



AMENDED CLINICAL TRIAL PROTOCOL 01

COMPOUND: LEMTRADA® /alemtuzumab/GZ402673

Collection of blood samples from patients with relapsing forms of Multiple Sclerosis (RMS) who have developed Immune thrombocytopenic purpura (ITP) after LEMTRADA® treatment

STUDY NUMBER: ASY15905

STUDY NAME: LEMTRADA ITP

NCT03784898

Version Number: 1	EudraCT IND Number(s) WHO universal trial number:	Not applicable Not applicable Not applicable
Date: 24-May-2019	Total number of pages:	40

Any and all information presented in this document shall be treated as confidential and shall remain the exclusive property of Sanofi (or any of its affiliated companies). The use of such confidential information must be restricted to the recipient for the agreed purpose and must not be disclosed, published or otherwise communicated to any unauthorized persons, for any reason, in any form whatsoever without the prior written consent of Sanofi (or the concerned affiliated company); 'affiliated company' means any corporation, partnership or other entity which at the date of communication or afterwards (i) controls directly or indirectly Sanofi, (ii) is directly or indirectly controlled by Sanofi, with 'control' meaning direct or indirect ownership of more than 50% of the capital stock or the voting rights in such corporation, partnership or other entity

**NAMES AND ADDRESSES OF
INVESTIGATOR**

Name:
Address:

[Redacted]
[Redacted]
[Redacted]
Los Angeles, CA 90094
[Redacted]
[Redacted]

Tel:

E-mail:

**STUDY MEDICAL
MANAGER**

Name:
Address:

[Redacted]

Tel:

E-mail:

**GLOBAL STUDY
MANAGER**

Name:
Address:

[Redacted]

Tel:

E-mail:

**SPONSOR'S MEDICAL
OFFICER**

Name:
Address:

[Redacted]

Tel:

E-mail:

SPONSOR

Company:
Address:

Genzyme Corporation
50 Binney Street
Cambridge, MA 02142
USA

**OTHER EMERGENCY
TELEPHONE NUMBERS**

Company:
Address:

[Redacted]

Tel:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/Countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01	US	24-May-2019, version 1 (electronic 1.0)
Original Protocol		31-Aug-2018, version 1 (electronic 1.0)

AMENDED PROTOCOL 01 (24-MAY-2019)

This amended protocol (amendment 01) 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 modifies the study primary objective.

OVERALL RATIONALE FOR THE AMENDMENT

This substantial protocol amendment introduces the following changes due to the modification the study primary objective.

In addition, Sanofi-Genzyme uses this opportunity to edit other sections of the protocol as listed below for better clarity. Inconsistencies, typographical and spelling errors throughout the document were also corrected.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title (page 1)	Title modified to "Collection of blood samples"	Due to change in the main objective of the study
Names and addresses	Name and address of the investigator was added	Update
4.2 Study rationale 5.1 Primary objective 9.2.1 Pharmacogenetic assessment 9.2.2 Sampling time	Update on the main focus (primary objective) of the study: collection of blood samples for DNA extraction	The DNA analysis (sequencing) will not be part of this study and will be included in a more global biomarker project
4.2 Study rationale 5.2 Exploratory objective	First exploratory objective was removed	This objective will not be part of the study

Section # and Name	Description of Change	Brief Rationale
6.2.1 Duration of study participation for each patient 9.5.2 Sample blood volume 12.1 Visit Schedule	Increase duration and implementation of one additional visit, if needed	To allow to complete blood drawn, if for any safety reason all samples cannot be collected at the initial blood draw visit
7.2 Inclusion criteria	Removal of "As per label" for Lemtrada	To allow enrollment of RMS patients who developed ITP during clinical trials involving Gz402673 (Lemtrada)
6.1 Description of the study Number of sites	Clarification on the number of site	Update
9.5.2 Sample blood volume	Updated <ul style="list-style-type: none"> • Addition of a discard tube • Less blood volume collection feasible 	Need a discard tube before blood DNA sample draw To increase subject safety if needed
9.2.6 Future use of samples	Detailed description of sample use	Clarification of the use of samples as the DNA analysis (sequencing) will not be part of this study and will be included in a more global biomarker project
11.2 Reasons for study withdrawal 14.2 Informed consent	"patient's representative" deleted	Requested by IRB as not applicable here
13.7 Analysis of pharmacogenetics variables	Pharmacogenetic statistical analysis is not in the scope of this study but will be part of a global biomarker program	Update due to modification of study objective

