NCT02255656

AMENDED CLINICAL TRIAL PROTOCOL 03

COMPOUND: GZ402673 (alemtuzumab)

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

STUDY NUMBER: LPS13649

STUDY NAME: TOPAZ

VERSION DATE/STATUS: 28-Jan-2020 / APPROVED

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03	All	28-Jan-2020, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	24-Jul-2019, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	27-Feb-2018, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 02 (US)	US only	27-Feb-2018, version 1 (electronic 3.0)
Protocol Amendment 02	All	27-Feb-2018, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01 (US)	US only	23-Mar-2016, version 1 (electronic 2.0)
Protocol Amendment 01 (US)	US only	23-Mar-2016, version 1 (electronic 2.0)
Clinical Trial Protocol	All	11-Apr-2014, version 1 (electronic 1.0)

AMENDED PROTOCOL 03 (28-Jan-2020)

This amended protocol 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 amendment addresses safety update based on recent post marketing safety monitoring findings. Sponsor has conducted a comprehensive review of safety data from post-marketing use with alemtuzumab, updated contraindications for retreatment with alemtuzumab, and updated Adverse Event of Special Interest (AESI) list and identified areas where risk mitigation measures will be implemented that include increasing frequency of liver function tests from every 3 months to every month.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.2.2 Re-treatment with alemtuzumab flow chart And Section 9.5.2.2 Patients exposed to alemtuzumab during this study And Section 10.1.6 Alemtuzumab treatment And Appendix A Recommendations for using alemtuzumab in countries where it is not yet available	Changed the frequency of LFT evaluation from every three months to every month. And Added ECG to be performed before alemtuzumab infusion.	Monitoring potential autoimmune hepatitis and updated the safety monitoring information
Section 10.1.6.2 Post-alemtuzumab treatment monitoring	Changed the frequency of LFT evaluation from every three months to every month.	Monitoring potential autoimmune hepatitis
Section 1.2.2 Re-treatment with alemtuzumab flow chart (footnote [b]) And Section 9.5.2.2 Patients exposed to alemtuzumab during this study And Section 10.1.6.1 Prior to alemtuzumab treatment visit Section 10.1.6.2 Post-alemtuzumab treatment monitoring	Updated wording of bilirubin assessment to total and direct bilirubin	Clarification of wording

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary endpoint(s) Primary endpoints: Safety And Section 4 Introduction and rationale And Section 9.1 Primary endpoints: safety And Section 10.4.1.3 Adverse event of special interest And Section 10.4.4 Guidelines for reporting adverse events of special interest, Table 2 - Summary of adverse event reporting instructions	The current list of AESIs is updated with below list: • Acquired hemophilia A • Progressive multifocal leukoencephalopathy (PML) • Temporally associated* pulmonary alveolar hemorrhage • Temporally associated* myocardial ischemia, myocardial infarction • Temporally associated* stroke • Temporally associated* cervicocephalic arterial dissection (* Temporally associated: 1 to 3 days after the last infusion) • 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	Updated as per recent safety findings and benefit risk assessment
Section 4 Introduction and rationale	Reference to “section 10.1.6 Alemtuzumab treatment” added for infusion monitoring procedure.	Reference for clarity and details
Section 6.3 Interim Analysis And Section 11.5 Interim Analysis	Updated wording to below text: No interim analysis is planned; an annual partial database lock will be made available for publication purpose.	Clarification of wording
Section 8.1.2 Pre-treatment	Added below text: Physician should also consider the contraindications of alemtuzumab when retreating patient in this study (Section 10.1.6).	Updated the safety monitoring information
Section 9.1 Primary Endpoints: Safety	Added Hemophagocytic lymphohistiocytosis (HLH). in project-specific Adverse Events of Special Interest (AESIs), which was missed in this section in Amendment 2	Omitted in previous amendment

Section # and Name	Description of Change	Brief Rationale
Section 10.1.6 Alemtuzumab treatment Pre-Infusion And Appendix A Recommendations for using alemtuzumab in countries where it is not yet available	Updated/added the contra-indications list as below: - 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	Updated the safety monitoring information
Section 10.1.6 Alemtuzumab treatment	Updated the pre-infusion, during infusion, and post-infusion text: The following infusion management procedures must be utilized for each infusion and each treatment course to reduce serious reactions temporally associated with LEMTRADA 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), evaluate infusion-related risks, and review HCP checklist. It is at investigator's discretion to re-treat or not re-treat patient with alemtuzumab after clinical evaluation. Updated the during infusion with following text: The following are recommendations in case of clinical abnormalities/severe adverse event: - Interrupt infusion - Medically evaluate the patient guided by the adverse event profile of LEMTRADA prior to considering restarting therapy - Provide appropriate treatment as needed - Consider permanently discontinuing the LEMTRADA infusion if the patient shows clinical symptoms suggesting development of	Updated the safety monitoring information

Section # and Name	Description of Change	Brief Rationale
	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: - Observation for infusion reactions is recommended for a minimum of 2 hours after LEMTRADA infusion. - 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 seek appropriate medical care.	
Section 10.1.6.1 Prior to alemtuzumab treatment visit	Added below parameters - ECG -vital signs (including heart rate and blood pressure measurement	Updated the safety monitoring information
Section 14.2 Record Retention in Study Sites	The duration of archiving of study document has been updated to 25 years	Administrative change
Appendix A Recommendations for using alemtuzumab in countries where it is not yet available	Added HPV and platelet count in baseline tests to be conducted before re-treatment with alemtuzumab Added LFT in baseline tests (to be performed before re-treatment with alemtuzumab) and in monitoring activities (to be performed during treatment and for 48 months after last treatment)	Updated safety monitoring information
Whole document	Minor editorial and format changes were done throughout the document. In Title page, header, and table of contents, amended protocol 02 was changed to amended protocol 03. LFT abbreviation was added in list of abbreviations. Page numbers were updated.	Formatting/Administrative change

CLINICAL TRIAL SUMMARY

COMPOUND: GZ402673 (Alemtuzumab) **STUDY No: LPS13649**	
TITLE	A long-term follow-up study for Multiple Sclerosis patients who have completed the alemtuzumab Extension Study (CAMMS03409)
INVESTIGATOR/TRIAL LOCATION	Multinational, multicenter: Argentina, Australia, Belgium, Brazil, USA, Canada, Croatia, Czech Republic, Denmark, Germany, Israel, Italy, Mexico, Netherlands, Poland, Russia, Serbia, Spain, Sweden, Ukraine, United Kingdom.
PHASE OF DEVELOPMENT	Phase 3B/4
STUDY OBJECTIVE(S)	**Primary objective** • To evaluate long-term safety of alemtuzumab. **Secondary objective(s)** • To evaluate long term efficacy of alemtuzumab. • To evaluate the safety profile of patients who received other Disease Modifying Treatments (DMT) following alemtuzumab treatment. • To evaluate patient-reported quality of life (QoL) outcomes and health resource utilization of patients who received alemtuzumab. • To evaluate as needed re-treatment with alemtuzumab and other DMTs.
STUDY DESIGN	This study is a Phase 3B/4, international, multicenter, open-label, non-comparative study to evaluate the long-term safety, efficacy and QoL of alemtuzumab in patients who have completed at least 48 months of the extension Study CAMMS03409. In addition, impact of treatment on pharmaco-economic data will also be evaluated. Scheduled visits for safety and efficacy assessments will be performed every six months. Quality of life and pharmaco-economic data will be collected every twelve months. Patients must contact the treating neurologist at the study site (Study Investigator) as soon as they experience any sign or symptom of multiple sclerosis (MS) relapse. The Study Investigator will decide on the need to schedule extra visits (unscheduled visits) to evaluate the patient's status. At the Study Investigator's discretion patients can be treated with additional courses of alemtuzumab (not sooner than 12 months from the previous course) or with any commercial DMT. If the patient is re-treated with additional courses of alemtuzumab, the patient will be followed using the specific recommendations indicated in the IB or in the local approved label (when available). Patients will be followed for 48-months after the last infusion of alemtuzumab received in the current trial setting. During the 48-month period, laboratory safety sampling should be collected every month, in a local laboratory and they must be reviewed in a timely manner by the Study Investigator. If the 48-month period of safety follow-up continues after the study ends, the patient will be followed by their physician in a regular healthcare setting, in line with the local approved Risk Minimization Plan for alemtuzumab, until the 48-month period is completed.

	A pharmacogenomics (PGx) substudy will be conducted for exploratory analysis of genetic variations predictive of autoimmune conditions, including thyroid and immune thrombocytopenia (ITP), related to MS disease and/or the effects of alemtuzumab. For research purposes only and on a voluntary basis, a blood sample will be proposed to approximately 300 ongoing patients in the TOPAZ study who have not provided a PGx sample in the previous studies (CAMMS03409, CAMMS223, CAMMS323 and CAMMS324). A blood sample will be collected from consenting patients. Objectives of the substudy are as follows: • To develop biomarkers predictive of autoimmune conditions including thyroid disorders and immune thrombocytopenia. This will include collection of samples from patients who have not yet developed any auto immune conditions; these samples would be used as controls. • To explore efficacy and safety markers through data analysis. • To explore genetic variation related to MS disease manifestation through data analysis. Sample collection, handling, storage, and analysis will conform to all applicable national guidance and regulations. Details of the PGx sub-study are presented in Appendix C.
STUDY POPULATION **Main selection criteria** **Total expected number of patients**	**Inclusion criteria** I 01. Patient has completed at least 48 months of the Extension Study CAMMS03409. I 02. Signed written informed consent form (ICF). **Exclusion criteria** E 01. Patient participating in another investigational interventional study. Approximately (up to) 1248 eligible patients from the Extension Study (CAMMS03409) In approximately (up to) 180 study centers
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation** **Route(s) of administration** **Dose regimen** **Noninvestigational medicinal product(s) (if applicable)** **Formulation** **Route(s) of administration** **Dose regimen**	Alemtuzumab Concentrate for solution for infusion (sterile concentrate) IV infusion in a supervised medical setting 12 mg/day for 3 consecutive days (36 mg total dose) at least 12 months after the prior treatment course. Each single-use vial contains 12 mg alemtuzumab (10 mg/mL; total extractable volume 1.2 mL). NA

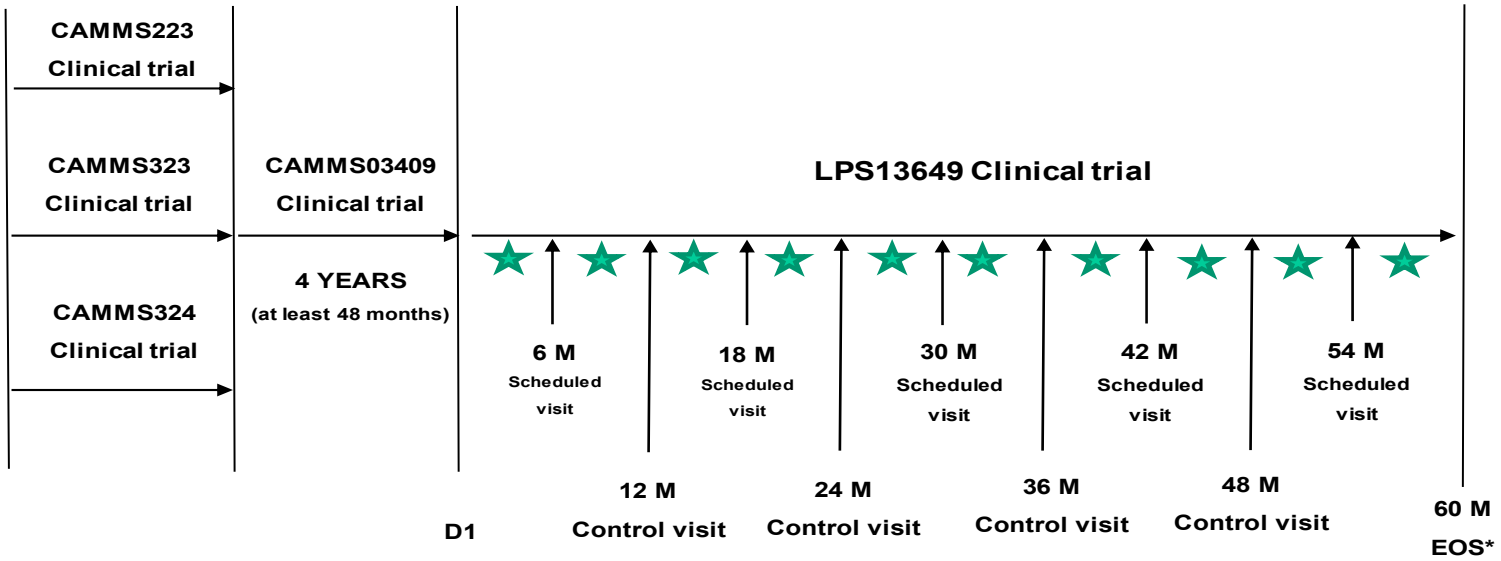
ENDPOINT(S)	**Primary endpoints: Safety** • Incidence, duration, grade/intensity, relationship to study drug, and outcome of the following: - Serious Adverse Events (SAEs). - Adverse Events (AEs). - Infusion-associated reactions (IAR). • Incidence, nature, seriousness, grade/intensity, relationship to study drug, and outcome of the following Adverse Events of Special Interest (AESI): - Autoimmune mediated conditions including, but not limited to: - Immune thrombocytopenic purpura (ITP). - Nephropathies including anti-glomerular basement membrane (GBM) disease. - Cytopenias. - Thyroid disorders. - Autoimmune hepatitis. - Acquired hemophilia A - Hemophagocytic lymphohistiocytosis (HLH). - Progressive multifocal leukoencephalopathy (PML) - Temporally associated* pulmonary alveolar hemorrhage - Temporally associated* myocardial ischemia, myocardial infarction - Temporally associated* stroke - Temporally associated* cervicocephalic arterial dissection (*Temporally associated: 1 to 3 days after the last infusion) - Serious infections including serious opportunistic infections (eg, Listeria infections, CMV, EBV), HPV associated with cervical dysplasia - Malignancy. - Pneumonitis • Changes in laboratory parameters. **Secondary endpoints: Efficacy** • Annualized relapse rate (ARR). • Proportion of patients relapse free. • Change over time in Expanded Disability Status Scale (EDSS) scores. • Change over time in brain imaging findings to include: - Number of Gadolinium (Gd)-enhancing, and new Gd-enhancing lesions. - Number of new/enlarging T2 lesions. - Number of new T1 (and new hypointense T1) lesions. - T1 and T2 lesion volume. - Brain Parenchymal Fraction (BPF).

