°C (+36°F to +46°F). Do not freeze and do not shake. Do not use alemtuzumab beyond the use by date provided on the label or other documentation. Protect from light.

Prior to administration, protect diluted alemtuzumab solution from light and store for as long as 8 hours either at room temperature 15°C to 25°C (59°F to 77°F) or keep refrigerated at conditions 2°C to 8°C (36°F to 46°F). From a microbiological point of view, it is recommended that the product should be used immediately. Partially used, unused or damaged drug vials should be disposed according to institutional policies.

Alemtuzumab will be used in accordance with the approved protocol and must not be used for any other purpose.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor (see Section 10.4.7). Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

As alemtuzumab will be administered by daily IV infusions in a day hospital supervised medical setting, by qualified center personnel, responsibility for compliance with mandatory safety assessments resides with the Study Investigator.

8.7.2 Return and/or destruction of treatments

For IMP provided by the Sponsor:

Reconciliation of all used, partially-used or unused treatments must be performed at the site by the Investigator and the monitoring team using treatment log forms.

Written authorization for destruction will be given by the sponsor once the reconciliation has been completed. This destruction can be performed at the site depending on local regulations and site specific capabilities; alternatively, study drug may be returned to the sponsor or designee for destruction. The Investigator will not destroy the used and unused IMP unless the Sponsor provides written authorization.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s). Concomitant treatments have been detailed for all phases of the study and are not limited to the treatment received with the IMP (treatment phase). Concomitant use of alternative medications (eg, herbal treatments, botanicals, etc) for treatment of MS is discouraged due to concerns of possible interactions with study treatment. Patients should be questioned about their use of such nonprescription therapies, all of which will be listed as concomitant medications.

Prior DMT period

Therapy with disease-modifying MS treatments that the patient is currently being administered (ie, limited to interferons and GA only) will be permitted during the screening and prior DMT Treatment Phase. If the investigator determines that the patient needs to be treated with another DMT, the patient will be discontinued from the study.

Prior DMT will be discontinued 7 days before alemtuzumab first administration. Refer to Section 6.1 for further details.

No concomitant therapy with any other disease-modifying MS treatments either licensed or investigational will be permitted during the screening and prior DMT period.

Concomitant use of systemic corticosteroids for the treatment of MS relapse is allowed during the DMT period.

Alemtuzumab treatment phase

Patients who receive any alemtuzumab treatment will continue study participation even if they do not complete the planned treatment regimen. Patients who discontinue study treatment can continue study participation. If a patient is not willing to continue study participation, all efforts should be made to have the EOTP visit performed by the patient.

No concomitant therapy with any disease-modifying MS treatments either licensed or investigational, including interferons and GA, will be permitted during the alemtuzumab treatment phase. If the investigator determines that the patient needs to be treated with another DMT, the patient will be discontinued from the study.

In addition, no other investigational MS therapy, including investigational symptomatic therapy, will be permitted. Use of live vaccines is specifically prohibited for alemtuzumab-treated patients for the 30 days prior to the first alemtuzumab administration at Month 0 and for the 2 years duration of the alemtuzumab treatment phase of the study.

Concomitant use of systemic corticosteroids for the treatment of MS relapse is allowed during this period.

Safety monitoring phase

The safety of MS disease-modifying drugs in patients who receive alemtuzumab has not been established. Alemtuzumab treatment may have long-lasting, unknown effects on a patient's immune system. Concomitant therapy with any disease-modifying MS treatments following treatment with alemtuzumab has not been studied in a controlled study conducted by Sanofi Genzyme. Investigators should consider the potential for adverse effects associated with subsequent or concomitant treatment with cytotoxic or immunosuppressant drugs in patients who have received alemtuzumab.

Participating patients are prohibited from use of any investigational MS therapy.

It is investigator criteria to determine if the patient needs to be treated with another DMT, and in which case the patient will be discontinued from the study.

Concomitant use of systemic corticosteroids for the treatment of MS relapse is allowed during the course of the Study. Relapses may be treated with systemic corticosteroids if clinically necessary and as per Investigator judgment in doses appropriate for paediatric population.

The use of systemic corticosteroids or adrenocorticotrophic hormone within 2 weeks prior to MRI assessment is not permitted due to potential interference with MRI assessment.

It is recommended that patients complete local immunization requirements at least 6 weeks prior to treatment with alemtuzumab. The ability to generate an immune response to any vaccine following alemtuzumab treatment has not been studied.

The safety of immunization with live viral vaccines following a course of alemtuzumab treatment has not been formally studied in controlled clinical trials in MS. Live vaccines must not be administered to MS patients who have recently received a course of alemtuzumab. Also, some experts urge caution in using live pathogen vaccinations in people with MS (National MS Society web site).

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

The assessments will be performed according to the schedule presented in the Study Flowchart. See Section 1.2 and Section 10 for further details.

9.1 PRIMARY ENDPOINT

9.1.1 Primary efficacy endpoint

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

9.1.1.1 Brain MRI

For primary endpoint assessment, two periods have been defined

- **Period 1**: will occur from M-4 up to M0. An MRI will be performed during the screening period and another at Visit 3. Both MRI will be taken while patients are on their prior DMT. The two MRIs will be compared by a central assessor to count the number of new or enlarging T2 lesions. It is important to ensure that these 2 MRI assessments are performed 4 months (±7 days) apart.
- **Period 2**: will occur from M4 to M8: The MRI performed at the M4 visit will be the baseline MRI for Period 2. A second MRI will be performed after alemtuzumab first course of treatment at M8. The two MRIs will be compared by a central assessor to count the number of new or enlarging T2 lesions. It is important to ensure that these 2 MRI assessments are performed 4 months (±7 days) apart.

It is expected that Periods 1 and 2 will be of the same length ±7 days.

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

Screening MRI is expected to be reviewed locally by PI only for study eligibility confirmation. The MRI assessments will also be available to the investigators to assess safety.

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

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

An MRI manual explaining the instructions for standard image acquisition requirements, data transfer, archiving and shipping, and outlining the phantom data approval process will be provided to all centers.

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).

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:

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

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.

The Tanner scale (also known as the Tanner stages I-V) is a scale of physical development in children, adolescents and adults (23, 24). The scale defines physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitalia, and development of pubic hair. Tanner scale is performed either at the study site by the paediatric neurologist or paediatrician or at a designated site arranged by the Investigator.

9.3.6 Other safety endpoints

The other safety endpoints will be assessed by:

- Antidrug antibody formation (ADA).

Assessment of ADA formation will be performed at M0/D1 (baseline), post dose, M1, M3, M12 (prenext dose), M13, M15, M24/at EOTP, and annually in the safety monitoring phase.

IV infusion of alemtuzumab has been associated with the development of antialemtuzumab antibodies and inhibitory antibodies. Serum samples will be tested by established assay methods for the presence of antialemtuzumab antibodies and titers will be quantified for positive samples.

9.4 EXPLORATORY ENDPOINT

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

9.5 FUTURE USE OF SAMPLES

9.5.1 Immune markers (optional)

Based on the increased risk of autoimmune events observed with alemtuzumab, serum will be collected to support investigation of potential biomarkers predictive of the response to alemtuzumab. The markers to be tested may include cytokines and possibly other serum components; the specific markers to be assessed will be guided by results of ongoing biomarker investigations with alemtuzumab.

If the patient accepts to sign the specific informed consent form (ICF), “Future Use of Samples”, serum samples and peripheral blood mononuclear cell will be collected at the visit specified in the study flow chart (designated “immune markers”) and these samples will be stored to support future investigation of potential biomarkers predictive of autoimmunity, such as serum cytokines.

9.6 APPROPRIATENESS OF MEASUREMENTS

The primary endpoint is the number of new or enlarging T2 lesions during continuation of prior DMT (Period 1) and during an approximately equal period of time after Course 1 of alemtuzumab treatment (Period 2) This endpoint was agreed upon by the Paediatric Committee (PDCO to protect the study population from any significant treatment-free period and provide an analysis of

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).

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),

- 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.

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.

On days of alemtuzumab infusion, and 1 hour prior to the infusion, H1 antagonist IV should be administered immediately followed by 1000mg IV methylprednisolone (whichever is lower), on the first 3 days of alemtuzumab administration and ≥500 mg on infusion Days 4 and 5. H2 antagonist medications and NSAID/antipyretic should be administered on the 5 days of alemtuzumab administration as needed. Study patients should also receive antiviral prophylaxis for herpetic viral infection beginning on Day 1 and continuing for a minimum of 1 month. If diphenhydramine IV is not available, an equivalent H1 antagonist can be used at an equivalent dosing, via IV route. If no H1 antagonist is available in IV formulation, an oral formulation of an equivalent compound can be used at an equivalent dosing, 2 hours prior to infusion.

Alemtuzumab will be administered as daily IV infusion on 5 consecutive days in a supervised medical setting. Calculation of the dose used will be based on patient weight .Vital signs during infusion days will be monitored.

The following assessments should be done as listed in the study flow chart (refer to Section 1.2.1):

- Physical examination and vital signs.
- Check for compliance.
- Preinfusion blood samples collection for clinical laboratory assessments and for ADA.
- Blood sample collection for serum creatinine and ALT.
- Blood samples collection for immune markers (optional) and PK.
- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).
- The Investigator or designee will contact the IVRS to obtain a treatment kit number.

The following infusion management procedures must be utilized for each infusion and each treatment course:

- Pre-infusion : Physicians should obtain a baseline ECG and vital signs (including heart rate and blood pressure measurement), screen for pre-existing hemorrhagic, cardiovascular (including venous thromboembolism) and cerebrovascular risk factors, screen for lung disease, review concomitant medications (eg, antiplatelet agents, anticoagulants), perform laboratory tests (complete blood count with differential, serum transaminases, serum creatinine, test of thyroid function and urinalysis with microscopy), and evaluate infusion-related risks. Physician should also apply the following contraindications when treating patients in this study:
    - Hypersensitivity to the active substance, or to any of the excipients
    - Human Immunodeficiency Virus (HIV) infection
    - Severe active infection
    - Uncontrolled hypertension
    - History of arterial dissection of the cervicocephalic arteries
    - History of stroke
    - History of angina pectoris or myocardial infarction
    - Known coagulopathy or on concomitant anti-coagulant therapy

It is at investigator's discretion to treat or not treat patient with alemtuzumab after clinical evaluation.

- During infusion: Continuous/frequent monitoring of heart rate, blood pressure assessment (at least hourly) and overall clinical status of the patients including consideration of the volume of fluids administered. The following are recommendations in case of clinical abnormities/severe adverse event:
    - Interrupt infusion
    - Medically evaluate the patient guided by the adverse event profile of alemtuzumab prior to considering restarting therapy
    - Provide appropriate treatment as needed
    - Consider permanently discontinuing the alemtuzumab infusion if the patient shows clinical symptoms suggesting development of a serious adverse event associated with the infusion (myocardial ischemia, hemorrhagic stroke, cervico-cephalic arterial dissection or pulmonary alveolar hemorrhage).
    - Implement appropriate measures for patients at risk of venous thromboembolism: repeated ambulation during infusion and/or compression stockings.

- Post-infusion: Observation and education of patients
    - Observation for infusion reactions is recommended for a minimum of 2 hours after alemtuzumab infusion; 2 hours after infusion, patients should be cautious and reporting if any of the infusion reactions develop within 48 hours.
    - Patients with clinical symptoms suggesting development of a serious adverse event temporarily associated with the infusion (myocardial ischemia, hemorrhagic stroke, cervico-cephalic arterial dissection or pulmonary alveolar hemorrhage) should be closely monitored until complete resolution of the symptoms. The observation time should be extended as appropriate.
    - Patients with persistent blood pressure elevation should be referred to an appropriate medical facility for continued monitoring and treatment.
    - The patients should be educated on the potential for delayed onset of infusion associated reactions and symptoms and signs of cardiovascular or cerebrovascular events, and instructed to report symptoms and/or seek appropriate medical care.

10.1.5 Visit 5 to Visit 7/M1 to M3

The following assessments should be done as listed in the study flow chart:

- Blood sample collection for clinical laboratory assessments and urinalysis.
- Blood samples collection for ADA at Visit 5 and Visit 7 and for lymphocyte phenotyping at Visit 5.
- Blood sample collection for thyroid function test at Visit 7.

- Blood samples collection for PK on Visit 5 and Visit 6.
- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).

10.1.6 Visit 8/M4

The following assessments should be done as listed in the study flow chart:

- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).
- Physical examination and vital signs.
- Blood samples collection for clinical laboratory assessments, clinical chemistry, and urinalysis.
- Blood sample collection for lymphocyte phenotyping.
- Perform MRI scan without contrast.
- Perform EDSS assessment.
- Perform SDMT and BVMT-R test.
- Recording of PedsQL/ Ped NeuroQoL.
- Blood samples collection for immune markers (optional).

10.1.7 Visit 9 to Visit 11 /M5 to M7

The following assessments should be done as listed in the study flow chart:

- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).
- Blood samples collection for clinical laboratory assessments, serum creatinine, ALT, and urinalysis, including thyroid function test only at Visit 10.

10.1.8 Visit 12/M8

The following assessments should be done as listed in the study flow chart:

- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).
- Physical examination and vital signs.
- Blood samples collection for clinical laboratory assessments (hematology and chemistry) including urinalysis.
- Blood samples collection for lymphocyte phenotyping.

- Perform MRI scan without contrast.
- Perform EDSS assessment.
- Perform SDMT and BVMT-R test.
- Recording of PedsQL/Ped NeuroQoL.

10.1.9 Visit 13 to Visit 15/M9 to M11

The following assessments should be done as listed in the study flow chart:

- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).
- Blood samples collection for clinical laboratory assessments, serum creatinine, ALT, and urinalysis.
- Perform thyroid function test only at Visit 13.
- The day prior to alemtuzumab administration patient should take the premedication as specified in Section 1.2.1 and Section 8.2.

10.1.10 Visit 16/M12 (second course of alemtuzumab)

Visit 16 (M12) can occur within -7 days or +30 days of the scheduled visit.