CLINICAL TRIAL SUMMARY

COMPOUND: LEMTRADA®
/alemtuzumab/GZ402673

STUDY No : ASY15905

TITLE	Collection of blood samples from patients with relapsing forms of Multiple Sclerosis (RMS) who have developed Immune thrombocytopenic purpura (ITP) after LEMTRADA® treatment
INVESTIGATOR/TRIAL LOCATION	USA; may be expanded to Canada
STUDY OBJECTIVE(S)	<p>Primary objective:</p> <p>To collect blood samples, in a new cohort of RMS patients who have developed Immune thrombocytopenic purpura (ITP) after LEMTRADA treatment, for future DNA analysis as part of a global biomarker project assessing pre-identified candidate SNPs associated to the development of ITP after LEMTRADA treatment.</p> <p>Exploratory objectives:</p> <ul style="list-style-type: none"> To collect from these patients additional serum, plasma, circulating peripheral blood mononuclear cells (PBMCs), and RNA samples together with their retrospective demographic and clinical data related to MS disease and ITP status.
STUDY DESIGN	<p>Phase IV, single-center, non-randomized study.</p> <p>Some retrospective demographic and clinical data will be captured through the patient's physician, patient reporting, and medical records. The only intervention will be the blood draws performed during study visit(s).</p> <p>This study is part of a global biomarker project that aims to collect samples from different studies to potentially confirm correlations between ITP and other autoimmune conditions and specific single nucleotide polymorphism (SNP) genetic set.</p>
<p>STUDY POPULATION</p> <p>Main selection criteria:</p> <p>Total expected number of patients:</p> <p>Expected number of sites:</p>	<p>Inclusion criteria:</p> <p>I 01. Male and female adult patients who have been treated with LEMTRADA, with development of ITP subsequent to treatment. Patients do not need to be currently on LEMTRADA treatment.</p> <p>I 02. Patients who have signed the study informed consent form (ICF).</p> <p>Approximately 35</p> <p>1 center</p>
STUDY TREATMENT(s)	No investigational medicinal product(s) will be administered to patients.
PRIMARY ENDPOINT(S) AND MAIN SECONDARY ENDPOINT(S)	<p>Primary endpoints: DNA will be extracted from peripheral blood</p> <p>Exploratory endpoints:</p> <ul style="list-style-type: none"> Peripheral blood will be collected for the preparation of serum, plasma, and PBMCs, which will be stored for up to 5 years, and RNA, which will be stored up to 15 years after completion of the study.

	<ul style="list-style-type: none"> Retrospective demographic and clinical data related to MS disease and ITP status will be collected for correlative analysis. <p>Safety: Adverse events and serious adverse events related to study procedures during the visit(s).</p>
<p>ASSESSMENT SCHEDULE</p>	<p>The study will consist of one single visit which includes a subject interview and a blood draw. However, for safety reason and at the discretion of the medical team, the blood draw might occur in more than one visit,</p> <p>Blood draw will be performed to collect samples from which DNA, serum, plasma, PBMCs, and RNA will be further extracted.</p> <p>Additionally the following data points will be captured if available from the prescriber, patient, and/or medical records:</p> <ul style="list-style-type: none"> Age/date of birth, gender, race/ethnicity Body mass index (BMI) if possible, otherwise most recent weight and height from medical records Time since MS symptom onset/ MS diagnosis Previous MS therapies Prior history of ITP / coagulation disorders, thyroid or renal problems; date of ITP symptoms/diagnosis onset Prior evidence of other autoimmunity disorders Symptoms associated with ITP prior to time of diagnosis Details of laboratory and medical confirmation of ITP clinical diagnosis Treatments and duration to achieve response/resolution of ITP Smoking history Recent laboratory data (last data available): platelets, thyroid function, urinalysis Present MS clinical status: <ul style="list-style-type: none"> Medical record documentation of time and intensity of relapses Recent magnetic resonance imaging reports Recent (1-2 years) evidence of disability progression
<p>STATISTICAL CONSIDERATIONS</p>	<p>Sample size determination Sample size for this study was based upon empirical considerations. No sample size calculation was performed.</p> <p>Pharmacogenomic analysis</p> <p>The statistical analysis of pharmacogenetics variables will be part of a global biomarker program and is not in the scope of this study.</p> <p>Safety Safety analysis (AEs and SAEs) will be based on the review of individual values, and descriptive statistics.</p>
<p>DURATION OF STUDY PERIOD (per patient)</p>	<p>One to 70 days.</p> <p>One visit is required for blood draw. However, for safety reason and at the discretion of the medical team, the blood draw might occur in more than one visit.</p>