	• Change over time in self-reported QoL as assessed by the Medical Outcome Study (MOS) 36-Item Short-Form Health Survey (SF-36) Version 2. • Change over time in the Functional Assessment of Multiple Sclerosis (FAMS), and • Change over time in the EuroQoL in 5 Dimensions (EQ-5D). **Other endpoint: Pharmaco-economic** • The modified Health Resources Utilization Questionnaire (HRUQ) and Health Related Productivity Questionnaire (HRPQ) will be administered to obtain pharmaco-economic data.
ASSESSMENT SCHEDULE	Safety assessments will be made at each visit and include all AEs, SAEs, and AESI. Vital signs will be assessed and recorded at each visit. Physical examination will be assessed and recorded once a year. Efficacy Assessments will be performed as described in the flowchart, including Expanded Disability Status Scale (EDSS); Brain imaging; MOS 36-Item Short-Form Health Survey (SF-36); FAMS and EQ-5D questionnaires. Potential MS relapse will be considered at each scheduled visit by the Study Investigator. Patients will be informed to contact the treating neurologist at the study site (Study Investigator) as soon as they observe any sign/symptom compatible with a possible relapse between scheduled visits and the Study Investigator will determine the need for an unscheduled visit. In case of relapse, the Study Investigator will decide on the therapeutic approach. The reason(s) for any change in the MS therapy must be collected as well as the relapse treatment. If the patient is re-treated with a new course of alemtuzumab, the patient will be followed during the 48-month period of safety follow-up after the last infusion of alemtuzumab. For patients treated with alemtuzumab, laboratory safety sampling should be collected every month for 48 months, in a local laboratory and the results will be reviewed in a timely manner by the Study Investigator. If the 48-month period of safety follow-up continues after the study ends, the patient will be followed by their physician in a regular healthcare setting until the 48-month period is completed. PGx samples obtained from consenting patients will be used for exploratory biomarker analysis.

STATISTICAL CONSIDERATIONS	The following represents an overview of planned analyses. Further elaboration of statistical issues will be specified in the Statistical Analysis Plan (SAP). Safety Analysis: All patients will be evaluated for safety based on incidence, duration, grade/intensity, seriousness, and relationship of AEs to alemtuzumab. AESIs, deaths, and other SAEs will also be evaluated. Efficacy Analysis: The long-term effects of alemtuzumab will be examined by summarizing the efficacy endpoints, including ARR, proportion of patients relapse free, changes in EDSS score over time, changes in MRI, QoL, changes in the FAMS, EQ-5d and pharmaco-economy, from original study baseline through the last visit in the study.
DURATION OF STUDY	The study duration will be 5 years (plus a window of 6 months) counted from the enrolment date of the first patient.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



★ **Only for patients treated with alemtuzumab: monthly laboratory safety variables collection for 48 months after last infusion**

- **For patients who received alemtuzumab in CAMMS03409 study less than 48 months before entering in LPS13649 study, and**
- **For patients receiving retreatment with alemtuzumab during the LPS13649 study**

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

1.2 STUDY FLOW CHARTS

1.2.2 Re-treatment with alemtuzumab flow chart

For all the patients re-treated with alemtuzumab and for 48 months after last infusion.

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

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

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

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

1.2.1 Study flow chart

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

a If not performed in the previous 3 months.

b Note that weight assessment is included in the vital signs assessment module in the eCRF instead of the physical examinations module. Nevertheless, it is to be performed at baseline and on yearly basis and not every 6 months.

c If not performed in the previous 6 months.

d If the HRUQ questionnaire was administered in the previous 3 months, then only questions 1 through 9 of the Modified HRUQ/HRPQ need to be completed at baseline.

e For consenting patients only.

f Omit if collected at a previous visit.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

AE:	adverse events
AESI:	adverse events of special interest
ARR:	annualized relapse rate
BPF:	brain parenchymal fraction
CI:	confidence intervals
CNS:	central nervous system
DMT:	disease modifying treatment
EDSS:	expanded disability status scale
EOS:	end of study
FAMS:	functional assessment of multiple sclerosis
Gd:	gadolinium
HLA:	human leukocyte antigen
HLH:	hemophagocytic lymphohistiocytosis
HPV:	human papilloma virus
HRPQ:	health related productivity questionnaire
HRUQ:	health resources utilization questionnaire
IAR:	infusion-associated reaction
IB:	investigator's brochure
ICF:	informed consent form
IMP:	investigational medical product
ITP:	immune thrombocytopenic purpura
LFT:	liver function tests
MOS:	medical outcome study
MS:	multiple sclerosis
NFD:	nephrogenic fibrosing dermopathy
NSF:	ephrogenic systemic fibrosis
PGx:	pharmacogenomics
QoL:	quality of life
SAE:	serious adverse events
SAP:	statistical analysis plan
SC:	subcutaneous
SNP:	single nucleotide polymorphism
UK:	United Kingdom

4 INTRODUCTION AND RATIONALE

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) that affects approximately 2.5 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 relapsing 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 believed to arise from the interplay of polygenic inherited susceptibility and as yet unidentified environmental agents. Age of onset typically ranges from 10 to 59 years, with most cases occurring between 20 and 40 years of age. As with most other autoimmune disorders, MS is more than twice as common among women. Pathologically, MS is characterized by focal and non-focal tissue injury of the brain and spinal cord due to the complex interplay of inflammation, demyelination, axonal injury, astrocytosis, and tissue atrophy. Lymphocytes are believed to play a central role in MS pathogenesis.

Alemtuzumab (Lemtrada®) is a humanized monoclonal antibody that binds to CD52, a cell surface antigen present at high levels on T and B lymphocytes, and at lower levels on natural killer cells, monocytes, and macrophages (2).

There is little or no CD52 detected on neutrophils, plasma cells, or bone marrow stem cells. Alemtuzumab acts through antibody-dependent cellular cytolysis and complement mediated lysis following cell surface binding to T and B lymphocytes.

The mechanism by which alemtuzumab exerts its therapeutic effects in MS is unknown, but may involve immunomodulation through the depletion and repopulation of lymphocytes.

Research suggests that potential immunomodulatory effects in MS may include alterations in the number, proportions, and properties of some lymphocyte subsets post-treatment (3).

Pilot studies in MS patients were conducted at Addenbrooke's Hospital in the United Kingdom (UK). Genzyme Corporation (Genzyme, a Sanofi company) has sponsored Phase 2 and Phase 3 randomized, comparator-controlled studies in patients with relapsing remitting MS that have established superior efficacy for alemtuzumab compared with subcutaneous interferon beta-1a (SC IFNB-1a, Rebif®) on clinical and imaging endpoints (4, 5, 6, 7, 8).

Identified risks of alemtuzumab in patients with MS include:

- Infusion-associated reactions (IAR)
- Serious infections
- Autoimmunity (notably, Immune thrombocytopenic purpura (ITP), thyroid dysfunction and nephropathies)

The most important adverse reactions are autoimmunity (eg, ITP, thyroid disorders, nephropathies, cytopenias), IARs, and serious infections. The most common adverse events

reported after alemtuzumab treatment (in ≥20% of patients) are rash, headache, pyrexia, and respiratory tract infections. Of note, Listeriosis/Listeria meningitis has been reported in LEMTRADA treated patients, generally within one month of LEMTRADA infusion. To reduce the risk of infection, patients receiving LEMTRADA should avoid ingestion of uncooked or undercooked meats, soft cheeses and unpasteurized dairy products two weeks prior to, during, and for at least one month after LEMTRADA infusion.

The Sponsor has conducted a comprehensive review of safety data from post-marketing use of alemtuzumab and added the following to the current list of AESIs:

- Autoimmune hepatitis
- Acquired hemophilia A
- Hemophagocytic lymphohistocytosis (HLH)
- Progressive multifocal leukoencephalopathy (PML)
- Temporally associated* pulmonary alveolar hemorrhage
- Temporally associated* myocardial ischemia, myocardial infarction
- Temporally associated* stroke
- Temporally associated* cervicocephalic arterial dissection

* Temporally associated: 1 to 3 days after the last infusion

Cases of serious and life-threatening stroke (including hemorrhagic and ischemic), myocardial infarction and cervicocephalic (ie, vertebral, carotid) arterial dissection have been reported within three days of alemtuzumab administration, with most cases occurring within one day. Cases of pulmonary alveolar hemorrhage have been reported with onset within 48 hours of alemtuzumab infusion. Long term auto immune risks, such as cases of Hemophagocytic lymphohistiocytosis (HLH) and autoimmune hepatitis causing clinically significant liver injury, including acute liver failure requiring transplant, has been reported. To minimize the risk of these serious adverse events, recommendations are provided for infusion related management and long term safety monitoring for patients receiving re-treatment of alemtuzumab during the course of the trial:

- Pre infusion: assess overall health status and risk factors; baseline BP/HR, bleeding risk, platelets count. Baseline liver function test.
- During infusion: continuous or hourly monitoring BP/HR; intermittently ambulation, compressive stocking.
- Post infusion: inform/remind patient any abnormal clinical sign/symptoms related to infusion.
- Periodic liver function test.

Please refer to Section 10.1.6 for details.

Study CAMMS03409 is an open-label extension study designed to provide additional safety monitoring for up to 60 months, and as-needed alemtuzumab retreatment to qualifying patients who received alemtuzumab in prior Genzyme-sponsored studies CAMMS223, CAMMS323 and CAMMS324. In addition, patients who received SC IFNB-1a in the earlier studies had the opportunity to receive 2 annual courses of alemtuzumab, and possibly subsequent as-needed alemtuzumab retreatment.

In CAMMS03409, “as needed” retreatment with alemtuzumab could be offered to patients upon documented evidence of resumed MS disease activity, subject to safety-related disqualifications. The additional course(s) of alemtuzumab were administered at 12 mg/day on 3 consecutive days (36 mg total dose) at least 12 months after the prior treatment course. The benefits and risks of >2 treatment courses have not been fully established, but results suggest that the safety profile does not appear to change with additional courses.

The present study LPS13649 will provide long term safety and efficacy data on the patients who completed the extension study CAMMS03409, as well as on additional as-needed alemtuzumab retreatment. In addition, the study will provide information about the safety profile of patients who received other commercial DMTs following alemtuzumab treatment.

5 STUDY OBJECTIVES

5.1 PRIMARY

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

5.2 SECONDARY

The secondary objectives are:

- To evaluate long term efficacy of alemtuzumab.
- To evaluate the safety profile of patients who received other DMT following alemtuzumab treatment.
- To evaluate patient-reported quality of life (QoL) outcomes and health resource utilization of patients who received alemtuzumab.
- To evaluate as needed re-treatment with alemtuzumab and other DMTs.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

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

Patients treated with alemtuzumab within 48 months prior to enrollment in the LPS13649 study must be followed-up at monthly intervals until 48 months after the last infusion of alemtuzumab (Section 10.1.6.2).

