NCT02201108

STATISTICAL ANALYSIS PLAN

A two year, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate efficacy, safety, tolerability, and pharmacokinetics of teriflunomide administered orally once daily in pediatric patients with relapsing forms of multiple sclerosis followed by an open-label extension

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For the double-blind period

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADEM:	acute disseminated encephalomyelitis
AE:	adverse event
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
ATC:	Anatomic Therapeutic Chemical
BMI:	body mass index
BUN:	blood urea nitrogen
BVMI:	beery visual-motor integration
CI:	confidence interval
CNS:	central nervous system
CRF:	case report form
CSR:	clinical study report
DBL:	database lock
D-KEFS:	Delis-Kaplan executive function system
ECG:	electrocardiogram
EDSS:	expanded disability status scale
EOT:	end of treatment
FSS:	functional system scores
GGT:	gamma glutamyl transferase
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
ILD:	interstitial lung disease
IMP:	investigational medicinal product
IVRS:	interactive voice response system
LDH:	lactate dehydrogenase
LLOQ:	lower limit of quantification
LLT:	lower-level term
LS means:	least-squares means
MedDRA:	Medical Dictionary for Regulatory Activities
MMRM:	mixed-effect model with repeated measures
MRI:	magnetic resonance imaging
MS:	multiple sclerosis
PK:	pharmacokinetic(s)
PT:	preferred term
RAP:	relapse adjudication panel
SDMT:	symbol digit modalities test
SOC:	system organ class
T2:	T2-weighted hyperintense lesions

TEAE:	treatment emergent adverse event
TSH:	thyroid stimulating hormone
WHO-DD:	World Health Organization Drug Dictionary
β-HCG:	serum β-human chorionic gonadotropin

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study followed by an open-label extension period in children and adolescents 10 to 17 years of age with relapsing forms of multiple sclerosis. It consists of:

- A screening period up to 4 weeks.
- A double-blind period of up to 96 weeks treatment for each patient.
- An open-label period including the remainder of the initial 96 weeks treatment, where applicable, and a 96-week extension, ie, up to a maximum of 192 weeks after randomization.
- An optional additional extension period for young patients with teriflunomide until the patients are 18 years old and/or able to switch to commercial product, whichever comes first.
- A follow-up period of 4 weeks for patients discontinuing treatment.

After a screening, eligible patients will be randomly assigned to receive either teriflunomide or placebo in a 2:1 randomization ratio (110 teriflunomide and 55 placebo) via Interactive Voice Response System (IVRS). Randomization will be stratified by the country and patient's pubertal status.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to assess the effect of teriflunomide in comparison to placebo on disease activity as measured by time to first clinical relapse after randomization in children and adolescents 10 to 17 years of age with relapsing forms of multiple sclerosis.

1.2.2 Secondary objectives

The secondary objectives of this study are as follows:

- To assess the effect of teriflunomide in comparison to placebo on disease activity/progression measured by brain MRI and on cognitive function.
- To evaluate the safety and tolerability of teriflunomide in comparison to placebo.
- To evaluate the pharmacokinetics (PK) of teriflunomide.

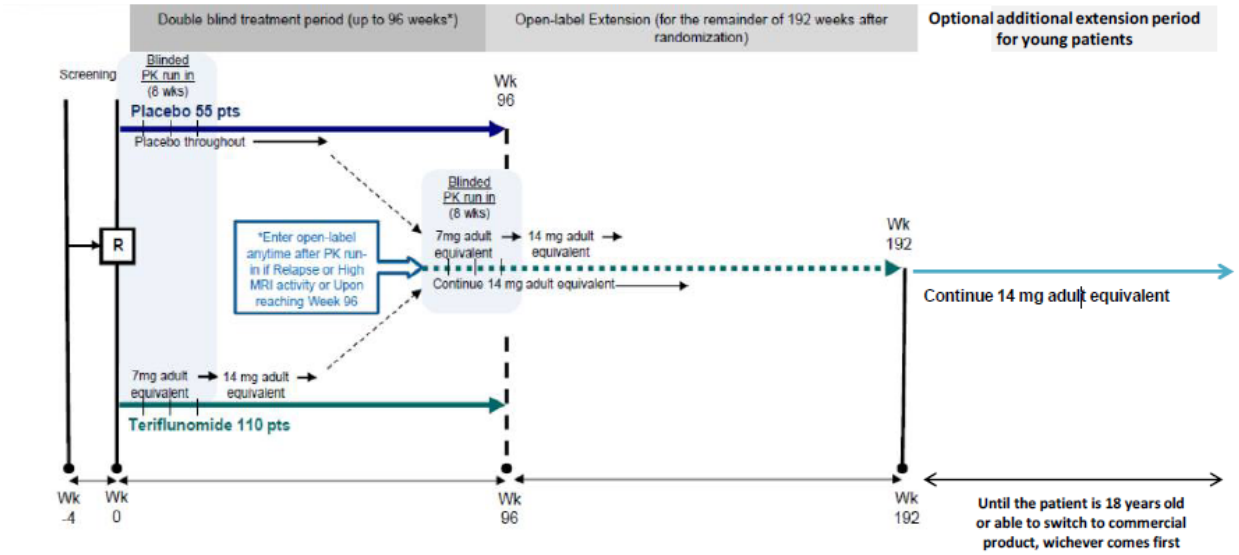
1.3 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the primary efficacy endpoint, time to first confirmed clinical relapse after randomization. Assuming 60% of placebo patients will experience a relapse by 2 years, 165 children aged 10 to 17 years (110 teriflunomide and 55 placebo; with at least 22 and 11, pre-pubertal, respectively) are needed for 80% power to detect a hazard ratio (teriflunomide versus placebo) of 0.5 (2-sided alpha 0.05). The 2-year rate of relapse in the teriflunomide group would be 36.8% and the corresponding hazard rates, assuming the time-to-relapse is exponentially distributed with a constant hazard rate, would be 0.4581 for placebo and 0.2291 for teriflunomide. The sample size is adjusted assuming 20% of patients discontinue the study in 2 years due to reasons other than relapse. Calculations are performed using nQuery Advisor 7.

The assumption for the percentage of placebo patients with relapse at 2 years is based on the combined data from the completed Phase III monotherapy adult studies (EFC6049/TEMSO and EFC10531/TOWER), where 58.7% of placebo patients aged ≤30 (n=167) experienced at least 1 relapse in a 2-year treatment period. Of note, the corresponding percentage was 38.7% in the 163 patients aged ≤30 treated with teriflunomide 14 mg.

1.4 STUDY PLAN

The study design is briefly described in the following graphical presentation:



R: Randomization

Note: An optional additional extension period with teriflunomide is offered to young patients when they complete the study, to provide treatment until they are 18 years old and/or can switch to commercial product, whichever comes first. The optional additional extension period will be reported separately.

Table 1 - Study schedule for the double-blind period

Variable	Visit
Brain MRI	Screening, Weeks 24, 48, 72 and Week 96/end of treatment (EOT)[a] visit, Week 36 if necessary
EDSS	Screening, randomization, Weeks 24, 48, 72, Week 96/EOT[a] visit, and unscheduled relapse visits
SDMT	Randomization, Weeks 24, 48, 72, and Week 96/EOT[a] visit,
Cognitive Battery Test	Randomization and EOT[a] visit
Clinical Laboratory	Screening, randomization, every 4 weeks up to 24 weeks and then every 6 weeks up to the Week 96/EOT[a]
Vital signs	Screening, randomization, weeks 4, 8, 12, 24, and every 12 weeks up to Week 96/EOT[a]
ECG	randomization, Week 96/EOT[a] and after EOT[a] if abnormality
Immunoglobulins and TSH	Randomization, Weeks 24, 48, 72 and Week 96/EOT[a] visit
PK	Weeks 2, 3, 4, 8, 12, 24, 36, Week 96/EOT[a]
Physical examinations	Screening, randomization, weeks 12, 24, and every 12 weeks up to Week 96/EOT[a]
Tanner assessment	Randomization, at Week 24, 48, 72, and at Week 96/EOT[a] for all patients (until complete sexual maturity).

a Patients who complete the treatment period or who prematurely discontinue, should complete EOT visit

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled).

There is no major change in statistical section of protocol in amendments.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

In this section summarize major changes in statistical analysis features made in approved SAP versions, with emphasis on changes after study start (after the first patient was enrolled).

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan. Changes also incorporated in a protocol amendment are cross-referenced to Table 2.

Table 2 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
1	11-Nov-2016	To control the multiplicity issue in secondary endpoint	Stepwise testing was added for key secondary endpoints
1	11-Nov-2016	Many of the patients will be studied during the period of age-expected brain volume increase, thus brain atrophy is not appropriate	Replace “brain atrophy” to “percentage change of brain volume”
1	11-Nov-2016	For pediatric patients, Brain volume change is significantly influenced by age and gender. Also SDMT is closely related with age for pediatric patients	Add covariate age and gender in MMRM model for brain volume change, and add covariate age in MMRM model for SDMT
2	This version	To clarify definitions of relapse in primary endpoint and in analysis of primary efficacy endpoint	Updated term “relapse” into “clinical relapse” in Section 2.1.3.1 and Section 2.4.4.1; Updated term “RAP confirmed relapse” into “Confirmed clinical relapse” in Section 2.1.3.1 and Section 2.4.4.1; Added definition for “not confirmed clinical relapse” in Section 2.1.3.1.

2 STATISTICAL AND ANALYTICAL PROCEDURES

The data from the double-blind and the open label teriflunomide treatment periods will be the focus of the CSR of their respective phase. The following statistical methods/considerations in this SAP relate to the analysis of the data from the double-blind period. The analysis of the data from the open-label and optional additional extension period will be addressed in separate documents.

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value before the first intake of IMP, unless otherwise specified.

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

Demographic characteristics

Demographic variables are gender (Male, Female), race (Caucasian/white, Black, Asian/Oriental, other), region (definition of the regions are provided in Section 2.5.5), age at study consent in years (quantitative and qualitative variable: <13, and ≥13 years), pubertal status, tanner staging.

