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 open-label period

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADEM:	acute disseminated encephalomyelitis
AE:	adverse event
ALT:	alanine aminotransferase
ARR:	annualized relapse rate
AST:	aspartate aminotransferase
ATC:	Anatomic Therapeutic Chemical
BMI:	body mass index
BUN:	blood urea nitrogen
CI:	confidence interval
CNS:	central nervous system
CRF:	case report form
CSR:	clinical study report
DBL:	database lock
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
MedDRA:	Medical Dictionary for Regulatory Activities
MRI:	magnetic resonance imaging
MS:	multiple sclerosis
PK:	pharmacokinetic(s)
PT:	preferred term
SDMT:	symbol digit modalities test
SOC:	system organ class
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.

The unblinding of this Phase 3 study will be taken place after the core database lock (DBL), which is expected to be done approximately 28 days after the last patient last visit (LPLV) in the double-blind period/core part of the study. An interim clinical study report (CSR) of the open-label period of this study will be planned upon the core DBL.

The data from the placebo-controlled and the open label teriflunomide treatment periods will be the focus of the CSR of their respective phase. Relevant statistical methods/considerations that mainly relate to the analysis of the data from the placebo-controlled period are employed for data analysis of the open-label period. The data from the open label teriflunomide treatment arm are non-controlled and supportive in nature; summary statistics will be provided for efficacy variables and safety data. More details on interim analysis for the interim CSR of the open-label period are provided in Section 3 Interim Analysis.

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.

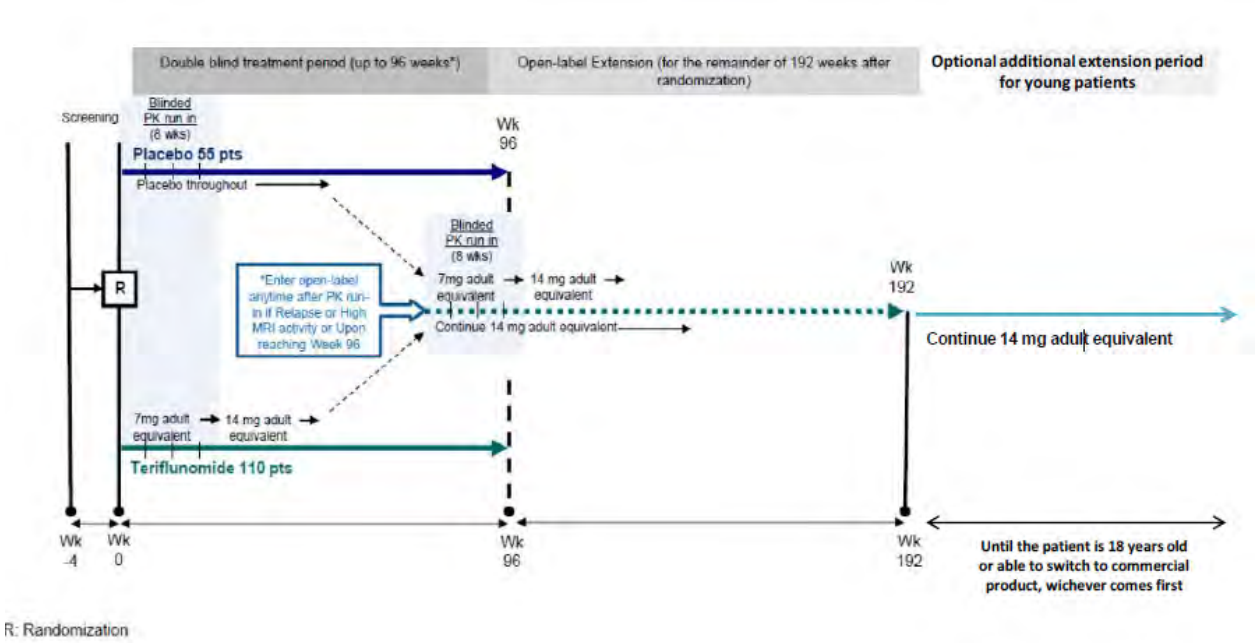
1.3 DETERMINATION OF SAMPLE SIZE

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.

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] visit
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 and Week 96/EOT[a] visit
Physical examinations	Screening, randomization, Weeks 12, 24, and every 12 weeks up to Week 96/EOT[a] visit
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 double-blind treatment period or who prematurely discontinue, should complete EOT visit.