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

Patients must contact the treating neurologist at the study site (Study Investigator) as soon as they experience any sign or symptom of MS relapse. The Study Investigator will decide on the need to schedule extra visits (unscheduled visits) to evaluate the patient's status. All procedures and assessments will be collected in the e-CRF.

At the Study Investigator discretion patients can be treated:

- Patients may receive additional courses of alemtuzumab but not sooner than 12 months from any previous alemtuzumab treatment course, or
- Patients may receive other commercial DMTs.

In the event that a Study Investigator decides to treat a patient (with alemtuzumab or another DMT) the factors contributing to the decision to treat (eg, patient is experiencing clinical and/or imaging activity) should be documented in the e-CRF.

For treatment courses of alemtuzumab the Study Investigator should refer to the safety information in the Investigator's Brochure (IB) or in the approved label in the country/region when available. All treatment courses will consist of 12 mg/day alemtuzumab intravenously infused once daily on 3 days (Section 8.1).

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

If the 48-month period of required safety follow-up continues after the study ends, the patient will be followed by their physician in a regular healthcare setting, in line with the local approved Risk Minimization Plan for alemtuzumab, until the 48-month period is completed.

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

- To develop biomarkers predictive of autoimmune conditions including thyroid disorders and immune thrombocytopenia. This will include collection of samples from patients who have not yet developed any auto immune conditions; these samples would be used as controls.
- To explore efficacy and safety markers through data analysis.
- To explore genetic variation related to MS disease manifestation through data analysis.

For research purposes only and on a voluntary basis, a blood sample will be collected from approximately 300 ongoing patients who signed the optional pharmacogenomic informed consent form and who have not previously provided a PGx sample. Details of the PGx substudy are presented in Appendix C, “Exploratory Pharmacogenomics Assessment Substudy”.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation

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

6.2.2 Determination of end of clinical trial (all patients)

The end of the clinical trial occurs 5 years (plus a window of 6 months) after the inclusion of the first patient.

6.3 INTERIM ANALYSIS

No interim analysis is planned; an annual partial database lock will be made available for publication purpose.

6.4 STUDY COMMITTEES

No study committees are planned.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Patient has completed at least 48 months of the Extension Study CAMMS03409.

I 02. Signed written informed consent form (ICF).

7.2 EXCLUSION CRITERIA

E 01. Patient participating in another investigational interventional study.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Name of the Investigational Medical Product (IMP):

- Alemtuzumab.

Pharmaceutical form:

- Concentrate for solution for infusion (sterile concentrate).

Dose of drug per administration:

- 12 mg/day on 3 consecutive days (36 mg total dose).
- Missed doses should not be given on the same day as a scheduled dose.

Route of administration:

- Intravenous infusion.

8.1.1 Administration

There is no fixed treatment requirement or schedule. Administration of alemtuzumab will only be done following a decision from the Study Investigator that an additional "as needed" course is indicated.

Alemtuzumab will be then administered by IV infusions in a supervised medical setting at a dose of 12 mg/day on 3 consecutive days (36 mg total dose) at least 12 months after the prior treatment course.

8.1.1.1 Method of preparation at the clinical site

Alemtuzumab must be diluted before infusion. The diluted solution should be administered by intravenous infusion over a period of approximately 4 hours.

8.1.1.2 Special precautions for disposal and other handling

The vial contents should 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 intravenous administration, withdraw 1.2 mL 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 should be inverted gently to mix the solution.

Alemtuzumab contains no antimicrobial preservatives and, therefore, care should 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 unused medicinal product or waste material should be disposed of in accordance with local requirements.

8.1.2 Pre-treatment

All the specific recommendations indicated in the IB or in the local approved label (when available) should be checked before starting the re-treatment with alemtuzumab. Physician should also considered the contraindications of alemtuzumab when retreating patient in this study (Section 10.1.6.1).

Patients should be pre-treated with corticosteroids (eg, 1000 mg methylprednisolone IV) immediately prior to alemtuzumab administration on each of the 3 days of treatment.

Additionally, pretreatment with antihistamines and/or antipyretics prior to alemtuzumab administration may also be considered.

Oral prophylaxis for herpes infection should be administered to all patients starting on the first day of treatment and continuing for a minimum of 1 month following treatment with alemtuzumab. The choice of the therapy and the dose will be at the discretion of the Study Investigator.

8.1.3 Post-treatment

Observation for infusion associated reactions is recommended during and for a minimum of 2 hours after alemtuzumab infusion.

Patients treated with alemtuzumab must commit to 48-months of follow-up after the last infusion. It is possible that this period continues after study completion, in a regular healthcare setting.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Not applicable.

8.3 BLINDING PROCEDURES

No blinding procedures are planned.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

No method of assigning patients to treatment group is planned.

8.5 PACKAGING AND LABELING

The content of the labeling is in accordance with the local regulatory specifications and requirements.

Alemtuzumab will be packaged in 3-vial cartons. Each vial contains 12 mg of alemtuzumab per 1.2 mL of solution. The vials are single use only and contain no preservatives. The label text for the alemtuzumab vial will, at a minimum, include the protocol number, the contents of the vial (ie, alemtuzumab 10 mg/mL, 1.2 mL vial), lot number, appropriate cautionary statements, route of administration, storage conditions, and name and address of Genzyme (a Sanofi company). Labels comply with Good Manufacturing Practices and national legislation.

8.6 STORAGE CONDITIONS AND SHELF LIFE

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

Alemtuzumab diluted product may be stored at room temperature (15° to 25°C) or refrigerated conditions (2° to 8°C), and should be used within 8 hours after dilution. From a microbiological point of view, it is recommended that the product should be used immediately. Protect from light. 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 Study 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 Study 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) should be promptly notified to the Sponsor. 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 Study Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Study 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 supervised medical setting, on an outpatient basis, 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

The Study Investigator will not destroy the unused IMP unless the Sponsor provides written authorization. A detailed treatment log of the destroyed IMP will be established with the Study Investigator (or the pharmacist) and countersigned by the Study Investigator and the monitoring team.

8.8 CONCOMITANT MEDICATION

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

Patients who need to be re-treated with alemtuzumab and who are receiving treatment with other DMTs, should discontinue the other DMTs according to their local approved label. The potential for additive effects on the patient's immune system must be taken into account. Concomitant use of alemtuzumab with some therapies could increase the risk of immunosuppression.

8.8.1 Forbidden concomitant medications

Patients should not receive live vaccines 6 weeks prior to alemtuzumab administration or during the study.

All the specific recommendations indicated in the IB or in the local approved label (when available) should be checked before starting the re-treatment with alemtuzumab.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINTS: SAFETY

Safety assessments will include the following:

- Incidence, duration, grade/intensity, relationship to study drug, and outcome of the following:
  - Serious Adverse Events (SAEs).
  - Adverse Events (AEs).
  - Infusion-associated reactions (IAR).
- Incidence, nature, seriousness, grade/intensity, relationship to study drug, and outcome of the following project-specific Adverse Events of Special Interest (AESIs):
  - Autoimmune mediated conditions including, but not limited to:
    - Immune thrombocytopenic purpura (ITP).
    - Nephropathies including anti-glomerular basement membrane (GBM) disease.
    - Cytopenias.
    - Thyroid disorders.
    - Acquired hemophilia A
    - Autoimmune hepatitis.
    - Hemophagocytic lymphohistiocytosis (HLH).
    - Progressive multifocal leukoencephalopathy (PML)
    - Temporally associated* pulmonary alveolar hemorrhage
    - Temporally associated* myocardial ischemia, myocardial infarction
    - Temporally associated* stroke
    - Temporally associated* cervicocephalic arterial dissection

      (* Temporally associated: 1 to 3 days after the last infusion)

    - Serious infections including serious opportunistic infections (eg, Listeria infections, CMV, EBV), HPV associated with cervical dysplasia
  - Malignancy.
  - Pneumonitis
- Changes in laboratory parameters.

9.2 SECONDARY ENDPOINTS: EFFICACY

The long-term effects of alemtuzumab will be examined by summarizing from baseline (date of the inclusion in the initial studies: CAMMS223, CAMMS323 or CAMMS324) through the last study visit the following efficacy endpoints:

- Annualized relapse rate (ARR).
- Proportion of patients relapse free.
- Change over time in Expanded Disability Status Scale (EDSS) scores.
- Change over time in brain imaging findings to include:
  - Number of Gadolinium (Gd)-enhancing, and new Gd-enhancing lesions.
  - Number of new/enlarging T2 lesions.
  - Number of new T1 (and new hypointense T1) lesions.
  - T1 and T2 lesion volume.
  - Brain Parenchymal Fraction (BPF).
- Change over time in self-reported quality of life (QoL) as assessed by the Medical Outcome Study (MOS) 36-Item Short-Form Health Survey (SF-36) Version 2.
- Change over time in the Functional Assessment of Multiple Sclerosis (FAMS), and
- Change over time in the EuroQoL in 5 Dimensions (EQ-5D).

9.3 OTHER ENDPOINTS

The modified HRUQ/HRPQ will be administered to obtain pharmaco-economic data.

9.4 APPROPRIATENESS OF MEASUREMENTS

The assessments used in this study are standard for evaluation of therapy in patients with MS.

9.5 SAFETY MEASUREMENTS

9.5.1 Adverse events

Collection of AEs (refer to Section 10.4 for details) spontaneously reported by the patient or observed by the Study Investigator extends from the signing of the informed consent form until the end of the study visit. All reported AEs will be recorded in the patient's records and in the e-CRF at all visits.

Patients will be asked to volunteer information concerning AEs with a non-leading question such as: "How have you been since your last visit?"

An IAR is defined as any adverse event occurring during and within 24 hours of alemtuzumab infusion.

9.5.2 Laboratory safety variables

9.5.2.1 Patients exposed to alemtuzumab within 48 months prior to inclusion in this study

- The following parameters must be obtained at monthly intervals until 48 months after the last infusion of alemtuzumab administered in the study CAMMS03409:
  - CBC with differential (including platelet count).
  - Serum creatinine.
  - Urinalysis (minimally including determination of urine protein and red blood cells) with microscopy.[1]
- TSH must be obtained every 3 months until 48 months after the last infusion of alemtuzumab administered in the study CAMMS03409.
- For women, a Human Papilloma Virus (HPV) screening must be performed as follows:
  - For women within 48 months follow-up at time of study transition from CAMMS03409 to TOPAZ, the date of the last alemtuzumab infusion administered in the study CAMMS03409 must be checked, and then an HPV screening performed approximately 1 year after the last infusion of alemtuzumab, and then every 12 months until 48 months safety FU is completed.

9.5.2.2 Patients exposed to alemtuzumab during this study

- For women of childbearing potential, a pregnancy test must be obtained prior to treatment with alemtuzumab.
- For women, an HPV screening must be performed as follows:
  - For women patients re-treated with alemtuzumab during the TOPAZ study, an HPV screening should be performed prior to re-treatment (if not done in the previous 12 months) and then every 12 months until 48 months safety FU is completed.
- The following parameters must be obtained prior to treatment with alemtuzumab if not performed in the previous 2 weeks:
  - ECG

[1] Note: For sites using homecare nurses service, or where microscopy is not routinely done if urine dipstick analysis is negative, the following procedure will be implemented: Homecare nurses/investigator site staff will perform a urine dipstick which will secure the detection of any potential haematuria and/or proteinuria. If urine dipstick is positive, the investigator would need to ask the patient to come to the site to have microscopy performed at the local lab. At any time, as per investigator criteria, according to the patient's status, the patient can be asked to have a microscopy at the local lab to confirm any potential diagnosis.

- CBC with differential (including platelet count).
- Serum creatinine.
- TSH.
- Liver function test (ALT, AST, ALP, albumin, total protein, direct bilirubin, and total bilirubin)
- Urinalysis (minimally including determination of urine protein and red blood cells) with microscopy. (Please also refer to footnote in Section 9.5.2).

- The following parameters must be obtained at monthly intervals until 48 months after the last infusion of alemtuzumab:
  - CBC with differential (including platelet count).
  - Serum creatinine.
  - Liver function test (ALT, AST, ALP, albumin, total protein, total bilirubin and direct bilirubin)
  - Urinalysis (minimally including determination of urine protein and red blood cells) with microscopy. (Please also refer to footnote in Section 9.5.2).
- TSH must be obtained every 3 months until 48 months after the last infusion of alemtuzumab if retreated. LFT may be performed at any time if clinically indicated at Investigators' discretion.

9.5.3 Vital signs

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]).

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

If clinically significant vital sign changes from previous visit are noted the changes will be documented as AEs in the e-CRF. Clinical significance is defined as any variation that has medical relevance and may result in an alteration in medical care. The Study Investigator will continue to monitor the patient until the parameter returns to baseline or until the Study Investigator determines that follow-up is no longer medically necessary.