Medical or surgical history

Medical (or surgical) history includes concurrent illnesses, detailed neurological history and detailed vaccination history.

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

Disease characteristics at baseline

Specific disease history includes the following:

- Time since first diagnosis of Multiple sclerosis (MS) relative to randomization (in years)
- Time since first symptoms of MS relative to randomization (in years)
- Time since most recent relapse onset relative to randomization (in months)
- MS type (relapsing remitting, progressive relapsing)
- Number of relapses experienced within past 1 year (quantitative variable and qualitative variable: 0, 1, 2 and ≥3)

- Number of relapses experienced within past 2 years (quantitative variable and qualitative variable: 0, 1, 2, 3 and ≥4)
- Number of relapses experienced overall (quantitative variable and qualitative variable: 0, 1, 2, 3 and ≥4)
- With previous MS medication in the last 2 years (Yes, No)
- Total number of any events since onset of MS (0, 1, 2-5 and >5) and the subtype (Non encephalopathic Central nervous system (CNS) clinical events, Acute Disseminated Encephalomyelitis (ADEM), other event)

Vital signs

Vital signs at baseline are weight in kilograms (quantitative variable and qualitative variable: ≤40, >40), height in cm, Body Mass Index (BMI) in kg/m^2.

Other

Alcohol habits within the last 12 months and smoking habits will also be summarized.

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

2.1.2 Prior or concomitant medications

All medications taken within 4 weeks (2 years for MS treatments) before screening and until the end of the study are to be reported in the case report form (CRF) pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used prior to first investigational medicinal product (IMP) intake. Prior medications can be discontinued before first IMP administration or can be ongoing during treatment period.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from the first IMP intake to the day of last double-blind IMP intake
- Follow-up medications are those the patient took running from the day after the last double-blind IMP intake up to the end of the double-blind period

A given medication can be classified both as a prior medication and as a concomitant medication.

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

2.1.3 Efficacy endpoints

Evaluation schedule for efficacy variables is presented in Table 1.

Note that all efficacy evaluations up to closeout measurement will be included for analysis unless otherwise specified. Baseline for efficacy variable is defined as the last non-missing value on or before the date of randomization. For patients who have no value on or before randomization date, the last non-missing value on (at pre-dosing) or before the date of first dose intake will be used as baseline.

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is the time to first clinical relapse after randomization up to the end of double-blind treatment period.

Clinical relapses are defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the Examining Neurologist and documented by the Functional System Scores (FSS). New or recurrent symptoms that occur less than 30 days following the onset of a relapse are considered part of the same relapse.

Confirmed clinical relapse must have objective signs on the Examining Neurologist's examination confirming the event and must then be reviewed and confirmed by an independent Relapse Adjudication Panel (RAP).

Not confirmed clinical relapses are those clinical relapses not confirmed by an independent Relapse Adjudication Panel.

Time to first clinical relapse is defined as "the date of first confirmed clinical relapse - randomization date +1", ie, the randomization day will be Day 1. If a patient has no confirmed clinical relapse, then the patient is considered as clinical relapse free until the end of the double-blind period. His/her data will be censored on the end date of the double-blind period.

2.1.3.2 Secondary efficacy endpoint(s)

The secondary efficacy endpoints are the following:

- Proportion of clinical relapse free patients at 24, 48, 72 and 96 weeks
- MRI endpoints:
  - Number of new/newly enlarged T2 lesions
  - Number of Gd-enhancing T1 lesions
  - Change in volume of T2 lesions
  - Change in volume of T1 hypointense lesions
  - Number of new hypointense T1 lesions

- Proportion of patients free of new or enlarged MRI T2 lesions at 48 weeks and 96 weeks
- Percentage change of brain volume

- The number of new/newly enlarged T2 lesions and the number of Gd-enhancing T1 lesions will be considered the key secondary imaging endpoints.
- Cognitive outcome measured by the SDMT and Cognitive Battery Tests
- Teriflunomide PK
- Exploratory endpoint: proportion of disease-free patients.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data, vital signs, ECG, etc.

Observation period

The observation period will be divided into epochs:

- The **screening** epoch is defined as the time from the signed informed consent date up to the first dose of IMP
- The **treatment** epoch is defined as the time from the first administration of the IMP to the last administration of the double-blind IMP
- The **accelerated elimination** epoch is defined as the time from 1 day after treatment epoch up to 4 weeks (28 days) after the last administration of the double-blind IMP or up to the first administration in open label period, whichever occurs first

The treatment-emergent adverse event (TEAE) period will include both **treatment** and **accelerated elimination** epochs.

- The **posttreatment** epoch is defined as the period of time starting the day after the end of the treatment-emergent adverse event period up to the end of the double-blind period (defined as first dose of open label IMP for patients enter open label extension period, or the last protocol-planned visit, EOT+4W, in the double-blind period or the resolution/stabilization of a followed-up AE for patients do not enter).

The on-study observation period for double-blind period is defined as the combination of TEAE period and posttreatment epoch.

2.1.4.1 Adverse events variables

Adverse event observation period

- Pretreatment adverse events are adverse events that developed or worsened or became serious from the signed informed consent date up to first administration of IMP

- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period
- Posttreatment adverse events are adverse events that developed or worsened or became serious during the posttreatment period

All adverse events including serious adverse events (SAEs) and adverse events of special interest (AESI) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Record the occurrence of adverse events (including serious adverse events and AESI) from the time of signed informed consent until the end of the study.

AESIs include the following terms:

- Gastrointestinal disorders (Nausea and diarrhea)
- Hepatic disorders
- Pancreatic disorders
- Bone marrow disorders
- Infections and Infestations
- Hypersensitivity
- Severe skin reaction
- Malignancy
- Hypertension
- Cardiac Arrhythmias
- Pulmonary disorders (ILD)
- Embolic and Thrombotic
- Hemorrhage
- Peripheral neuropathy
- Convulsions
- Alopecia
- Psychiatric disorders

Additional AESIs may be identified through the ongoing studies. The complete list of AESIs and details of the grouping algorithm will be finalized prior to the Database Lock (DBL).

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period
- Death post-study: deaths occurring after the end of the study (ie, the end of double-blind period)

2.1.4.3 Laboratory safety variables

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

Blood samples for routine clinical laboratories will be taken at screening, randomization, Weeks 4, 12, 24 and then every 12 weeks up to the EOT (Week 96, premature treatment discontinuation visit and the time when patient switches to the open label period due to high MRI activity). The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells and platelets and coagulation**: hemoglobin, hematocrit, mean corpuscular hemoglobin, red blood cell count, platelet count, prothrombin time, activated partial thromboplastin time
  - **White blood cells:** white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry
  - **Metabolism:** glucose, cholesterol, triglycerides, total protein, albumin, globulin, albumin/globulin ratio, creatine phosphokinase(CPK), serum amylase and lipase
  - **Electrolytes**: sodium, potassium, chloride, calcium, inorganic phosphorus, bicarbonate, magnesium
  - **Renal function**: creatinine, creatinine clearance, blood urea nitrogen (BUN), uric acid
  - **Liver function**: alanine aminotransferase(ALT), aspartate aminotransferase(AST), alkaline phosphatase, Gamma Glutamyl Transferase(GGT), lactate dehydrogenase (LDH), total bilirubin, direct/indirect bilirubin
  - **Pregnancy test**: Serum β-human chorionic gonadotropin (β-HCG) for pubescent females (NOTE: This test is performed at baseline and every 12 weeks and at EOT or premature treatment discontinuation)
- Urinalysis - quantitative analyses: pH, ketones, protein, glucose, blood, urobilinogen, bilirubin, microscopic sediment and specific gravity

The following safety laboratory testing will be conducted in between clinical routine lab at Weeks 8, 16, 20, 30 and then every 12 weeks up to the EOT measuring

- Hematology (as above)
- Liver function tests (ALT, AST, GGT, total bilirubin, and direct/indirect bilirubin)
- Pancreatic enzymes (serum amylase and lipase)

At EOT +2 weeks and EOT +4 weeks:

- Uric acid and inorganic phosphorus will also be performed

Laboratory assessment for TSH will also be performed at baseline, every 24 weeks and EOT.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs include: radial heart rate, systolic and diastolic blood pressure and body temperate. Weight and height will be documented in the growth charts.

2.1.4.5 Electrocardiogram variables

A standard 12-lead ECG will be performed at baseline and at EOT and will be evaluated centrally.

ECG parameters include heart rate, PR interval, QRS interval, QT, and corrected QTc (QTc interval calculated by Bazett's method) and QTcF (QTc interval calculated by Fridericia's method).

2.1.4.6 Tanner scales

The Tanner scale (also known as the Tanner Stages I-V) will be used to define physical measurements of growth and development (including sexual development and endocrine function), based on external primary and secondary sex characteristics, such as the size of the breasts, genitalia, and development of pubic hair.

Tanner staging will be performed at baseline, every 24 weeks and EOT (until the patient completes sexual maturity (defined by Tanner Stage 5).

2.1.5 Pharmacokinetic variables

Blood samples will be collected at pre-dose (through PK samples) on Week 2, 3 and 4 (PK run-in [8 weeks] period), 8, 12, 24, 36 and EOT visit or in case of overdose during the double-blind period. An additional sample may be required during the PK run-in period in case of inadequate sampling or information/variability.

2.1.6 Immunoglobulins

Serum immunoglobulins concentration (IgG, IgM and IgA) will be performed at randomization and every 24 weeks up to Week 96/EOT in double-blind treatment period.

In addition if a patient has a vaccination, antibody titers will be assessed before and after vaccination (only inactivated vaccines are allowed).

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations. The summary statistics will be displayed based on treatment arm as randomized (Placebo versus Teriflunomide).

Screened patients are defined as any patient who met the inclusion criteria and where signed informed consent/assent was obtained from the patient and patient's legal representative (parents or guardians) according to local regulations.