Table 2 - Study schedule for the open-label period

Variable	Visit
Brain MRI	Weeks 48, 96,144 and Week 192/end of treatment (EOT)[0] visit
EDSS	Weeks 24, 48, 72, 96, 120, 144, 168, Week 192/EOT[0] visit, and unscheduled relapse visits
SDMT	Weeks 24, 48, 72, 96, 120, 144, 168, Week 192/EOT[0] visit
Cognitive Battery Test	Week 96 and Week 192/EOT[0] visit
Clinical Laboratory	Transition, Weeks 4, 12, and then every 12 weeks up to the Week 192/EOT[0]
Vital signs [b]	Transition, Weeks 4, 8, 12, and then every 12 weeks up to the Week 192/EOT[0]
ECG	Week 192/EOT[0] and after EOT[0] if abnormality on EOT or ECG could not be performed at EOT (in exceptional circumstances).
Immunoglobulins and TSH	Week 96 and Week 192/EOT[0] visit
PK	Weeks 2, 3, 4, 8, 12, 24, 36 and Week 192/EOT[0] visit
Physical examinations	Weeks 12, 24, and then every 24 weeks up to the Week 192/EOT[0]
Tanner assessment	Every 24 weeks up to the Week 192/EOT[0] for all patients (until complete sexual maturity).

Note: For a regional or national emergency declared by a governmental agency, contingency measures are included in the protocol section 17.7. Remote visits and unscheduled visits may be planned for the collection of possible safety and/or efficacy data.

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

b During remote visits, only weight should be collected.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This statistical analysis plan (SAP) is specified for efficacy and safety analyses with all data collected in the open-label period for the open label CSR.

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

The statistical section of the protocol for open label period was never changed in an amendment.

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).

Statistical analysis for open-label period was not addressed in previous version of SAP or in amended protocol. 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 3.

Table 3 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
1	05-May-2019	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	05-May-2019	To explore long-term treatment effect in teriflunomide/teriflunomide and placebo/teriflunomide group	Add annualized relapse rate (ARR) and time to sustained disability progression as additional endpoint in section 2.1.3.3 and 2.4.4.3.
2		To fulfill requirement from health authorities	Added ethnicity in the demographic section
2		To investigate Covid-19 impact on study conduct and assessment of safety and efficacy of teriflunomide	1) Added Covid-19 related disposition summary 2) Added extent of exposure and compliance summary for Covid-19 impact. 3) Added Covid-19 related adverse event analysis. 3) Modified censoring rule for time-to-event endpoint and OL EOT analysis visit window for potential Covid-19 delay.
2		To correct typo	Added 1 day for each of the target day and analysis visit windows in section 2.5.3

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 period. The following statistical methods/considerations in this SAP relate to the analysis of the data from the open label period. The analysis of the data from the double-blind period was addressed in a separate SAP. The optional additional extension period will be reported separately.

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 in the double-blind period, 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), ethnicity (Hispanic or Latino, Not Hispanic or Latino), region (definition of the regions are provided in Section 2.5.5), age in years at study consent of the double-blind period (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 as well as extension baseline (defined as the last available value before the first intake of IMP in the open-label extension period) 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 imputation for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

All medications taken during the open-label period 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 in the double-blind period. 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 day of first IMP intake in the double-blind period to the day of last IMP intake in the open-label period
- Follow-up medications are those the patient took running from the day after the last IMP intake in the open-label period up to the end of the open-label period

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 and Table 2.

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 in the double-blind period. 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 in the double-blind period 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 end of double-blind treatment period, which is not directly applicable for the open-label treatment period since Relapse Adjudication Panel (RAP) of the double-blind period was not continued into the open-label period. Refer to the SAP for the double-blind period of the study.

However, time to first clinical relapse after randomization in double-blind period up to the end of the open-label treatment period will be performed on relapses with objective signs on the Examining Neurologist's examination (which is the basis for RAP confirming relapses) as a primary efficacy endpoint for analysis period from randomization to the end of the open-label period.

2.1.3.2 Secondary efficacy endpoint(s)

The secondary efficacy endpoints pertaining to the open-label period are the following:

- Time to first clinical relapse since enrollment into the open-label period up to the exit of the open-label treatment period
- Proportion of clinical relapse free patients at 24, 48, 72, 96, 120, 144, 168 and 192 weeks
- MRI endpoints at 48, 96, 144 and 192 weeks:
  - 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
  - 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.

2.1.3.3 Additional efficacy endpoints

The following endpoints, which have not been planned in the protocol for the double-blind period, are added as relevant for efficacy analysis of the open-label period.