9.5.4 Physical examination

A physical examination, including weight, will be performed at D1 (if not performed in the previous 3 months) and then every 12 months. Any clinically significant abnormalities should be reported in the patient e-CRF as an AE. Weight should be taken with the patient wearing undergarments or very light clothing and no shoes and with an empty bladder. It is recommended to use the same scale throughout the study.

9.6 EFFICACY MEASUREMENTS

9.6.1 Relapse

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

EDSS must be completed to confirm the relapse.

If the MS relapse is confirmed, the therapeutic approach will be decided by the Study Investigator, and all the treatments will be described in the e-CRF. Patients will be followed up at the discretion of the Study Investigator and all the procedures and assessments will be collected in the e-CRF.

MS relapse will be verified at each visit. On the other hand, patients will be informed to contact the Study Investigator as soon as they observe any sign/symptom compatible with a possible relapse, in order to schedule an extra visit (see Section 10.1.4).

Relapses will not be considered as AEs (see Section 10.4.1.2).

9.6.2 Expanded disability status scale (EDSS)

Patient disability will be evaluated using the EDSS, which has long been considered the standard for assessing disability in patients with MS. The EDSS must be performed by a qualified practitioner who has completed the Neurostatus certification training.

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, cerebral, and other) in the context of a standard neurological examination and then uses these 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.

EDSS will be collected at D1 (if not collected in the previous 3 months) and then at each scheduled visit (every 6 months) and unscheduled visits for MS relapse.

9.6.3 Brain imaging

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

9.6.3.1 Pre- and post-Gadolinium-MRI

The most frequently used surrogate marker of inflammatory disease activity in Phase 1 and Phase 2 studies in MS is the rate of new gadolinium-enhancing MRI lesion formation. Gadolinium-enhancing lesions in MS patients generally indicate active foci of inflammatory demyelination in the CNS. In 2 studies, alemtuzumab has been shown to have a profound effect on this measure.

Gadolinium-containing contrast agents have been linked with Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD) in patients with impaired kidney function. There have been no reported cases in alemtuzumab-treated MS patients to date. Nonetheless, the Study Investigator should confirm that the patient is eligible to receive gadolinium according to their imaging center's guidelines, for example based on age, medical status, and most recent creatinine level, prior to performing gadolinium-enhanced imaging.

9.6.3.2 MRI-T1

These brain scans can be used to assess the number and volume of T1 hypointense lesions ("Black Holes"), which also indicate axonal loss and tissue matrix damage. Three dimensional (3D) T1 weighted Gradient Echo imaging will also be performed as it affords greater spatial resolution and thus enhances detection of smaller lesions.

9.6.3.3 MRI-T2

The total MRI T2 lesion volume has been used as a surrogate marker of disease activity in the beta-interferon studies. T2-weighted MRI assessments will also include proton density and fluid attenuated inversion recovery (FLAIR) sequences. The inflammatory demyelination and edema characteristic of active MS lesions as well as the sclerotic gliosis of end-stage MS plaques contribute to the MRI T2 lesion volume, which thus reflects the "burden of disease" in these patients.

Cerebral volume is also estimated from MRI-T2/PD acquisitions to quantify global neuro-degeneration, which is largely due to axonal loss in MS. In this study the rate of cerebral atrophy will be determined from the MRI T2/PD brain scans as changes in the BPF.

The number of new or enlarging hyperintense lesions as detected by T2 weighted MRI has been used as a surrogate marker of efficacy in recent MS studies.

9.6.4 MOS 36-item short-form health survey (SF-36) Version 2

The SF-36 is a self-administered questionnaire designed to assess generic Health Related Quality of Life (HRQoL) in healthy and ill adult populations. The SF-36 consists of 36 items organized into the 8 scales shown below (see Table 1). The SF-36 also yields 2 summary measures of physical health (the Physical Component Summary [PCS]) and mental health (the Mental Component Summary [MCS]) derived from scale aggregates. Higher global scores are associated with better quality of life.

Table 1 - Components of the SF-36

Scale	Number of items	Definition of scale
Physical Functioning (PF)	10	Limitations in physical activity because of health problems
Social Functioning (SF)	2	Limitations in social activities because of physical or emotional problems
Role Limitations Physical (RP)	4	Limitations in usual role activities because of physical health problem
Bodily Pain (BP)	2	Presence of pain and limitations due to pain
General Medical Health (GH)	5	Self-evaluation of personal health
Mental Health (MH)	5	Psychological distress and well-being.
Role Limitations Emotional (RE)	3	Limitations in usual role activities because of emotional problems.
Vitality (VT)	4	Energy and fatigue
General Health Perceptions	Single item	(Not applicable)

The reliability of the 8 scales and 2 summary measures has been estimated using both internal consistency and test-retest methods. With rare exceptions, published reliability statistics have exceeded the minimum standard of 0.70 recommended for measures used in group comparisons in more than 25 studies; most have exceeded 0.80. Reliability estimates for physical and mental summary scores usually exceed 0.90.

SF-36 will be collected at D1 (if not collected in the previous 3 months) and then every 12 months, and the end of study visit.

9.6.5 FAMS, Version 4

The FAMS is a widely accepted, MS-specific, quality of life questionnaire. It has been developed and validated in 23 languages, and shows adequate test-retest reliability and internal consistency. The FAMS is a self-report multidimensional index comprising a total of 58 items on 7 subscales: mobility (7 items); symptoms (7 items); emotional well being (7 items); general contentment (7 items); thinking and fatigue (9 items); family/social well being (7 items); and additional concerns (14 items, these are not scored). The response period for this measure is the past 7 days. Each item (except those for “additional concerns”) is rated on a 5-point scale of 0 to 4. The sum of the 44 scored items is the total score, which ranges from 0 to 176, with higher numbers reflecting

a higher quality of life. The total score is the primary criterion by which the effect of treatment on quality of life will be assessed; however, subscale totals will also be evaluated.

FAMS will be collected at D1 (if not collected in the previous 3 months) and then every 12 months and the end of study visit.

9.6.6 EuroQoL in 5 dimensions (EQ-5D)

The EQ-5D is a generic, standardized instrument that provides a simple, descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The EQ-5D comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension consists of 3 levels (some, moderate, extreme problems), generating a total of 243 theoretically possible health states.

The index has been validated in 36 languages. The response period is the day of assessment only. Assessments will also be made using the EuroQol Visual Analogue Scale (EQ-VAS), which captures the self-rating of current health status using a visual "thermometer" with the end points of 100 (best imaginable health state) at the top and zero (worst imaginable health state) at the bottom.

EQ-5D will be collected at D1 (if not collected in the previous 3 months) and then every 12 months, and at the end of study visit.

9.7 OTHER MEASUREMENTS

9.7.1 Modified healthcare resource utilization questionnaire (HRUQ)/health related productivity questionnaire (HRPQ)

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

The questionnaire addresses the following content areas:

- Employment situation and changes in employment situation due to MS.
- Admissions and stays in hospital, rehabilitation centers, or nursing homes.
- Typical MS-related investments (eg, stair and bed lift, ramps, rails) and devices (eg, walking aids, wheelchairs).
- Assistance by community or social services (eg, home nurse, transportation), or help from family or friends.
- Patient reported data regarding employment status.

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

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

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

9.7.2 Exploratory pharmacogenomic assessment

For research purposes only and on a voluntary basis, a blood sample will be collected from consenting patients for exploratory analysis of genetic variations related to MS disease and/or alemtuzumab effects. The results of these analyses will not be provided to the Investigator or the patient. DNA sample collection, handling, storage, and analysis will conform to all applicable guidance and regulations. Details can be found in Appendix C.

10 STUDY PROCEDURES

Procedures will be performed following the standard clinical practice of each study center.

10.1 VISIT SCHEDULE

10.1.1 Visit 1: selection (D1)

This visit must be conducted within 3 months (6 months for US, see Appendix D) after completion of the Extension Study CAMMS03409. When possible, Visit 1 will be performed at the same time as the last visit of the Extension Study CAMMS03409.

Prior to any assessments, information for the patient regarding the aims and methods of the study, its constraints and risks will be reviewed with the patient and a written summary in the form of an informed consent will be given to the patient. The patient must sign the informed consent before continuing the visit. The patient will keep the same patient number as used in the Extension Study CAMMS03409.

The following items will be checked/performed and recorded:

- Informed consent signature.
- Eligibility by review of Inclusion/Exclusion criteria (Section 7).
- Date of the last infusion of alemtuzumab.
  - If the treatment was administered within the previous 48 months, the patient must be followed-up as described in Section 10.1.6.2.
- Safety assessments (Section 9.5).
  - Collection of AEs still ongoing at the end of the Extension Study CAMMS03409.
  - Collection of the AE that occurred between the final visit of the CAMMS03409 study and Visit 1.
  - Collection of laboratory results, if any, performed between the final visit of the CAMMS03409 study and Visit 1.
  - Vital signs and physical examination (only if not performed and collected in the previous 3 months).
- Efficacy assessments (Section 9.6).
  - MS relapse verification.
  - EDSS (only if not performed and collected in the previous 3 months).
  - Brain imaging to include: G-MRI, MRI-T1 and MRI-T2 T1 pre- and post-Gadolinium (Gd), T2/PD, FLAIR and T1 sagittal sequences (only if not performed and collected in the previous 6 months).

  - Health questionnaires: SF-36, FAMS and EQ-5D (only if not performed in the previous 3 months).
- Pharmaco-economic assessment: modified HRUQ/HRPQ (Section 9.7) (only if not collected in the previous 3 months).
- Previous medication (from the end of the Extension Study CAMMS03409 to Visit 1 of LPS13649 study).
- Concomitant medication.

An appointment should be scheduled for next visit in 6 months (±14 days).

10.1.2 Scheduled visits at 6 months (M6±14D, M18±14D, M30±14D, M42±14D, M54±14D)

The following items will be checked/performed and recorded:

- Safety assessments (Section 9.5).
  - AE collection.
  - Vital signs.
- Efficacy assessments (Section 9.6).
  - MS relapse verification.
  - EDSS.
- Concomitant medication.
- Blood sample collection for pharmacogenomic analysis (for consenting patients only).

An appointment should be scheduled for the next visit in 6 months (±14 days).

10.1.3 Scheduled visits at 12 months (M12±14D, M24±14D, M36±14D, M48±14D)

The following items will be checked/performed and recorded:

- Safety assessments (Section 9.5).
  - AE collection.
  - Vital signs and physical examination.
- Efficacy assessments (Section 9.6).
  - MS relapse verification.
  - EDSS.
  - Brain imaging to include: G-MRI, MRI-T1 and MRI-T2 T1 pre- and post-Gadolinium (Gd), T2/PD, FLAIR and T1 sagittal sequences.
  - Health questionnaires: SF-36, FAMS and EQ-5D.
- Pharmaco-economic assessment: modified HRUQ/HRPQ (Section 9.7).

- Concomitant medication.
- Blood sample collection for pharmacogenomic analysis (for consenting patients only). Omit if already collected during a prior study visit.

An appointment should be scheduled for the next visit in 6 months (±14 days).

10.1.4 End of study (EOS) visit

This visit will be performed in one of the following situations:

- At the end of the study. This visit corresponds to the Visit M60±14D.
- At the end of the study period of 5 years, for all the ongoing patients, the next scheduled site visit will be changed into an EOS visit.
- If the patient is prematurely withdrawn from the study.

The following items will be checked/performed and recorded:

- Safety assessments (Section 9.5).
  - AE collection.
  - Vital signs and physical examination.
- Efficacy assessments (Section 9.6).
  - MS relapse verification.
  - EDSS.
  - Brain imaging to include: G-MRI, MRI-T1 and MRI-T2 T1 pre- and post-Gadolinium (Gd), T2/PD, FLAIR and T1 sagittal sequences (only if not performed in the previous 6 months).
  - Health questionnaires: SF-36, FAMS and EQ-5D.
- Pharmaco-economic assessment: modified HRUQ/HRPQ (Section 9.7).
- Concomitant medication.
- Blood sample collection for pharmacogenomic analysis (for consenting patients only). Omit if already collected during a prior study visit.

10.1.5 Unscheduled visits

At any time during the study the Study Investigator can schedule an extra visit if necessary.

The Study Investigator will decide on the procedures to be performed. Data of all performed procedures will be collected in the e-CRF. At least the following items will be checked/performed and recorded:

- Safety assessments (Section 9.5).
  - AE collection.
  - Vital signs.

- Efficacy assessments (Section 9.6).
  - MS relapse verification.
  - EDSS.
- Concomitant medication.

The Study Investigator determines whether patients are eligible for treatment:

- Patients may receive additional courses of alemtuzumab (see Section 8.1.1) but not sooner than 12 months from any previous alemtuzumab treatment course, or
- Patients may receive other commercial DMTs.

In case of treatment the Study Investigator must document:

- Clinical factors for deciding treatment, and/or
- Imaging factors for deciding the treatment.