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients
- Screen failure patients and reasons for screen failure
- Nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who completed the double-blind treatment period
    - Patients who completed the double-blind treatment period and had a confirmed relapse since randomization until the end of double-blind treatment period
    - Patients who completed the double-blind treatment period and met the high MRI activity criteria since randomization until the end of double-blind treatment period.
    - Patients who completed the 96-week double-blind treatment period
- Patients who did not complete the double-blind treatment period as per protocol
- Patients who discontinued double-blind treatment by main reason for permanent treatment discontinuation

- Patient's decision to permanently discontinue the treatment in the double-blind treatment period
- Patients who entered open label treatment period

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

Patients who did not complete the study and for whom no end-of-treatment data are available will be considered as lost to follow-up.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group.

Kaplan-Meier estimates of the cumulative incidence of permanent double-blind IMP discontinuation for any reason will be provided. Time to withdrawal will be defined as the number of days from the randomization date until the date of last double-blind IMP intake. Patients who complete the double-blind period will be censored at the date of end of the double-blind period. A listing of patients, along with reasons for treatment discontinuation, will be provided.

Additionally, the analysis populations for safety, efficacy, and pharmacokinetics (see Section 2.3) will be summarized in a table by number of patients on the randomized population.

- Efficacy population: intent-to-treat (ITT) population
- Safety population
- Pharmacokinetics population

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IRT transaction
Erroneous kit dispensation
Randomization by error
Patient randomized twice
Stratification error

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered as "randomized" and will not be included in any efficacy population.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

2.3.1 Efficacy populations

2.3.1.1 Intent-to-treat population

The intent-to-treat population is the randomized population analyzed according to the treatment group allocated by randomization.

2.3.2 Safety population

The safety population is defined as all randomized patients exposed to double-blind study medication, regardless of the amount of treatment administered.

The safety analyses will be conducted according to the treatment patients actually received.

In addition:

- Nonrandomized but treated patients will not be part of the safety population; however, their safety data will be presented separately
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized
- For patients receiving more than 1 IMP during the trial, the treatment group allocation for as-treated analysis will be teriflunomide treatment.

2.3.3 Pharmacokinetic population

The PK population is a subset of the safety population containing patients who have at least one PK sample taken. Patients will be analyzed in the treatment group corresponding to the treatment actually received as defined for the safety population.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients with non-missing data (unless otherwise noted) in each treatment group.

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the ITT population for any treatment group.

Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics.

Medical and surgical history

Medical and surgical history will be summarized by primary SOC and HLT for each treatment group. The table will be sorted by SOC internationally agreed order and decreasing frequency of HLT based on the overall incidence in the overall treatment group.

P-values on demographic and baseline characteristic data will not be calculated.

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

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

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the randomized population. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the ITT population for any treatment group.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the Anatomic Therapeutic Chemical (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The tables for concomitant and follow-up medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the teriflunomide group. In case of equal frequency regarding ATCs, alphabetical order will be used.

In addition, prior MS medication, the inducers and systemic corticosteroid treatment for MS relapse will be analyzed by number and percentage of confirmed relapse requiring steroid treatment.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment within the safety population (see Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure.

Duration of double-blind IMP exposure is defined as last double-blind dose date - first dose date +1 day, regardless of unplanned intermittent discontinuations (see Section 2.5.2 for calculation in case of missing or incomplete data).

Duration of double-blind IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories: >0 to ≤4 weeks, >4 to ≤12 weeks, >12 to ≤24 weeks, >24 to ≤48 weeks, >48 to ≤72 weeks, >72 to <96 weeks, and ≥96 weeks.

The number and percentage of patients by final double-blind IMP dose and by dose at the end of PK run-in will also be presented by each treatment group. A list of the patients who changed dose after the end of the PK run-in will be provided. The number and percentage of patients with each double-blind IMP dose level by visit and with dose increase/decrease/unchanged by visit will also be presented by each treatment group if necessary.

2.4.3.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Percentage of compliance for a patient will be defined as the number of administrations that the patient was compliant divided by the total number of administrations that the patient was planned to take during the treatment epoch defined in Section 2.1.4.

Above-planned dosing percentage for a patient will be defined as the number of administrations that the patient took a higher dose than planned divided by the total number of administrations that the patient was planned to take during the treatment epoch.

Under-planned dosing percentage for a patient will be defined as the number of administrations that the patient took a lower dose than planned divided by the total number of administrations that the patient was planned to take during the treatment epoch.

Treatment compliance, above-planned, and under-planned dosing percentages will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized. In addition, numbers and percentages of patients with at least 1 above-planned dose administration will also be provided, as well as numbers and percentages of patients with 0, (0, 20%], and >20% under-planned dose administrations.

Treatment compliance will also be summarized by group (placebo, 3.5 mg, 7 mg, and 14 mg teriflunomide at the end of PK run-in phase of the double-blind period) and baseline body weight (≤40, >40 kg); where applicable, additional summary of treatment compliance by baseline weight of >0 to <30, ≥30 to <40, ≥40 to <50, and ≥50 kg will be presented.

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint(s)

Main statistical model and adjustment for covariates

Time to first confirmed clinical relapse will be analyzed using a stratified log-rank test with time to first clinical relapse as the dependent variable, treatment group as a test variable, region (definition of the regions are provided in Section 2.5.5), and pubertal status as covariates. The first confirmed clinical relapse occurring from randomization (including relapses during the PK run-in (8 weeks) phase) to the end of the randomized, placebo-controlled study treatment period, will be included for analysis. Treatment effect as measured by the hazard ratio and its associated 95% confidence interval will be estimated using a Cox proportional-hazards model with robust variance estimation (1). Cox model will include factors for treatment group, region, pubertal status, age, and number of relapses in the year prior to randomization. Statistical significance will be claimed for the primary endpoint if the p-value for the 2-sided log-rank test is <0.05.

Censoring rule

If a patient has no confirmed clinical relapse before treatment discontinuation/completion in the double-blind period, the patient will be considered as free of relapse till the date of last IMP administration reported on the EOT page of the double-blind period. If this date is missing, last dose date on the IMP administration page will be used.

Sensitivity analysis

The following sensitivity analyses for the primary endpoint will be performed using the similar log-rank test and Cox proportional-hazards model as described above.

- Time to first confirmed clinical relapse or high MRI activity meeting protocol criteria for switching into open-label period, whichever comes first, after randomization before the treatment discontinuation/completion in the double-blind period.
- Time to first clinical relapse (ie, clinical relapse confirmed or not) after randomization before the treatment discontinuation/completion in the double-blind period.
- Time to first confirmed clinical relapse occurring after the PK run-in (8 weeks) phase but before the treatment discontinuation/completion in the double-blind period. The patients who have a relapse during the PK run-in (8 weeks) phase will be included in the analysis with the time to first clinical relapse right censored at the time of treatment discontinuation.
- Time to first clinical relapse with objective signs on the Examining Neurologist's examination including relapses during the PK run-in (8 weeks) phase and relapses reported after the study drug discontinuation and up to 96 weeks after randomization.

Subgroup analysis

Subgroup analyses will be performed for the primary efficacy endpoint by:

- Intrinsic factors
  - Age group at study consent (<13, ≥13 years)
  - Gender
  - Race
  - Pubertal status (at study consent, and at disease onset)
  - Baseline weight group (≤40, >40 kg)
  - MS subtypes (relapsing-remitting MS, other forms)
  - Number of relapses experienced within past 1 year (0, 1, 2 and ≥3)
  - Number of relapses experienced overall (0, 1, 2, 3 and ≥4)
  - High disease activity at baseline defined as 2 or more relapses in past year, and 1 or more Gadolinium enhancing lesions on baseline MRI (Yes, No)
- Extrinsic factors
  - Region (as defined in Section 2.5.5)
  - Previous MS treatment (Yes, No)

Summaries and Cox regression model results will be presented for different patient subpopulations. The Cox model will include treatment, pubertal status, region, subgroup, and treatment-by-subgroup interaction as fixed factors. If the p-value for an interaction is smaller than 0.05, a further investigation will be performed for the possibility of a qualitative interaction. Summary statistics will be provided for each subgroup, as well as the Forest plot. Subgroup factors might be combined if sample within one sub-category is too small (n <5 or no event per treatment group per subtype). If the size is still too small after combination, only summary statistics will be provided.

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 The proportion of clinical relapse-free patients

The proportion of patients with clinical relapse-free (no confirmed clinical relapse) at Weeks 24, 48, 72 and 96 will be estimated based on Kaplan-Meier methods. The complementary log-log transformation will be used to construct 95% confidence intervals. A Kaplan-Meier graph summarizing the event probability over time will be presented.

Censoring rule

If a patient has no confirmed clinical relapse before treatment discontinuation/completion in the treatment period, the patient will be considered as free of clinical relapse till the date of last IMP administration reported on the EOT page of the treatment period. If this date is missing, last dose date on the IMP administration page will be used.

2.4.4.2.2 Magnetic resonance imaging (MRI) variables

Key MRI variables: The number of new/newly enlarged T2 lesions, the number of T1 Gd-enhancing T1 lesions, as well as the change from baseline in volume of T2 lesions and in volume of T1 hypointense lesions at Week 48 and Week 96.

General rules for MRI variables

The protocol requires that the MRI should not be performed until after a minimum of 14 days following completion of corticosteroid therapy. Thus, MRI values obtained within 14 days of systemic corticosteroid therapy will be excluded from the analysis.

Baseline for MRI variables is defined as the last non-missing, valid MRI value that was measured before or on the day of first administration of IMP. A previous MRI performed in the 6 weeks preceding randomization could be used as the baseline if performed according to the specifications for this study. For valid MRI values in subsequent post baseline visits, time windows (see Table 3) between visits will be used to capture MRI measurements. For multiple records within a visit window, the one closest to the targeted visit date will be used.

Number of lesions

The number of new or enlarged T2 lesions per MRI scan will be analyzed using a negative binomial regression model with robust variance estimation. The model will include the total number of new or enlarged T2 lesions as the response variable, with treatment group, region, pubertal status and age as covariates. In order to account for different numbers of MRI scans performed among patients, the log-transformed number of scans will be included in the model as an offset variable. The robust error variances can be estimated by specifying the patient identifier in the repeated statement using SAS PROC GENMOD. The estimated number of lesions per scan and associated 2-sided 95% confidence interval (CI) will be provided for each treatment group. The relative risk, 2-sided 95% CI and p-value will be provided for comparing teriflunomide to placebo.