- Annualized relapse rate (ARR) since the enrollment into the open-label period up to the exit of the open-label treatment period.
- Time to sustained disability progression (using EDSS) since randomization in double-blind period up to the end of open-label treatment period.

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 of the open-label period will be divided into 3 epochs:

- The **treatment** epoch is defined as the time from the first administration of the IMP in the open-label period to the last administration of the IMP in the open-label period.
- The **accelerated elimination** epoch is defined as the time from 1 day after the open-label treatment epoch up to 4 weeks (28 days) after the last administration of the IMP in the open-label period or up to the first administration in optional additional extension 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 from the day after the end of the treatment-emergent adverse event period up to the end of the open-label period (defined as the first dose of optional additional extension IMP for patients enter optional additional extension period, or the last protocol-planned visit, EOT +4W, in the open-label period or the resolution/stabilization of a followed-up AE for patients do not enter).

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

2.1.4.1 Adverse events variables

Adverse event observation period

- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period in the open-label period of the study.
- Posttreatment adverse events are adverse events that developed or worsened or became serious during the posttreatment period in the open-label period of the study.

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
  - A specific analysis of Covid-19 related adverse events will be performed, using the search terms described in Appendix D
- 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 periods 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 open-label 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 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 after a clinical confirmed relapse or high MRI activity whichever comes first) in the double-blind period, and then at transition, Weeks 4, 12 and then every 12 weeks up to the EOT (Week 192 or premature treatment discontinuation visit whichever comes first) in the open-label period. 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 screening, randomization and then every 12 weeks and EOT in the double-blind period, and then every 12 weeks and EOT in the open-label period)
- 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 in the double-blind period, and then at Weeks 8, 16, 20, 30 and then every 12 weeks up to EOT in the open-label period 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 randomization, every 24 weeks and EOT in the double-blind period, and then at Week 96 and EOT in the open-label period.

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 (standing and supine) and body temperature. 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 randomization, EOT in the double-blind period and EOT in the open-label period 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 stage 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 Week 2, 3 and 4 (PK run-in [8 weeks] period), 12, 24, 36 and EOT visit or in case of overdose in the double-blind and open-label 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 the double-blind period, and then at Week 96 and Week 192/EOT in the open-label 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.

All the tables in this section will be presented by the treatment groups the patients were allocated to in the double-blind and open-label period (placebo/teriflunomide versus teriflunomide/teriflunomide) as well as the overall treatment group.

Enrolled patients are defined as any patient who entered the open-label period and where signed informed consent/assent was re-obtained from the patient and patient's legal representative (parents or guardians) according to local regulations when they enter the open-label period of the study.

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:

- Patients who were randomized and treated in the double-blind period
- Patients who completed the double-blind period
- Patients who discontinued from the double-blind period
- Enrolled patients in the open-label period
- Patients who enrolled but were not treated in the open-label period
- Patients who completed the open-label treatment period
- Patients who discontinued open-label treatment period
- Patients who discontinued open-label treatment by main reason for permanent treatment discontinuation in the open-label period
- Patient's decision to permanently discontinue the treatment in the open-label period.

For all categories of patients, percentages will be calculated using the number of enrolled patients as the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group.

The Covid-19 related disposition information will be summarized separately including number of patients were impacted by the Covid-19, Covid-19 related reasons for permanent treatment discontinuation. The summary of disposition by visit impacted by the Covid-19 will be summarized if applicable.

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, drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group. The critical or major deviations that related to the Covid-19, regardless of deviation categories, will be summarized by treatment group separately.

Kaplan-Meier estimates of the cumulative incidence of permanent IMP discontinuation for any reason will be provided for open-label period. Time to withdrawal will be defined as the number of days from the first open-label IMP intake date until the last IMP intake date for the open-label period. Patients who complete the open-label period will be censored at the date of end of the open-label period. A listing of patients, along with reasons for treatment discontinuation, will be provided with their relationship with Covid-19.

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 enrolled population.

- Efficacy population
- Safety population
- Pharmacokinetics population.

2.3 ANALYSIS POPULATIONS

2.3.1 Enrolled population

The enrolled population is defined as patients who were randomized in the double-blind period and enrolled in open-label period analyzed according to the treatment group allocated by randomization in double-blind period (ie, placebo/teriflunomide versus teriflunomide/teriflunomide).

2.3.2 Efficacy population

The efficacy population is defined as all patients enrolled and were treated with at least 1 dose of teriflunomide in the open-label treatment period analyzed according to the treatment group allocated by randomization in the double-blind period (ie, placebo/teriflunomide versus teriflunomide/teriflunomide).