10.1.6 Alemtuzumab treatment

At any time during the study, the Study Investigator can decide to treat the patient with alemtuzumab (provided that the patient has not had alemtuzumab in prior 12 months).

All the specific recommendations indicated in the IB or in the local approved label (when available) should be checked before starting the re-treatment with alemtuzumab.

The following infusion management procedures must be utilized for each infusion and each treatment course to reduce serious reactions temporally associated with LEMTRADA 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), evaluate infusion-related risks, and review HCP checklist. Physician should also consider following contraindications of alemtuzumab when retreating patient 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 re-treat or not re-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 abnormalities/severe adverse event:
  - Interrupt infusion
  - Medically evaluate the patient guided by the adverse event profile of LEMTRADA prior to considering restarting therapy
  - Provide appropriate treatment as needed
  - Consider permanently discontinuing the LEMTRADA 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 LEMTRADA infusion.
  - 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 seek appropriate medical care.

For monitoring potential risk of autoimmune hepatitis, liver function test must be performed for patients who newly initiate retreatment of alemtuzumab, LFT to be performed prior infusion of retreatment as baseline, and monthly for 48 months after the last infusion of retreatment of alemtuzumab. In addition, LFT may be performed at any time if clinically indicated at Investigators' discretion

10.1.6.1 Prior to alemtuzumab treatment visit

The following items will be checked and recorded:

- Clinical factors for deciding treatment.
- Imaging factors for deciding the treatment.
- For women, an HPV screening must be performed if not done in the previous 12 months.

The following parameters must be obtained prior to initiation of treatment with alemtuzumab:

- ECG
- vital signs (including heart rate and blood pressure measurement
- Pregnancy test (for women of childbearing potential).
- CBC with differential, including platelet count (if not performed in the previous two weeks).
- Serum creatinine (if not performed in the previous two weeks).
- TSH and liver function test (ALT, AST, ALP, albumin, total protein, direct and total bilirubin) (if not performed in the previous 2 weeks).
- Urinalysis (minimally including determination of urine protein and red blood cells) with microscopy (if not performed in the previous 2 weeks). (Please also refer to footnote in Section 9.5.2).

10.1.6.2 Post-alemtuzumab treatment monitoring

The following parameters must be obtained at monthly intervals (± 3 days) until 48 months after the last infusion of alemtuzumab:

- CBC with differential (including platelet count).
- Serum creatinine.
- Liver function test (ALT, AST, ALP, albumin, total protein, direct and total bilirubin)
- Urinalysis (minimally including determination of urine protein and red blood cells) with microscopy (if not performed in the previous 2 weeks). (Please also refer to footnote in Section 9.5.2).

TSH must be obtained every 3 months (±3 days) until 48 months after the last infusion of alemtuzumab.

For women, an HPV screening must be performed every 12 months (±14 days) until 48 months safety FU is completed.

The blood and urine sampling will be performed in local laboratories at the patients' convenience. Results must be sent to the Study Investigator. The Study Investigator must review laboratory data as soon as the results are available and they will be recorded in the e-CRF.

If the 48-month period of safety follow-up continues after the study ends, the patient will be followed by their physician in a regular healthcare setting, in line with the local approved Risk Minimization Plan for alemtuzumab, until the 48-month period is completed.

10.2 DEFINITION OF SOURCE DATA

Source documents 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, MRI, chest X-ray or signed documented X-ray and reports, ECG tracings and reports, laboratories reports, medication dispensing records, computer printouts, electronic data/information sources and any other documentation regarding the patient.

10.3 HANDLING OF PATIENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

Any IMP discontinuation should be fully documented in the e-CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Permanent treatment discontinuation with investigational medicinal product(s)

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

10.3.2 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 Study Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

10.3.3 Handling of patients after permanent treatment discontinuation

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

Patients re-treated with alemtuzumab must be followed as described in Section 10.1.6.

10.3.4 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.

If possible, the patients are assessed using the procedure normally planned for the EOS visit (Section 10.1.4).

If a patient has consented to participate in the PGx substudy and withdraws from the TOPAZ study, the patient's PGx sample will be stored for analysis unless the patient specifically indicates that it cannot be used following the time of study withdrawal. If the patient withdraws consent of sample use, the samples must be destroyed.

For patients who fail to return to the site, the Study Investigator should make the best effort to recontact the patient (eg, contacting patient's family or private physician, reviewing 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).

At time of withdrawal, any patient who has received an infusion with alemtuzumab less than 48 months ago should be reminded of the importance to continue to check for symptoms of autoimmune conditions and to have monthly laboratory tests performed until the 48-month period is completed.

The SAP will specify how these patients lost to follow-up 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 **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily must have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

A **serious adverse event** (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 should 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 must be considered as 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.
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Study 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).

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Study 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 or removed during a study by protocol amendment.

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

The following AE will be considered as AESI:

- Hypersensitivity or anaphylaxis

- Pregnancy of a woman entered in the study;
  - Pregnancy occurring in a woman patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2).
  - Follow-up of the pregnancy in a woman participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or non-serious) with IMP.
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Study Investigator or spontaneously notified by the patient and defined as increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.

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

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

10.4.1.4 Events not to be considered as AEs/SAEs

Medical conditions present at the initial trial visit (Visit1) that do not worsen in severity or frequency during the trial are defined as baseline medical conditions, and are not to be considered AEs. However, baseline medical conditions other than the disease under trial that worsen in severity or frequency during the trial should be recorded and reported as AEs.

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 eCRF. Therefore, symptoms, relapses or worsening of MS will not be considered as AEs nor captured on the AE module of the eCRF 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).

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP, spanning from the signature of the informed consent 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 CRF. At Visit 1 the ongoing AEs started during the Extension Study CAMMS03409, or occurred between the final visit of the CAMMS03409 study and Visit 1, are also to be recorded.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Study 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 Study 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.
- 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 or ECG abnormalities 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.
- AEs/AESIs that are ongoing at the end of the patient's participation in CAMMS03409 should be followed during the LPS13649 study.

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Study Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Study Investigator within the e-CRF or after a standard delay.
- 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.
- 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. 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 Study 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.

10.4.4 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 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF.

Table 2 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case report form completion		
			AE form	Safety comple-mentary form[a]	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Hypersensitivity or anaphylaxis	Yes	Yes	No
		Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	No
		ALT ≥3 ULN or ≥2 baseline	Yes	Yes	Yes
		Autoimmune mediated conditions including, but not limited to: • Immune thrombocytopenic purpura (ITP) • Nephropathies including anti-glomerular basement membrane (GBM) disease • Cytopenias • Thyroid disorders • Autoimmune hepatitis • Acquired hemophilia A	Yes	Yes	No
		Serious infections including serious opportunistic infections (eg, Listeria infections, CMV, EBV), HPV associated with cervical dysplasia	Yes	Yes	No
		Hemophagocytic lymphhostiocytosis (HLH)	Yes	Yes	No

Event category	Reporting timeframe	Specific events in this category	Case report form completion		
			AE form	Safety comple-mentary form[a]	Other specific forms
		Progressive Multifocal Leukoencephalopathy (PML)	Yes	Yes	No
		Pneumonitis	Yes	Yes	No
		Temporally associated* pulmonary alveolar hemorrhage	Yes	Yes	No
		Temporally associated* myocardial ischemia, myocardial infarction	Yes	Yes	No
		Temporally associated* stroke	Yes	Yes	No
		Temporally associated* cervicocephalic arterial dissection	Yes	Yes	No
		(* Temporally associated: 1 to 3 days after the last infusion)			
		Malignancy	Yes	Yes	No

AE = adverse event; AESI = adverse event of special interest; GBM = Glomerular Basement Membrane; SAE = serious adverse event.

a If an SAE or an AESI ongoing from the CAMMS study is reported in TOPAZ study, the Safety Complementary Form need not be completed.

10.5 OBLIGATIONS OF THE SPONSOR

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, IECs/IRBs as appropriate and to the Study Investigators.
- All SAEs that are expected and at least reasonably related to the IMP to the regulatory authorities, according to local regulations.
- The following AESI, to those regulatory authorities who require such reporting:
  - Malignancy.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected.

Any other AE not listed as an expected event in the IB will be considered unexpected.

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

10.6 SAFETY INSTRUCTIONS FOR USING ALEMTUZUMAB

For more information about alemtuzumab, please refer to IB or to the approved label in the country/region when available.

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

11.1 DETERMINATION OF SAMPLE SIZE

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

11.2 DISPOSITION OF PATIENTS

All CAMMS03409 patients that fulfill the inclusion/exclusion criteria are eligible for enrollment.

A detailed description of patient disposition will be provided. It will include:

- A summary of data on patient discontinuation
- A summary of data on overall Screening and qualification status of all patients
- An account of all identified protocol deviations

In addition, the treatment regimen for all patients will be summarized. This includes summarizing the percentage of patients receiving alemtuzumab on an as-needed basis, and the time to treatment.

11.3 ANALYSIS POPULATIONS

11.3.1 Safety population

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

11.3.2 Efficacy populations

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

11.4 STATISTICAL METHODS

All data collected in this study will be reported using summary tables, figures, and patient data listings. Summary statistics will be computed and displayed by treatment group (assigned in the original study) and scheduled assessment time. Summary statistics for continuous variables will minimally include n, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate. No formal inferential hypothesis tests will be performed, however 2-sided 95% confidence intervals (CI) will be provided where appropriate.

11.4.1 Analyses of efficacy endpoints

The long-term effects of alemtuzumab in patients who received alemtuzumab prior to the extension Study CAMMS03409 (eg, in Studies CAMMS223, CAMMS323, or CAMMS324) will be examined by summarizing the efficacy endpoints from prior study baseline through the end of study participation for each patient. Efficacy will be evaluated using proportion of patients relapse free, relapse rate, ARR, change over time in EDSS, MRI, and QoL measures, starting at baseline of the earlier studies.

The same efficacy evaluations will be made for patients who received SC IFNB-1a prior to the extension Study CAMMS03409 and who subsequently received alemtuzumab in the extension study. For these patients, efficacy will be assessed from the time of their first study treatment in CAMMS323 and CAMMS324 or from the time of randomization in CAMMS223.

The number of patients with a relapse event, the total number of relapses, and the annualized relapse rate over the years of follow-up will be produced. The annualized relapse rate will be estimated using a negative binomial model with robust variance estimation. The model will be stratified by clinical study.

A detailed description of the methods utilized to analyze each of the efficacy endpoints will be provided in the SAP.

11.4.2 Analyses of safety data

All patients in the study will be evaluated for safety. A summary of safety will be evaluated based on incidence, duration, grade/intensity, seriousness, and relationship of AEs to study drugs, and on changes in physical examination, vital signs, and clinical laboratory results, particularly hematological parameters and biochemical, immunological, and clinical indications of ITP, infection, and thyroid dysfunction observed in this study. Deaths and other SAEs will also be evaluated. Particular attention will be paid to the development of autoimmune disorders including the incidence of ITP, autoimmune thyroid disorders and anti-GBM disease. Further elaboration of statistical issues will be provided in the SAP.

11.4.3 Analyses of patient reported outcomes (health-related quality of life/health economics variables

Change over time in self-reported quality of life (QoL) as assessed by the Medical Outcome Study (MOS) 36-Item Short-Form Health Survey (SF-36) Version 2, the Functional Assessment of Multiple Sclerosis (FAMS), and the EuroQoL in 5 Dimensions (EQ-5D), will be analyzed relative to the baseline obtained at the start of the original studies.

Change over time in modified HRUQ/HRPQ will also be analyzed.

11.4.4 Analysis of blood samples for exploratory pharmacogenomics substudy

PGx samples obtained from consenting patients will be used for exploratory biomarker analysis, including (1) targeted gene sequencing to validate the candidate ITP biomarker panel and (2) de novo association analysis to identify predictive markers using whole exome sequencing (WES)/genome-wide association study (GWAS) data. Details can be found in Appendix C.

11.5 INTERIM ANALYSIS

No interim analysis is planned; an annual partial database lock will be made available for publication purpose.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Study Investigator, delegated Study Investigator staff and Subinvestigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, 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 Study Investigator (according to applicable regulatory requirements), or a person designated by the Study Investigator, and under the Study Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (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 informed consent form 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 informed consent form will be provided to the patient.

Ongoing patients agreeing to participate in the exploratory PGx substudy must sign an additional, separate informed consent.

The informed consent form used by the Study 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.

12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Study Investigator or the Sponsor must submit this clinical trial protocol to 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, informed consent form, IB, Study Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

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

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB/IEC before implementation according to applicable regulations, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should 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 IB will be sent to the IRB/IEC, except in countries where alemtuzumab is already approved for treatment in MS.