The following assessments should be done as listed in the study flow chart:

- Physical examination and vital signs.
- Perform Tanner staging.
- Blood and urine samples collection for clinical laboratory assessments including pregnancy test (for females of childbearing potential), thyroid function test, urinalysis and for ADA.
- Blood samples collection for lymphocyte phenotyping.
- Blood samples collection for PK and immune markers (optional).
- Assess and confirm eligibility for alemtuzumab administration.
- Alemtuzumab will be administered as daily IV infusion on 3 consecutive days in a supervised medical setting. Calculation of the dose used will be based on patient weight. Observation for infusion reactions is recommended during and for at least 2 hours (based on local requirements) after alemtuzumab infusion.
- The Investigator or designee will contact the IVRS to obtain a treatment kit number.
- On days of Alemtuzumab infusion, and 1 hour prior to the infusion, H1 antagonist IV should be administered immediately followed by 30mg/kg or 1000mg IV methylprednisolone (whichever is lower). H2 antagonist medications and NSAID/antipyretic should be administered on the 3 consecutive days of alemtuzumab

administration as needed. Study patients should also receive antiviral prophylaxis for herpetic viral infection beginning on Day 1 and continuing for a minimum of 1 month. If diphenhydramine IV is not available, an equivalent H1 antagonist can be used at an equivalent dosing, via IV route. If no H1 antagonist is available in IV formulation, an oral formulation of an equivalent compound can be used at an equivalent dosing, 2 hours prior to infusion.

- Vital signs during infusion days will be monitored.
- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).

The following infusion management procedures must be utilized for each infusion and each treatment course:

- Pre-infusion :

  Physicians should obtain a baseline ECG and vital signs (including heart rate and blood pressure measurement), screen for pre-existing hemorrhagic, cardiovascular (including venous thromboembolism) and cerebrovascular risk factors, screen for lung disease, review concomitant medications (eg, antiplatelet agents, anticoagulants), perform laboratory tests (complete blood count with differential, serum transaminases, serum creatinine, test of thyroid function and urinalysis with microscopy), and evaluate infusion-related risks. Physician should also apply the following contraindications when treating patients in this study:
    - Hypersensitivity to the active substance, or to any of the excipients
    - Human Immunodeficiency Virus (HIV) infection
    - Severe active infection
    - Uncontrolled hypertension
    - History of arterial dissection of the cervicocephalic arteries
    - History of stroke
    - History of angina pectoris or myocardial infarction
    - Known coagulopathy or on concomitant anti-coagulant therapy

  It is at investigator's discretion to treat or not treat patient with alemtuzumab after clinical evaluation.

- During infusion: Continuous/frequent monitoring of heart rate, blood pressure assessment (at least hourly) and overall clinical status of the patients including consideration of the volume of fluids administered. The following are recommendations in case of clinical abnormities/severe adverse event:
    - Interrupt infusion
    - Medically evaluate the patient guided by the adverse event profile of alemtuzumab prior to considering restarting therapy
    - Provide appropriate treatment as needed
    - Consider permanently discontinuing the alemtuzumab infusion if the patient shows clinical symptoms suggesting development of a serious adverse event associated

with the infusion (myocardial ischemia, hemorrhagic stroke, cervico-cephalic arterial dissection or pulmonary alveolar hemorrhage).
    - Implement appropriate measures for patients at risk of venous thromboembolism: repeated ambulation during infusion and/or compression stockings.

- Post-infusion: Observation and education of patients
    - Observation for infusion reactions is recommended for a minimum of 2 hours after alemtuzumab infusion; 2 hours after infusion, patients should be cautious and reporting if any of the infusion reactions develop within 48 hours.
    - Patients with clinical symptoms suggesting development of a serious adverse event temporarily associated with the infusion (myocardial ischemia, hemorrhagic stroke, cervico-cephalic arterial dissection or pulmonary alveolar hemorrhage) should be closely monitored until complete resolution of the symptoms. The observation time should be extended as appropriate.
    - Patients with persistent blood pressure elevation should be referred to an appropriate medical facility for continued monitoring and treatment.
    - The patients should be educated on the potential for delayed onset of infusion associated reactions and symptoms and signs of cardiovascular or cerebrovascular events, and instructed to report symptoms and/or seek appropriate medical care.

- Perform MRI scan without contrast.
- Perform EDSS assessment.
- Perform SDMT and BVMT-R test.
- Recording of PedsQL/Ped NeuroQoL.

10.1.11 Visit 17 to Visit 18/M13 to M14

The following assessments should be done as listed in the study flow chart:

- AE/SAE will be monitored (if any).
- Concomitant medication (if any) will be checked at Visit 17 and Visit 18.
- Blood samples collection for hematology, ALT, serum creatinine, and urinalysis.
- Blood samples collection for lymphocyte phenotyping and for ADA at Visit 17 only.
- Blood samples collection for PK.

10.1.12 Visit 19/M15

The following assessments should be done as listed in the study flow chart:

- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).

- Physical examination, including vital signs.
- Perform EDSS assessment.
- Blood samples collection for hematology, clinical chemistry laboratory assessments including thyroid function test and urinalysis.
- Blood samples collection for lymphocyte phenotyping and ADA.

10.1.13 Visit 20 to Visit 21/M16 to 17

The following assessments should be done as listed in the study flow chart:

- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).
- Blood samples collection for hematology, ALT, serum creatinine, and urinalysis.

10.1.14 Visit 22/M18

The following assessments should be done as listed in the study flow chart:

- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).
- Physical examination including vital signs.
- Blood samples collection for clinical laboratory assessments, clinical chemistry, thyroid function test, and urinalysis.
- Blood samples collection for lymphocyte phenotyping.
- Blood samples collection for immune markers (optional).
- Perform EDSS assessment.
- Perform SDMT and BVMT-R test.
- Recording of PedsQL/Ped NeuroQoL.

10.1.15 Visit 23 to Visit 24/M19 to M20

The following assessments should be done as listed in the study flow chart:

- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).
- Blood samples collection for hematology, ALT, serum creatinine, and urinalysis.

10.1.16 Visit 25/M21

The following assessments should be done as listed in the study flow chart:

- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).
- Physical examination including vital signs.
- Blood samples collection for clinical laboratory assessments including thyroid function test and urinalysis.
- Perform EDSS assessment.
- Blood samples collection for lymphocyte phenotyping.

10.1.17 Visit 26-Visit 27/M22-23

The following assessments should be done as listed in the study flow chart:

- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).
- Blood samples collection for hematology, ALT, serum creatinine and urinalysis.

10.1.18 Visit 28/M24 EOTP

The following assessments should be done as listed in the study flow chart:

- AE/SAE will be monitored (if any).
- Concomitant medication will be checked and reported (if any).
- Physical examination including vital signs.
- Blood samples collection for clinical laboratory assessments including thyroid function test, ADA, and urinalysis.
- Blood samples collection for lymphocyte phenotyping.
- Blood samples collection for immune markers (optional).
- Perform Tanner staging.
- Perform MRI scan without contrast.
- Perform EDSS assessment.
- Perform SDMT and BVMT-R test.
- Recording of PedsQL/Ped NeuroQoL.

10.1.19 Safety monitoring phase Year 3 to Year 5

The following assessments should be done as listed in the study flow chart:

- AE/SAE will be monitored (if any).
- Perform EDSS assessment at every 6 months.

- Concomitant medication will be checked and reported (if any).
- Physical examination including vital signs at every 6 months.
- Blood sample collection for hematology, urinalysis, ALT, and serum creatinine every month.
- Perform clinical chemistry assessments including thyroid function test every 3 months.
- Perform MRI scan without contrast, PedsQL/Ped NeuroQoL, and cognitive tests yearly.
- Perform Tanner staging yearly.
- Blood samples collection for lymphocyte phenotyping and ADA yearly.

10.1.20 Relapse Visit

The following assessments should be done as listed in the study flow chart:

- Physical examination, including vital signs.
- AE/SAE will be recorded (if any).
- Perform EDSS assessment.
- Concomitant medication will be checked and reported (if any).

10.2 DEFINITION OF SOURCE DATA

Source data are defined as original documents, data, and records. This includes, but is not limited to the following: hospital records, clinic and office charts, study-specific source document worksheets including Neurostatus-EDSS worksheets, phone logs, memoranda, evaluation checklists, laboratory requisitions, and reports, MRI reports and images, local laboratory reports (if applicable), medication dispensing records, patient questionnaires, computer printouts, electronic data/information sources including IVRS/IWRS notifications, and any other documentation regarding the patient.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

During infusion courses, the IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation must be fully documented in the electronic-Case Report Form (e-CRF). In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best

medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

For all temporary treatment discontinuations, duration must be recorded by the Investigator in the appropriate pages of the e-CRF.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reason(s) for treatment discontinuation and this should be documented in the e-CRF in the EOTP Visit.

Patients must discontinue the IMP for the following reasons:

- Pregnancy or intention for pregnancy.
- At patient/parents request (ie, withdrawal of the consent for treatment).
- If, in the Investigator's opinion, continuation with the administration of the IMP would be detrimental to the patient's well-being.
- Intercurrent condition that requires discontinuation of the IMP (eg, laboratory abnormalities, please refer to decision tree in Appendix B).
- Life threatening events (such as such as myocardial ischemia, pulmonary alveolar hemorrhage, HLH,…)
- At the specific request of the Sponsor.

Any abnormal laboratory value will be immediately repeated for confirmation (within 24 hours if possible), before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

All cases of permanent treatment discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for nonpatient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study.

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited must be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All study withdrawals must be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator must make the best effort to recontact the patient (eg, contact patient's family or private physician, review available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The statistical analysis plan (SAP) will specify how these patients lost to follow-up for their primary endpoints will be considered.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

An SAE is any untoward medical occurrence that at any dose:

- Results in death, or,

- 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

10.4.2 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.

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.

11.3.2 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.

There are two courses. The first treatment course includes 5 consecutive days of infusion, and the second treatment course is administered 12 months after the first treatment course and includes 3 consecutive days of infusion. The numbers and percentages of patients that received each possible level of total dose will be presented in the clinical study report.

11.4.2 Analyses of efficacy endpoints

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

11.4.2.1 Analysis of primary efficacy endpoint

The number of new or enlarging T2 lesions during continuation of prior DMT (Period 1) and in an equal-length period after the first course of alemtuzumab treatment (Period 2) will be analyzed and compared using a repeated measures negative binomial regression model with GEE. The default log link function will be used to model the expected number of lesions. The robust, sandwich covariance matrix will be constructed assuming an unstructured/exchangeable working correlation matrix.

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

11.4.2.2 Analyses of secondary efficacy endpoints

The annualized relapse rate at Year 2 will be estimated using a negative binomial model with robust variance estimation.

The EDSS, descriptive statistics, (eg, percentages of stable/improved/worsened since the end of Period 1) will be calculated.

Descriptive statistics (eg, mean, median, min, max, SD, quartiles) and 95% confidence interval for the means, when appropriate, will be calculated for the change from baseline in cognitive outcomes and QoL measures at each prescheduled, postbaseline assessment visit.

The proportion of patients with new or enlarging T2 lesions during Period 1 and Period 2 will be analyzed and compared using repeated measures logistic regression model with GEE and robust variance estimation. The analyses will be similar to the primary endpoint analyses with the exception of the use of the logit link function and the Bernoulli distribution.

11.4.2.3 Multiplicity considerations

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

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.

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.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules).
The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the e-CRF, discrepancy resolution form or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner.
The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the e-CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the e-CRF entries against the source documents, except for the preidentified source data directly recorded in the e-CRF. The ICF will include a statement by which the patient allows the Sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the e-CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF ELECTRONIC CASE REPORT FORMS AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate e-CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All e-CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (discrepancy resolution form) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 25 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the e-CRFs, the Investigator's Brochure, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Subinvestigator not to mention any information or the product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.
- Subject race or ethnicity will be collected in this study because these data are required by several regulatory authorities.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, good clinical practice, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Noncompliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- The total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the ICF. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised ICF prior to implementation of the change and patient signature should be recollected if necessary.

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17 APPENDICES

Appendix A Guidance on contraceptive methods and collection of pregnancy information

Women Of Child Bearing Potential

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Women of Child Bearing Potential must use one of the highly effective methods from the lists below:

Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of <1% per year when used consistently and correctly[a]

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral,
  - Intravaginal,
  - Transdermal.
- Progestogen-only hormone contraception associated with inhibition of ovulation:
  - Oral,
  - Injectable.

Highly Effective Methods That Are User Independent

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).

Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

NOTE:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

COLLECTION OF PREGNANCY INFORMATION

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- In this study pregnancy is considered to be an AESI and will be reported as such, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Section 10.4.1.3. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Male subjects with partners of reproductive potential who become pregnant

- The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner’s pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Appendix B General guidance for the follow-up of laboratory abnormalities by sanofi

Immune thrombocytopenia

All patients will be monitored with monthly laboratory tests. The table below summarizes the minimum recommendations for ITP monitoring.

Summary of Minimum Recommendations for ITP Monitoring of All Patients

Test	Result	Action Items	Changes In Monitoring
Platelet Count	<LLN	Immediate repeat Hematology	If Repeat <LLNWeekly Hematology Until Stable*
	<100,000/µL	Immediate repeat Hematology; Hematology Consult if confirmed	If Repeat <LLN Weekly Hematology Until Stable*
	<50,000/µL	Immediate repeat Hematology; Emergency Hematology Consult if confirmed	If Repeat <LLN Weekly Hematology Until Stable*
Platelet Drop (but still within normal range)	100,000/µL from prior	Investigator Notified	Investigator Discretion
	140,000/µL from prior	Repeat Hematology	If Repeat < LLN Weekly Hematology Until Stable
ITP Signs or Symptoms	Any ITP Signs or Symptoms	Immediate site contact to determine further evaluation	As outlined above

*Weekly CBC Protocol: Weekly platelet counts for at least 8 weeks.
Return to Monthly when:
- Platelet counts × 8 are within the normal range
(or)
- Platelet counts stabilize (8 consecutive readings ≥100,000/µL and average of last 4 counts ≥ average of 4 prior counts)
After documenting stabilization, continue monthly monitoring as long as platelet counts remain ≥100,000/µL; If a subsequent platelet count is confirmed to be <100,000, the patient should resume weekly monitoring.

In addition to the above recommendations, the ongoing and long-term management of all patients with ITP will be subject to the clinical judgment of the treating hematologist.

Definition of ITP: For the purposes of this study, patients will be considered to have a diagnosis of ITP if they have all of the following:

- Normal Hgb.
- Normal WBC, though the differential will likely reflect lymphopenia as a result of the alemtuzumab treatment.
- No splenomegaly.
- No evidence of alternative nonautoimmune etiology of thrombocytopenia (eg, cytomegalovirus [CMV] infection).
- Normal peripheral smear except for a decrease in platelets without clumping.