2.3.3 Safety population

The safety population is defined as all patients enrolled in the open-label treatment period and received any dose of teriflunomide in the open-label period. It will be used for the safety analyses in the open-label period.

The safety analyses will be conducted according to the treatment patients actually received in the double-blind and open-label period (placebo/teriflunomide versus teriflunomide/teriflunomide) as well as the overall treatment group.

2.3.4 Pharmacokinetic population

The PK population is a subset of the safety population containing patients who have at least one PK sample taken in the open-label period. 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

All demographics and baseline characteristics parameters will be summarized on the enrolled population analyzed in the treatment group to which they were allocated to in the double-blind and open-label period (placebo/teriflunomide versus teriflunomide/teriflunomide) as well as the overall treatment group. 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 efficacy population for any treatment group.

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

Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics. P-values or statistics tests on demographic and baseline characteristic data will not be calculated.

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.

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 or concomitant medications will be presented for the enrolled 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 efficacy population for any treatment group.

Medications will be summarized by placebo/teriflunomide, teriflunomide/teriflunomide and overall treatment groups 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 incidence in the overall 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 overall treatment 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 in the open-label period will be assessed and summarized by actual treatment (placebo/teriflunomide, teriflunomide/teriflunomide and overall treatment group) within the safety population (Section 2.3.3).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure in the open-label period of the study.

Duration of open-label IMP exposure is defined as last dose date of teriflunomide - first dose date of teriflunomide +1 day in the open-label period, regardless of unplanned intermittent discontinuations (see Section 2.5.2 for calculation in case of missing or incomplete data). Duration of open-label 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, >96 to ≤120 weeks, >120 to ≤144 weeks, >144 to ≤168 weeks, >168 to <192 weeks and ≥192 weeks. The number and percentage of patients by final open-label IMP dose and by dose at the end of PK

run-in of the open-label period will also be presented by each treatment group. A list of the patients who changed dose after the end of the PK run-in of the open-label period will be provided. The number and percentage of patients with each open-label IMP dose level by visit and with dose increase/decrease/unchanged by visit will also be presented by each treatment group if necessary. Cumulative exposure of the IMP taken in the double-blind and open-label treatment periods will be summarized with descriptive statistics from the first dose of IMP in the double-blind period to the last dose of IMP in the open-label period for each treatment group.

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.

In order to address impact of the Covid-19 pandemic, Covid-19 impacted compliance summary will be provided based on safety population including but not limit to the below items.

- Number of patients who used Direct-to-patient (DTP)
- Number of patients who did not compliant to the protocol IMP administration due to the Covid-19 (e.g. dose interruption, dose prolongation, etc.)
- Number of patients who had dose interruption due to the Covid-19
- Duration of non-compliant period due to the Covid-19
- Duration of dose interruption period due to the Covid-19.

Treatment compliance will also be summarized by group (3.5 mg, 7 mg, and 14 mg teriflunomide at the end of PK run-in phase of the open-label period) and baseline body weight (≤40, >40 kgs).

2.4.4 Analyses of efficacy endpoints

All the following efficacy analysis will be conducted on efficacy population, according to the treatment group allocated by randomization in the double-blind period (ie, placebo/teriflunomide versus teriflunomide/teriflunomide). Baseline values of the double-blind period will be used as the baseline in the efficacy analysis for the open-label CSR, unless otherwise noted.

Analyses of efficacy endpoints of the open-period period are of exploratory intent in principle. Long-term treatment effects and the 95% confidence intervals, where applicable, will be assessed since the randomization date in the double-blind period throughout the last visit of the open-label period of the study; unless otherwise noted. P-values will be provided if applicable. No confirmative conclusion should be drawn based on p-value because of exploratory nature of open-label period analysis.

2.4.4.1 Analysis of primary efficacy endpoint

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.

Note that the process of confirmation of clinical relapse is different between the double-blind period and the open-label period. Confirmation in the double-blind period involves the Relapse Adjudication Panel (RAP), whereas confirmation in the open-label period is done by the investigative center. However, some analyses will combine confirmed relapses from both treatment periods, as the criteria used in the two processes are similar.

The first clinical confirmed relapse occurring from randomization in the double-blind period (including relapses during the PK run-in (8 weeks) phase) to the end of the open-label 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. The duration of time to the event will be included in the modeling to offset the lengths of individual observations. Kaplan-Meier estimates of probability of clinical relapse at Week 24, 48, 72, 96, 120, 144, 168 and 192 will be estimated. The complementary log-log transformation will be used to construct 95% confidence intervals. A Kaplan-Meier survival curve from randomization in double-blind period to the end of open-label period will be presented. 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 will be provided as supportive.