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 Study 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 Study Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] 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 Study 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 Study Investigator. The Study 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 CRFs. Thus, the main duty of the monitoring team is to help the Study 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, Study 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 CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form 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 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 CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Study Investigator to maintain adequate and accurate 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 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 (DRF) to which the Study 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 Study 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 Study Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

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

If the Study Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Study 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 CRFs, the IB and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Study 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 Study Investigator. The Study Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Study 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 Study 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 Study 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 Study 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 Study 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 Study Investigator in compliance with all applicable laws and regulations.

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 Study 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 Study Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Study 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 Study 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 Study 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 Study 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 Study 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;
- Non-compliance of the Study 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 Study Investigator of its decision by written notice.

14.8.2 By the Investigator

The Study 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 Study Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Study 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 Study Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Study 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 Study 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 Study 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

The Study Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, 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 Study 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 according to applicable local regulations, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Study Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

16 BIBLIOGRAPHIC REFERENCES

1. National Multiple Sclerosis Society. Multiple sclerosis: Just the facts [Online]. 2011 [cited 2011 Oct 27]. Available from: URL:http://www.nationalmssociety.org/about-multiple-sclerosis/index.aspx.

2. Moreau T, Coles A, Wing M, Thorpe J, Miller D, Moseley I, et al. CAMPATH-IH in multiplesclerosis. Mult Scler. 1996;1(6):357-65.

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6. Coles AJ, Wing M, Smith S, Coraddu F, Greer S, Taylor C, et al. Pulsed monoclonal antibodytreatment and autoimmune thyroid disease in multiple sclerosis. Lancet. 1999;354(9191):1691-5.

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17 APPENDICES

Appendix A Recommendations for using alemtuzumab in countries where it is not yet available

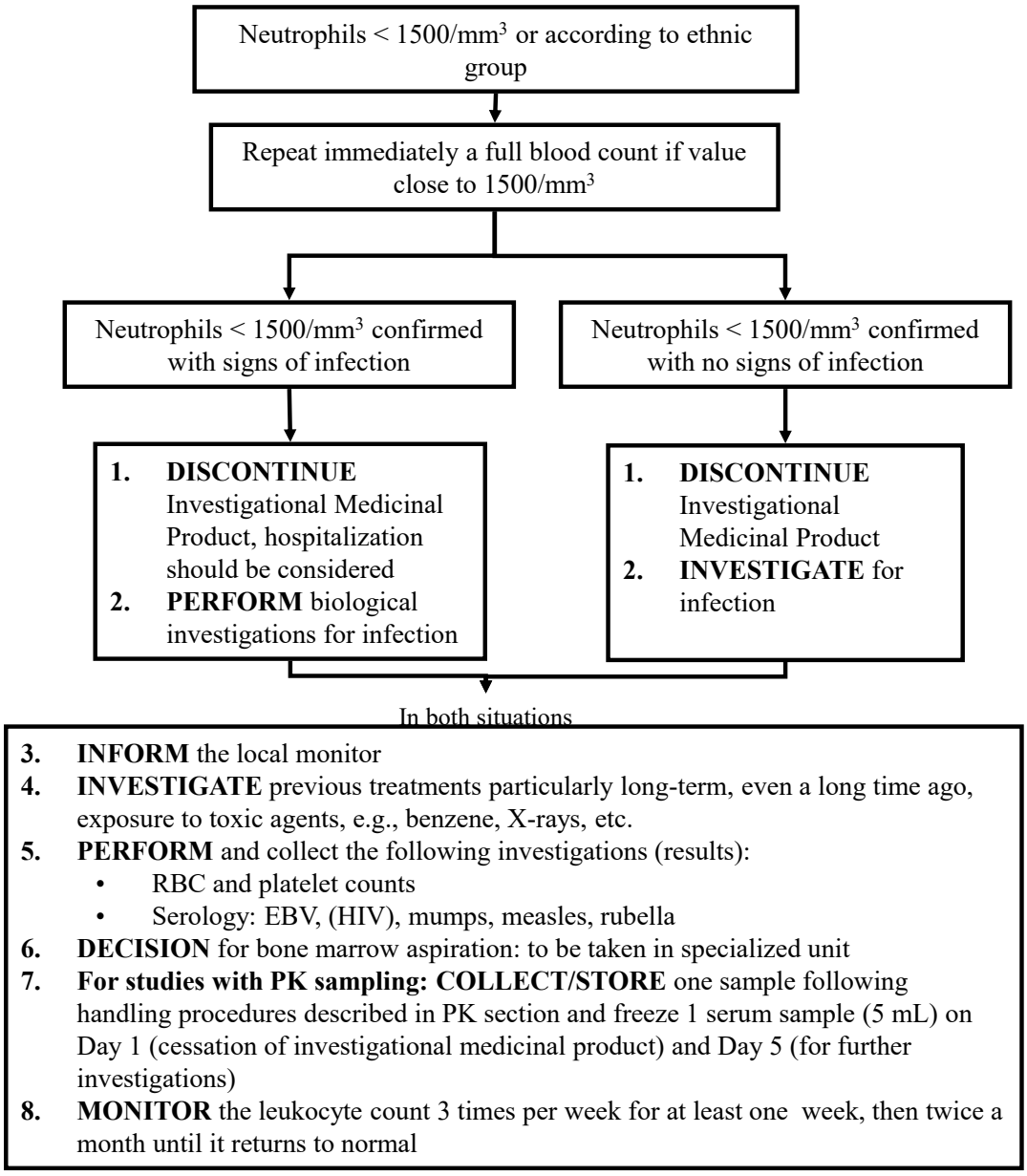
Timing	Activity	Detail
Before re-treatment with alemtuzumab	Contraindications	• Hypersensitivity to the active substance, or to any of the excipients. • Human Immunodeficiency Virus (HIV) infection. • Severe active infection • Uncontrolled hypertension • History of arterial dissection of the cervicocephalic arteries • History of stroke • History of angina pectoris or myocardial infarction • Known coagulopathy or on concomitant anti-coagulant therapy
	Recommended screening	Evaluate for active and inactive ("latent") TB (per local guidelines). Consider screening patients at high risk of HBV and/or HCV infection. Exercise caution in prescribing alemtuzumab to patients identified as carriers of HBV and/or HCV.
	Baseline tests	ECG HPV Complete Blood Count with differential (including platelet count). Serum creatinine, LFT. Thyroid function tests, such as TSH. Urinalysis with microscopy[a].
	Understanding of Benefits & Risks	The patient has been informed about and understands the risks of serious autoimmune disorders, infections and malignancies, and the measures to minimize risk (eg, watching for symptoms, carrying the Patient Alert Card and the need to commit to periodic monitoring for 48 months after the last treatment).
6 weeks prior to treatment (if needed)	Vaccinations	It is recommended that patients have completed local immunization requirements. Consider VZV vaccination of antibody negative patients before initiating a course of alemtuzumab treatment.
Immediately prior to treatment	Pre-treatment	Immediately prior to alemtuzumab pre-treat with corticosteroids on each of the first 3 days of any treatment course.
	Pre-treatment for IARs	Pretreatment with antihistamines and/or antipyretics prior to alemtuzumab administration may also be considered.
	Oral prophylaxis for herpes	Administer 200 mg aciclovir (or equivalent) twice a day from first day of treatment and continuing for a minimum of 1 month following treatment.
	General health	Consider delaying initiation of alemtuzumab administration in patients with active infection until the infection is fully controlled
	Pregnancy & contraception	Ensure women of child bearing potential use effective contraceptive measures when receiving a course of treatment with alemtuzumab and for 4 months following the course of treatment. If patient is pregnant, administer only if the potential benefit justifies the potential risk to the fetus.

Timing	Activity	Detail
During treatment and for 48 months after last treatment	Monitoring Activities	Complete Blood Count w/Differential and Serum creatinine, LFT: Monthly until 48 months from last treatment.
		Urinalysis with microscopy[a]. Monthly until 48 months from last treatment.
		Thyroid function tests: Every 3 months until 48 months from last treatment.

a Note: For sites using homecare nurses service, or where microscopy is not routinely done if urine dipstick analysis is negative, the following procedure will be implemented: Homecare nurses/investigator site staff will perform a urine dipstick which will secure the detection of any potential haematuria and/or proteinuria. If urine dipstick is positive, the investigator would need to ask the patient to come to the site to have microscopy performed at the local lab. At any time, as per investigator criteria, according to the patient's status, the patient can be asked to have a microscopy at the local lab to confirm any potential diagnosis.

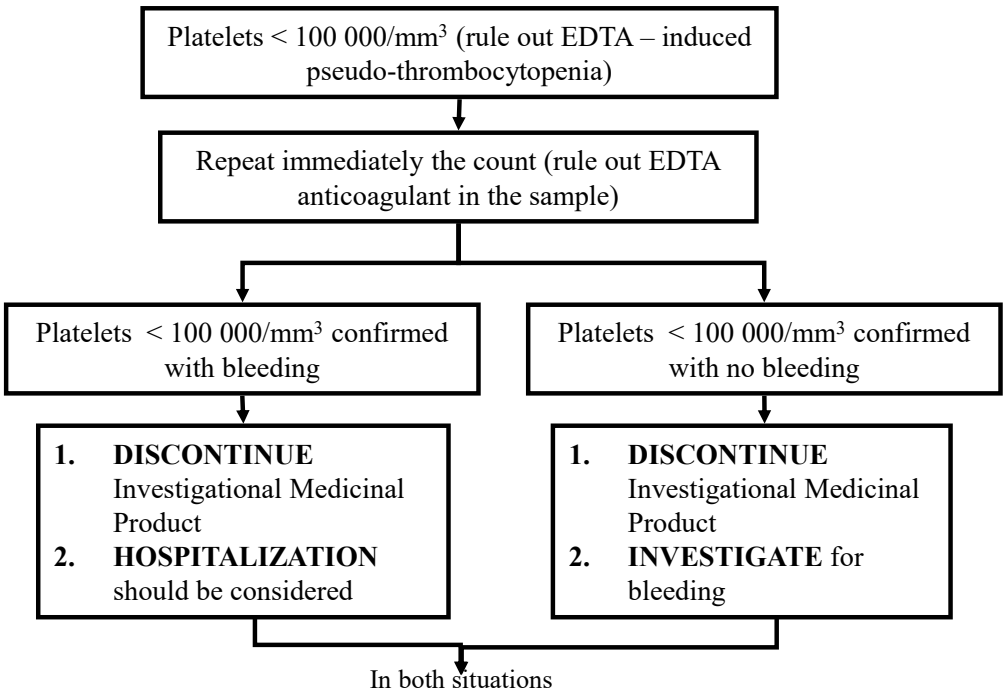
Appendix B General guidance for the follow-up of laboratory abnormalities as required by Sanofi

NEUTROPENIA



Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•For individuals of African descent, the relevant value of concern is <1000/mm3

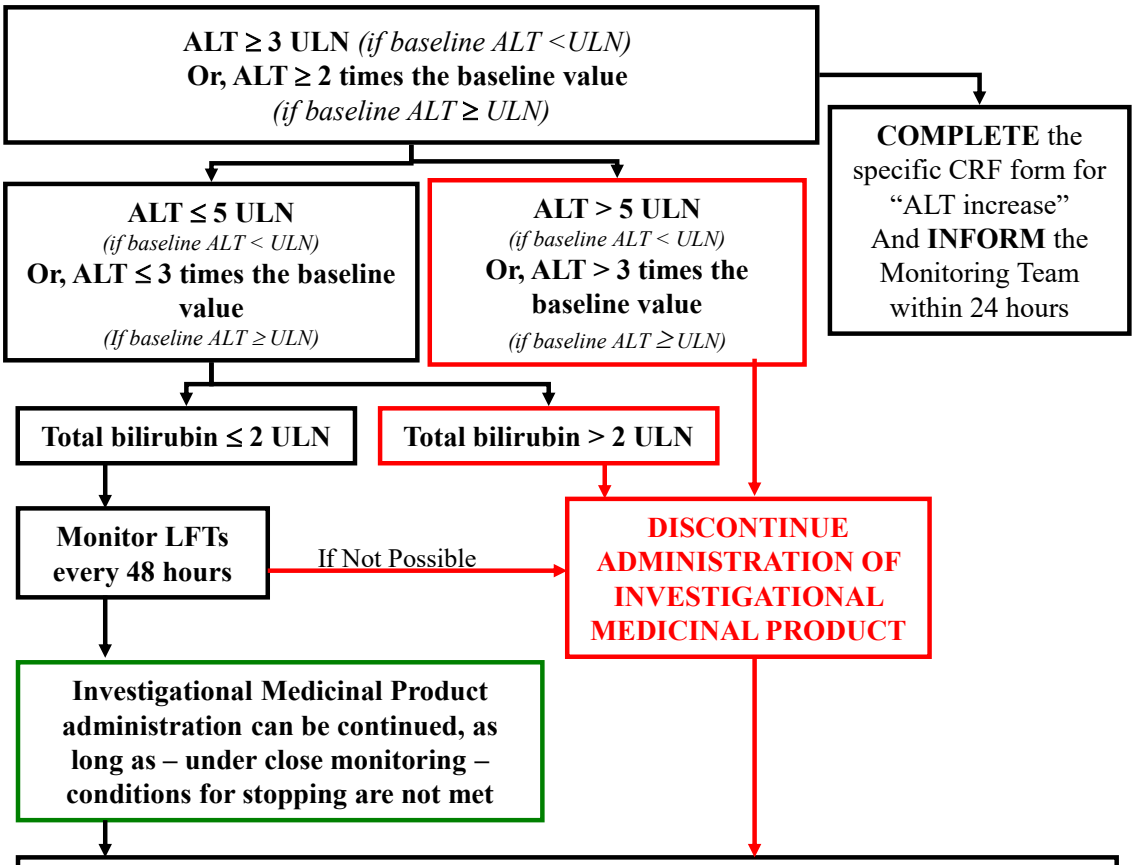
THROMBOCYTOPENIA



3. **INFORM** the local Monitor
4. **QUESTION** about last intake of quinine (drinks), alcoholism, heparin administration
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Bleeding time and coagulation test (fibrinogen, INR or PT, aPTT), Fibrin Degradation Product
   - Viral serology: EBV, HIV, mumps, measles, rubella
6. **For studies with PK sampling: COLLECT/STORE** 1 sample following handling procedures described in PK sections and freeze 1 serum sample (5 mL) on Day 1 (end of treatment) and Day 5 to test for drug-induced antiplatelets antibodies
7. **DECISION** for bone marrow aspiration: to be taken in specialized unit
   - On Day 1 in the case of associated anemia and/or leukopenia
   - On Day 8 if platelets remain < 50 000/mm^3
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