The number of T1 Gd-enhancing lesions per MRI scan and the number of new T1 hypointense lesions per MRI scan will be analyzed using a similar negative binomial regression model as described above for T2 lesions.

Volume of lesions and brain

The change from baseline in volume of T2 lesions, T1 hypointense lesions and the percentage change of brain volume will be analyzed using a mixed-effect model with repeated measures (MMRM) approach with appropriate transformation if necessary (eg, cubic root transformation). If significant violation from normality exists after transformation, rank Analysis of covariance (ANCOVA) with LOCF will be used.

The MMRM analyses will be implemented via PROC MIXED in SAS by fitting change from baseline values to all post randomization visits in the treatment period. For the change in volume of T2 lesions, T1 hypointense lesions, the model will include factors (fixed effects) for treatment,

puberty strata, region, visit, treatment-by-visit interaction and baseline value. The factor visit with nominal visits as defined in Section 2.5.3 will have 4 levels (eg, Week 24, Week 48, Week 72, and Week 96). An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. Adjusted least-squares means (LS means) estimates by treatment group will be provided, as well as the differences of these estimates versus placebo, with their corresponding standard errors and associated 95% CIs.

For the percentage change of brain volume, the MMRM model will include factors (fixed effects) for treatment, puberty strata, region, visit, treatment-by-visit interaction, age, gender and baseline brain volume.

Descriptive statistics of the change in volume of T2 lesions, T1 hypointense lesions and the percentage change of brain volume in the original scale will be summarized at each visit by treatment group.

The proportion of patients free of new or enlarged T2 lesions

The proportion of patients free of new or enlarged T2 lesions at Weeks 48 and 96 will be summarized based on all patients having an MRI at these time points. Kaplan-Meier methods will be used for estimation.

Censoring rule

If a patient has no new or enlarged T2 lesions detected by MRI scan before treatment discontinuation/completion in the double-blind period, the patient will be considered as free of new or enlarged T2 lesions till the date of last during-treatment MRI assessment. The last during-treatment MRI assessment is defined as last MRI assessment before treatment discontinuation/completion in the double-blind period.

2.4.4.2.3 EDSS

EDSS score and the change from baseline in EDSS score will be summarized descriptively at each visit by treatment group.

2.4.4.2.4 Cognitive outcome

Cognitive outcome measured by the SDMT and Cognitive Battery Tests. SDMT will be analyzed by MMRM model similar as done for volume of lesions and brain in Section 2.4.4.2.2. No data transformation is needed. The visits windows for SDMT are defined in Section 2.5.3. The MMRM model will include factors (fixed effects) for treatment, puberty strata, region, visit, treatment-by-visit interaction, age and baseline value.

The change from baseline in Cognitive Battery Tests (except SDMT) will be summarized descriptively. Box plot will be provided as well.

2.4.4.2.5 Disease free patient

Disease-free patients was defined as patients with

- No confirmed clinical relapse
- No 24-week sustained disability progression (≥0.5-point EDSS score increase if baseline EDSS score >5.5 or ≥1-point EDSS score increase from baseline if baseline EDSS score ≤5.5, persisting for ≥24 weeks)
- Free of MRI activity: No Gd-enhancing T1 lesions and no new/enlarging T2 lesions

Alternative definitions of disease-free status, eg, using cognitive information may be additionally explored.

The proportion of disease-free patient at Weeks 48 and 96 will be summarized based on all patients having an MRI at these time points. Kaplan-Meier methods will be used for estimation.

2.4.4.3 Multiplicity issues

Statistical significance will be claimed for the primary efficacy endpoint (time to the first clinical relapse after randomization) if the computed p-value from the primary analysis with a 2-sided log-rank test is <0.05.

To strongly control Type-I error rate for this family, a step down testing procedure will be applied to the 2 key secondary efficacy endpoints in the order specified below.

- Number of new/newly enlarged T2 lesions
- Number of Gd-enhancing T1 lesions

Each hypothesis will be formally tested only if the preceding one is significant at 5% level. The results of this step-down testing procedure will be of supplemental intent.

2.4.4.4 Accidental unblinding or erroneous kit dispensation during the double-blind period

Potential operational biases, associated with accidental unblinding of treatment allocation of individual patients or erroneous kit dispensation leading a placebo patient to receive teriflunomide (or vice versa) during the double-blind period, will be assessed with sensitivity analysis of the primary endpoint and selected secondary endpoints, if at least 5% of all patients in either group were affected by such incidence, regardless of the root causes.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group.

General common rules

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

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately.
- The baseline value is defined as the last available value before the first intake of IMP in the double-blind period.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (PCSA version dated May 2014 [Appendix A]).
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by treatment group on the safety population.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group. Summaries will include the endpoint value and/or the minimum and maximum value. The endpoint value is commonly defined as the value collected at the same day/time of the last administration of IMP. If this value is missing, this endpoint value will be the closest value prior to the last dose intake.
- All of the values including unscheduled measurements will be assigned to the appropriate safety analysis visit window. In the presence of multiple measurements of the same test in the same window (see Table 4), the one closest to the targeted visit date will be used for the by-visit summaries.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events (TEAEs). Pretreatment and posttreatment adverse events will be described separately.

TEAEs will be further differentiated as “TEAEs during treatment epoch” and “TEAEs during accelerated elimination epoch”. TEAEs during treatment epoch and TEAEs during accelerated elimination epoch will be analyzed separately and combined, as applicable.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment, treatment-emergent, or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment or posttreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.2.

Adverse event incidence tables will present by SOC, HLGT, HLT, and PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment period. The denominator for computation of percentages is the safety population within each treatment group.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pretreatment, treatment-emergent, and posttreatment). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the teriflunomide treatment arm.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - Treatment-emergent adverse event
  - Serious treatment-emergent adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified.

- Common TEAEs (incidence ≥2% in any treatment group for PT) by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least one common TEAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All treatment-emergent adverse events regardless of relationship and related by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above
- Number (%) of patients experiencing treatment-emergent adverse event(s) presented by primary and secondary SOC, HLGT, HLT, and PT sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT
- By-patient listing of TEAE(s) occurred within 2 months after first dose increase for teriflunomide treated patients showing treatment group, patient identified, age, gender, race, primary SOC decode, PT decode, verbatim (diagnosis), onset date and study day, date of death (if relevant), recovery date/time, event duration, outcome, intensity/grade, relationship to study treatment, action taken with study treatment and corrective treatment/therapy, AE serious criteria, flag for AE status

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- Number (%) of patients with at least one treatment-emergent serious adverse events by seriousness criteria
- By-patient listing of treatment-emergent SAEs showing treatment group, patient identified, age, gender, race, primary SOC decode, PT decode, verbatim (diagnosis), onset date and study day, date of death (if relevant), recovery date/time, event duration, outcome, intensity/grade, relationship to study treatment, action taken with study treatment and corrective treatment/therapy, AE serious criteria, flag for AE status.

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

- All treatment-emergent adverse events leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events leading to treatment discontinuation, by primary SOC and PT, showing the number (%) of patients sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC
- By-patient listing of TEAEs leading to treatment discontinuation showing treatment group, patient identified, age, gender, race, primary SOC decode, PT decode, verbatim (diagnosis), onset date and study day, date of death (if relevant), recovery date/time, event duration, outcome, intensity/grade, relationship to study treatment, action taken with study treatment and corrective treatment/therapy, AE serious criteria, flag for AE status, flag for seriousness.

AESIs summaries

- All treatment emergent adverse events of special interest, by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least one TEAE sorted by SOC internationally agreed order. The other level (HLGT, HLT, PT) will be presented in an alphabetic order

In addition, the following exposure adjusted analyses will be performed for treatment emergent adverse events with prespecified monitoring adverse events.

The frequency of TEAEs across pre-defined time intervals will be provided for the treatment emergent AESIs, where the time intervals will be defined as: >0- ≤1 week, >1- ≤4 week, >4- ≤12 weeks, >12- ≤24 weeks, >24- ≤36 weeks, >36- ≤48 weeks, >48- ≤60 weeks, >60- ≤72 weeks, >72- ≤84 weeks, >84- ≤96 weeks, and >96 weeks. In each time interval, the denominator for calculation of percentage will be the number of patients exposed at the beginning of the time interval who did not report the given TEAE in the preceding intervals and the numerator will be the number of patients with at least one TEAE occurring in this time interval. Only the first event will be counted and all recurrent events will not be included.

Analysis of pretreatment and posttreatment adverse events

- All pretreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All pretreatment adverse events leading to study discontinuation by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All posttreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 posttreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

- All pretreatment or posttreatment serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 posttreatment serious adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

Safety Subgroup Analysis

Safety subgroup analyses will be performed for key tables of TEAEs/SAEs/AESIs, AEs leading to treatment discontinuation during the treatment-emergent adverse event period by:

- Intrinsic factors
  - Age group at study consent (<13, ≥13 years)
  - Gender
  - Race
  - Pubertal status (at study consent, and at disease onset)
  - Baseline weight group (≤40, >40 kg)
  - MS subtypes (relapsing-remitting MS, other forms)
  - Number of relapses experienced within past 1 year (0, 1, 2 and ≥3)
  - Number of relapses experienced overall (0, 1, 2, 3 and ≥4)
  - High disease activity at baseline (defined as 2 or more relapses in the past year, and 1 or more Gadolinium enhancing lesions on baseline MRI) (Yes, No)
- Extrinsic factors
  - Region (as defined in Section 2.5.5)
  - Previous MS treatment (Yes, No)

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-study, on-treatment, post-study)
- Deaths in nonrandomized patients or randomized but not treated patients
- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC.
- By-patient listing of deaths showing treatment group, patient identified, age, gender, race, duration of exposure, date of death, primary reason of death.

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or minimum and maximum value during the treatment-emergent adverse event period) by treatment group. Mean changes from baseline with the corresponding standard error will be plotted over time (at same time points) in each treatment group for laboratory parameters of primary interest. This section will be organized by biological function.