1 STUDY FLOW CHART

Assessments	Screening & Inclusion Visit ^a
Inclusion criteria	X
Informed consent	X
Patient demography (age, date of birth, gender, race/ethnicity)	X ^b
Detailed patient history of clinical and pathological characteristics: <ul style="list-style-type: none"> • Time since MS symptom onset/ MS diagnosis • Previous MS therapies • Prior history of ITP / coagulation disorders, thyroid or renal problems; date of ITP symptoms/diagnosis onset • Prior evidence of other autoimmunity disorders • Symptoms associated with ITP prior to time of diagnosis • Details of laboratory and medical confirmation of ITP clinical diagnosis • Treatments and duration to achieve response/resolution of ITP • Smoking history • BMI if possible, otherwise most recent weight and height from medical records • Recent laboratory data (last data available): platelets, thyroid function, urinalysis • Present MS clinical status: <ul style="list-style-type: none"> - Medical record documentation of time and intensity of relapses - Recent MRI reports - Recent (1-2 years) evidence of disability progression 	X ^b
Blood draw for further pharmacogenetic analysis and sample storage	X ^c
AE collection	X

AE = adverse event; BMI = body mass index; ITP = Immune thrombocytopenic purpura; MRI = magnetic resonance imaging; MS = multiple sclerosis.

^a Screening and inclusion visit can be performed the same day or on separate days with a maximum timeframe of 30 days apart. The visit may be performed either at the study center or at the patient's home if he/she cannot reach the study center. The visit will occur late in the day to comply with sample management requirements.

^b If available from the prescriber, patient, and/or medical records.

^c One visit is required for blood draw. However, for safety reason and at the discretion of the medical team, the blood draw might occur in more than one visit. If a second visit occurs, it must take place within 40 days of the first visit.

2 TABLE OF CONTENTS

AMENDED CLINICAL TRIAL PROTOCOL 01	1
PROTOCOL AMENDMENT SUMMARY OF CHANGES	3
DOCUMENT HISTORY	3
AMENDED PROTOCOL 01 (24-MAY-2019)	3
OVERALL RATIONALE FOR THE AMENDMENT	3
1 STUDY FLOW CHART	7
2 TABLE OF CONTENTS	8
2.1 LIST OF TABLES	11
3 LIST OF ABBREVIATIONS	12
4 INTRODUCTION AND RATIONALE	13
4.1 INTRODUCTION	13
4.2 STUDY RATIONALE	14
5 STUDY OBJECTIVES	15
5.1 PRIMARY OBJECTIVE	15
5.2 EXPLORATORY OBJECTIVES:	15
6 STUDY DESIGN	16
6.1 DESCRIPTION OF THE STUDY	16
6.2 DURATION OF STUDY PARTICIPATION	16
6.2.1 Duration of study participation for each patient	16
6.2.2 Determination of end of clinical trial (all patients)	16
6.3 INTERIM ANALYSIS	16
7 SELECTION OF SUBJECTS	17
7.1 NUMBER OF SUBJECTS PLANNED	17
7.2 INCLUSION CRITERIA	17
7.3 EXCLUSION CRITERIA	17
8 STUDY TREATMENTS	18

8.1	INVESTIGATIONAL MEDICINAL PRODUCT	18
8.2	OTHER PRODUCTS	18
8.3	PACKAGING AND LABELING	18
8.4	STORAGE CONDITIONS AND SHELF LIFE	18
8.5	RESPONSIBILITIES	18
8.6	CONCOMITANT MEDICATION.....	18
8.7	TREATMENT ACCOUNTABILITY AND COMPLIANCE	18
9	ASSESSMENTS	19
9.1	SAFETY	19
9.1.1	Baseline demographic characteristics	19
9.1.2	History of clinical and pathological characteristics.....	19
9.1.3	Safety assessment.....	20
9.2	PHARMACOGENETICS	20
9.2.1	Pharmacogenetic assessment.....	20
9.2.2	Sampling times.....	20
9.2.3	Number of samples	20
9.2.4	Sample handling procedure	20
9.2.5	Sampled blood volume	21
9.2.6	Future use of samples	21
9.2.7	Sample destruction	22
10	SUBJECT SAFETY	23
10.1	ADVERSE EVENT MONITORING	23
10.2	DEFINITIONS OF ADVERSE EVENTS.....	23
10.2.1	Adverse event	23
10.2.2	Serious adverse event	24
10.3	OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING	24
10.3.1	General guidelines for reporting adverse events.....	24
10.3.2	Guidelines for reporting serious adverse events	25
10.4	OBLIGATIONS OF THE SPONSOR	25
11	HANDLING OF PATIENT WITHDRAWAL	26
11.1	LIST OF TREATMENT WITHDRAWAL CRITERIA.....	26