Censoring rule

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

Given that confirmation of relapse in the open-label period is based on objective neurological examinations, it is possible that a patient remained on treatment but did not perform any objective neurological examinations due to Covid-19 pandemic. If a patient reported suspected MS relapse and had no objective neurological examinations assessed afterwards due to the pandemic, the censor date will be the date of the last EDSS or FSS assessment.

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 Time to first clinical relapse after enrollment of open-label period up to the end of open-label period

The first clinical relapse occurring from enrollment of open-label period to the end of the open-label period will be included for analysis. Hazard ratio with associated 95% confidence interval, Kaplan-Meier estimates and its 95% confidence interval will be presented using the same method as described in Section 2.4.4.1. 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 will be provided.

Censoring rule

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

Given that confirmation of relapse in the open-label period is based on objective neurological examinations, it is possible that a patient remained on treatment but did not perform any objective neurological examinations due to Covid-19 pandemic. If a patient reported suspected MS relapse and had no objective neurological examinations assessed afterwards due to the pandemic, the censor date will be the date of the last EDSS or FSS assessment.

2.4.4.2.2 The proportion of clinical relapse-free patients

The proportion of patients with clinical relapse-free at Weeks 24, 48, 72, 96, 120, 144, 168 and 192 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.

2.4.4.2.3 Magnetic resonance imaging (MRI) variables

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 in the double-blind period. 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 4 and Table 5 in Section 2.5.3) 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 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

Descriptive statistics of the change from baseline 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, 96, 144 and 192 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 open-label treatment 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 treatment period. In rare cases, if a patient had a delayed MRI scheduled during the open-label period but performed after the open-label EOT visit due to the Covid-19 pandemic, then the delayed MRI result will be considered in the open-label analysis. This MRI assessment is considered as during-treatment assessment.

2.4.4.2.4 EDSS

EDSS score and the change from baseline in EDSS score in the double-blind period will be summarized with descriptive statistics at each visit by treatment group.

2.4.4.2.5 Cognitive outcome

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

2.4.4.2.6 Disease free patient

Disease-free patients were 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, 96, 144 and 192 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 Analysis of additional efficacy endpoint

2.4.4.3.1 Annualized relapse rate

The annualized relapse rate (ARR) is defined as the number of confirmed clinical relapses occurred during the study per patient-year. It will be analyzed in open-label period only. A confirmed clinical relapse is defined as the appearance of a new clinical sign/symptom or clinical worsening of a previous sign/symptom (one that had been stable for at least 30 days) that persists for a minimum of 24 hours in the absence of fever. Each episode of relapse must be confirmed by the treating neurologist, based on the objective assessments by an independent evaluator (the examining neurologist) by documenting either of the following:

A) A 1-point increase in at least two FS functions, or a 2-point increase in at least one FS function (excluding bowel/bladder and cerebral) from the previous clinically stable assessment, or;

B) An increase of at least 0.5 point in EDSS score (unless EDSS=0, then an increase of at least 1.0 point is required) from the previous clinically stable assessment.

Relapses are collected on CRF page "MS relapse". The objective confirmation, based on the protocol-defined criteria, is reported (Yes/No) in the CRF. Only confirmed clinical relapses will be used in the analysis.

A gross estimate of annualize d relapse rate for a treatment group would be the total number of relapses for patients in the treatment group divided by the sum of standardized study durations for patients in the treatment group. Total number of confirmed clinical relapses and standardized study duration will be calculated for each patient.

- Total number of confirmed clinical relapses is defined as the number of confirmed clinical relapses with onset between enrollment date of the open-label period and treatment discontinuation/completion date (same as last dose IMP intake date).
- Standardized study duration (in year) will be calculated by (last dose IMP intake date - enrollment date of the open-label period + 1) / 365.25.

Adjusted ARR will be performed using a Poisson regression model with robust error variance that would accommodate the potential over-dispersed data appropriately. The model will include the total number of clinical relapses as the response variable, treatment group as the test variable, pubertal status, and region as covariates. In order to account for different treatment durations among subjects, the log-transformed standardized treatment duration will be included in the model as an "offset" variable for appropriate computation of relapse rate. The robust error variances can be estimated by specifying the patient identifier in the repeated statement using SAS PROC GENMOD, and this is equivalent to the Generalized Estimating Equation (GEE) model. In comparison to the regular Poisson model, the GEE estimator is robust against

violation of the correlation structure and the distributional assumptions. The treatment-by-strata and treatment-by-region interactions will be evaluated separately at the 5% level of significance by adding the corresponding interaction term to the model. If a statistically significant interaction is detected at $p < 0.05$, further investigations will be performed for the possibility of qualitative interaction.