PCSA will be assessed based on age group at each visit. After subjects turn to be adult, the adult criteria will be applied. The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period will be summarized by biological function and treatment group whatever the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

A listing of patients with at least one post-baseline PCSA will be provided and will display the whole profile over time at any time of all parameters of the corresponding biological function. In this listing, baseline, endpoint value and individual values will be flagged when lower or higher than the lower or upper laboratory limits and/or when reaching the absolute limit of abnormality criteria.

Drug-induced liver injury

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any postbaseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any postbaseline visit will also be displayed by duration of exposure for each treatment group.

Time to onset of the initial ALT and AST elevation (>3 x upper limit of normal range [ULN]) and total bilirubin elevation (>2 x ULN) (time to first observation of ALT >3 x ULN or total bilirubin >2 x ULN, whichever comes first) will be analyzed using Kaplan-Meier estimates, presented by treatment group. Consideration should be given to the impact of the spacing of scheduled tests. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

Listing of possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin ≥2 x ULN),), presented with ALT,

AST, alkaline phosphatase, total bilirubin, and the following complementary parameters: conjugated bilirubin and prothrombin time/international normalized ratio, creatine phosphokinase and serum creatinine.

Summarize the normalization by parameter (to ≤1 x ULN or return to baseline) of elevated liver function tests by categories of elevation (3 x, 5 x, 10 x, 20 x ULN for ALT and AST, 1.5 x ULN for alkaline phosphatase, and 1.5 x and 2 x ULN for total bilirubin), with the following categories of normalization: never normalized, normalized despite treatment continuation of IMP, or normalized after IMP discontinuation. Note that a patient will be counted only under the maximum elevation category.

Proportion of patients with ALT >1 x ULN and ALT >2 x ULN at post-baseline visits will be presented by treatment group.

Summarize the incidence of liver-related adverse events by treatment group. The selection of preferred terms will be based on the hepatic disorder SMQ.

TSH

TSH will also be summarized for each study assessment by treatment group.

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all vital signs variables (raw data and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or minimum and maximum value during the treatment-emergent adverse event period)by treatment group. For blood pressure, height and weight, mean changes from baseline with the corresponding standard error will be plotted over time (at same time points) in each treatment group. Listing of weight for patients with baseline body weight <40 kg will also be presented.

PCSA will be assessed based on age group at each visit. After subjects turn to be adult, the adult criteria will be applied. The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

2.4.5.5 Analyses of electrocardiogram variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all ECG variables (central reading and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or minimum and maximum value during the treatment-emergent adverse event period) by treatment group. Mean changes from baseline with the corresponding standard error will be plotted over time (at the same time points) in each treatment group.

PCSA will be assessed based on age group at each visit. After subjects turn to be adult, the adult criteria will be applied. The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

2.4.5.6 Analyses of Tanner scales

Summary of raw value and change of Tanner scales (including number, mean, median, standard deviation, minimum and maximum) from baseline will be presented for each location (pubic hair and breasts in girls, pubic hair and testes in boys) for each visit by gender and treatment group. The distribution of number of days to the first Tanner stage increase by 1 point, 2 points, and 3 or more points in each location will be estimated by gender and treatment group using the Kaplan-Meier product limit estimator. The Kaplan-Meier plot for patients first achieving Tanner Stage 5 in either location during the double-blind period also will be provided by treatment group for each gender.

Shift table for Tanner scales shifted from pre-treatment scales at study consent to post-treatment scales at Week 96/EOT will be summarized by gender and location in each treatment group.

2.4.6 Analyses of pharmacokinetic variables

The summary statistics (including number, mean, standard deviation, geometric mean, coefficient of variation, median, minimum and maximum) of teriflunomide plasma concentrations will be calculated by dose level for each visit or study assessment for teriflunomide-treated patients.

If date and/or time of the drug intake and/or sampling are missing then the concentration will not be taken into account. Where concentration values are below the lower limit of quantification (LLOQ), one-half of the LLOQ will be used at given study visits.

By-patient listing will be presented for placebo-treated patients showing teriflunomide PK levels greater than a value of zero during the double-blind period, if applicable.

Population pharmacokinetic analysis will be to be conducted per separate analysis plan and reported separately.

2.4.7 Analyses of immunogenicity variables

The summary statistics (including number, mean, standard deviation, geometric mean, coefficient of variation, median, minimum and maximum) of serum immunoglobulins concentration (IgG, IgM and IgA) will be provided for each visit or study assessment by treatment group.

Listing will be provided for patients with concomitant vaccine administration.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

Age = integer part of (date of study consent – date of birth) / 365.25

BMI (in kg/m²) = weight in kg/ (height [in m] x height [in m])

Renal function formulas

Creatinine clearance (CrCl) value for children up to 18 years old will be derived from body length and plasma creatinine (Scr) using the updated Schwartz (Bedside Schwartz) equation:

For children/adolescents: CrCl (mL/min/1.73m^2) = 0.413 x (height [cm] /Scr [µmol/L]), where eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2

Creatinine clearance value for adults will be derived using the equation of Cockcroft and Gault:

For males: $\boldsymbol{crcl(mL/min) = \frac{(140-age)\times weight\,(kg)}{0.814\times creatinine\,(\mu mol/L)}}$

$$\boldsymbol{crcl(mL/min) = \frac{(140-age)\times weight\,(kg)}{0.814\times creatinine\,(\mu mol/L)}}$$

$$\boldsymbol{crcl(mL/min) = \frac{(140-age)\times weight\,(kg)}{0.814\times creatinine\,(\mu mol/L)}}$$

$$\boldsymbol{crcl(mL/min) = \frac{(140-age)\times weight\,(kg)}{0.814\times creatinine\,(\mu mol/L)}}$$

$$\boldsymbol{crcl(mL/min) = \frac{(140-age)\times weight\,(kg)}{0.814\times creatinine\,(\mu mol/L)}}$$

For females: $\boldsymbol{crcl(mL/min) = \frac{(140-age)\times weight\,(kg)}{0.814\times creatinine\,(\mu mol/L)} \times 0.85}$

$$\boldsymbol{crcl(mL/min) = \frac{(140-age)\times weight\,(kg)}{0.814\times creatinine\,(\mu mol/L)} \times 0.85}$$

$$\boldsymbol{crcl(mL/min) = \frac{(140-age)\times weight\,(kg)}{0.814\times creatinine\,(\mu mol/L)} \times 0.85}$$

$$\boldsymbol{crcl(mL/min) = \frac{(140-age)\times weight\,(kg)}{0.814\times creatinine\,(\mu mol/L)} \times 0.85}$$

$$\boldsymbol{crcl(mL/min) = \frac{(140-age)\times weight\,(kg)}{0.814\times creatinine\,(\mu mol/L)} \times 0.85}$$

$$\boldsymbol{crcl(mL/min) = \frac{(140-age)\times weight\,(kg)}{0.814\times creatinine\,(\mu mol/L)} \times 0.85}$$

The last height or weight measurement on or before the visit of the creatinine measurement will be used. The age collected at the visit will be used.

2.5.2 Missing data

For data listings, the character date will always be used to present the date collected in the CRF.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of multiple sclerosis medical history missing/partial dates

If the date of first MS diagnosis, first symptoms of MS or most recent relapse onset is incomplete, earliest possible day will be imputed for calculation, ie, unknown day will be set in 1st day of the month, and unknown month will be set in January. Unknown year will not be imputed.

Handling of medication missing/partial dates

For the purpose of determination whether the medication is prior or concomitantly, no imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and posttreatment medication.

For concomitant systemic corticosteroid used to identify invalid MRI scans (MRI should be done after a minimum of 14 days following the completion of a course of corticosteroid).Below is the imputation rule:

If start day is missing, and start month and year are not missing:

Impute the start day using the first day of the month. Imputation flag is “D”.

If start month is missing, and start year is not missing:

If end date is not missing/partial date, and the start year are the same as end date -5, then impute the start date using end date -5; if the year are earlier than end date -5, then impute the month and day using December 31. Imputation flag is “M”. If the end date is also missing/partial date, this record will not be imputed and will not be used to identify invalid MRI scans.

If start year is missing:

If end date is not missing/partial date, impute the start date using end date -5. Imputation flag is “Y”. If the end date is also missing/partial date, this record will not be imputed and will not be used to identify invalid MRI scans.

If end day is missing and end month and year are not missing:

If the end month and year are the same as start date +5, then impute the end date using start date +5; If the month and year are earlier than start date +5, then impute the day using the last day of the month; If the month and year are later than start date +5, then impute the day using the first day of the month. If this leads to a date after end of study follow up date, use the end of follow up date instead. Imputation flag is “D”.

If end month is missing and year is not missing:

If the end year are the same as start date +5, then impute the end date using start date +5; If the year are earlier than start date +5, then impute the month and day using December 31; If the year are later than start date +5, then impute the month and day using January 01. If this leads to a date after end of study follow up date, use the end of follow up date instead. Imputation flag is “M”.

If end year is missing:

Impute the end date using start date +5. If this leads to a date after end of study follow up date, use the end of follow up date instead. Imputation flag is “Y”.

A special note, if the systemic corticosteroid start day is missing and month and year are not missing, the rule of 5 days after the start would not apply for the initial imputation. Thus for these cases, after imputation of start date, the end date will be re-imputed by repeating the above rules. If the start month and/or year are missing, the end date will not be imputed and this record will not be used to identify invalid MRI scans.

The above data imputations will only be used to identify invalid MRI scans.

Handling of adverse events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

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

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity of adverse events

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category “normal/missing at baseline”.

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is >0.5 GIGA/L or > ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

2.5.3 Windows for time points

Time window for MRI measurements and SDMT will be used to capture data collected between visits. It is defined in Table 3. All days are relative to randomization date.