AND either of the following:

- A confirmed platelet count equal to or above 50,000/μL but below 100,000/μL on at least 2 consecutive occasions over a period of at least 1 month, or,
- A confirmed platelet count below 50,000/μL without clumping documented on at least 2 consecutive occasions over any period of time.

It is recognized that confounding medical conditions may result in other abnormalities to the CBC, which can render diagnosis more difficult. **Nonetheless, any alemtuzumab-treated patient who meets the ITP criteria specified immediately above will receive no further alemtuzumab and will be immediately referred for hematologic consultation.**

If upon review of the peripheral smear platelet clumping is present indicative of pseudothrombocytopenia, the Hematology Panel should be repeated at a laboratory using an anticoagulant other than ethylenediamine tetraacetic acid (EDTA). In addition, examination of the peripheral smear should reveal a normal platelet estimate.

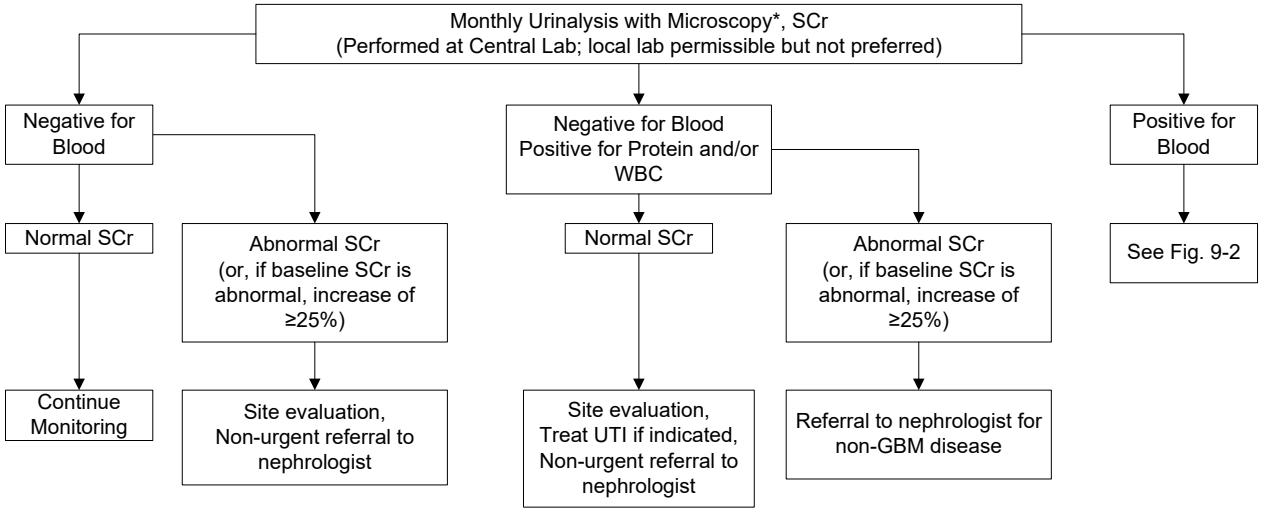
Anti-Glomerular Basement Membrane Disease

Alemtuzumab has also been associated with anti–GBM disease, which can cause a pulmonaryrenal syndrome known as Goodpasture's disease. (Clatworthy, 2008, N Engl J Med; Coles, 2006, J Neurol) Anti–GBM 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. Signs and symptoms that commonly occur in patients with antiGBM disease include:

- Gross hematuria (red or tea colored urine).
- Hemoptysis.
- Edema (particularly lower extremity edema).
- Nonspecific symptoms can include malaise, fatigue, upper respiratory infection, rash.

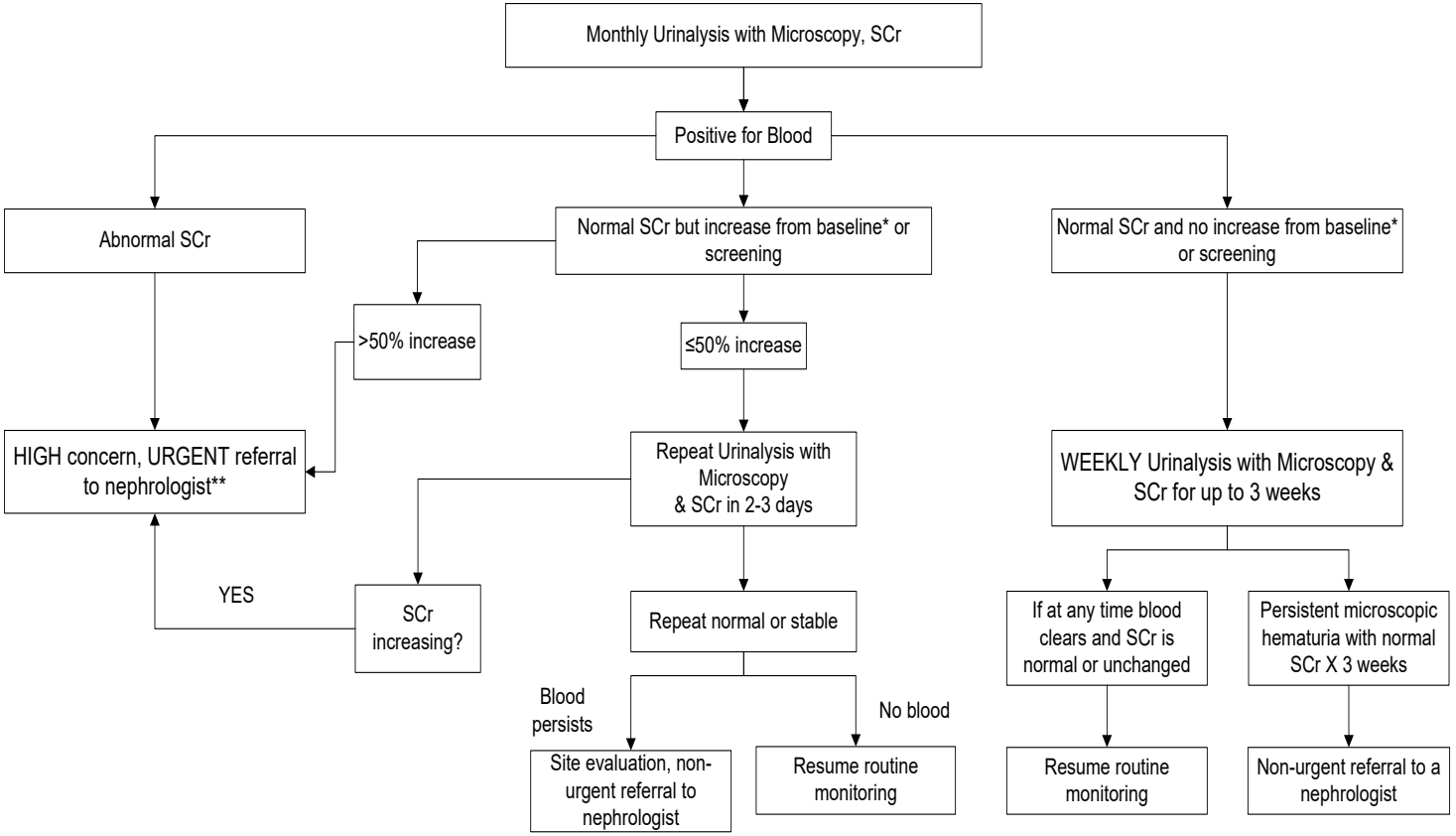
In an effort to identify potential cases of antiGBM disease early, all patients will undergo monthly evaluation of serum creatinine levels alone or as part of a full chemistry panel and laboratory urinalysis (minimally including examination of protein and hemoglobin) with microscopy. Follow up of abnormal results will be guided by the algorithm below in 2 the figures below.

Monthly Urinalysis and Serum Creatinine

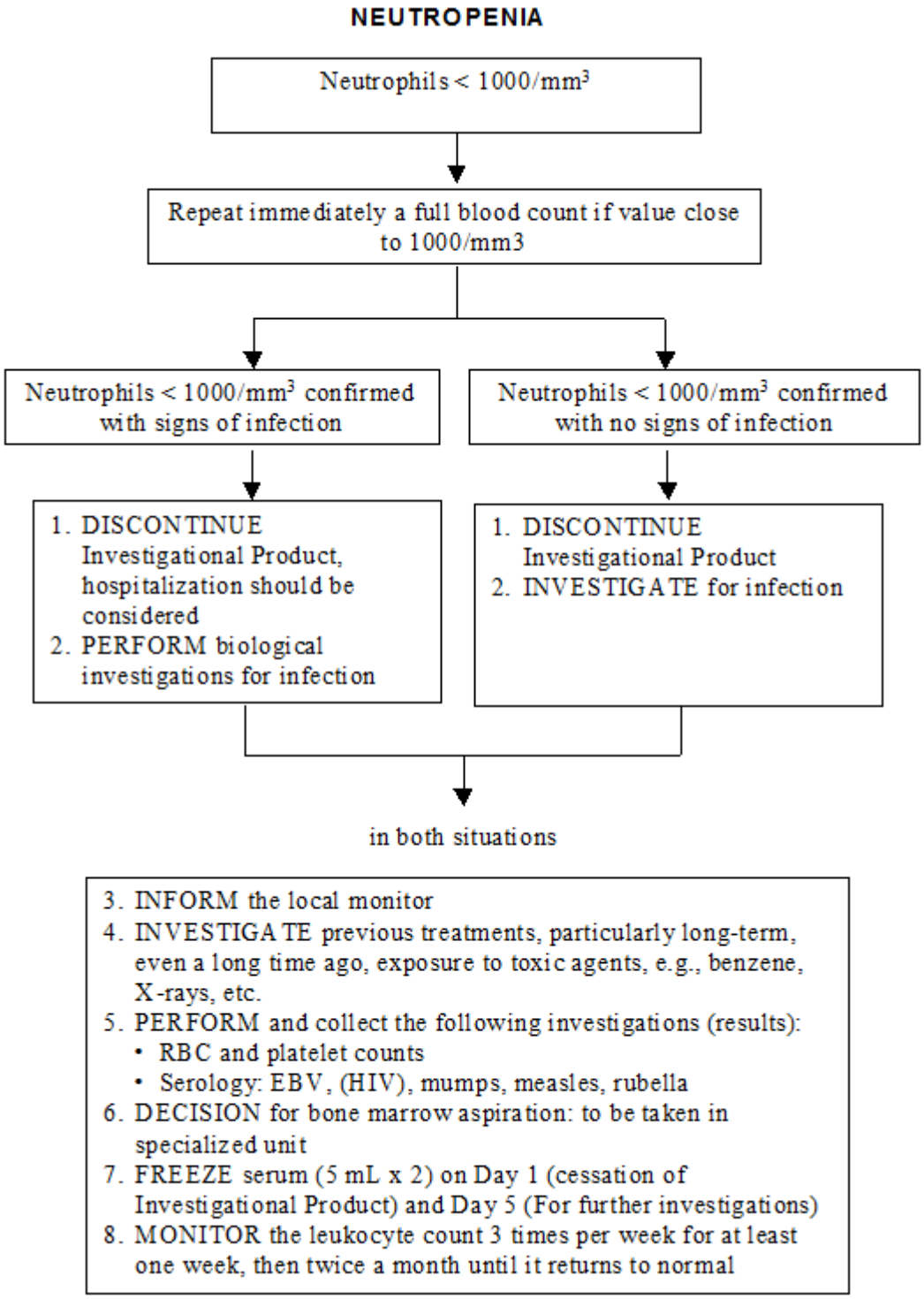


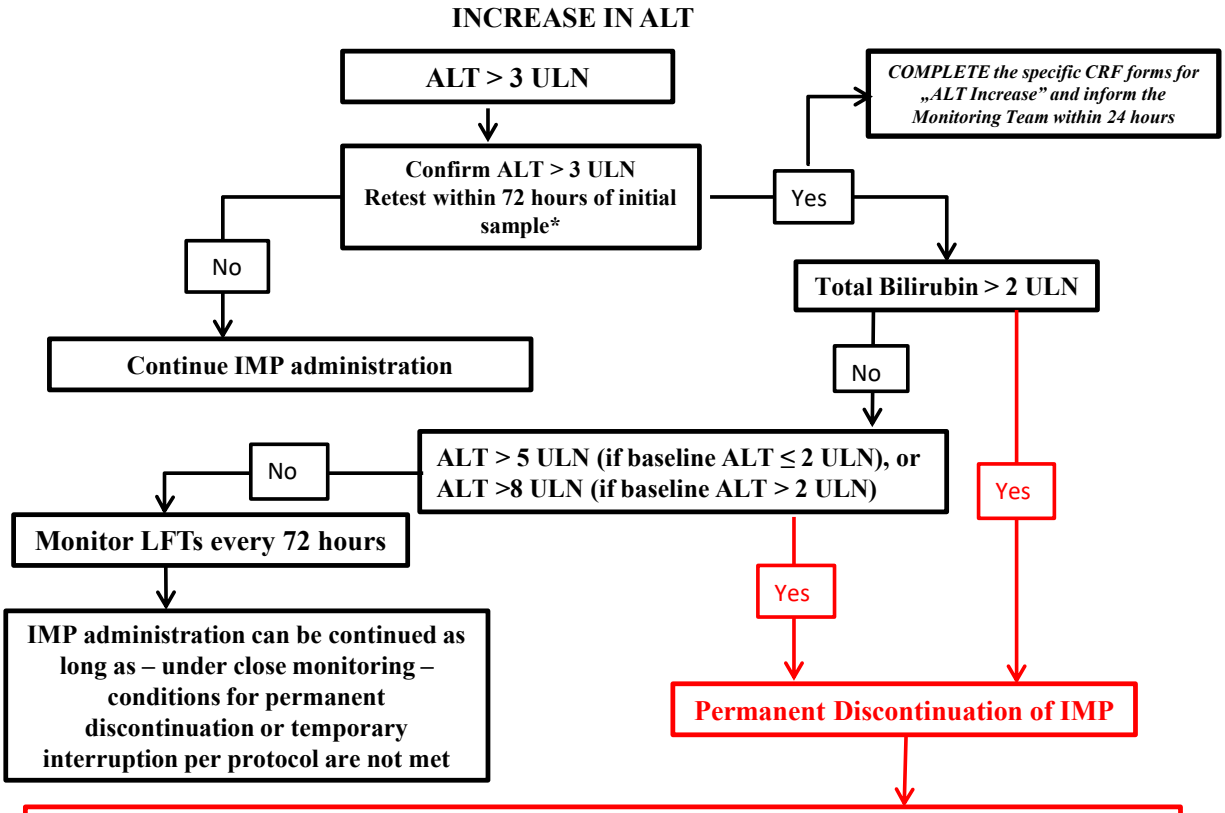
Abbreviations: SCr=Serum creatinine; GBM=glomerular basement membrane; UTI=urinary tract infection; WBC=white blood cells
*Morning urine preferred; false positive rate high during menses and one week after. If monthly urinalysis is positive for blood, SCr is normal, and the patient is menstruating, the urinalysis should be repeated one week following menses. If a patient has chronic microscopic hematuria or proteinuria that is being evaluated or already adequately evaluated, monthly surveillance should focus on changes in these levels and on SCr.