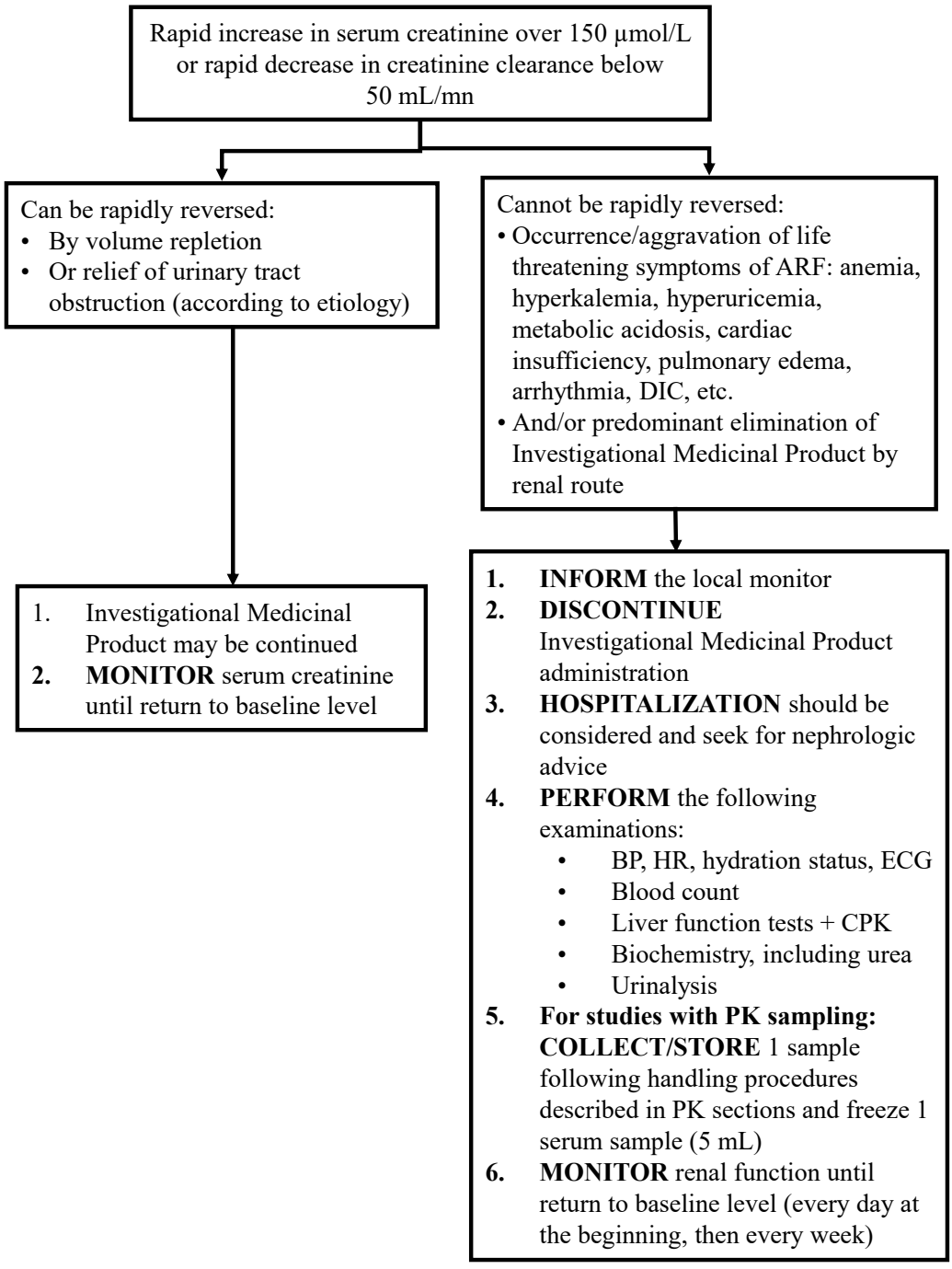
INCREASE IN ALT



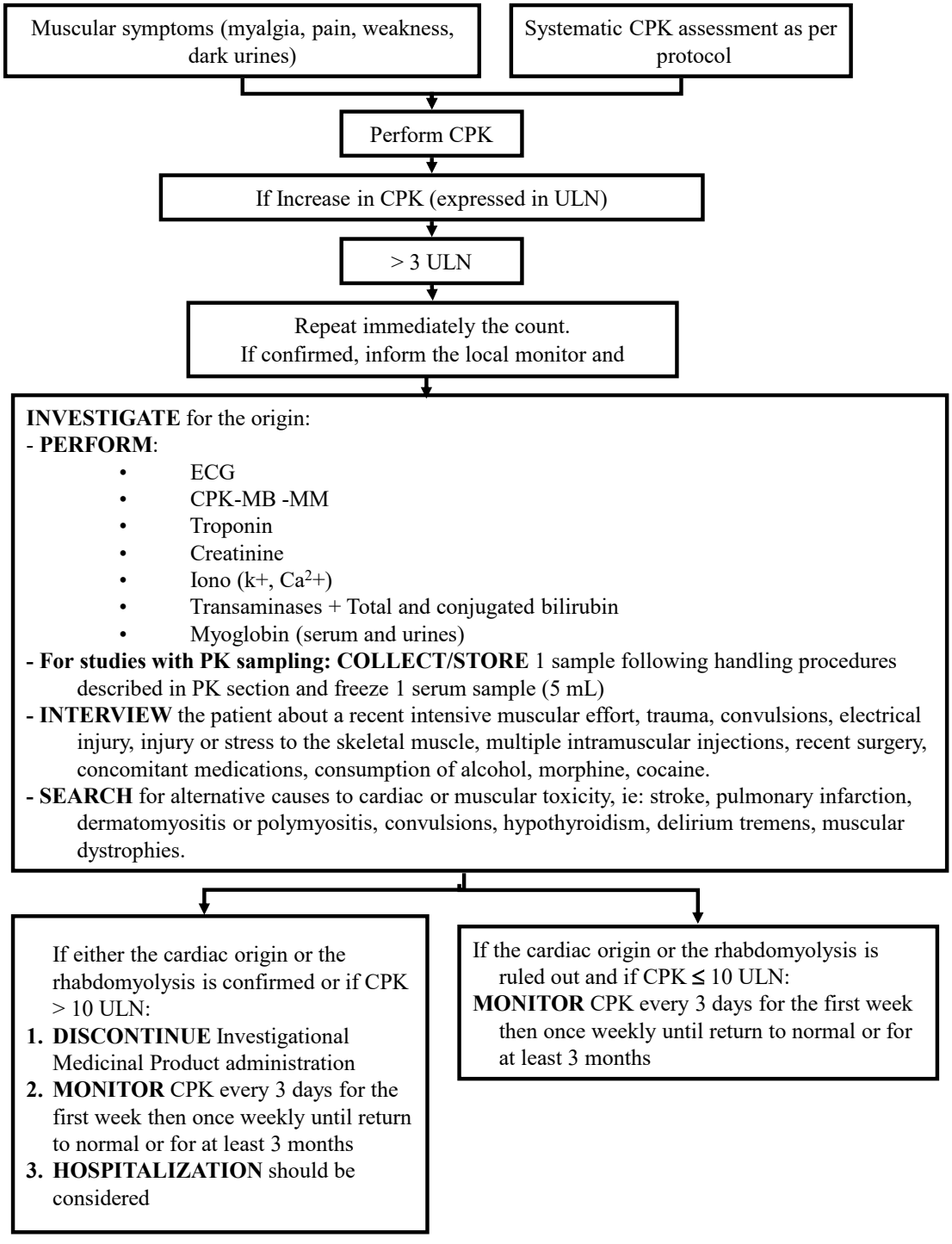
In ANY CASE, FOLLOW the instructions #1 to 7 listed in the box below.

1. **INVESTIGATE THE CLINICAL CONTEXT** in the previous 72 hours, specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia; rule out muscular injury
2. **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, anti-HCV and HCV RNA , anti-CMV IgM and anti-HEV IgM antibodies, and depending on the clinical context, check for recent infections, eg, EBV, Herpes viruses and toxoplasma
   - Hepatobiliary ultrasonography (can be completed by other imaging investigations if needed)
3. **CONSIDER** auto-antibodies: anti-nuclear, anti-DNA, anti-smooth muscle, anti-LKM
4. **CONSIDER** consultation with hepatologist
5. **CONSIDER** patient hospitalization if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy
6. **MONITOR LFTs**
   - **If investigational medicinal product is continued: every 48 hours** until return to normal (<2ULN) or baseline. If ALT elevation persists beyond 2 weeks then perform LFTs every 2 weeks and 15 to 30 days after the last dose according to the study protocol.
   - **If investigational medicinal product is discontinued**: as closely as possible to every 48 hours until stabilization then every 2 weeks until return to normal (<2ULN) or baseline or for at least 3 months, whichever comes last.
7. **For studies with PK sampling: COLLECT/STORE** 1 sample following handling procedures described in PK sections and freeze 1 serum sample (5 mL)

ACUTE RENAL FAILURE



SUSPICION OF RHABDOMYOLYSIS



Appendix C Exploratory pharmacogenomics assessment substudy

Background information

The autoimmunity adverse events associated with LEMTRADA are identified potential risks and pose a potential barrier to a greater use of the product, including autoimmune thyroid disorders (36%), immune thrombocytopenia (ITP; 2%), and nephropathies (0.3%). If biomarkers for autoimmunity were known, more patients could potentially benefit from LEMTRADA treatment.

A team effort has been under way to discover a panel of biomarkers that could predict which patients are at risk of developing autoimmunity events. Blood samples collected from LEMTRADA-treated MS patients within clinical studies were preserved for biomarker discovery. Genomics and proteomics profiling were conducted on a cohort of LEMTRADA-treated MS patients, including patients who developed treatment-emergent autoimmune disorders and patients who, to date, have not developed such disorders. The search for the associated markers was focused on single nucleotide polymorphism (SNP), human leukocyte antigen (HLA)-allele, HLA-amino acid polymorphism, serum cell-free microRNA, serum protein, and serum autoantibody.

Correlative analysis of this biomarker data with the development of autoimmune conditions indicated no robust signals for protein biomarkers. Interestingly, we identified candidate SNPs that are potentially associated with the development of ITP with this preliminary discovery data set. Although potential predictors have been identified, more samples are needed to validate this data. Samples from the TOPAZ study together with samples from patients from previous clinical trials (CAMMS03409, CAMMS223, CAMMS323 and CAMMS324) and from post-marketing patients will provide a large enough cohort to validate the to validate the preliminary findings (and potentially efficacy/non-responders). Samples from patients who have not yet developed any autoimmune conditions would be used as controls.

The goal of this exploratory substudy is to obtain additional data to identify a biomarker for autoimmune events so that LEMTRADA can be safely administered to patients who need the treatment.