11.2	REASONS FOR STUDY WITHDRAWAL.....	26
11.3	WITHDRAWAL FOLLOW-UP PROCEDURE.....	26
12	STUDY PROCEDURES	27
12.1	VISIT SCHEDULE.....	27
12.1.1	Screening procedures.....	27
12.1.2	Description of the inclusion visit.....	27
12.2	DEFINITION OF SOURCE DATA.....	27
13	STATISTICAL CONSIDERATIONS	28
13.1	DETERMINATION OF SAMPLE SIZE.....	28
13.2	SUBJECT DESCRIPTION	28
13.3	ANALYSIS POPULATION	28
13.4	DEMOGRAPHIC AND BASELINE CHARACTERISTICS	28
13.5	EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE.....	28
13.6	PRIOR/CONCOMITANT MEDICATION/THERAPY	28
13.7	ANALYSIS OF PHARMACOGENETIC VARIABLES	29
13.8	ANALYSIS OF SAFETY DATA.....	29
13.9	ANALYSIS OF PHARMACOKINETIC DATA.....	29
13.10	PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS.....	29
13.11	INTERIM ANALYSIS.....	29
14	ETHICAL AND REGULATORY CONSIDERATIONS.....	30
14.1	ETHICAL AND REGULATORY STANDARDS	30
14.2	INFORMED CONSENT	30
14.3	HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD (IRB)	31
15	STUDY MONITORING.....	32
15.1	RESPONSIBILITIES OF THE INVESTIGATOR(S).....	32
15.2	RESPONSIBILITIES OF THE SPONSOR.....	32
15.3	SOURCE DOCUMENT REQUIREMENTS.....	33

15.4	USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST	33
15.5	USE OF COMPUTERIZED SYSTEMS.....	33
16	ADDITIONAL REQUIREMENTS.....	34
16.1	CURRICULUM VITAE.....	34
16.2	RECORD RETENTION IN STUDY SITE(S).....	34
16.3	CONFIDENTIALITY	34
16.4	PROPERTY RIGHTS.....	35
16.5	DATA PROTECTION	35
16.6	INSURANCE COMPENSATION.....	35
16.7	SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES	36
16.8	PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE	36
16.8.1	By the Sponsor.....	36
16.8.2	By the Investigator	37
16.9	CLINICAL TRIAL RESULTS	37
16.10	PUBLICATIONS AND COMMUNICATIONS	37
17	CLINICAL TRIAL PROTOCOL AMENDMENTS	38
18	BIBLIOGRAPHIC REFERENCES.....	39
19	APPENDICES.....	40

2.1 LIST OF TABLES

Table 1 - Sampled blood volume per patient	21
--	----

3 LIST OF ABBREVIATIONS

ADL:	activity of daily living
AE:	adverse event
ALT:	alanine aminotransferase
BMI:	body mass index
CNS:	central nervous system
CRF:	case report form
CTCAE:	Common Terminology Criteria for Adverse Events
eCRF:	electronic case report form
GCP:	Good Clinical Practice
ICF:	informed consent form
IMP:	investigational medicinal product
IRB:	Institutional Review Board
ITP:	immune thrombocypenic purpura
MS:	multiple sclerosis
NCI:	National Cancer Institute
PBMC:	peripheral blood mononuclear cell
RMS:	relapsing multiple sclerosis
SAE:	serious adverse event
SNP:	single nucleotide polymorphism
ULN:	upper limit of normal

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) that affects more than 2.3 million people worldwide (1). Its clinical course is typically characterized by initial episodes of transient neurological compromise with full recovery, followed by a phase of cumulative deficits that may increase with each new episode. Most 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 nonfocal 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). Alemtuzumab acts through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity 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 lymphocyte subsets. It effects rapid and sustained lymphocyte depletion and has shown potent efficacy in treatment-naïve as well as treatment-refractory patients with relapsing remitting multiple sclerosis (RRMS). Treatment with alemtuzumab 12 mg/day is efficacious in patients with RRMS and is associated with clinically meaningful and statistically significant improvements in clinical endpoints, imaging endpoints and composite disease measures, compared with subcutaneous (SC), high-dose, high-frequency interferon-beta-1a (IFNB-1a).