Follow-up of Abnormal Urine or Serum Creatinine Results



Abbreviations: SCr=serum creatinine
*Comparison is versus the lowest of pre-treatment values for that patient.
**While awaiting nephrology consult, consider repeating SCr in 2-3 days and refer emergently/consider hospitalization if SCr rising.


NEUTROPENIA
Neutrophils < 1000/mm3
Repeat immediately a full blood count if value close to 1000/mm3
Neutrophils < 1000/mm3 confirmed with signs of infection
Neutrophils < 1000/mm3 confirmed with no signs of infection
1. DISCONTINUE Investigational Product, hospitalization should be considered
2. PERFORM biological investigations for infection
1. DISCONTINUE Investigational Product
2. INVESTIGATE for infection
in both situations
3. INFORM the local monitor
4. INVESTIGATE previous treatments, particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. PERFORM and collect the following investigations (results):
• RBC and platelet counts
• Serology: EBV, (HIV), mumps, measles, rubella
6. DECISION for bone marrow aspiration: to be taken in specialized unit
7. FREEZE serum (5 mL x 2) on Day 1 (cessation of Investigational Product) and Day 5 (For further investigations)
8. MONITOR the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal



In ANY CASE, FOLLOW the instructions listed in the box below:

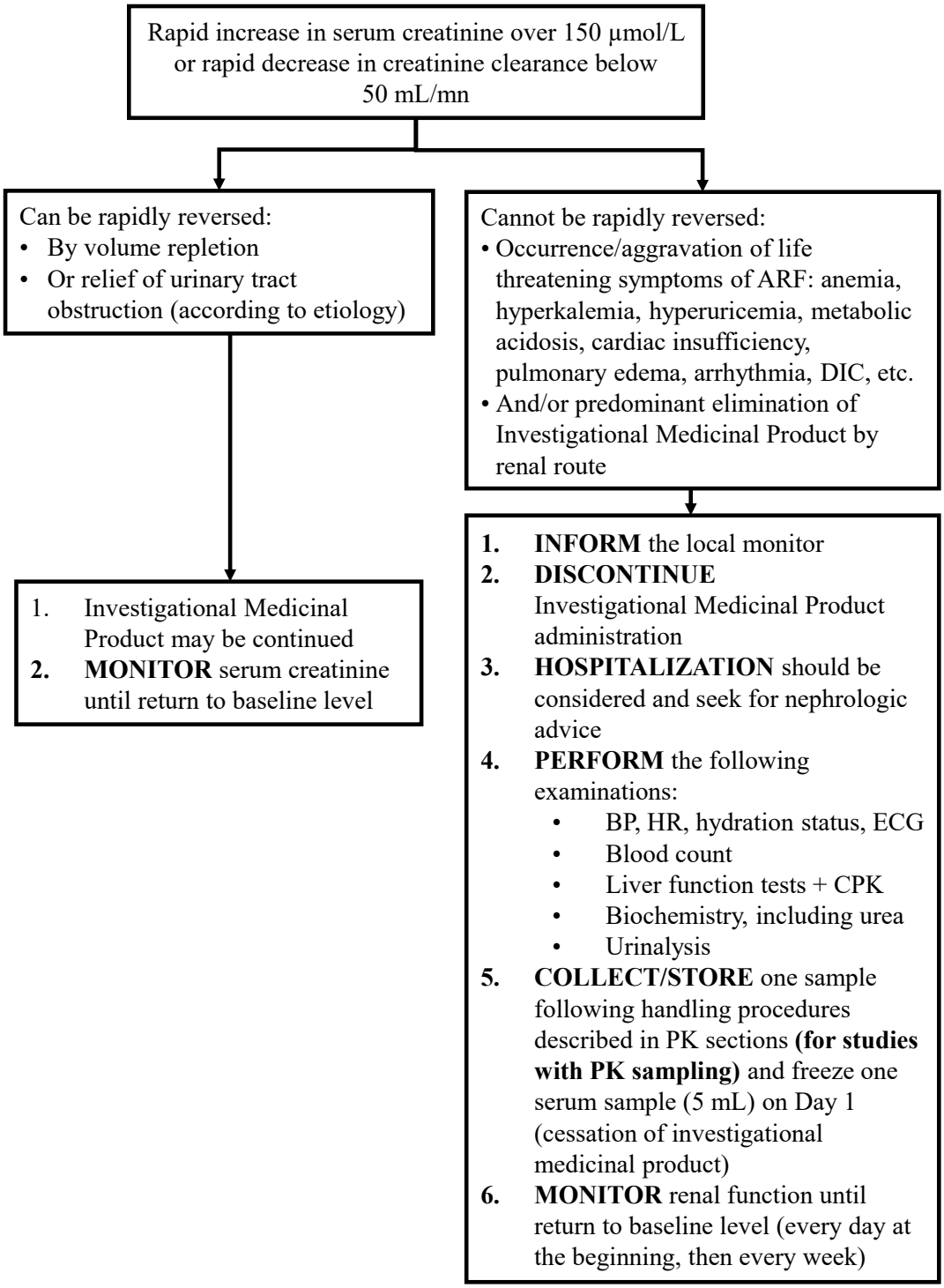
1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

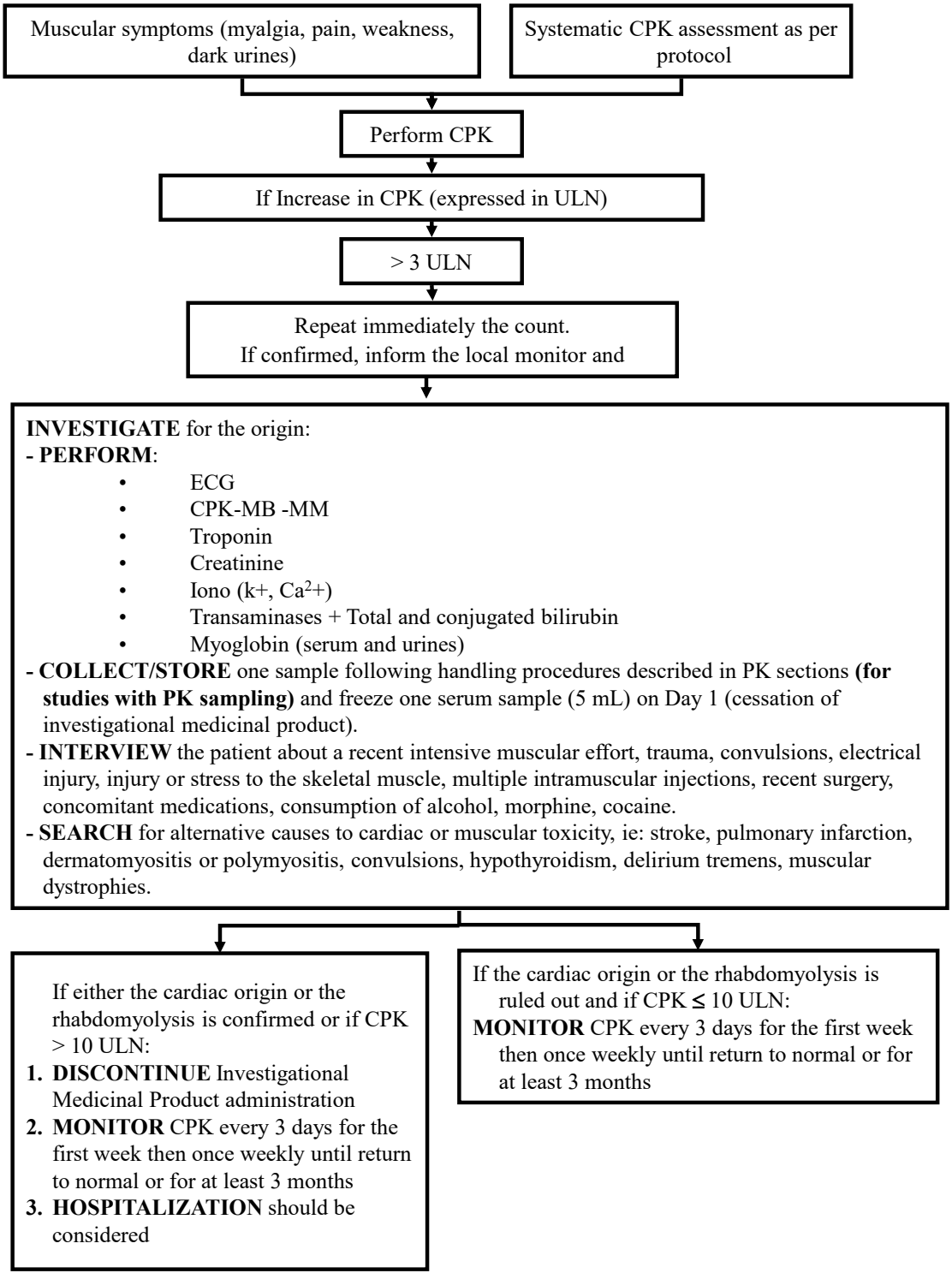
- "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 10.4 for guidance on safety reporting.
- Normalization is defined as ≤ ULN or baseline value, if baseline value is >ULN.

ACUTE RENAL FAILURE



Acute renal failure is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.5 is met.

SUSPICION OF RHABDOMYOLYSIS



Suspicion of rhabdomyolysis is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in Section 10.4.5 is met.

Appendix C Mc Donald's criteria for diagnosis of MS

TABLE 4: The 2010 McDonald Criteria for Diagnosis of MS

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥2 attacks[a]; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
≥2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a second clinical attack[a] implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria[d]: 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

If the Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is "MS"; if suspicious, but the Criteria are not completely met, the diagnosis is "possible MS"; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is "not MS."

[a]An attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

[b]Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

[c]No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

[d]Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

MS = multiple sclerosis; CNS = central nervous system; MRI = magnetic resonance imaging; DIS = dissemination in space; DIT = dissemination in time; PPMS = primary progressive multiple sclerosis; CSF = cerebrospinal fluid; IgG = immunoglobulin G.

Appendix D Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

Definitions for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

Slightly modified from J.F. Kurtzke, Neurology 1983:33,1444-52
©2011 Ludwig Kappos, MD, Neurology, University Hospital Basel, 4031 Basel, Switzerland; Version 04/10.2

EQUIVALENCE WITH PREVIOUS VERSIONS

This version of the neurostatus scoring guidelines is fully compatible with previous versions. Additional help is provided by clarifying some definitions and by introducing an ambulation score in order to reduce measurement noise. But these changes do not imply changes in scoring levels.

GENERAL GUIDELINES

To ensure unbiased EDSS assessment in controlled clinical trials, the EDSS rater should not inquire about the patients' condition except as necessary to perform the EDSS assessment. Patients must be observed to walk the required distance.
The functional system and EDSS scores should reflect the MS related deficits only. In case of doubt the examining physician should assume a relation to MS.
Temporary signs or symptoms that are not due to multiple sclerosis, e.g. temporal immobilisation after fracture of one limb, as well as permanent signs or symptoms that are not due to multiple sclerosis, e.g leg amputation after accident, will not be taken into consideration when assessing the FS scores and EDSS steps, but need to be noted in neurostatus and commented by adding "P" next to the respective field on the scoring sheet for permanent findings and "T" for temporary findings.

FUNCTIONAL SYSTEMS (FS)

A neurostatus score "signs only" is noted when the examination reveals signs of which the patient is unaware.
A score of 1 in a Functional System implies that the patient is not aware of the deficit and that the deficit or sign does not interfere with normal daily activities. However, this general rule does not apply to the Visual, Bowel/Bladder and Cerebral FS.

EXPANDED DISABILITY STATUS SCALE (EDSS)

The EDSS step should not be lower than the score of any individual FS, with the exception of the Visual and Bowel/Bladder FS before conversion.

EDSS steps from 0 up to 4.0 should not change compared to the previous examination, unless there is a change by one grade in at least one FS score.
EDSS steps from 0 up to 1.5 can only apply if ambulation is "unrestricted".
EDSS steps from 2.0 up to 5.0 are defined by the Functional System (FS) scores and/or walking range restriction. As an example, EDSS step 5.0 is possible with an unrestricted ambulation. EDSS steps from 2.0 up to 4.0 does only apply in individuals when at least "fully ambulatory" (able to walk ≥500 meters). If ambulation is assessed as "restricted" the pyramidal or cerebellar FS must be ≥2.
EDSS steps ≥ 5.5 are exclusively defined by the ability to ambulate, the assistance required or the use of a wheelchair.

1 VISUAL (OPTIC) FUNCTIONS

VISUAL ACUITY

The visual acuity score is based on the line in the Snellen chart at 20 feet (5 meters) for which the patient makes no more than one error, using best available correction. Alternatively, best corrected near vision can be assessed, but this should be noted and consistently performed during follow-up examinations. Switching from near to distance visual acuity measurements should be avoided in follow-up examinations.

VISUAL FIELDS

0 normal
1 signs only: deficits present only on formal (confrontational) testing
2 moderate: patient aware of deficit, but incomplete hemianopsia on examination
3 marked: complete homonymous hemianopsia or equivalent

SCOTOMA

0 none
1 small: detectable only on formal (confrontational) testing
2 large: spontaneously reported by patient

* DISC PALLOR

0 not present
1 present

NOTE

When determining the EDSS step, the Visual FS score must be converted to a lower score as follows:

Visual FS Score	6	5	4	3	2	1
Converted Visual FS Score	4	3	3	2	2	1

FUNCTIONAL SYSTEM SCORE

0 normal
1 disc pallor and/or small scotoma and/or visual acuity (corrected) of worse eye less than 20/20 (1.0) but better than 20/30 (0.67)
2 worse eye with maximal visual acuity (corrected) of 20/30 to 20/59 (0.67–0.34)
3 worse eye with large scotoma and/or moderate decrease in fields and/or maximal visual acuity (corrected) of 20/60 to 20/99 (0.33–0.21)
4 worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20/100 to 20/200 (0.2–0.1);
grade 3 plus maximal acuity of better eye of 20/60 (0.33) or less
5 worse eye with maximal visual acuity (corrected) less than 20/200 (0.1);
grade 4 plus maximal acuity of better eye of 20/60 (0.33) or less
6 grade 5 plus maximal visual acuity of better eye of 20/60 (0.33) or less

* = optional part of the examination.