Objectives

The following high level objectives are proposed:

- Develop biomarkers predictive of autoimmune conditions including thyroid and ITP. This will include collection of samples from patients who have not yet developed any autoimmune conditions. These samples would be used as controls.
- Explore efficacy and safety markers through data analysis
- Explore genetic variation related to MS disease manifestation through data analysis

Rationale

TOPAZ patients have >7 years post LEMTRADA treatment experience. The intent is to collect blood samples from approximately 300 consenting patients for the purpose of exploratory analyses of genetic variations related to MS disease and/or alemtuzumab effects.

Investigational plan

For research purposes only and for those patients who signed the optional pharmacogenomic informed consent form, a blood sample will be collected at the study visit for exploratory analysis of genetic variations related to MS disease and/or alemtuzumab effects as specified in the study flow chart, and this sample will be stored.

Samples will be processed for DNA isolation and for genetics analysis. Genomic data generated from these samples (including samples collected from TOPAZ patients with no autoimmunity) will be used to validate a predictive marker panel from discovery cohort analysis. DNA sample collection, handling, storage, and analysis will conform to all applicable national guidance and regulations as follows.

This blood sample will be transferred to a site that will, on behalf of Sanofi, store it until the time of analysis.

The blood sample, and the DNA that is extracted from it, will be assigned a second number, a Genetic ID (deidentification code) that is different from the Subject ID. This “double coding” is performed to separate a subject’s medical information and DNA data.

The clinical study data (coded by Subject ID) will be stored in the clinical data management system (CDMS), which is a distinct database in a separate environment from the database containing the pharmacogenetic data (coded by Genetic ID). The key linking Subject ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The samples will be stored at a secure site specialized for such investigations under the responsibility of the Sponsor for up to 15 years after completion of the final study report of the LPS13649 study. All data is anonymized. If the patient withdraws consent to participate in the PGx substudy, the patient’s PGx sample will be destroyed.

Patient selection criteria

Sample size will be based on elective participation of approximately 300 patients who are enrolled into the TOPAZ study.

Pharmacogenomic sampling

PGx samples will be collected from consenting TOPAZ patients that have not previously provided a PGx sample in parent studies.

Three aliquots at 2.5 mL each of whole blood (from each patient) will be drawn.

Detailed information about samples storage will be provided by the sponsor in the laboratory manual.

PGx blood samples will be maintained until the end of this study, when the conclusion is finalized, or 15 years, or as approved locally

Planned sample analysis

These samples will be used for exploratory analysis of genetic variations predictive of autoimmune conditions related to MS and or the effects of alemtuzumab and or MS disease manifestation using genetic analysis platform technologies

Appendix D Country-specific requirements

1. Requirements for US

Section 10.1.1

This visit must be conducted within 6 months after completion of the Extension Study CAMMS03409. When possible, Visit 1 will be performed at the same time as the last visit of the Extension Study CAMMS03409.

Appendix E Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located before the Clinical Trial Summary.

1. Amended Clinical Trial Protocol 01 (US) based on Amendment 01 (US) [23-Mar-2016]

This amendment 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

To extend the time-window between CAMMS03409 and TOPAZ study from 3 to 6 months to allow as many patients as possible to enroll in the TOPAZ study for a long term follow-up.

Section # and Name	Description of Change	Brief Rationale
10.1.1. Visit 1: Selection (D1)	This visit has to be conducted within 6 months after completion of extension study CAMMS03409	See above

2. Amended Clinical Trial Protocol 02 (US), Amended Clinical Trial Protocol 01 based on Amendment 02 [27-Feb-2018]

This amendment 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

- **To add an optional pharmacogenomics substudy**

TOPAZ patients have >7 years post Lemtrada treatment experience. The intent is to collect a blood sample from consenting patients (who have not already provided a PGx sample in parent studies) for the purpose of exploratory analysis of genetic variations predictive of autoimmune conditions related to MS disease and/or alemtuzumab effects.

The samples from TOPAZ patients will be used for validating preliminary findings to identify a biomarker for autoimmune events.

- **To harmonize the list of Adverse Events of Special Interest (AESI) within sections**

To harmonize different sections of the protocol and for consistency with other Lemtrada projects.

- **To clarify procedure for routine urinalysis and microscopy**

To be in line with urinalysis procedures in a real life setting.

- **To clarify timing of HPV screening in women**

HPV screening was not mandatory in previous studies and it was necessary to clarify the timing of HPV screening in TOPAZ study.

- **To clarify interim analysis objective**

An annual partial database lock will be done instead of an Interim analysis.

- **To update information regarding risk of Listeria infection according new Lemtrada SmPC**

To be in line with new Lemtrada SmPC.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary; Section 1.2.1 Study flow chart; 6.1 Description of the protocol, 9.7.2 Exploratory Pharmacogenomic assessment; 10.1 Visit schedule; 11.4.4 Analysis of blood samples for exploratory pharmacogenomics substudy; 12.2 Informed consent; Appendix C Exploratory Pharmacogenomics Assessment Substudy	Add the following text: A pharmacogenomics (PGx) substudy will be conducted for exploratory analysis of genetic variations predictive of autoimmune conditions, including thyroid and immune thrombocytopenia (ITP), related to MS disease and/or the effects of alemtuzumab. For research purposes only and on a voluntary basis, a blood sample will be proposed to approximately 300 ongoing patients in the TOPAZ study who have not provided a PGx sample in the previous studies (CAMMS03409, CAMMS223, CAMMS323 and CAMMS324). A blood sample will be collected from consenting patients. Objectives of the substudy are as follows: • To develop biomarkers predictive of autoimmune conditions including thyroid disorders and immune thrombocytopenia. This will include collection of samples from patients who have not yet developed any auto immune conditions; these samples would be used as controls. • To explore efficacy and safety markers through data analysis. • To explore genetic variation related to MS disease manifestation through data analysis. Sample collection, handling, storage, and analysis will conform to all applicable national guidance and regulations. Details of the PGx sub-study are presented in Appendix C.	To add an optional pharmacogenomics substudy
Clinical Trial Summary; 9.1 Primary endpoints: Safety; 10.4.1.3 Adverse Events of Special Interest; 10.4.4 Guidelines for reporting adverse events of special interest	Replaced with the following text: Other project specific AESI(s) Autoimmune mediated conditions including, but not limited to: - Immune thrombocytopenic purpura (ITP) - Nephropathies including anti-glomerular basement membrane (GBM) disease	See above

Section # and Name	Description of Change	Brief Rationale
	- Cytopenias - Thyroid disorders Serious infections, including serious opportunistic infections Malignancy Cervical dysplasia	
9.5.2 Laboratory safety variables; 10.1.6 Alemtuzumab treatment; Appendix A Recommendations for using Alemtuzumab in countries where it is not yet available.	Replaced with the following text: Urinalysis (minimally including determination of urine protein and red blood cells) with microscopy.[1] A footnote has been added: [1] Note: For sites using homecare nurses service, or where microscopy is not routinely done if urine dipstick analysis is negative, the following procedure will be implemented: Homecare nurses/investigator site staff will perform a urine dipstick which will secure the detection of any potential haematuria and/or proteinuria. If urine dipstick is positive, the investigator would need to ask the patient to come to the site to have microscopy performed at the local lab. At any time, as per investigator criteria, according to the patient's status, the patient can be asked to have a microscopy at the local lab to confirm any potential diagnosis.	See above
1.2.2 Re-treatment with Alemtuzumab flow chart; 9.5.2 Laboratory Safety Variables; 10.1.6 Alemtuzumab Treatment.	Add the following text: For women, a Human Papilloma Virus (HPV) screening must be performed as follows: For women within 48 months follow-up at time of study transition from CAMMS03409 to TOPAZ, the date of the last alemtuzumab infusion administered in the study CAMMS03409 must be checked, and then an HPV screening performed approximately 1 year after the last infusion of alemtuzumab, and then every 12 months until 48 months safety FU is completed. For women, an HPV screening must be performed as follows: For women patients re-treated with alemtuzumab during the TOPAZ study, an HPV screening should be performed prior to re-treatment (if not done in the previous 12 months) and then every 12 months until 48 months safety FU is completed.	See above
6.3 Interim analysis; 11.5 Interim analysis	An annual partial database lock will be made available	See above
4 Introduction and rationale	Add the following text: Of note, Listeriosis/Listeria meningitis has been reported in LEMTRADA treated patients, generally within one month of LEMTRADA infusion. To reduce the risk of infection, patients receiving LEMTRADA should avoid ingestion of uncooked or undercooked meats, soft cheeses, and unpasteurized dairy products two weeks prior to, during, and for at least 1 month after LEMTRADA infusion.	See above

3. Amended Clinical Trial Protocol 02 (24-Jul-2019)

This amended protocol 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 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 # and Name	Description of Change	Brief Rationale
1.2.2 Re-treatment with alemtuzumab chart flow	Add liver function test along with TSH footnote b: … LFT includes: ALT, AST, ALP, albumin, total protein and bilirubin.	Monitoring potential autoimmune hepatitis
4 INTRODUCTION AND RATIONALE	Add the following text: … During post-marketing use, additional risks of alemtuzumab have been identified recently that include: • Stroke (hemorrhagic and ischemic). • Cervicocephalic (ie, vertebral, carotid) arterial dissection. • Pulmonary alveolar hemorrhage. • Acute acalculous cholecystitis. • Autoimmune hepatitis. • Hemophagocytic lymphohistiocytosis (HLH). Cases of serious and life-threatening stroke (including hemorrhagic and ischemic), myocardial infarction and cervicocephalic (ie, vertebral, carotid) arterial dissection have been reported	Update recent safety findings and benefit risk assessment

Section # and Name	Description of Change	Brief Rationale
	within three days of alemtuzumab administration, with most cases occurring within one day. Cases of pulmonary alveolar hemorrhage have been reported with onset within 48 hours of alemtuzumab infusion. Long term auto immune risks, such as cases of Hemophagocytic lymphohistiocytosis (HLH) and autoimmune hepatitis causing clinically significant liver injury, including acute liver failure requiring transplant, has been reported. To minimize the risk of these serious adverse events, recommendations are provided for infusion related management and long term safety monitoring for patients receiving re-treatment of alemtuzumab during the course of the trial • Pre infusion: assess overall health status and risk factors; baseline BP/HR, bleeding risk, platelets count. Baseline liver function test. • During infusion: continuous or hourly monitoring BP/HR; intermittently ambulation, compressive stocking. • Post infusion: inform/remind patient any abnormal clinical sign/symptoms related to infusion. • Periodic liver function test.	
9.5.2.2 Patients exposed to alemtuzumab during this study	Liver function test must be performed prior retreatment with alemtuzumab and repeated every 3 months for 48 months. … LFT may be performed at any time if clinically indicated at Investigators' discretion.	Monitoring potential autoimmune hepatitis
10.1.6 Alemtuzumab treatment	Add the following text: The following infusion management procedures must be utilized for each infusion and each treatment course: • Pre-infusion: Physicians should identify potential cardiovascular and cerebrovascular risk factors (eg, screen for pre-existing hemorrhagic, cardiovascular (including venous thromboembolism) and cerebrovascular risk factors, lung disease, concomitant medications (eg, antiplatelet agents, anticoagulants) and review of infusion-related risks, and HCP checklist. • During infusion: in addition to continuous/frequent monitoring of heart rate, blood pressure assessment (at least hourly) and overall clinical status of the	See above

Section # and Name	Description of Change	Brief Rationale
	patients including consideration of the volume of fluids administered. The following are recommendations in case of clinical abnormities: - Adjust or interrupt infusion, as necessary; if clinically significant changes in vital functions are observed, additional monitoring, including ECG, should be considered. - When re-starting, consider a slower rate of infusion. - Appropriate management of blood pressure during infusion, including pharmacotherapy as necessary. - 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. - Minimum until 2 hours after infusion has ended or longer until stabilization. - Patients with persistent blood pressure elevation should be referred to an appropriate medical facility for continued monitoring and treatment. - Education on delayed infusion associated reactions and symptoms and signs of cardiovascular or cerebrovascular events. - Instructions to patients to seek urgent medical care if there are signs and symptoms of cardiovascular, pulmonary or cerebrovascular events. For monitoring potential risk of autoimmune hepatitis, liver function test must be performed for patients who newly initiate retreatment of alemtuzumab, LFT to be performed prior infusion of retreatment as baseline, every 3 months for 48 months after the last infusion of retreatment of alemtuzumab. In addition, LFT may be performed at any time if clinically indicated at Investigators' discretion.	

Section # and Name	Description of Change	Brief Rationale
10.1.6.1 Prior to alemtuzumab treatment visit	Add liver function test (ALT, AST, ALP, albumin, total protein and bilirubin)	See above
10.1.6.2 Post-alemtuzumab treatment monitoring	Add liver function test (ALT, AST, ALP, albumin, total protein and bilirubin) and editorial correction	See above
10.4.1.3 Adverse event of special interest and Table 2	Add hemophagocytic lymphohistiocytosis (HLH)	See above

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