Table 3 - Visit window for MRI variables and SDMT

Week of study	Visit	Target day	Schedule A[a]	Schedule B[b]
0	Baseline	0	Up to 1st dose date	Up to 1st dose date
24	Visit 8	168	after 1st dose date -251	after 1st dose date -209
36	Visit 10	252	Not applicable	210 - 293
48	Visit 12	336	252 - 419	294 - 419
72	Visit 16	504	420 - 587	420 - 587
96	Visit 20	756	588 - Last double-blind dose date +60 days and before 1st open label dose	588 - Last double-blind dose date + 60 days and before 1st open label dose

a SDMT and MRI variables for patients without MRI assessment for Week 36
b MRI variables for patients with MRI assessment for Week 36

For multiple records within a visit window, the one closest to the targeted visit date will be used.

Selected safety variables will be summarized by the analysis window defined in Table 3 for the by visit descriptive analysis. All available values obtained between 2 visits including unscheduled measurements will be pooled according to the visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary.

Table 4 - Visit window for safety variables

Week of study	Visit	Schedule A[a]	Schedule B[b]	Vital signs
0	Baseline	Up to 1st dose date	Up to 1st dose date	Up to 1st dose date
4	Visit 3	after 1st dose date - 55	after 1st dose date - 41	after 1st dose date - 41
8	Visit 4	Not applicable	42 - 69	42 - 69
12	Visit 5	56 - 125	70 - 97	70 - 125
16	Visit 6	Not applicable	98 - 125	Not applicable
20	Visit 7	Not applicable	126 - 153	Not applicable
24	Visit 8	126 - 209	154 -188	126 - 209
30	Visit 9	Not applicable	189 - 230	Not applicable
36	Visit 10	210 - 293	231 - 272	210 - 293
42	Visit 11	Not applicable	273 - 314	Not applicable
48	Visit 12	294 - 377	315 - 356	294 - 377

54	Visit 13	Not applicable	357 -398	Not applicable
60	Visit 14	378 - 461	399 - 440	378 - 461
66	Visit 15	Not applicable	441 - 482	Not applicable
72	Visit 16	462 - 545	483 - 524	462 - 545
78	Visit 17	Not applicable	525 - 566	Not applicable
84	Visit 18	546 - 629	567 - 608	546 - 629
90	Visit 19	Not applicable	609 - 650	Not applicable
96	Visit 20	630- end of double-blind period[c]	651- end of double-blind period[c]	630- end of double-blind period[c]

a Schedule A includes: Coagulation panel (prothrombin time, and activated partial thromboplastin time); Complete chemistry panel (glucose, creatinine, BUN, sodium, potassium, chloride, bicarbonate, magnesium, calcium uric acid, LDH, alkaline phosphatase, inorganic phosphorus, total protein, albumin, globulin, albumin/globulin ratio, triglycerides, cholesterol and CPK. Urinalysis (pH, ketones, protein, glucose, blood, urobilinogen, bilirubin, microscopic sediment, specific gravity).

b Schedule B includes: Hematology and differential panel (hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin, white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets); liver function tests [ALT, AST, GGT, total bilirubin, and direct/indirect bilirubin] and pancreatic enzymes [serum amylase and lipase]).

c End of double-blind period is defined as last double-blind dose date + 28 days and before 1st open label dose, whichever comes first.

2.5.4 Unscheduled visits

Unscheduled MRI scans and SDMT will be assigned to the appropriate analysis window (defined in Table 3). Otherwise, only scheduled visit efficacy measurements will be used for by visit analysis to exclude the temporary fluctuations in the clinical status that may occur with a relapse.

Laboratory and vital sign data from unscheduled visits will be used in PCSA analysis. The unscheduled visits will also be assigned to the appropriate analysis time window (defined in Table 4) for the summary of change from baseline by visit. The one closest to the targeted visit date will be used in the presence of multiple measurements within the same time window.

2.5.5 Pooling of centers for statistical analyses

Study centers will be pooled into geographical regions for statistical analysis. Final adjustment to the region list will be made before the database lock.

- Europe: Belgium, Bulgaria, Estonia, France, Greece, Lithuania, Netherlands, Portugal, Russian federation, Serbia, Spain, Ukraine, United Kingdom
- North America: Canada, United States
- Asia: China
- Middle East: Turkey, Israel, Lebanon
- North Africa: Tunisia, Morocco

2.5.6 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

There is no interim analysis planned for the double-blind period of this study.

4 DATABASE LOCK

The database is planned to be locked approximately 28 days after last patient last visit in the double-blind period.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS Version 9.2 or higher.

6 REFERENCES

1. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. Journal of the American Statistical Association. 1989;84(408):1074-8.

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix B: Summary of statistical analyses

Appendix C: Study flow chart for the double-blind treatment period

Appendix A Potentially clinically significant abnormalities criteria

Criteria for potentially clinically significant abnormalities For studies in children (Version 3.0 May 2014)			
Parameter	**Age range**	**PCSA**	**Comments**
ECG parameters			Ref. : Rijnbeek P.R. et al., Eur Heart J 2001; Davignon A. et al., Ped Cardiol 1979/1980; Semizel E.et al., Cardiol Young 2008; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009
HR	Birth/0 to 27 days old (Neonates)	≤90 bpm and decrease from baseline ≥20 bpm ≥190 bpm and increase from baseline ≥20 bpm	
	28 days/1 month to 23 months old (Infants)	≤80 bpm and decrease from baseline ≥20 bpm ≥175 bpm and increase from baseline ≥20 bpm	
	24 months/2 years to <6 years old (Children)	≤75 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm	
	6 to <12 years old (Children)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
	12 to 16/18 years old (Adolescents)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	Birth/0 to 27 days old (Neonates)	≥120 ms	
	28 days/1 month to 23 months old (Infants)	≥140 ms	
	24 months/2 years to <6 years old (Children)	≥160 ms	
	6 to <12 years old (Children)	≥170 ms	
	12 to 16/18 years old (Adolescents)	≥180 ms	

Criteria for potentially clinically significant abnormalities
For studies in children
(Version 3.0 May 2014)

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

Criteria for potentially clinically significant abnormalities
For studies in children
(Version 3.0 May 2014)

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

Criteria for potentially clinically significant abnormalities
For studies in children
(Version 3.0 May 2014)

Parameter	Age range	PCSA	Comments
	6 to <12 years old (Children)	≤48 mmHg and decrease from baseline ≥10 mmHg ≥72 mmHg and increase from baseline ≥10 mmHg	
	12 to 16/18 years old (Adolescents)	≤54 mmHg and decrease from baseline ≥10 mmHg ≥78 mmHg and increase from baseline ≥10 mmHg	
Orthostatic hypotension	All age ranges	SBP: St - Su ≤ -20 mmHg DBP: St - Su ≤ -10 mmHg	
Temperature	All age ranges	Rectal, ear or temporal artery: ≥100.4°F/38.0°C Oral or pacifier: ≥99.5°F/37.5°C Axillary or skin infrared: ≥99°F/37.2°C	Ear temperature not accurate below 6 months of age
Respiratory rate	Birth/0 to 27 days old (Neonates)	<30 per minutes >60 per minutes	Based on normal range
	28 days/1 month to 23 months old (Infants)	<24 per minutes >40 per minutes	
	24 months/2 years to <6 years old (Children)	<22 per minutes >34 per minutes	
	6 to <12 years old (Children)	<18 per minutes >30 per minutes	
	12 to 16/18 years old (Adolescents)	<12 per minutes >20 per minutes	
Sa02	All age ranges	≤95%	
Weight	All ranges	≥5% weight loss from baseline	Based on identification of trends in the child's growth with a series of visits WHO Multicentre Reference Study Group, 2006; Center for Disease Control. Growth chart 2007

Criteria for potentially clinically significant abnormalities
For studies in children
(Version 3.0 May 2014)

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

Criteria for potentially clinically significant abnormalities
For studies in children
(Version 3.0 May 2014)

Parameter	Age range	PCSA	Comments
Total Bilirubin	All age ranges	≥1.3 ULN	CF = mg x 1.7 = µmol Based on normal ranges: <6 mg/dL (Term 0-1 day), <8 mg/dL (Term 1-2 days), <12 mg/dL (Term 3-5 days), <1 mg/dL (Term >5 days)
Conjugated Bilirubin	All age ranges	>35% Total Bilirubin and TBILI≥1.3 ULN	CF = mg x 1.7 = µmol Based on normal range: 0 to 0.4 mg/dL
ALT and Total Bilirubin	All age ranges	ALT ≥3 ULN and Total Bilirubin ≥2 ULN	
CPK	All age ranges	≥3 ULN	
Creatinine	Birth/0 to <6 years old (Neonates, Infants, Children)	>53 µmol/L or 0.6 mg/dL	CF = mg x 8.8 = µmol Based on normal ranges: ≤0.6 mg/dL (0-1 year), 0.5 to 1.5 mg/dL (1 to 16/18 years)
	6 years to <12 years old (Children)	≥90 µmol/L or 1.1 mg/dL	
	12 years to 16/18 years old (AdolescentsAdolescentsAdolsecentsAdolescents)	≥132µmol/L or 1.5 mg/dL	
Creatinine Clearance	All age ranges	50 % of normal <60 mL/min/1.73m^2 (After 1 year old)	Based on GFR Bedside Schwartz Formula Based on normal ranges: 20 to 50 (<8 days), 25 to 80 (8 days to 1 month), 30 to 90 (1-6 months), 40 to 115 (6-12 months), 60 to 190 (12-23 months), 90 to 165 (2-12 years), 80-120 (After 12 years)
Uric Acid	All age ranges	≤2.0 mg/dL or 119 µmol/L ≥8.0 mg/dL or 476 µmol/L	CF = mg x 5.95 = µmol Based on normal ranges: 2.4 to 6.4 mg/dL

Criteria for potentially clinically significant abnormalities
For studies in children
(Version 3.0 May 2014)