2 BRAINSTEM FUNCTIONS

EXTRAOCULAR MOVEMENTS (EOM) IMPAIRMENT

0 none
1 signs only: subtle and barely clinically detectable EOM weakness, patient does not complain of blurry vision, diplopia or discomfort
2 mild: subtle and barely clinically detectable EOM weakness of which patient is aware; or obvious incomplete paralysis of any eye movement of which patient is not aware
3 moderate: obvious incomplete paralysis of any eye movement of which patient is aware; or complete loss of movement in one direction of gaze in either eye
4 marked: complete loss of movement in more than one direction of gaze in either eye

NYSTAGMUS

0 none
1 signs only or mild: gaze evoked nystagmus below the limits of "moderate" (equivalent to a Brainstem FS score of 1)
2 moderate: sustained nystagmus on horizontal or vertical gaze at 30 degrees, but not in primary position, patient may or may not be aware of the disturbance
3 severe: sustained nystagmus in primary position or coarse persistent nystagmus in any direction that interferes with visual acuity; complete internuclear ophthalmoplegia with sustained nystagmus of the abducting eye; oscillopsia

TRIGEMINAL DAMAGE

0 none
1 signs only
2 mild: clinically detectable numbness of which patient is aware
3 moderate: impaired discrimination of sharp/dull in one, two or three trigeminal branches; trigeminal neuralgia (at least one attack in the last 24 hours)
4 marked: unable to discriminate between sharp/dull or complete loss of sensation in entire distribution of one or both trigeminal nerves

FACIAL WEAKNESS

0 none
1 signs only
2 mild: clinically detectable facial weakness of which patient is aware
3 moderate: incomplete facial palsy, such as weakness of eye closure that requires patching overnight or weakness of mouth closure that results in drooling
4 marked: complete unilateral or bilateral facial palsy with lagophthalmus or difficulty with liquids

HEARING LOSS

0 none
1 signs only: hears finger rub less in one or both sides and has lateralized Weber test but does not complain of any hearing problem
2 mild: as in 1 but is aware of hearing problem
3 moderate: does not hear finger rub on one or both sides, misses several whispered numbers
4 marked: misses all or nearly all whispered numbers

DYSARTHRIA

0 none
1 signs only
2 mild: clinically detectable dysarthria of which patient is aware
3 moderate: obv. dysarthria during ordinary conversation that impairs comprehensibility
4 marked: incomprehensible speech
5 inability to speak

DYSPHAGIA

0 none
1 signs only
2 mild: difficulty with thin liquids
3 moderate: difficulty with liquids and solid food
4 marked: sustained difficulty with swallowing; requires a pureed diet
5 inability to swallow

OTHER CRANIAL NERVE FUNCTIONS

0 normal
1 signs only
2 mild disability: clinically detectable deficit of which patient is usually aware
3 moderate disability
4 marked disability

FUNCTIONAL SYSTEM SCORE

0 normal
1 signs only
2 moderate nystagmus and/or moderate EOM impairment and/or other mild disability
3 severe nystagmus and/or marked EOM impairment and/or moderate disability of other cranial nerves
4 marked dysarthria and/or other marked disability
5 inability to swallow or speak

3 PYRAMIDAL FUNCTIONS

REFLEXES

0 absent
1 diminished
2 normal
3 exaggerated
4 nonsustained clonus (a few beats of clonus)
5 sustained clonus

Cutaneous Reflexes
0 normal
1 weak
2 absent

*Palmomental Reflex
0 absent
1 present

Plantar Response
0 flexor
1 neutral or equivocal
2 extensor

LIMB STRENGTH

The weakest muscle in each group defines the score for that muscle group. Use of optional functional tests (hopping on one foot and walking on heels/toes), is highly recommended in order to assess BMRC grades 3–5.

BMRC RATING SCALE

0 no muscle contraction detected
1 visible contraction without visible joint movement
2 visible movement only on the plane of gravity
3 active movement against gravity, but not against resistance
4 active movement against resistance, but not full strength
5 normal strength

FUNCTIONAL TESTS

*Pronator Drift (upper extremities) Pronation and downward drift:
0 none
1 mild
2 evident

*Position Test (lower extremities – ask patient to lift both legs together, with legs fully extended at the knee) Sinking:
0 none
1 mild
2 evident
3 able to lift only one leg at a time (grade from the horizontal pos. at the hip joints…°)
4 unable to lift one leg at a time

*Walking on heels/toes
0 normal
1 impaired
2 not possible

*Hopping on one foot
0 normal
1 6–10 times
2 1–5 times
3 not possible

LIMB SPASTICITY (AFTER RAPID FLEXION OF THE EXTREMITY)

0 none
1 mild: barely increased muscle tone
2 moderate: moderately increased muscle tone that can be overcome and full range of motion is possible
3 severe: severely increased muscle tone that is extremely difficult to overcome and full range of motion is not possible
4 contracted

GAIT SPASTICITY

0 none
1 barely perceptible
2 evident: minor interference with function
3 permanent shuffling: major interference with function

OVERALL MOTOR PERFORMANCE

0 normal
1 abnormal weakness (as compared to peers) in performing more demanding tasks, e.g. when walking longer distances, but no reduction in limb strength on formal (confrontational) testing
2 Reduction in strength of individual muscle groups at confrontational testing

FUNCTIONAL SYSTEM SCORE

0 normal
1 abnormal signs without disability
2 minimal disability: patient complains of motor-fatigability or reduced performance in strenuous motor tasks (motor performance grade 1) and/or BMRC grade 4 in one or two muscle groups
3 mild to moderate paraparesis or hemiparesis: usually BMRC grade 4 in more than two muscle groups;
and/or BMRC grade 3 in one or two muscle groups (movements against gravity are possible);
and/or severe monoparesis: BMRC grade 2 or less in one muscle group
4 marked paraparesis or hemiparesis: usually BMRC grade 2 in two limbs or monoplegia with BMRC grade 0 or 1 in one limb;
and/or moderate tetraparesis: BMRC grade 3 in three or more limbs
5 paraplegia: BMRC grade 0 or 1 in all muscle groups of the lower limbs;
and/or marked tetraparesis: BMRC grade 2 or less in three or more limbs;
and/or hemiplegia;
6 tetraplegia: BMRC grade 0 or 1 in all muscle groups of the upper and lower limbs

4 CEREBELLAR FUNCTIONS

HEAD TREMOR
0 none
1 mild
2 moderate
3 severe

TRUNCAL ATAXIA
0 none
1 signs only
2 mild: swaying with eyes closed
3 moderate: swaying with eyes open
4 severe: unable to sit without assistance

LIMB ATAXIA (TREMOR/DYSMETRIA AND RAPID ALTERNATING MOVEMENTS)
0 none
1 signs only
2 mild: tremor or clumsy movements easily seen, minor interference with function
3 moderate: tremor or clumsy movements interfere with function in all spheres
4 severe: most functions are very difficult

TANDEM (STRAIGHT LINE) WALKING
0 normal
1 impaired
2 not possible

GAIT ATAXIA
0 none
1 signs only
2 mild: problems with balance realized by patient and/or significant other
3 moderate: abnormal balance with ordinary walking
4 severe: unable to walk more than a few steps unassisted or requires a walking aid or assistance by another person because of ataxia

ROMBERG TEST
0 normal
1 mild: mild instability with eyes closed
2 moderate: not stable with eyes closed
3 severe: not stable with eyes open

OTHER CEREBELLAR TESTS
0 normal
1 mild abnormality
2 moderate abnormality
3 severe abnormality

NOTE
The presence of severe gait and/or truncal ataxia alone (without severe ataxia in three or four limbs) results in a Cerebellar FS score of 3.
If weakness or sensory deficits interfere with the testing of ataxia, score the patient's actual performance. To indicate the possible role of weakness make an "X" after the Cerebellar FS score.

FUNCTIONAL SYSTEM SCORE
0 normal
1 abnormal signs without disability
2 mild ataxia and/or moderate station ataxia (Romberg) and/or tandem walking not possible
3 moderate limb ataxia and/or moderate or severe gait/truncal ataxia
4 severe gait/truncal ataxia and severe ataxia in three or four limbs
5 unable to perform coordinated movements due to ataxia
X pyramidal weakness (BMRC grade 3 or worse in limb strength) or sensory deficits interfere with cerebellar testing

5 SENSORY FUNCTIONS

SUPERFICIAL SENSATION (LIGHT TOUCH AND PAIN)

0 normal
1 signs only: slightly diminished sensation (temperature, figure-writing) on formal testing of which patient is not aware
2 mild: patient is aware of impaired light touch or pain, but is able to discriminate sharp/dull
3 moderate: impaired discrimination of sharp/dull
4 marked: unable to discriminate between sharp/dull and/or unable to feel light touch
5 complete loss: anaesthesia

VIBRATION SENSE (AT THE MOST DISTAL JOINT)

0 normal
1 mild: graded tuning fork 5–7 of 8; alternatively, detects more than 10 seconds but less than the examiner
2 moderate: graded tuning fork 1–4 of 8; alternatively, detects between 2 and 10 sec.
3 marked: complete loss of vibration sense

POSITION SENSE

0 normal
1 mild: 1–2 incorrect responses, only distal joints affected
2 moderate: misses many movements of fingers or toes; proximal joints affected
3 marked: no perception of movement, astasia

*LHERMITTE'S SIGN

Does not contribute to the Sensory FS score
0 negative
1 positive

*PARAESTHESIAE (TINGLING)

Does not contribute to the Sensory FS score
0 none
1 present

FUNCTIONAL SYSTEM SCORE

0 normal
1 mild vibration or figure-writing or temperature decrease only in one or two limbs
2 mild decrease in touch or pain or position sense or moderate decrease in vibration in one or two limbs;
and/or mild vibration or figure-writing or temperature decrease alone in more than two limbs
3 moderate decrease in touch or pain or position sense or marked reduction of vibration in one or two limbs;
and/or mild decrease in touch or pain or moderate decrease in all proprioceptive tests in more than two limbs
4 marked decrease in touch or pain in one or two limbs;
and/or moderate decrease in touch or pain and/or marked reduction of proprioception in more than two limbs
5 loss (essentially) of sensation in one or two limbs;
and/or moderate decrease in touch or pain and/or marked reduction of proprioception for most of the body below the head
6 sensation essentially lost below the head

6 BOWEL AND BLADDER FUNCTIONS

URINARY HESITANCY AND RETENTION

0 none
1 mild: no major impact on lifestyle
2 moderate: urinary retention; frequent urinary tract infections
3 severe: requires catheterisation
4 loss of function: overflow incontinence

URINARY URGENCY AND INCONTINENCE

0 none
1 mild: no major impact on lifestyle
2 moderate: rare incontinence occurring no more than once a week; must wear pads
3 severe: frequent incontinence occurring from several times a week to more than once a day; must wear urinal or pads
4 loss of function: loss of bladder control

BLADDER CATHETERISATION

0 none
1 intermittent self-catheterisation
2 constant catheterisation

BOWEL DYSFUNCTION

0 none
1 mild: no incontinence, no major impact on lifestyle, mild constipation
2 moderate: must wear pads or alter lifestyle to be near lavatory
3 severe: in need of enemata or manual measures to evacuate bowels
4 complete loss of function

*SEXUAL DYSFUNCTION

Male

0 none
1 mild: difficulty to maintain erection during intercourse, but achieves erection and still has intercourse
2 moderate: difficulty to achieve erection, decrease in libido, still has intercourse and reaches orgasm
3 severe: marked decrease in libido, inability to achieve full erection, intercourse with difficulty and hypoorgasmia
4 loss of function

Female

0 none
1 mild: mild lack of lubrication, still sexually active and reaches orgasm
2 moderate: dysparunia, hypoorgasmia, decrease in sexual activity
3 severe: marked decrease in sexual activity, anorgasmia
4 loss of function

NOTE

When determining the EDSS step, the Bowel and Bladder FS score must be converted to a lower score as follows:

Bowel and Bladder FS Score	6	5	4	3	2	1
Converted Bowel and Bladder FS Score	5	4	3	3	2	1

Sexual dysfunction can be documented but in general does not impact on FS score because of obvious difficulties in assessment by examining physician

FUNCTIONAL SYSTEM SCORE

0 normal
1 mild urinary hesitancy, urgency and/or constipation
2 moderate urinary hesitancy/retention and/or moderate urinary urgency/incontinence and/or moderate bowel disfunction
3 frequent urinary incontinence or intermittent self-catheterisation; needs enemata or manual measures to evacuate bowels
4 in need of almost constant catheterisation
5 loss of bladder or bowel function; external or indwelling catheter
6 loss of bowel and bladder function

7 CEREBRAL FUNCTIONS

° DEPRESSION AND EUPHORIA

0 none
1 present: Patient complains of depression or is considered depressed or euphoric by the investigator or significant other.

° Depression and Euphoria are documented on the scoring sheet but are not taken into consideration for FS and EDSS calculation.

DECREASE IN MENTATION

0 none
1 signs only: not apparent to patient and/or significant other
2 mild: Patient and/or significant other report mild changes in mentation. Examples include: impaired ability to follow a rapid course of association and in surveying complex matters; impaired judgement in certain demanding situations; capable of handling routine daily activities, but unable to tolerate additional stressors; intermittently symptomatic even to normal levels of stress; reduced performance; tendency toward negligence due to obliviousness or fatigue.
3 moderate: definite abnormalities on brief mental status testing, but still oriented to person, place and time
4 marked: not oriented in one or two spheres (person, place or time), marked effect on lifestyle
5 dementia, confusion and/or complete disorientation

+FATIGUE

0 none
1 mild: does not usually interfere with daily activities
2 moderate: interferes, but does not limit daily activities for more than 50 %
3 severe: significant limitation in daily activities (> 50 % reduction)

+Because fatigue is difficult to evaluate objectively, in some studies it does not contribute to the Cerebral FS score or EDSS step. Please adhere to the study's specific instructions.