The most important adverse reactions are autoimmunity (eg, immune thrombocytopenic purpura (ITP), thyroid disorders, nephropathies, cytopenias), infusion-associated reactions, and serious infections. Serious events of ITP have been observed in approximately 2% of patients with relapsing multiple sclerosis (RMS) treated with alemtuzumab in clinical trials. The onset of ITP generally occurred between 14 and 36 months after the first alemtuzumab exposure but might also occur later. Fatality in the index case of ITP, which was reported in the Phase 2 study, highlights the seriousness of the risks associated with the disorder.

4.2 STUDY RATIONALE

In a previous analysis on a small number of patients from the Ph3 clinical trial population, a specific single nucleotide polymorphism (SNP) genetic set was identified showing a strong correlation with development of ITP after treatment by alemtuzumab (unpublished internal data). However samples from an independent cohort of post-marketing RMS patients who have developed ITP would be needed to confirm these data.

The current study will focus on the collection of blood samples to extract DNA from patients who developed ITP consequently to Lemtrada treatment. The DNA will be subjected to further sequencing pre-identified specific candidate genes of interest to evaluate their polymorphism status and correlate these assessments with demographic and clinical data from the patients as well as the occurrence of LEMTRADA-induced ITP. DNA sequencing and corresponding analysis are not part of this study.

Complementary to these objectives serum, plasma, peripheral blood mononuclear cells (PBMCs), and RNA samples will be collected and stored to be further explored in this patient population to potentially identify new safety and LEMTRADA treatment response markers.

This study is part of a global biomarker project that aims to collect samples from different studies to potentially confirm correlations between ITP and other autoimmune conditions and specific SNP genetic set. Genomic data collected in other studies from MS patients who are treated with LEMTRADA but did not develop any autoimmune condition will be used as controls to validate the preliminary findings. The ultimate goal of this global biomarker project is to enhance the benefit/risk ratio of LEMTRADA with the objective of discovering a panel of biomarkers to predict which patients are at risk of developing auto-immunity events.

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE

To collect blood samples, in a new cohort of RMS patients who have developed Immune thrombocytopenic purpura (ITP) after LEMTRADA treatment, for future DNA analysis as part of a global biomarker project assessing pre-identified candidate SNPs associated to the development of ITP after LEMTRADA treatment in RMS patients.

5.2 EXPLORATORY OBJECTIVES:

- To collect from these patients additional serum, plasma, circulating PBMCs, and RNA samples together with their retrospective demographic and clinical data related to MS disease and ITP status

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a phase 4, single-center, non-randomized study conducted in one site in the USA; the study may be expanded to Canada at an undetermined number of sites. No investigational medicinal product (IMP) administration will be performed.

Some retrospective demographic and clinical data will be captured through the patient's physician, patient reporting, and medical records.

The only intervention will be the blood draw performed during study visit(s).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

This duration is from one to 70 days. Screening and visit(s) can be performed the same day or on separate days with a maximum timeframe of 30 days apart. One visit is required for blood draw. However, for safety reason and at the discretion of the medical team, the blood draw might occur in more than one visit. If a second visit occurs, it must take place within 40 days of the first visit.

The study will be considered completed for a patient at the time he/she completes all the scheduled study procedures.

6.2.2 Determination of end of clinical trial (all patients)

The end of the clinical trial is defined as the day of last patient last visit.

6.3 INTERIM ANALYSIS

No interim analysis is planned.

7 SELECTION OF SUBJECTS

7.1 NUMBER OF SUBJECTS PLANNED

Approximately 35 patients

7.2 INCLUSION CRITERIA

- I 01. Male and female adult patients who have been treated with LEMTRADA, with development of ITP subsequent to treatment. Patients do not need to be currently on LEMTRADA treatment.
- I 02. Patients who have signed the study informed consent form (ICF).

7.3 EXCLUSION CRITERIA

None

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

No IMP will be administered to patients.

8.2 OTHER PRODUCTS

Not applicable.

8.3 PACKAGING AND LABELING

Not applicable.

8.4 STORAGE CONDITIONS AND SHELF LIFE

Not applicable.

8.5 RESPONSIBILITIES

Not applicable.

8.6 CONCOMITANT MEDICATION

Not applicable.

8.7 TREATMENT ACCOUNTABILITY AND COMPLIANCE

Not applicable.

9 ASSESSMENTS

9.1 SAFETY

9.1.1 Baseline demographic characteristics

Baseline demographic characteristics will consist of:

- Age (years)
- Date of birth
- Gender
- Race/ethnicity: Subject race (African/American, Caucasian, Asian, Other) and ethnicity (“Hispanic” or “Not Hispanic”) will be collected in this study because analysis of results according to race/ethnicity are required by several Regulatory Authorities (eg, African/American population for FDA in United States).