The estimated relapse rates and 2-sided 95% confidence intervals will be provided for each treatment group. Nelson-Aalen mean cumulative function plot will be provided for descriptive purposes.

2.4.4.3.2 Time to sustained disability progression (using EDSS)

The time to sustained disability progression will be assessed by EDSS during the study. The first disability progression (ie, confirmed disability worsening) is defined as a sustained increase of at least 1.0 point (0.5 for subjects with baseline EDSS >5.5) persisting for at least 24 weeks from baseline EDSS in the double-blind period of the study.

The minimum EDSS increase used to define disability progression is referred to as "minimum increase" in the following text. The initial EDSS increase that meets this "minimum increase" criterion is referred to as "the onset". An EDSS measurement at or after 24 weeks following the onset is necessary to confirm the initial increase and is referred to as "24-week EDSS confirmation". All EDSS measurements (with or without relapse) will be used to determine the onset of a disability progression. However, for the purpose of confirmation, only EDSS measured more than 30 days after the onset of a confirmed relapse will be used to avoid a confirmation caused by a temporary relapse. In order to confirm that the EDSS increase is persistent for at least 24 weeks, the following conditions have to be satisfied: (1) The 24-week EDSS confirmation needs to maintain at least the minimum increase; (2) all EDSS measurements between the onset and the 24-week EDSS confirmation need to maintain at least the minimum increase. Once a disability progression is confirmed, time to disability progression is defined as "date of onset - date of randomization (in the double-blind period) + 1". If a patient has no disability progression on or before last during treatment EDSS evaluation, then the patient is considered as disability progression free until the date of last during treatment EDSS evaluation. The last during treatment EDSS evaluation is defined as last measurement during treatment period (measurement at last scheduled visit for patients who complete the treatment, or measurement at the close-out visit for patients who discontinue the treatment).

If a patient dies for any reason without a 24-week EDSS confirmation, the disability progression will be considered as confirmed with the date of the onset as the date of progression unless any EDSS measured within the 24 weeks did not maintain the minimum increase. Death due to MS (EDSS=10) will be counted as confirmed progression. The progression date is the date of death if there is no prior qualifying EDSS increase and it is the date of the first qualifying EDSS increase if there is such an EDSS increase prior to the death. All the derivation will be based on the exact EDSS evaluation date. Since the actual visit may have been +/-7 days from the scheduled visit, a -7 days window will be used to define the period of 24 weeks.

Censoring rules

- If a patient has no EDSS increase that meets the criteria for progression before treatment discontinuation/completion, then the patient will be considered as free of progression till the date of last during-treatment EDSS evaluation.
- If a patient has an EDSS increase that meets the criteria for progression before treatment discontinuation, all available EDSS assessments obtained during the follow-up visits will be used to serve the purpose of progression confirmation. The patient will be considered as having disability progression if the first increase during treatment period is confirmed for at least 24 weeks during the follow-up visits. If the EDSS from the follow-up visit(s) does not confirm a sustained increase or despite all possible attempts, no confirmatory EDSS assessment is obtained after withdrawal, the patient will be considered as free of disability progression until the date of last during treatment EDSS evaluation.
- If a patient has an EDSS increase that meets the criteria for progression and completes the treatment period before the progression can be confirmed, then the patient will be considered as free of progression till the date of last during-treatment EDSS evaluation.
- In rare cases, if a patient had a delayed EDSS scheduled during the open-label period but performed during the optional extension period due to the Covid-19 pandemic, then this assessment will still be considered as during-treatment EDSS evaluation. The delayed EDSS result will be considered in the sustained disability progression determination process in the open-label analysis.
- In rare cases, if a patient had a delayed EDSS scheduled during the open-label period but performed after treatment discontinuation due to the Covid-19 pandemic, then the delayed EDSS result will be used for progression confirmation purpose only.

The hazard ratio and 95%CI for teriflunomide/teriflunomide versus placebo/teriflunomide will be estimated using Cox regression model with treatment group, region and baseline pubertal status as covariates, offset by the lengths of individual observations.

The Kaplan-Meier method will be used to estimate median time (if possible) to disability progression sustained for at least 24 weeks and cumulative disability progression rates specific to each treatment group. Kaplan-Meier graphs will be generated; quartiles and point probabilities will be calculated. Interval estimates will be calculated using 95% point wise confidence intervals.