FUNCTIONAL SYSTEM SCORE

0 normal
1 signs only in decrease in mentation; mild fatigue
2 mild decrease in mentation; moderate or severe fatigue
3 moderate decrease in mentation
4 marked decrease in mentation
5 dementia

8 AMBULATION

Unrestricted ambulation means the patient is able to walk a distance without assistance that is regarded as normal, compared with healthy individuals of similar age and physical condition. In this case the EDSS step can be anything between 0 and 5.0, depending on the FS scores.

Fully ambulatory means at least 500 meters of ambulation without assistance, but not unrestricted. The EDSS step can be anything between 2.0 and 5.0, depending on the FS scores. In this case, the pyramidal and/or cerebellar FS must be ≥ 2 to reflect this „restriction" of ambulation.

If ambulation is < 500 meters, the EDSS step must be ≥ 4.5 depending on the walking ranges provided by the ambulation score (see next page) and combination of FS scores. EDSS steps 5.5 to 8.0 are exclusively defined by the ability to ambulate and type of assistance required, or the ability to use a wheelchair.

If assistance is needed, the definitions of EDSS steps 6.0 or 6.5 include both a description of the type of assistance required when walking and the walking range. Assistance by another person is equivalent to bilateral assistance.

NOTE

The ambulation score represents both a description of walking range and the type of assistance required for ambulation. The score replaces the former use of several checkboxes (paragraph 8 ambulation on the scoring sheet) but does NOT introduce new definitions. The use of wheelchair can now be scored on the scoring sheet.
Please indicate the reported distance and time for the patient in the appropriate field on the scoring sheet, followed by the type of assistance and the walking distance measured during the assessment.

DISTANCE AND TIME REPORTED BY PATIENT

Maximal unassisted walking distance reported by patient (in meters) without rest or assistance and time required to walk max. distance according to patient (in minutes)

ASSISTANCE

0 Without help or assistance (allowing the use of an ankle foot orthotic device, without any other type of assistive device)
1 Unilateral assistance: one stick/crutch/brace
2 Bilateral assistance: two sticks/crutches/braces or assistance by another person
3 Wheelchair

DISTANCE

Measure the distance the patient is able to walk im meters.
Unassisted: observe the patient walking unassisted for a minimum distance of 500 meters and measure the time needed, if possible.
Assisted: observe the patient walking with the assistive device or help by another person for a minimum distance of 130 meters, if possible.

AMBULATION SCORE

0 Unrestricted
1 Fully ambulatory
2 ≥ 300 meters, but < 500 meters, without help or assistance (EDSS 4.5 or 5.0)
3 ≥ 200 meters, but < 300 meters, without help or assistance (EDSS 5.0)
4 ≥ 100 meters, but < 200 meters, without help or assistance (EDSS 5.5)
5 Walking range < 100 meters without assistance (EDSS 6.0)
6 unilateral assistance, ≥ 50 meters (EDSS 6.0)
7 bilateral assistance, ≥ 120 meters (EDSS 6.0)
8 unilateral assistance, < 50 meters (EDSS 6.5)
9 bilateral assistance, ≥ 5 meters, but < 120 meters (EDSS 6.5)
10 Uses wheelchair without help; unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day (EDSS 7.0)
11 Uses wheelchair with help; unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self (EDSS 7.5)
12 essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms (EDSS 8.0)

9 EXPANDED DISABILITY STATUS SCALE

0 normal neurological exam (all FS grade 0)
1.0 no disability, minimal signs in one FS (one FS grade 1)
1.5 no disability, minimal signs in more than one FS (more than one FS grade 1)
2.0 minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5 minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0 moderate disability in one FS (one FS grade 3, others 0 or 1) though fully ambulatory; or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5 fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one/two FS grade 2) and others 0 or 1; or fully ambulatory with two FS grade 3 (others 0 or 1);or fully ambulatory with five FS grade 2 (others 0 or 1)
4.0 ambulatory without aid or rest for ≥500 meters; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps
4.5 ambulatory without aid or rest for ≥300 meters; up and about much of the day, characterised by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps
5.0 ambulatory without aid or rest for ≥200 meters (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)
5.5 ambulatory without aid or rest for ≥100 meters
6.0 unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting (see chapter 8, Ambulation)
6.5 constant bilateral assistance (canes or crutches) required to walk at least 20 meters without resting (see chapter 8, Ambulation)
7.0 unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day
7.5 unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self
8.0 essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5 essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0 helpless bed patient; can communicate and eat
9.5 totally helpless bed patient; unable to communicate effectively or eat/swallow
10 death due to MS

neurostatus.net
Independent Internet Platform for training and certification of physicians participating in projects that use a standardized, quantified neurological examinationand Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis
neurostatus training
Interactive Training DVD-ROM for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis
neurostatus e-test
Interactive Test and Certification Tool for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis
neurostatus forum
Forum for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis
www.neurostatus.net

Appendix E Tanner stage classification

The Tanner stages assessment for each patient at each site should be performed, if possible by the same Investigator/designee trained to assess pubertal development.

Boys - development of external genitalia

Stage 1: Pre-adolescent. Testes, scrotum, and penis are of about the same size and proportion as in early childhood.

Stage 2: The scrotum and testes have enlarged and there is a change in the texture of the scrotal skin. There is also some reddening of the scrotal skin.

Stage 3: Growth of the penis has occurred, at first mainly in length but with some increase in breadth. There has been further growth of testes and scrotum.

Stage 4: Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged. There is also further darkening of the scrotal skin.

Stage 5: Genitalia adult in size and shape. No further enlargement takes place after Stage 5 is reached.

Girls - breast development

Stage 1: Pre-adolescent; elevation of papilla only.

Stage 2: Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areola diameter.

Stage 3: Further enlargement of breast and areola, with no separation of their contours.

Stage 4: Projection of areola and papilla to form a secondary mound above the level of the breast.

Stage 5: Mature stage; projection of papilla only, due to recession of the areola to the general contour of the breast.

Boys/Girls - pubic hair

Stage 1: Pre-adolescent; the vellus over the pubes is not further developed than that over the anterior abdominal wall, ie, no pubic hair.

Stage 2: Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly at the base of the penis (boys) or along the labia (girls).

Stage 3: Considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.

Stage 4: Hair is now adult in type, but the area covered by it is still considerably smaller than in most adults. There is no spread to the medial surface of the thighs.

Stage 5: Adult in quantity and type, distributed as an inverse triangle of the classically feminine pattern (girls). Spread to the medial surface of the thighs, but not up the *linea alba* or elsewhere above the base of the inverse triangle.

Appendix F 23-item PedsQL Generic Core Scales

ID# _____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

CHILD REPORT (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

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PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

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ID# _____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

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PedsQL 2

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

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Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

TEEN REPORT (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

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PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

ABOUT SCHOOL *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

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ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **TEENS** (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your teen**. Please tell us **how much of a problem** each one has been for **your teen** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

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PedsQL 2

*In the past **ONE month**, how much of a **problem** has your teen had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other teens	0	1	2	3	4
2. Other teens not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other teens	0	1	2	3	4
4. Not able to do things that other teens his or her age can do	0	1	2	3	4
5. Keeping up with other teens	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

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Appendix G NeuroQOL

Physical (fatigue and pain) and mental (cognitive function, anxiety, depression)

Neuro-QOL Item Bank 2.1 –Pediatric Fatigue – Short Form

Pediatric Fatigue –Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	None of the time	A little bit of time	Some of the time	Most of the time	All of the time
NQFTGped01	I felt tired……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped04	I had trouble starting things because I was too tired……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped05	I had trouble finishing things because I was too tired……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped06	I needed to sleep during the day……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped09	Being tired made it hard to play or go out with my friends as much as I would like...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped11r1	I was too tired to eat……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped12	Being tired makes me sad……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped13	Being tired makes me mad……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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English
July 11, 2014

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Neuro-QOL Item Bank v1.0 – Pediatric Pain – Short Form

Pediatric Pain– Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost never	Sometimes	Often	Almost always
NQPAped01	I had a lot of pain……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPAped02	My pain was so bad that I needed to take medicine for it……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPAped03	I missed school when I had pain……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPAped04	I had so much pain that I had to stop what I was doing……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPAped05	I hurt all over my body……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPAped06	I had pain……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPAped08	I had trouble sleeping when I had pain….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPAped09	I had trouble watching TV when I had pain……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPAped10	It was hard for me to play or hang out with my friends when I had pain……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	In the past 7 days…	Few seconds	Few minutes	Few hours	Few days (less than a week)	More than a week
NQPAped07	When you had pain, how long did it last?..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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English
March 14, 2014

Page 1 of 1

Pediatric Cognitive Function – Short Form

Please respond to each question or statement by marking one box per row.

		Not at all	A little bit	Somewhat	Quite a bit	Very much
NOCOGped03	I forget schoolwork that I need to do……	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NOCOGped05	I sometimes forget what I was going to say……	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NOCOGped09	I react slower than most people my age when I play games. ……	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NOCOGped15	I forget things easily……	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NOCOGped17	I have trouble remembering to do things (e.g., school projects)……	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NOCOGped18	It is hard for me to concentrate in school……	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NOCOGped19	I have trouble paying attention to the teacher……	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NOCOGped20	I have to work really hard to pay attention or I will make a mistake……	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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June 5, 2014

Neuro-QOL Item Bank v1.0 –Pediatric Anxiety – Short Form

Pediatric Anxiety – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost never	Sometimes	Often	Almost always
NQEMNped22	I felt afraid to go out alone.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQEMNped23	Being worried made it hard for me to be with my friends.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQEMNped24	It was hard to do schoolwork because I was nervous or worried.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQEMNped25	I felt afraid.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQEMNped28	I worried when I was at home.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQEMNped29	I felt worried.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
NQEMNped43	I worry that my health might get worse.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQEMNped46	I worry about doing well in school.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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English
March 14, 2014

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Neuro-QOL Item Bank v1.1 –Pediatric Depression – Short Form

Pediatric Depression – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost never	Sometimes	Often	Almost always
NQEMNped01	I felt too sad to do things with friends…...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQEMNped04	I felt sad……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQEMNped09	I felt lonely.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQEMNped21	I was less interested in doing things I usually enjoy……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQEMNped24	It was hard for me to care about anything……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQEMNped28	It was hard for me to have fun……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQEMNped40	I felt like I couldn't do anything right……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQEMNped41	I felt everything in my life went wrong….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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March 14, 2014

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Appendix H Country-specific requirements

AMENDMENT FOR RUSSIA:

Amendment 01 RU: 23-Jan-2017

This protocol amendment (Amendment 01 RU) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union [because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study].

Overall Rationale for the Amendment

I01. was modified at the request of the Ministry of Health of the Russian Federation.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 7.1, Inclusion criteria	Restrict inclusion to patients with RRMS aged 12 to <18 years at study entry	In the future, it is intended to also include children aged ≥10 to <12, as for the other countries, when the Russian Ministry of Health and Local Ethics Committees will grant an authorization for this age range.

AMENDMENTS FOR GREAT BRITAIN:

Amendment 02 GB: 05-May-2017

This protocol amendment (Amendment 02 GB) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union [because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study].

Overall Rationale for the Amendment

The protocol was modified at the request of the Medicines and Healthcare Products Regulatory Agency (MHRA) address concerns about contraceptive methods

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 6.3, Interim analysis	Replace “An interim analysis will be performed to assess the primary endpoint. A partial database lock will be done after the last patient has completed efficacy assessments including MRI at the end of Period 2. This data base lock will allow the comparison of lesion counts between Period 1 (M-4 to M0) and Period 2 (M4-M8).” With “Not applicable.”	Inconsistency between section 6.3 and section 11.5 on a pre-planned Interim Analysis

Section 7.2, Exclusion criteria	"Unwilling to agree to use a reliable and effective contraceptive method as defined for contraception in the informed consent form (ICF) when receiving a course of alemtuzumab treatment and for 4 months following that course of treatment (fertile patients only) (Appendix A)." is replaced with "Unwilling to agree to use a highly effective contraceptive method as defined in Appendix A when receiving a course of alemtuzumab treatment and for 4 months following that course of treatment fertile patients only) (Appendix A)."	To provide recommendations related to contraception requirements in line with the Clinical Trial Facilitation Group (CTFG) guidance 2014

Amendment 05 GB: 21-May-2018

This protocol amendment (Amendment 05 GB) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union [because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study].

Overall Rationale for the Amendment

The primary driver for this amendment was to make an H1 antagonist other than intravenous (IV) diphenhydramine available in countries where IV diphenhydramine is not available.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary	The clinical trial summary was edited to reflect changes to the protocol.	
Section 8.2, Noninvestigational medicinal products	The possibility to use an IV H1 antagonist other than diphenhydramine or an oral formulation, if no H1 antagonist IV formulation is available, at an appropriate dosing, is offered.	Lack of availability of IV diphenhydramine in some countries

AMENDMENT FOR ITALY:

Amendment 04 IT: 12-Mar-2018

This protocol amendment (Amendment 04 IT) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union [because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study].

Overall Rationale for the Amendment

The primary driver for this amendment was to make an H1 antagonist other than intravenous (IV) diphenhydramine available in countries where IV diphenhydramine is not available.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary	The clinical trial summary was edited to reflect changes to the protocol.	
Section 8.2, Noninvestigational medicinal products	The possibility to use an IV H1 antagonist other than diphenhydramine or an oral formulation, if no H1 antagonist IV formulation is available, at an appropriate dosing, is offered.	Lack of availability of IV diphenhydramine in some countries

AMENDMENT FOR FRANCE:

Amendment 06 FR: 21-May-2018

This protocol amendment (Amendment 05 FR) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union [because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study].

Overall Rationale for the Amendment

The primary driver for this amendment was to make an H1 antagonist other than intravenous (IV) diphenhydramine available in countries where IV diphenhydramine is not available.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary	The clinical trial summary was edited to reflect changes to the protocol.	
Section 8.2, Noninvestigational medicinal products	The possibility to use an IV H1 antagonist other than diphenhydramine or an oral formulation, if no H1 antagonist IV formulation is available, at an appropriate dosing, is offered.	Lack of availability of IV diphenhydramine in some countries

Appendix I Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly after the title page.

Amended protocol 04 (09 Mar 2020)

In Europe, this amended protocol 04 is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety or physical/mental integrity of participants.

OVERALL RATIONALE FOR THE AMENDMENT

The amendment provides additional updates and safety measures based on safety concerns that have been identified from post-marketing use of alemtuzumab in adults. Updates include additional safety measures, contraindications and adverse events of special interest (AESIs) important for patient safety. Details of updates are outlined below.