9.1.2 History of clinical and pathological characteristics

History of clinical and pathological characteristics, if available from the prescriber, patient, and/or medical records, will consist of:

- Time since MS symptom onset/MS diagnosis
- Previous MS therapies
- Prior history of ITP/coagulation disorders, thyroid or renal problems; date of ITP symptoms/diagnosis onset
- Prior evidence of other autoimmunity disorders
- Symptoms associated with ITP prior to time of diagnosis
- Details of laboratory and medical confirmation of ITP clinical diagnosis
- Treatments and duration to achieve response/resolution of ITP
- Smoking history
- Body mass index if possible, otherwise most recent weight and height from medical records
- Recent laboratory data (last data available): platelets, thyroid function, urinalysis
- Present MS clinical status:
 - Medical record documentation of time and intensity of relapses
 - Recent magnetic resonance imaging reports
 - Recent (1-2 years) evidence of disability progression

9.1.3 Safety assessment

Adverse events (AEs) and serious adverse events (SAEs) related to study procedures will be recorded spanning from the signature of the ICF until the end of the study. As there is no investigational product administration, assessment of the relationship of AEs or SAEs to procedures (ie, blood sampling) will be performed by both the Investigator and the Sponsor.

9.2 PHARMACOGENETICS

9.2.1 Pharmacogenetic assessment

Samples will be processed for DNA isolation.

These blood samples will be transferred to a site that will, on behalf of Sanofi, extract DNA. Material extracted will remain labelled with the same identifiers used during the study (ie, patient ID, sample ID). They will be transferred to a Sponsor site (or a subcontractor site) which can be located outside of the country where the study is conducted. DNA and RNA sample collection, handling, storage, and future analysis will conform to all applicable national guidance and regulations.

As part of a global biomarker program and outside the scope of this study, this DNA will be further subjected to sequencing analysis. Genomic data generated from these samples will be used to confirm previous findings of a potential set of SNPs observed in patients with RMS who have developed ITP after LEMTRADA treatment.

The DNA will be stored for up to 15 years from the completion of the clinical study report in the US.

9.2.2 Sampling times

A blood draw will be collected at the study visit(s) for DNA extraction and sample storage as specified in the study flow chart ([Section 1](#)).

Blood will be collected preferably late in the day to comply with sample management requirement – overnight shipment of the samples for first morning delivery to the central lab.

9.2.3 Number of samples

The number of sample per patient is indicated in [Table 1](#).

9.2.4 Sample handling procedure

Special procedures for collection, shipment, processing and storage of samples will be provided in the laboratory manual.

9.2.5 Sampled blood volume

A total of 69 ml of whole blood will be collected as shown in [Table 1](#) and under the priority rank indicated.

At the discretion of the medical team, for some patients the collection of 69 ml at one single draw may be inappropriate. In such cases, either additional draws may be performed or less blood volume may be collected but respecting the priority order indicated in [Table 1](#).

Table 1 - Sampled blood volume per patient

Priority	Type	Volume per sample	Sample number	Total
	discard tube	2 mL	1	2 mL
1	DNA PAXgene tubes	2.5 mL	2	5 mL
2	RNA PAXgene tubes	2.5 mL	2	5 mL
3	EDTA for PBMCs	8.5 mL	5	42.5 mL
4	SST tube	8.5 mL	1	8.5 mL
5	K2EDTA tube	6.0 mL	1	6.0 mL
	Total			69 mL

PMBC = peripheral blood mononuclear cells.

9.2.6 Future use of samples

The DNA samples will be stored for up to 15 years from the completion of the clinical study report in the US. A part of this DNA will be used for sequencing analysis. The DNA samples that will be unused or left over after testing may be used for additional research purposes related to better understanding MS disease pathogenesis, drug response or activity.

Additional blood samples collected during this study will be processed for serum, plasma, PBMCs, and RNA preparations and stored as described in the laboratory manual. These samples may be used for research purpose related to MS disease, ITP status, predictive and safety biomarker identification, or LEMTRADA mechanism of action. These samples will remain labelled with the same identifiers as the one used during the study (ie, patient ID, sample ID). They will be transferred to a Sanofi site (or a subcontractor site), which can be located outside of the countries where the study is conducted, and stored for up to 5 years (serum, plasma, PBMCs) or 15 years (RNA) after completion of the study.

9.2.7 Sample destruction

If a patient, via written request, asks for destruction of his/her samples, the Sponsor will destroy the samples per applicable guidelines; however, any data already generated will not be destroyed. The Sponsor will notify the Investigator in writing that the samples have been destroyed. However, any analyses of the sample(s) that have already been performed or data generated prior to patient's request will continue to be used as part of the research in this project and will be kept by the Sponsor.