2.4.4.4 Multiplicity issues

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

Efficacy analyses performed for primary and secondary endpoints of the open-label period are of exploratory intent in principle to better understand treatment effects of teriflunomide monotherapy beyond the double-blind period in the pediatric population. The step-down testing procedure for controlling multiplicity will not be applied to these exploratory analyses in the open-label period.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment patients actually received in the double-blind and open-label period (placebo/teriflunomide and teriflunomide/teriflunomide) and overall treatment group. Baseline values of the double-blind period will be used as the baseline in the safety analysis for the open-label CSR, unless otherwise noted.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.3, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population 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 of the double-blind period 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 in the open-label period. If this value is missing, this endpoint value will be the closest value prior to the last dose intake.
- All 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 6 and Table 7 in Section 2.5.3), 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) in the open-label period. 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 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 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 (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 overall treatment group.

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, and 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, and Covid-19 related flag.

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, and Covid-19 related flag.

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, and Covid-19 related flag.

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 pre-specified 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, >96-≤108 weeks, >108-≤120 weeks, >120-≤132 weeks, >132-≤144 weeks, >144-≤156 weeks, >156-≤168 weeks, >168-≤180 weeks, >180-≤192 weeks and >192 weeks for open-label period. 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* posttreatment *adverse events

- 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 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.

Long-term Safety Analysis

Long-term safety of teriflunomide exposure will also be analyzed by including all teriflunomide exposure, ie, from randomization in the double-blind period in the teriflunomide group and from start in the open-label period in the placebo group, for the complete study population analyzed in one overall group. Key safety analyses on TEAEs, SAEs, TEAEs leading to treatment discontinuation and AESIs.

Safety Subgroup Analysis

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

- Intrinsic factors
  - Age group at study consent of the double-blind period (<13, ≥13 years)
  - Gender
  - Race
  - Pubertal status (at study consent, and at disease onset)
  - Baseline weight group in the double-blind period (≤40, >40 kgs)
  - MS subtypes (relapsing-remitting MS, other forms)
  - High disease activity at baseline (defined as 2 or more relapses in the past year of screening, and 1 or more Gadolinium enhancing lesions on baseline MRI of the double-blind period) (Yes, No)
- Extrinsic factors
  - Region (as defined in Section 2.5.5).

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, poststudy).
- 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.

The proportion of patients with key PCSA values at any time during the treatment-emergent adverse event period will also be displayed by duration of exposure for each treatment group.

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.

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 Analysis 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 groups. 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 for patients first achieving Tanner Stage 5 in either location during the open-label blind period plot 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 192/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 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.

Population pharmacokinetic analysis will be conducted per a 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 consent in the double-blind period– 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: $$\boldsymbol{crcl(mL/min) = \frac{(140-age)\times weight\ (kg)}{0.814\times creatinine\ (\mu mol/L)}}$$

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

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 of the double-blind period 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 4 and Table 5. Baseline values will be the baseline defined in the double-blind period of the study. All days in the visit window tables for double-blind period (Table 4 and Table 6) and the open-label period (Table 5 and Table 7) are relative to the first dose date in each period respectively.

Table 4 - Visit window for MRI variables and SDMT in the double-blind period

Week	Visit	Target day	Schedule A[a]	Schedule B[b]
0	Baseline	1	Up to 1st dose date	Up to 1st dose date
24	Visit 8	169	after 1st dose date - 252	after 1st dose date -210
36	Visit 10	253	Not applicable	211 - 294
48	Visit 12	337	253 - 420	295 - 420
72	Visit 16	505	421 - 588	421 - 588
96	Visit 20	673	589 - Last double-blind dose date + 60 days and before 1st open label dose	589 - 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

Table 5 - Visit window for MRI variables and SDMT in the open-label period

Week	Visit	Target day	SDMT	MRI variables
0	OL transition visit	1	Up to the first dose in OL period	Up to the first dose in OL period
24	OL Visit 7	169	after 1st open-label dose date - 252	Not applicable
48	OL Visit 11	337	252 - 420	after 1st open-label dose date – 504
72	OL Visit 15	505	421 – 588	Not applicable
96	OL Visit 19	673	589 – 756	505 – 840
120	OL Visit 23	841	757 – 924	Not applicable
144	OL Visit 27	1009	925 – 1092	841 – 1176
168	OL Visit 31	1177	1093 – 1260	Not applicable
192	OL Visit 35	1345	1261 - Later of the Last open-label visit date or the 1st dose date in optional additional extension period	1177 - Later of the Last open-label visit date or before 1st dose date in optional additional extension period