Parameter	Age range	PCSA	Comments
Blood Urea Nitrogen (BUN)	Birth/0 to 27 days old (Neonates)	≥4.3 mmol/L or 12 mg/dL	CF = g x 16.66 = mmol Based on normal ranges: 3 to 12 mg/dL (NN; 5 to 18 mg/dL (other classes of age)
	28 days/1 month to 16/18 years old (Infants, Children, Adolescents)	≥6.4 mmol/L or 18 mg/dL	
Chloride	All age ranges	≤80 mmol/L or 80 mEq/L ≥115 mmol/L or 115 mEq/L	CF = 1 Based on normal range: 98 to 106
Sodium	All age ranges	≤129 mmol/L or 129 mEq/L ≥150 mmol/L or 150 mEq/L	CF = 1 Based on normal range : 134 to 146
Potassium	Birth/0 to 27 days old (Neonates)	≤3.0 mmol/L or 3.0 mEq/L ≥7.0 mmol/L or 7.0 mEq/L	CF = 1 Based on normal ranges: 3.0 to 7.0 (NN); 3.5 to 6.0 (Infants); 3.5 to 5.0 (>Infants)
	28 days/1 month to 23 months old (Infants)	≤3.5 mmol/L or 3.5 mEq/L ≥6.0 mmol/L or 6.0 mEq/L	
	24 months/2 years to 16/18 years old (Children, Adolescents)	≤3.5 mmol/L or 3.5 mEq/L ≥5.5 mmol/L or 5.5 mEq/L	
Bicarbonate	All age ranges	≤16 mmol/L or 16 mEq/L ≥30 mmol/L or 30 mEq/L	CF = 1 Based on normal range: 18 to 26
Calcium total	All age ranges	≤2.0 mmol/L or 8.0 mg/dL ≥2.9 mmol/L or 11.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 8.4 to 10.9 mg/dL
Calcium ionized	All age ranges	≤1.0 mmol/L or 4.0 mg/dL ≥1.4 mmol/L or 5.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 4.0 to 5.1 mg/dL
Total Cholesterol	All age ranges	≥6.20 mmol/L or 240 mg/dL	CF = g x 2.58 = mmol Based on normal ranges: 45 to 182 mg/dL (1-3 years), 109 to 189 mg/dL (4-6 years), 126 to 191 mg/dL (Boys 6-9 years), 122 to 209 mg/dL (Girls 6-9 years), 130 to 204 mg/dL (Boys 10-14 years), 124-217 mg/dL (Girls 10-14 years), 114 to 198 mg/dL (Boys 15-19 years), 125 to 212 mg/dL (Girls 14-19 years)

Criteria for potentially clinically significant abnormalities
For studies in children
(Version 3.0 May 2014)

Parameter	Age range	PCSA	Comments
Triglycerides	All age ranges	≥4.0 mmol/L or 350 mg/dL	After >12 hours of fast) CF = g x 1.14 = mmol Based on normal ranges: 30 to 86 mg/dL (Boys 0-5 years), 32 to 99 mg/dL (Girls 0-5 years), 31-108 mg/dL (Boys 6-11 years), 35 to 114 mg/dL (Girls 6 11 years), 36 to 138 mg/dL (Boys 12-15 years), 43 to 138 mg/dL (Girls 12-15 years), 40 to 163 mg/dL (Boys 16-19 years), 40-128 mg/dL (Girls 16-19 years)
Lipasemia	All age ranges	≥2 ULN	Based on normal ranges: 3 to 32 U/L (1-18 years)
Amylasemia	All age ranges	≥2 ULN	Based on normal ranges: 10 to 30 U/L (NN), 10 to 45 U/L (1-18 years)
Glucose	All age ranges	Hypoglycaemia <2.7 mmol/L or 50 mg/dL Hyperglycaemia ≥7 mmol/L or 120 mg/dL (fasted after >12 hours of fast); ≥10.0 mmol/L or 180 mg/dL (unfasted)	CF = g x 5.55 = mmol Based on normal ranges: 50 to 90 mg/dL (NN), 60 to 100 mg/dL (Child)
CRP	All age ranges	>2 ULN or >10 mg/L (if ULN not provided)	Based on normal ranges: <6 mg/L

Criteria for potentially clinically significant abnormalities
For studies in children
(Version 3.0 May 2014)

Parameter	Age range	PCSA	Comments
Hematology			Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 2006 ; Division of Microbiology and InfectiousInfectiousInfectious Diseases Pediatric Toxicity Tables, 2007 ; Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2004; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Family Practice Notebook, LLC, 2012; Tietz NW et al. Clinical Guide to Laboratory Testing, 3rd edition 1995
WBC	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4000/mm^3 >25.0 GIGA/L or 25 000/mm^3	To be used if no differential count available
	28 days/1 month to 23 months old (Infants)	<4.0 GIGA/L or 4000/mm^3 >20.0 GIGA/L or 20 000/mm^3	Based on normal ranges: 9000 to 30 000/mm^3 (birth), 9400 to 38 000/mm^3 (0-1 day), 5000 to 21 000/mm^3 (1 day-1 month), 6000 to 17 500/mm^3 (1 month-2 years), 5000 to 17 000/mm^3 (2-6 years), 4500 to 15 500/mm^3 (6-11 years), 4500 to 13 500/mm^3 (11-18 years)
	24 months/2 years to <6 years old (Children)	<3.0 GIGA/L or 3000/mm^3 >16.0 GIGA/L or 16 000/mm^3	
	6 to <12 years old (Children)	<5.0 GIGA/L or 5000/mm^3 >17.0 GIGA/L or 17 000/mm^3	
	12 to 16/18 years old (Adolescents)	<4,5 GIGA/L or 5000/mm^3 >13.5 GIGA/L or 17 000/mm^3	
Lymphocytes (ALC)	Birth/0 to 27 days old (Neonates)	<1.2 GIGA/L or 1200/mm^3 >17.0 GIGA/L or 17 000/mm^3	Based on normal ranges: 2000 to 11 500/mm^3 (0-1 days), 2000 to 17 000/mm^3 (2 days-1 month), 3000 to 13 500/mm^3 (1 month-2 years), 1500 to 9500/mm^3 (2-6 years), 1500 to 8000/mm^3 (6-10 years), 1200 to 5200/mm^3
	28 days/1 month to 23 months old (Infants)	<2.0 GIGA/L or 2000/mm^3 >13.5 GIGA/L or 13 500/mm^3	
	24 months/2 years to <6 years old (Children)	<1.0 GIGA/L or 1000/mm^3 >9.5 GIGA/L or 9500/mm^3	

Criteria for potentially clinically significant abnormalities
For studies in children
(Version 3.0 May 2014)

Parameter	Age range	PCSA	Comments
	6 to <12 years old (Children)	<1.0 GIGA/L or 1000/mm^3 >8.0 GIGA/L or 8000/mm^3	(10-18 years)
	12 to 16/18 years old (Adolescents)	<0.6 GIGA/L or 600/mm^3 >6.0 GIGA/L or 6000/mm^3	
Absolute Neutrophil Count (ANC)	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4000/mm^3 (1 day old) <1.5 GIGA/L or 1500/mm^3 (2-7 days old) <1.25 GIGA/L or 1250/mm^3 (>7 day-1 month old) > 1 ULN	Based on normal ranges: 5000 to 28 000/mm^3 (0-1 day), 1000 to 10 000 (1 day-1 month), 1000 to 8500 (1-12 months), 1500 to 8500 (1 to 6 years), 1500 to 8000 (6 to 10 years), 1800 to 8000 (10 to 18 years)
	28 days/1 month to 23 months old (Infants)	<1.0 GIGA/L or 1000/mm^3 (1-3 months) <1.2 GIGA/L or 1200/mm^3 (3-24 months) > 1 ULN	
	24 months/2 years to <6 years old (Children)	<1.2 GIGA/L or 1200/mm^3 > 1 ULN	
	6 to <12 years old (Children)	<1.2 GIGA/L or 1200/mm^3 >1 ULN	
	12 to 16/18 years old (Adolescents)	<1.2 GIGA/L or 1200/mm^3 >1 ULN	
Eosinophils	All age ranges	>0.5 GIGA/L or 500/mm^3 Or >ULN if ULN >0.5 GIGA/L or 500/mm^3	Based on normal ranges: 0 to 500/mm^3 (0-1 month), 0 to 300/mm^3 (1 month-18 years)
Hemoglobin	Birth/0 to 27 days old (Neonates)	<86 mmol/L or 12.0 g/dL or any decrease $\geq$0.31 mmol/L or 2 g/dL	CF = g x 1.55 = mmol Based on normal ranges: 15 to 20 g/dL (0-3 days), 12.5 to 18.5 g/dL (1-2 weeks), 10.0 to 13.0 g/dL (1-6 months), 10.5 to 13.0 g/dL (7 months-2 years), 11.5 to 13.0 g/dL (2-5 years), 11.5 to 14.5 (5-8 years), 12.0 to 15.2 g/dL (13-18 years)
	28 days/1 month to 23 months old (Infants)	<1.40 mmol/L or 9.0 g/dL or any decrease $\geq$0.31 mmol/L or 2 g/dL	
	24 months/2 years to <16/18 years old (Children, Adolescents)	<1.55 mmol/L or10.0 g/dL or any decrease $\geq$0.31 mmol/L or 2 g/dL	

Criteria for potentially clinically significant abnormalities
For studies in children
(Version 3.0 May 2014)

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for Phase 2/3 studies (oncology excepted)
(Version 3.0 May 2014)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI - FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI - FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI - FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurements.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for Phase 2/3 studies (oncology excepted)
(Version 3.0 May 2014)

Parameter	PCSA	Comments
CrCl (mL/min) (Estimated creatinine clearance based on the Cockcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for Phase 2/3 studies (oncology excepted)
(Version 3.0 May 2014)

Parameter	PCSA	Comments
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 GIGA/L (Non-Black); <2.0 GIGA/L (Black) ≥16.0 GIGA/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 GIGA/L	
Neutrophils	<1.5 GIGA/L (Non-Black);<1.0 GIGA/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 GIGA/L	
Basophils	>0.1 GIGA/L	
Eosinophils	>0.5 GIGA/L or >ULN (if ULN≥0.5 GIGA/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 GIGA/L ≥700 GIGA/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for Phase 2/3 studies (oncology excepted)
(Version 3.0 May 2014)

Parameter	PCSA	Comments
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SDB Orthostatic DBP	 ≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for Phase 2/3 studies (oncology excepted)
(Version 3.0 May 2014)

Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm >90 bpm >90 bpm and increase from baseline ≥20 bpm >100 bpm >100 bpm and increase from baseline ≥20 bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% >240 ms >240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 ms and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for Phase 2/3 studies (oncology excepted)
(Version 3.0 May 2014)

Parameter	PCSA	Comments
QTc	Absolute values (ms) >450 ms >480 ms >500 ms Increase from baseline Increase from baseline]30-60] ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula. Absolute values categories are cumulative QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.