10 SUBJECT SAFETY

The Investigator is the primary person responsible for making all clinically relevant decisions on safety issues.

10.1 ADVERSE EVENT MONITORING

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

10.2 DEFINITIONS OF ADVERSE EVENTS

10.2.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a subject which does not necessarily have to have a causal relationship with this treatment.

Adverse events and SAEs related to study procedures will be recorded spanning from the signature of the ICF until the end of the study. As there is no investigational product administration, assessment of the relationship of AEs or SAEs to procedures (ie, blood sampling) will be performed by both the Investigator and the Sponsor.

Adverse events will be graded according National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 and classified by system organ class / preferred term according the last available version of the MedDRA dictionary. For AEs not included in the NCI CTCAE, the Investigator will be required to assess the intensity of the adverse drug/biologic experience using the CTCAE general guideline:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE.

10.2.2 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 subject 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, or
- 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above.

Note: Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN) + total bilirubin > 2 x ULN or asymptomatic ALT increase > 10 x ULN, or development of drug dependence or drug abuse.

10.3 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.3.1 General guidelines for reporting adverse events

All AEs related to study procedures, regardless of seriousness, spanning from the signature of the ICF until the end of the study as defined by the protocol, are to be recorded on the corresponding page(s) or screen(s) of the case report form (CRF) for included subjects. For screen failed subjects, recording in the CRF is only performed in case of SAE occurring during the screening period or in case of AE when some screening procedures expose the subject to safety risks (eg, any substance administered as pretreatment or for phenotyping, invasive tests performed or chronic treatment interrupted).

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity (see definitions in [Section 10.2.1](#)), corrective treatment/therapy given, additional investigations performed (eg, in the case of dermatologic lesions photographs are required), outcome, and Investigator's/Sponsor's opinion.

In order to ensure the safety of the subjects, the Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death. 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.

10.3.2 Guidelines for reporting serious adverse events

In the case of a SAE, the Investigator must immediately:

- SEND (within 24 hours, preferably by fax or e-mail) the signed and dated corresponding page(s) in the CRF to the representative of the monitoring team whose name, fax number, and e-mail address appear on the clinical trial protocol.
- ATTACH the photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the subject's identity is protected and the subject's identifiers in the clinical trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further documentation should be sent to the monitoring team within 24 hours of knowledge. In addition, every effort should be made to further document within the week (7 days) following initial notification any SAE that is fatal or life threatening.

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

10.4 OBLIGATIONS OF THE SPONSOR

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

11 HANDLING OF PATIENT WITHDRAWAL

11.1 LIST OF TREATMENT WITHDRAWAL CRITERIA

Not applicable.

11.2 REASONS FOR STUDY WITHDRAWAL

- The patient may withdraw from the study if they decide to do so, at any time and irrespective of the reason, or upon the Investigator's decision or at the specific request of the Sponsor.
- In case of withdrawal, the patient should withdraw consent in writing and, if the patient refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

11.3 WITHDRAWAL FOLLOW-UP PROCEDURE

All study withdrawals should be recorded by the Investigator on the appropriate CRF pages or screens for electronic CRF (eCRF) when considered as confirmed.

Patients withdrawn from the study must not be reincluded in the study. Their Subject ID numbers must not be reused.

12 STUDY PROCEDURES

12.1 VISIT SCHEDULE

12.1.1 Screening procedures

The screening and visit(s) can be performed the same day or on separate days with a maximum timeframe of 30 days apart.

The patient will receive information on the study objective(s) and procedures from the Investigator. The patient must sign the informed consent prior to any action related to the study.

The screening visit will include the investigations listed in the Study Flow Chart ([Section 1](#)) and detailed in [Section 9.1](#).

Patients who meet all the inclusion criteria will be eligible for inclusion in the study.

12.1.2 Description of the inclusion visit

The visit will be performed either at the study center or at the patient's home if he/she cannot reach the study center.

The visit will occur late in the day to comply with sample management requirements.

Prior to any assessments an informed consent signed by the patients must be collected.

Blood draw will be performed and samples collected in the priority order specified in [Section 9.2](#). For any safety reason, several blood draw may be needed or less blood volume may be collected but respecting the priority order indicated in [Table 1](#). One visit is required for blood draw. However, for safety reason and at the discretion of the medical team, the blood draw might occur in more than one visit. If a second visit occurs, it must take place within 40 days of the first visit.