Protocol amendment summary of changes table

Section No. and name	Description of change	Brief rationale
Clinical trial summary And Section 7.2 Exclusion criteria	Added a note in the exclusion criteria with following text: NOTE: Prior to initiation of any alemtuzumab treatment course, contraindications should be reviewed as pre-treatment verification of eligibility.	Update of safety information following Pharmacovigilance Risk Assessment Comittee (PRAC) recommendations during the EU Article 20 Procedure.
Section 1.2.1 Schedule of events Part 1 (Year 1)	Added additional footnote 'v' in flow chart 1.2.1 part 1 (year 1) with below text: Contraindications, including the following must be checked before infusion: severe active infection, uncontrolled hypertension, history of arterial dissection of the cervicocephalic arteries, history of stroke, history of angina pectoris or myocardial infarction, known coagulopathy or on concomitant anti-coagulant therapy	Update of the safety information following the PRAC recommendations
Section 4 Introduction and Rationale	In sub-section “Alemtuzumab Post-Marketing Updates in Adult”, added “temporally associated” before “pulmonary alveolar haemorrhage, myocardial ischemia…” In sub-section “Alemtuzumab Post-Marketing Updates in Adult”, added acquired hemophilia A and PML in Post-marketing PV monitoring identified events	Update based on adult post-marketing data
Section 8.6 Storage Conditions and Shelf Life And Section 10.1.4 Visit 4/M0/D1 (first course of alemtuzumab)	LEMTRADA has been replaced by alemtuzumab.	Administrative change

Section No. and name	Description of change	Brief rationale
And Section 10.1.10 Visit 16/M12 (second course of alemtuzumab)		
Section 9.3.1 Adverse events	Added thrombocytopenia and myocardial infarction in assessment of IARs	Update of the safety information
Section 10.1.4 Visit 4/M0/D1 (first course of alemtuzumab) And Section 10.1.10 Visit 16/M12 (second course of alemtuzumab)	Updated the pre-infusion text: The following infusion management procedures must be utilized for each infusion and each treatment course to reduce serious reactions temporally associated with alemtuzumab infusion: • Pre-infusion: Physicians should obtain a baseline ECG and vital signs (including heart rate and blood pressure measurement), screen for pre-existing hemorrhagic, cardiovascular (including venous thromboembolism) and cerebrovascular risk factors, screen for lung disease, review concomitant medications (eg, antiplatelet agents, anticoagulants), perform laboratory tests (complete blood count with differential, serum transaminases, serum creatinine, test of thyroid function and urinalysis with microscopy), and evaluate infusion-related risks. It is at investigator's discretion to treat or not treat patient with alemtuzumab after clinical evaluation. Physician should also apply the following contraindications when treating patients in this study: • Hypersensitivity to the active substance, or to any of the excipients • Human Immunodeficiency Virus (HIV) infection • Severe active infection • Uncontrolled hypertension • History of arterial dissection of the cervicocephalic arteries • History of stroke • History of angina pectoris or myocardial infarction • Known coagulopathy or on concomitant anti-coagulant therapy Deleted review of HCP checklist. Updated the during infusion with following text: The following are recommendations in case of clinical abnormities/severe adverse event: - Interrupt infusion - Medically evaluate the patient guided by the adverse event profile of alemtuzumab prior to considering restarting therapy - Provide appropriate treatment as needed - Consider permanently discontinuing the alemtuzumab infusion if the patient shows clinical symptoms suggesting development of a serious adverse event associated with the infusion (myocardial ischemia, hemorrhagic stroke, cervico-cephalic arterial dissection or pulmonary alveolar hemorrhage). Updated the post infusion with following text:	Update of patient monitoring and safety procedures

Section No. and name	Description of change	Brief rationale
	- Observation for infusion reactions is recommended for a minimum of 2 hours after alemtuzumab infusion; 2 hours after infusion, patients should be cautious and reporting if any of the infusion reactions develop within 48 hours. - Patients with clinical symptoms suggesting development of a serious adverse event temporarily associated with the infusion (myocardial ischemia, hemorrhagic stroke, cervico-cephalic arterial dissection or pulmonary alveolar hemorrhage) should be closely monitored until complete resolution of the symptoms. The observation time should be extended as appropriate. - The patients should be educated on the potential for delayed onset of infusion associated reactions and symptoms and signs of cardiovascular or cerebrovascular events, and instructed to report symptoms and/or seek appropriate medical care.	
Section 10.4.1.3 Adverse event of special interest	Added following AESIs: • Autoimmune mediated conditions including but not limited to autoimmune hepatitis, acquired Hemophilia A • 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) • Progressive multifocal leukoencephalopathy (PML) Updated wording of serious and opportunistic infections to below text: Serious infections including serious opportunistic infections (eg, Listeria infections, CMV, EBV), HPV associated with cervical dysplasia Moved cervical dysplasia with HPV. Deleted hemolytic anemia, autoimmune neutropenia, autoimmune pancytopenia	Update of the safety information following the Article 20 Procedure.
Section 10.4.4 Instructions for reporting serious adverse events	The following old text: SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges. Is replaced by:	Administrative change

Section No. and name	Description of change	Brief rationale
	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	
Section 10.4.6 - Table 9 - Summary of adverse event reporting instructions	Added following AESIs: • Autoimmune mediated conditions including but not limited to autoimmune hepatitis, nephropathies including anti-glomerular basement membrane (GBM) disease, acquired Hemophilia A • 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) • Progressive multifocal leukoencephalopathy (PML) • Pneumonitis Updated wording of serious and opportunistic infections to below text: Serious infections including serious opportunistic infections (eg, Listeria infections, CMV, EBV), HPV associated with cervical dysplasia Moved cervical dysplasia with HPV. Deleted hemolytic anemia, autoimmune neutropenia, autoimmune pancytopenia, and glomerulonephritis	Update of the safety information following the Article 20 Procedure.
Section 14.2 Record Retention in Study Sites	The duration of archiving of study document has been updated to 25 years	Administrative change

Amended protocol 03 (21 June 2019)

In Europe, this amended protocol (amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety or physical/mental integrity of participants.

OVERALL RATIONALE FOR THE AMENDMENT

This amended protocol is written to provide information about new safety concerns that have been identified from post-marketing use with alemtuzumab. This includes reports of autoimmune hepatitis and hemophagocytic lymphohistiocytosis (HLH), as well as temporally associated serious cardiovascular reactions. Substantial changes in this amended protocol are related to

providing information on the new safety concerns and measures to minimize the risks of patients included in clinical trials.

The Sponsor has conducted a comprehensive review of safety data and identified two areas where risk mitigation measures will be implemented in this pediatric study; 1. infusion-related risks, specifically hemorrhagic risks, and 2. autoimmune hepatitis where additional laboratory tests may be of value.

Protocol amendment summary of changes table

Section No. and name	Description of change	Brief rationale
Clinical trial summary	ALT assessments	Update to match changes to other part of document
Section 1.2.1 Schedule of events Part 1 (Year 1) and Section 10.1.10	Change of the window visit for second infusion to allow a slightly bigger window for scheduling Monitoring of postinfusion period increased	To allow more flexibility for second visit Highlight of the monitoring cytopenia and postinfusion
Section 4 Introduction and rationale	Details of the rationale for the amendment	
Schedule of events, Part 1, Part 2, Part 3	Monitoring of cytopenia and additional assays of alanine aminotransferase were added	Additional monitoring and risk mitigation measures
Section 9.3.1 Adverse event	Some infusion associated reactions (IARs) may occur beyond 24 hours	Clarification of IAR
Section 9.3.2, Laboratory safety variables	Monitoring of cytopenia was added If a cytopenia or autoimmune hepatitis is confirmed, appropriate medical intervention should be promptly initiated, including referral to specialist. In case of such symptoms or signs, alemtuzumab should only be re-administered following careful consideration.	Clarification for additional monitoring
Section 9.3.3, ITP and antiGBM surveillance and monitoring	Monitoring of cytopenia was added	Additional monitoring
Section 9.3.4 HLH	Description of HLH and monitoring	Additional monitoring
Section 9.3.5 Physical examination and vital signs	Added to postinfusion monitoring: until 2 hours after infusion has ended or longer until stabilization	Reinforcement of alemtuzumab postinfusion monitoring
Section 10.1.1, Visit 1 Screening visit	Monitoring of cytopenia is added	Additional monitoring
Section 10.1.4 Visit 4/M0/D1 (first course of alemtuzumab) and Section 10.1.10 Visit 16/M12 (second course of alemtuzumab)	Indications are provided for rigorous infusion management •	Detail of the risk mitigation measures for alemtuzumab infusion

Section No. and name	Description of change	Brief rationale
Section 10.1.4 Visit 4/M0/D1 (first course of alemtuzumab), Section 10.1.7 Visit 9 to Visit 11 /M5 to M7, Section 10.1.10 Visit 16/M12, Section 10.1.9 Visit 13 to Visit 15/M9 to M11 , Section 10.1.11 Visit 17 to Visit 18/M13 to M14, Section 101.13 Visit 20 to Visit 21/M16 to 17, Section 10.1.15 Visit 23 to Visit 24/M19 to M20, Section 10.1.17 Visit 26-Visit 27/M22-23, Section 10.1.19 Safety monitoring phase Year 3 to Year 5	• ALT assay added	Additional monitoring and risk mitigation measures
10.3.3 List of criteria for permanent treatment discontinuation	• Permanent discontinuation in case of life threatening events (such as such as myocardial ischemia, pulmonary alveolar hemorrhage, HLH,…) were added.	Additional criteria for permanent discontinuation
Section 10.4.1.3 Adverse events of specific interest	• HLH added	Additional monitoring
Section 10.4.6 (Table 9)	• Addition of autoimmune hepatitis and HLH	Additional monitoring
Section 11.4.3.1	TEAEs that occur from start of infusion up to 72 hours postinfusion will be summarized if applicable.	Additional analyses
Section 11.4.3.2 Laboratory safety variables	Description of the analyses of hepatic enzymes	Additional analyses

Amended Protocol 02: 04-Jan-2019

The primary driver for this amendment is to make an H1 antagonist other than intravenous (IV) diphenhydramine available in countries where IV diphenhydramine is not available. This and secondary drivers for the amendment are described in the Protocol amendment summary of changes table immediately below. Nonsubstantial changes such as to those to improve readability, consistency, grammar, and adherence to the Sponsor's stylistic guidelines are not described specifically.

Protocol amendment summary of changes table

Section No. and name	Description of change	Brief rationale
Clinical trial summary	Update	Update to match changes to other part of document
Schedule of events, Part 1	For recommended visit windows: "D-7" was replaced with "D-14 to D-7" and was reflected in the flowchart. For Visit 3: "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." was added. For tuberculosis testing: "Only if the QuantiFERON TB Gold test is used" was appended to "Tuberculosis skin testing on site and tuberculosis skin testing via local laboratories are allowed." "Home nursing visits or visits to local laboratories followed by shipping of samples to the central laboratory are allowed for study visits that require only laboratory tests. These are to be followed by telephone calls from the study site to assess AEs. If Quantiferon test results are indeterminate, confirmation via skin testing is required." was added. For hematology, urinalysis and thyroid function: "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." was added.	Clarification. Ease of operation for sites; minimize office visits for patients.
Schedule of events, Part 2	For recommended visit windows: "D-7 day visit" was replaced by "D-14 to D-7 visit: For hematology, urinalysis and thyroid function: "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." was added.	Clarification. Minimize office visits for patients.
Schedule of events, Part 3	For clinical chemistry, hematology, thyroid function, and serum creatinine: "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." has been added. For urinalysis: "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." was added.	Minimize office visits for patients.
Section 6.1 Description of the study	"As late as possible" was appended to "A baseline MRI will be performed close to." Two instances of "D-7" were replaced with "D-14 to D-7." **"**A baseline MRI will be performed as late as possible during the screening period and another at Day -7 visit." was replaced with **"**A baseline MRI will be performed close to M-4 during the screening period and another at Visit 3."	Clarification.
Section 6.4.1 Scientific advisory committee	"First" was deleted in "PIs at the first 3 sites enrolling the most patients will also be included as authors for the primary publication, in addition to the other SAC members.	Clarification.

Section No. and name	Description of change	Brief rationale
Section 7.1, Inclusion criteria	"Should" was replaced by "must" in the requirement for patients to meet the criteria of diagnosis of MS as defined by the International Paediatric Multiple Sclerosis Study Group criteria for pediatric MS and the criteria of MS based on the 2010 McDonald criteria.	Clarification.
Section 7.2.1 Exclusion criteria related to study methodology	"If a patient has been enrolled in a clinical trial and treated with a comparator agent that is an approved agent for screening inclusion (INF or GA), they may be considered for this trial if they meet all inclusion and exclusion criteria otherwise." was added.	Clarification for countries in which there are no approved treatments for pediatric MS.
Section 7.2.3 Exclusion criteria related to the current knowledge of alemtuzumab and study methodology	"If a patient was deemed a screen failure, he or she may be re-screened for this study up to 2 times. If a patient who previously failed screening for any reason is re-screened, the patient must sign a new informed consent form and be assigned a new patient number by IWRS/IVRS (the next sequential patient number at the site). All screening assessments need to be repeated to confirm eligibility for the study. Rescreening assessments may be discussed with the Sponsor on a case-by-case basis." was added.	Clarification.
	"Note: If the treating physician suspects out-of-range cell count results are based upon issues of sample transportation or environmental conditions, the treating physician may request a repeat sample to be evaluated locally to confirm the patient is not excluded from the trial. If out-of-range cell counts are not confirmed through evaluations performed locally, the treating physician should document (in source data and in a CRF comment) that the central laboratory results are considered falsely exclusive, and proceed to enroll the patient." was added.	For resolution of suspected issues involving shipping from certain study sites.
Section 8.1.1.1 Method of preparation at the clinical site	"Should" was replaced by "must" in "The diluted solution should be administered by IV infusion".	Clarification.
Section 8.1.1.2 Special precautions for disposal and other handling	"Should" was replaced by "must" in "The vial contents should be inspected …", "The bag should be inverted gently …", and "care should be taken to ensure the sterility …"	Clarification.
Section 8.2, Noninvestigational medicinal products	The possibility to use an IV H1 antagonist other than diphenhydramine or an oral formulation, if no H1 antagonist IV formulation is available, at an appropriate dosing, is added.	Lack of availability of IV diphenhydramine in some countries.
	IV methylprednisolone dosing was updated.	Update to current standard of care.
Section 8.6, Storage conditions and shelf life	"Should" was replaced by "must" in "Lemtrada, in vials, should be stored …"	Clarification.
Section 8.7, Return and/or destruction of treatments	"The Investigator will not destroy the used and unused IMP unless the Sponsor provides written authorization" was added.	Clarification.
Section 8.8 Concomitant medication	"Should" was replaced by "must" in "Live vaccines should not be administered …"	Clarification.