Appendix B Summary of statistical analyses

EFFICACY ANALYSIS IN THE DOUBLE-BLIND PERIOD

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoint					
Time to first clinical relapse after randomization	ITT	Log-rank test	Cox proportional-hazards model	Subgroups: demographic (eg, age, sex, race, pubertal status, weight) and other (eg, MS subtypes, number of relapse experienced, high disease activity based on MRI, region and previous MS treatment)	Time to first confirmed clinical relapse or high MRI activity meeting criteria for switching into open-label period, whichever comes first; time to first clinical relapse (clinical relapse confirmed or not), time to first clinical relapse occurring after the PK run-in; clinical relapse including relapses during the PK run-in (8 weeks) phase and relapses reported after the study drug discontinuation up to 96 weeks after randomization.
Secondary endpoints					
The number of new or enlarged T2 lesions, T1 Gd-enhancing lesions and new T1 hypointense lesions	ITT	Negative binomial regression model	No	No	No
Change from baseline in volume of T2 lesions, T1 hypointense lesions, the percentage change of brain volume;	ITT	Mixed-effect model with repeated measures	Rank Analysis of covariance (ANCOVA) with LOCF	No	No

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
The proportion of clinical relapse-free patients at weeks 24, 48, 72 and 96,	ITT	Kaplan-Meier methods.	No	No	No
The proportion of patients free of new or enlarged T2 lesions at Weeks 48 and 96	ITT	Kaplan-Meier methods.	No	No	No
SDMT	ITT	Mixed-effect model with repeated measures;	No	No	No
Cognitive outcomes (except for SDMT) and EDSS	ITT	Descriptive summary	No	No	No

SAFETY ANALYSES IN THE DOUBLE-BLIND PERIOD

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Adverse events	Safety	Descriptive summary	No	Subgroups: demographic (eg, age, sex, race, pubertal status, weight) and other (eg, MS subtypes, number of relapse experienced, high disease activity based on MRI, region and previous MS treatment)	No
Lab/vital signs/ECG	Safety	Descriptive summary	No	No	No
Tanner scales	Safety	Descriptive, Kaplan-Meier methods.	No	No	No

Appendix C Study flow chart for the double blind treatment period

	Baseline		Treatment period																	Post drug elimination follow up		Unscheduled
Week (W)[a]	**W-4**	**Rand**[b]	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W30**	**W36**	**W42**	**W48**	**W54**	**W60**	**W66**	**W72**	**W78**	**W84**	**W90**	**W96/ EOT**	**EOT +2W**	**EOT +4W**	**Relapse visit**[v]
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**[c]	**21**[d]	**22**[d]	
Entry procedures																							
Informed consents[e] and assent	X																						X[e]
Review inc/excl criteria	X	X																					
Demographics	X																						
Medical/surgical history	X																						
Tuberculosis test[s]	X																						
Prior medications	X	X																					
Randomization		X																					
Efficacy																							
EDSS	X	X						X				X				X				X			X[p]
SDMT		X						X				X				X				X			
Cognitive Battery Test[u]		X																		X			
Brain MRI [q]	X[f]							X				X				X				X			
Safety																							
Adverse event reporting[g]		<- ->																					
Vital signs[h]	X	X	X	X	X			X		X		X		X		X		X		X	X	X	X
Physical examination[l]	X	X			X			X		X		X		X		X		X		X	X		
ECG 12-leads		X																		X	X[r]	X[r]	
Tanner[i]		X						X				X				X				X			
Clinical routine laboratories[k, j]	X	X	X		X			X		X		X		X		X		X		X			
Clinical safety laboratories[j, l, o]				X		X	X		X		X		X		X		X		X		X	X	

	Baseline		Treatment period																	Post drug elimination follow up		Unscheduled
Week (W)[a]	**W-4**	**Rand[b]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W30**	**W36**	**W42**	**W48**	**W54**	**W60**	**W66**	**W72**	**W78**	**W84**	**W90**	**W96/ EOT**	**EOT +2W**	**EOT +4W**	**Relapse visit[v]**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20[c]**	**21[d]**	**22[d]**	
Immunoglobulins/TSH		X						X				X				X				X			
Treatments																							
Concomitant medications		<--->																					
Dispense study drugs/IVRS call		X		X	X			X		X		X		X		X		X		X[v]			
Accountability/compliance				X	X			X		X		X		X		X		X		X			
Teriflunomide PK sampling[m]			X	X	X			X		X										X	X[n]	X[n]	

EOT = end of treatment (EOT= First visit after last study drug intake), EDSS = expanded disability status scale, FS = functional score, BVMTR = brief visuospatial memory test-revised, SDMT=symbol digit modalities test, MRI = magnetic resonance imaging, PK = pharmacokinetic

a Recommended windows: The window for obtaining biological samples at any given visit will be ±7 days. All other treatment period assessments should be completed within ±7 days of the scheduled visit date relative to the randomization visit. Post drug elimination follow-up visits should be ±7 days of scheduled visit relative to end of treatment.

b Randomization visit up to 28 days from signing of informed consent.

c End-of-treatment and premature discontinuation visit. This visit does not need to be performed when the patient switches to the open label period after a confirmed relapse or high MRI activity (as per protocol criteria). The drug elimination procedure must be initiated at this visit if applicable.

d For discontinuing treatment, 2 post drug elimination follow up visits should be scheduled 2 weeks and 4 weeks after study medication discontinuation and initiation of the drug elimination procedure. All patients who prematurely and permanently discontinue study medication will be asked to continue until the planned end of double-blind period.

e Re-consent must follow any RAP confirmed MS relapse for continuing in study when occurrence during PK run-in, for switching into open-label period when occurrence after PK run-in.

f To be prescribed at Visit 1 and report checked at Visit 2. MRI scan performed within 6 weeks prior to randomization can be used as the baseline MRI if performed according to the operations manual and accepted by the central reader.

g During the adverse event reporting process, specific questions about pulmonary symptoms and peripheral neuropathy symptoms will be asked. (Patients will be instructed to alert the treating physician of symptoms suggestive of immunodeficiency).

h Including systolic and diastolic blood pressure, heart rate, body temperature, weight and height (Height only at V2 and EOT); patient standing in bare or stocking feet. Height and weight is to be documented in the growth charts –Blood pressure (BP) and heart rate to be measured in both the supine and the standing positions (measures taken 3 minutes after supine and 3 minutes after standing). A sphygmomanometer with a blood pressure cuff appropriate to the patient's arm girth is used.

i Tanner stage to be assessed at baseline, every 24 weeks and at EOT for all patients (until complete sexual maturity).

j Pancreatic ultrasound must be performed if there are clinical or lab abnormalities suggesting pancreatitis or enzymes elevation ≥3 x ULN and must be followed up with a computed tomography (CT) with contrast or MRI in case of ultrasound with abnormal pancreatic findings

k The following routine parameters will be measured at screening, randomization, Weeks 4, 12, 24, 36, 48, then every 12 weeks and at EOT: Hematology and differential panel (hemoglobin, hematocrit, red blood cell count and red blood cell morphology, mean corpuscular volume, white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets); Coagulation panel (prothrombin time, and activated partial thromboplastin time); Complete chemistry panel (glucose, creatinine, blood urea nitrogen (BUN), sodium, potassium, chloride, bicarbonate, magnesium, calcium uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total bilirubin, direct/indirect bilirubin, alkaline phosphatase, inorganic phosphorus, total protein, albumin, globulin, albumin/globulin ratio, triglycerides, cholesterol and creatine phosphokinase (CPK). Pancreatic enzymes (serum amylase and lipase); Urinalysis (pH, ketones, protein, glucose, blood, urobilinogen, bilirubin, microscopic sediment, specific gravity). For pubescent females serum pregnancy test β- Human chorionic gonadotropin; (β-HCG) will be performed at screening, randomization and then every 12 weeks

l The following safety laboratory tests will be conducted in between clinical routine lab at Weeks 8, 16, 20, 30 and then every 12 weeks up to the end of the study (EOT). Study nurse visit at patient's home can be provided (except at Week 8). In addition at EOT+2 weeks and EOT+4 weeks. The following safety laboratory testing will be conducted: (measuring hematology and differential panel [as above], liver function tests [ALT, AST, GGT, total bilirubin, and direct/indirect bilirubin] and pancreatic enzymes [serum amylase and lipase]). In addition, uric acid and inorganic phosphorus will be done at EOT+2 weeks and EOT+4 weeks.

m PK samples will be collected at Week 2, 3, and 4 (PK run-in (8 weeks) period); an additional 4th sample may be required in case of inadequate sampling or information/variability from 3 samples. Study nurse visit at patient's home can be provided when PK sampling is not synchronized with routine lab visit (W2, W3 or in the event the 4th sample is needed).

n Post drug elimination procedure sample to be collected for verification of plasma teriflunomide concentrations ≤0.02 µg/mL

o In addition if a patient has a vaccination, antibody titers will be assessed before and after vaccination (inactivated vaccines only)

p EDSS required also after each clinical relapse, to be performed within 7 days.

q If patient is treated with steroids the MRI should be performed after 14 days discontinuation of the steroids

r ECG should be performed only for patients who had new abnormalities on the EOT ECG

s A tuberculosis test should be performed at screening. An additional test should be performed during the study if deemed clinically indicated. Skin test or blood testing are allowed

t The date of first menarche should be captured if applicable

u Cognitive Battery Tests: TMT-A and B, SRT, Beery visual-motor integration (BVMI), D-KEFS Fluencies (Letter and Category); BVMTR and WASI Vocabulary potentially supplemental. When available

v IVRS only if treatment is stopped

Signature Page for VV-CLIN-0282382 v2.0
efc11759-16-1-9-sap

Approve & eSign	[redacted]
Approve & eSign	[redacted]