12.2 DEFINITION OF SOURCE DATA

All evaluations that are reported in the CRF must be supported by appropriately identified source documentation.

13 STATISTICAL CONSIDERATIONS

For the current study, data from patients with ITP only will be collected. Statistical data processing and quality control steps will be performed. Descriptive statistics and sensitivity analysis will be provided.

The formal statistical analysis to find predictive biomarkers for ITP events will be conducted retrospectively when data from the control patients (those patients who did not develop ITP) are available from other studies.

Safety analysis of AEs will be based on the review of individual values, and descriptive statistics.

13.1 DETERMINATION OF SAMPLE SIZE

Sample size for this study was based upon empirical considerations. No sample size calculation was performed.

13.2 SUBJECT DESCRIPTION

Not applicable.

13.3 ANALYSIS POPULATION

The safety population will consist of all patients included into the study.

13.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Continuous variables (age) and qualitative variables (gender, race/ethnicity) will be summarized by descriptive statistics for the safety population.

13.5 EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE

Not applicable.

13.6 PRIOR/CONCOMITANT MEDICATION/THERAPY

Not applicable.

13.7 ANALYSIS OF PHARMACOGENETIC VARIABLES

The statistical analysis of pharmacogenetics variables will be part of a global biomarker program and is not in the scope of this study.

13.8 ANALYSIS OF SAFETY DATA

The safety evaluation will be based on the review of individual values and descriptive statistics of AEs related to study procedures during the study visit.

13.9 ANALYSIS OF PHARMACOKINETIC DATA

Not applicable.

13.10 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

Not applicable.

13.11 INTERIM ANALYSIS

No interim analysis is planned.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 ETHICAL AND REGULATORY STANDARDS

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

14.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the ethics committee (Institutional Review Board [IRB]). 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 electronic ICF should be signed, name filled in, and personally dated by the patient, and by the person who conducted the informed consent discussion. A copy of the signed and dated ICF will be provided to the patient by e-mail.

The ICF used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB) for approval/favorable opinion.

The electronic ICF and any other written information to be provided to patients should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised ICF, and information should receive the IRB's approval/favorable opinion in advance of use. The patient should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented. In case of study suspension due to safety concerns, patient will be informed of this study suspension and the reason for it. Once it is confirmed that it is safe for the study to continue, study patients will be asked to confirm their agreement to continue the study.

14.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD (IRB)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the Health Authorities (Competent Regulatory Authority) and the appropriate IRB, 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 composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, ICF, Investigator's Brochure, Investigator's curriculum vitae, etc.) and the date of the review should be clearly stated on the written IRB approval/favorable opinion.

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

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the Health Authorities (Competent Regulatory Authority), as required by local regulation, in addition to the IRB before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the Health Authorities (Competent Regulatory Authority) and the IRB should be informed as soon as possible. They 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 Investigator's Brochure will be sent to the IRB and to Health Authorities (Competent Regulatory Authority), as required by local regulation.

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

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

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

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

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

15.2 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 Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

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

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the preidentified source data directly recorded in the CRF. The ICF will include a statement by which the patient allows the Sponsor's duly authorized personnel, the IRB, 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 confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

15.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the 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 eCRF 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 eCRF.

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

15.5 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.

16 ADDITIONAL REQUIREMENTS

16.1 CURRICULUM VITAE

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

16.2 RECORD RETENTION IN STUDY SITE(S)

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

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

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

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

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

16.3 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 Investigator's Brochure, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

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

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

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

16.4 PROPERTY RIGHTS

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

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

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

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

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

16.5 DATA PROTECTION

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

The data collected in this study will only be used for the purpose(s) of the study. They may be further processed if they have been pseudonymized.

16.6 INSURANCE COMPENSATION

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

16.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

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

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

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

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

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

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

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

16.8.1 By the Sponsor

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

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;
- The Investigator has received from the Sponsor all 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 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;

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

16.8.2 By the Investigator

The Investigator may terminate his/her participation upon 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 and regulatory authorities should be informed according to applicable regulatory requirements.

16.9 CLINICAL TRIAL RESULTS

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

16.10 PUBLICATIONS AND COMMUNICATIONS

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

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

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

17 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB 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 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 prior to its implementation, unless there are overriding safety reasons.

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

18 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 multiple sclerosis. *Mult Scler*. 1996;1(6):357-65.

19 APPENDICES

Not applicable.

Signature Page for VV-CLIN-0539965 v1.0
asy15905-16-1-1-amended-protocol01

Approve & eSign		
-----------------	--	--

Approve & eSign		
-----------------	--	--