Section No. and name	Description of change	Brief rationale
Section 9.1.1.1 Brain MRI	"A baseline MRI" was replaced with "An MRI." "Day -7 visit" was replaced with "Visit 3". "It is expected that Periods 1 and 2 will be of the same length ±7 days." was added.	Clarification.
Section 9.2.2.2.1 Assessment methods	"D-7" was replaced with "D-14 to D-7."	Clarification.
Section 9.2.2.3 Quality of life endpoints	"D-7" was replaced with "D-14 to D-7."	Clarification.
9.3 Safety endpoints	"D-7" was replaced with "D-14 to D-7" in 6 places.	Clarification.
Section 9.3.2, Laboratory safety variables	"Animotransaminase" was replaced by "aminotransferase" in the chemistry panel. Details for the amount of blood taken during the study were provided to reflect compliance with international guidelines on blood withdrawal in the pediatric population.	Correction. Commitment to Federal Agency for Medicines and Health Products (Belgium).
9.3.4 Physical examination and vital signs	"D-7" was replaced with "D-14 to D-7."	Clarification.
Section 9.6 Appropriateness of measurements	The section "Appropriateness of measurements" was added.	Unintentional omission.
Section 10.1.1 Visit 1 Screening visit	"The parents/patient will be provided with educational material consisting of a patient guide containing a description of the risks associated with the use of alemtuzumab as well as a description of the best course of action if sign and symptoms of those risks present themselves (eg, how to reach your doctors)." was deleted.	This text was deleted because the patient guide wasn't implemented.
Section 10.1.3 Visit 3/Day -7 to -14	The section title was changed to "Visit 3/Days -14 to -7." "Visit 3 assessments can be performed over multiple days as long as the time windows below are respected." was added. "Investigator will assess and confirm eligibility fo alemtuzumab administration. If patient is eligible for alemtuzumab administration, prior DMT will be discontinued" was moved and was edited to read, "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." "Blood sample collection for lymphocyte phenotyping" was deleted.	Clarification. Deletion of repeated information.
Section 10.1.4 Visit 4/M0/D1 (first course of alemtuzumab)	"Should" was replaced by "must" in "Specialists and equipment required for the timely diagnosis and management of the most frequent adverse reactions, especially autoimmune conditions and infections, should be available." "Should" was replace by "must" in "Alemtuzumab treatment should be initiated …" The possibility to use an IV H1 antagonist other than diphenhydramine or an oral formulation, if no IV H1 antagonist formulation is available, at an appropriate dosing, was added.	Clarification. Lack of availability of IV diphenhydramine in some countries. Update to current standard of care.

Section No. and name	Description of change	Brief rationale
	The premedication regimen for IV methylprednisolone was revised (half dose on infusion Days 4 and 5).	
Section 10.1.10 Visit 16/Month 12 (alemtuzumab Course 2)	The possibility to use an IV H1 antagonist other than diphenhydramine or an oral formulation, if no IV H1 antagonist formulation is available, at an appropriate dosing, was added.	Lack of availability of IV diphenhydramine in some countries.
Section 10.3.3 List of criteria for permanent treatment discontinuation	"Should" was replaced by "must" in "Patients should discontinue the IMP for the following reasons."	Clarification.
Section 10.3.5, Procedure and consequence for patient withdrawal from study	"Should" was replaced by "must" in "and AE information elicited should be documented," All study withdrawals should be recorded …", and "Investigator should make the best effort to …"	Clarification.
Section 10.4.1.2, Serious adverse event	"Should" was replaced by "must" in "Medical and scientific judgment should be exercised …"	Clarification.
Section 11.2, Disposition of patients	Screened patients are defined as those who signed the informed consent form.	Clarification.
Section 11.4.3.1, Adverse events	On treatment AEs are defined as those AEs that developed or worsened after the first alemtuzumab dose and until the end of the study (Month 60).	Clarification.

Amended Protocol 01: 08-Nov-2017

This amended protocol (Amended Protocol 01) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union [because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study].

Overall Rationale for the Amendment

This amendment provides mainly clarifications of various existing contents in the protocol. Additionally, clarifications sought by Belgian Health Authority are addressed in this amendment.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary, Study design	The "current DMT" is clarified as being limited to beta interferon therapy or glatiramer acetate.	Clarification

Clinical trial summary, Main selection criteria	"Signed informed consent/assent" is replaced with "Signed written informed consent/assent". "after having been on that therapy for at least 6 months" is replaced with "after having been on that therapy for at least 6 months and is currently still taking the same therapy".	Clarification
Clinical trial summary, Dose regimen	"For patients <50 kg: 0.24 mg/kg/day" is replaced with "For patients <50 kg: 0.24 mg/kg/day (this equates to 12 mg/day for a 50 kg patient)."	Clarification
Clinical trial summary, NIMP formulation	"Oral prednisone/prednisolone,1 mg/kg or 50 mg, whichever is lower" is replaced with "Oral prednisone/prednisolone,1 mg/kg or 50 mg, whichever is lower or equivalent"	Clarification
Clinical trial summary, Secondary endpoints	"EDSS (descriptive statistics, e.g., percentages of stable/ improved/worsened since the end of Period 1)" is added	Clarification
Clinical trial summary, Planned database lock date	"There will be two database locks in this study. The first database lock will be after the last patient has completed efficacy assessments including MRI at the end of Period 2" is replaced by "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."	Clarification
Clinical trial summary, Study committees	"The members will remain blinded until completion of the study" was removed from the description of the Scientific Advisory Committee.	Clarification
Section 1.2.1, Schedule of events Part 1 (Year 1)	The following footnotes were added: *e* Subject race will be collected in this study because these data are required by several regulatory authorities. *i* 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. "The MRI assessments will be available to investigators to assess safety" was appended to footnote *l*.	Clarification
Section 1.2.2, Schedule of events Part 2 (Year 2)	The following footnotes were added: *c* The MRI assessments will be available to investigators to assess safety. *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.	Clarification. HPV test added per local health authority request.
Section 1.2.3, Schedule of events (safety monitoring phase (Year 3-5))	The following footnotes were added: *c* The MRI assessments will be available to investigators to assess safety. *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	Clarification. HPV test added per local health authority request.

	per the Investigator opinion (eg, follow-up HPV test is negative or cervical abnormality has been effectively treated). An annual follow-up is recommended.	
Section 1.2.4, Schedule of events Part 4: Table for PK sampling (Year 1)	The possibility of sample collection via local labs was added.	Patient convenience
Section 1.2.5, Schedule of events Part 5: Table for PK sampling (Year 2)	The possibility of sample collection via local labs was added.	Patient convenience
Section 4, Introduction and rationale	"The MS disease activity criteria include having at least 2 recorded MS attacks; at least 1 MS relapse in the last year during treatment with an IFNB or GA after having been on that therapy for at least 6 months," is appended by "and is currently still taking the same therapy". "For patients <50 kg: 0.24 mg/kg/day" is appended by "(this equates to 12 mg/day for a 50 kg patient)." "MRI assessments will be available to investigators to assess safety" is added.	Clarification
Section 6.1, Description of the study	"During this visit patients will be reminded to continue their prior DMT" is appended by "(limited to interferon or GA only)."	Clarification
Section 6.3, Interim analysis	The two database locks are clarified as a partial, informal interim lock and the final lock.	Clarification
Section 6.4.1 Scientific advisory committee	"The members will remain blinded until completion of the study" is removed.	Clarification
Section 7.1, Inclusion criteria	I02. Signed informed consent/assent …" is replaced with "Signed written informed consent/assent …" I04. "treatment with an IFNB or GA after having been on that therapy for at least 6 months" is appended with "months, and is currently still taking the same therapy."	Clarification
Section 7.2.2 Exclusion criteria related to alemtuzumab and/or mandatory background therapies	E08 "Unwilling to agree to use a reliable and effective contraceptive method as defined for contraception in the informed consent form (ICF) when receiving a course of alemtuzumab treatment and for 4 months following that course of treatment (fertile patients only) (Appendix A)" is replaced with: E08 "Unwilling to agree to use a highly effective contraceptive method as defined (Appendix A) when receiving a course of alemtuzumab treatment and for 4 months following that course of treatment (fertile patients only).	Local health authority request
Section 7.2.3, Exclusion criteria related to the current knowledge of alemtuzumab and study methodology	The following was added: "Re-screening could be possible due to logistic reasons (eg, blood samples defective, lost, or other reason, non-medical) or the conditions resolved for eligibility." E29 "Infection with hepatitis B, C viruses (positive serology)." Was appended with "but not due to hepatitis immunization).	Clarification
Section 8.1.1, Administration	"For patients <50 kg: 0.24 mg/kg/day" is appended with "(this equates to 12 mg/day for a 50 kg patient)."	Clarification
Section 8.1.1.1, Method of preparation at the clinical site	The time of infusion relative to dilution is clarified. It is allowed to extend the infusion time if clinically indicated. Additional requirements for infusion and monitoring are referenced.	Clarification
Section 8.2, Noninvestigational medicinal products	An equivalent medication to "oral prednisone/prednisolone 1 mg/kg or 50 mg one dose, whichever is lower" is allowed.	Clarification

Section 8.3.1, Methods of blinding	"The MRI assessments will be available to the investigators to assess safety" is added.	Clarification
Section 8.7 Responsibilities	"Should" is replaced by "must" in "Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified …"	Clarification
Section 8.7.2, Return and/or destruction of treatments	"Authorization for destruction will be given by the sponsor" is prepended by "Written".	Clarification
Section 8.8, Concomitant medication	"Concomitant use of alternative medications (eg, herbal treatments, botanicals, etc) .." is prepended with "A concomitant medication is any treatment received by the patient concomitantly to any IMP(s). Concomitant treatments have been detailed for all phases of the study and are not limited to the treatment received with the IMP (treatment phase)." "Therapy with disease-modifying MS treatments that the patient is currently being administered (ie interferons and GA) will be permitted during the screening and prior DMT Treatment Phase. Prior DMT will be discontinued 7 days before alemtuzumab first administration. Refer to Section 6.1 for further details" is replaced with "Therapy with disease-modifying MS treatments that the patient is currently being administered (ie, limited to interferons and GA only) will be permitted during the screening and prior DMT Treatment Phase. If the investigator determines that the patient needs to be treated with another DMT, the patient will be discontinued from the study. Prior DMT will be discontinued 7 days before alemtuzumab first administration. Refer to Section 6.1 for further details." "No concomitant therapy with any disease-modifying MS treatments either licensed or investigational, including interferons and GA, will be permitted during the alemtuzumab treatment" is replaced appended with "phase. If the investigator determines that the patient needs to be treated with another DMT, the patient will be discontinued from the study."	Clarification
Section 9.1.1.1, Brain MRI	"The MRI assessments will also be available to the investigators to assess safety" is added.	Clarification
Section 9.2, Secondary endpoints	A summary of secondary endpoints is added.	Clarification
Section 9.2.1.3.1, Brief visuospatial memory test – revised	"Central scoring will be performed by an independent rater who is blinded to treatments (ie, current DMT or alemtuzumab)" is added.	Clarification
9.2.1.3.2 ,Symbol digit modality test	It is clarified that oral responses are expected of the patient, which will be written down by the person administering the test.	Clarification
Section 9.3.2, Laboratory safety variables	Text regarding HPV testing is added.	Request of local health authorities
Section 10.1.1, Visit 1 Screening visit:	Race is added to the demographic variables collected. HPV testing is added to the list of serology tests performed. "The MRI assessments will be available to investigators to assess safety" is added.	Clarification
Section 10.1.3, Visit 3/Day-7:	The section title is changed to Visit 3/Day -14 to -7. Urine sampling is added.	Clarification
Section 10.1.10, Visit 16/M12 (second course of alemtuzumab):	Urine sampling is added	Clarification

Section 10.3, Handling of patient temporary or permanent treatment discontinuation and of patient study discontinuation	"Should" is replaced with "must" in "Any IMP discontinuation should be fully documented in the electronic-Case Report Form (e-CRF)."	Clarification
Section 10.3.1, Temporary treatment discontinuation with investigational medicinal product(s)	"Should is replaced with "must" in "For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF."	Clarification
Section 10.3.4, Handling of patients after permanent treatment discontinuation	"Should" is replaced with "must" in "All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed."	Clarification
Section 10.4.1.3, Adverse event of special interest	"Adverse events of special interest may be added, modified or removed during a study by protocol amendment" is added. "Caused" is replaced with "suspected" in "An overdose (accidental or intentional) with the IMP is an event caused by the Investigator or a nurse and defined as an increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration." Listeria infection is added to the list of serious opportunistic infections considered to be AESIs.	Clarification
Section 10.4.3, General Guidelines for reporting adverse events	Following of AEs, SAEs, and AESIs by Investigators after the last planned visit is clarified.	Clarification
Section 10.4.6, Guidelines for management of specific laboratory abnormalities	Cervical dysplasia and thyroid malignancy are added to the list of malignancies among specific laboratory abnormalities.	Clarification
Section 10.4.7, Guidelines for reporting product complaints (IMP/NIMP/device)	This section was added to the protocol.	Clarification
Section 10.5, Obligations of the Sponsor	The text "Adverse events that are considered expected will be specified by the reference safety information (label)" was added.	Clarification
Section 10.6, Safety instructions	"IB" is replace by "label" in For more information about alemtuzumab, please refer to IB."	Clarification
Section 11.1, Determination of sample size	"Approximately 60 patients aged from 10 years to less than 18 years will be enrolled in this study to account for screen failures, and to ensure at least 50 patients are evaluable" is replaced with "At least 60 patients aged from 10 years to less than 18 years will be enrolled in this study to account for screen failures to ensure at least 50 patients are evaluable."	Clarification
Section 11.4.2.2, Analyses of secondary efficacy endpoints	"For EDSS, descriptive statistics, (e.g., percentages of stable/improved/worsened since the end of Period 1) will be calculated" is added.	Clarification
Section 11.5, Interim analysis	That there will be a partial, informal database lock for the interim analysis is clarified.	Clarification
Section 14.5, Data protection	The reason for collection of race and ethnicity data is clarified.	Clarification
Appendix F – 23 –Item PedsQL Generic Core scales	This was deleted.	Clarification

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