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 6 and Table 7 of Section 2.5.3 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 6 - Visit window for safety variables in the double-blind period

Week	Visit	Schedule A[a]	Schedule B[b]	Vital signs
0	Baseline	Up to 1st double-blind dose date	Up to 1st double-blind dose date	Up to 1st double-blind dose date
4	Visit 3	after 1st double-blind dose date - 56	after 1st double-blind dose date - 42	after 1st double-blind dose date - 42
8	Visit 4	Not applicable	43 - 70	43 - 70
12	Visit 5	57 - 126	71 - 98	71 - 126
16	Visit 6	Not applicable	99 - 126	Not applicable
20	Visit 7	Not applicable	127 - 154	Not applicable
24	Visit 8	127 - 210	155 -189	127 - 210
30	Visit 9	Not applicable	190 - 231	Not applicable
36	Visit 10	211 - 294	232 - 273	211 - 294
42	Visit 11	Not applicable	274 - 315	Not applicable
48	Visit 12	295 - 378	316 - 357	295 - 378

Week	Visit	Schedule A[a]	Schedule B[b]	Vital signs
54	Visit 13	Not applicable	358 -399	Not applicable
60	Visit 14	379 - 462	400 - 441	379 - 462
66	Visit 15	Not applicable	442 - 483	Not applicable
72	Visit 16	463 - 546	484 - 525	463 - 546
78	Visit 17	Not applicable	526 - 567	Not applicable
84	Visit 18	547 - 630	568 - 609	547 - 630
90	Visit 19	Not applicable	610 - 651	Not applicable
96	Visit 20	631 - end of double-blind period[c]	652- end of double-blind period[c]	631 - 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.

Table 7 - Visit window for safety variables in the open-label period

Week	Visit	Schedule A[a]	Schedule B[b]	Vital signs[d]
0	OL transition visit	Up to the first dose in OL period	Up to the first dose in OL period	Up to the first dose in OL period
4	OL Visit 2	after 1st open-label dose date - 56	after 1st open-label dose date - 42	after 1st open-label dose date - 42
8	OL Visit 3	Not applicable	43 - 70	43 - 70
12	OL Visit 4	57 - 126	71 - 98	71 - 126
16	OL Visit 5	Not applicable	99 - 126	Not applicable
20	OL Visit 6	Not applicable	127 - 154	Not applicable
24	OL Visit 7	127 - 210	155 -189	127 - 210
30	OL Visit 8	Not applicable	190 - 231	Not applicable
36	OL Visit 9	211 - 294	232 - 273	211 - 294
42	OL Visit 10	Not applicable	274 - 315	Not applicable
48	OL Visit 11	295 - 378	316 - 357	295 - 378
54	OL Visit 12	Not applicable	358 -399	Not applicable
60	OL Visit 13	379 – 462	400 - 441	379 - 462
66	OL Visit 14	Not applicable	442 - 483	Not applicable
72	OL Visit 15	463 - 546	484 - 525	463 - 546
78	OL Visit 16	Not applicable	526 - 567	Not applicable
84	OL Visit 17	547 - 630	568 - 609	547 - 630

Week	Visit	Schedule A[a]	Schedule B[b]	Vital signs[d]
90	OL Visit 18	Not applicable	610 - 651	Not applicable
96	OL Visit 19	631 - 714	652 - 693	631 - 714
102	OL Visit 20	Not applicable	694 - 735	Not applicable
108	OL Visit 21	715 - 798	736 - 777	715 - 798
114	OL Visit 22	Not applicable	778 - 819	Not applicable
120	OL Visit 23	799 - 882	820 - 861	799 - 882
126	OL Visit 24	Not applicable	862 - 903	Not applicable
132	OL Visit 25	883 - 966	904 - 945	883 - 964
138	OL Visit 26	Not applicable	946 - 987	Not applicable
144	OL Visit 27	967 - 1050	988 - 1029	967 - 1050
150	OL Visit 28	Not applicable	1030 - 1071	Not applicable
156	OL Visit 29	1051 - 1134	1072 - 1113	1051 - 1134
162	OL Visit 30	Not applicable	1114 - 1155	Not applicable
168	OL Visit 31	1135 - 1218	1156 - 1197	1135 - 1218
174	OL Visit 32	Not applicable	1198 - 1239	Not applicable
180	OL Visit 33	1219 - 1302	1240 - 1281	1219 - 1302
186	OL Visit 34	Not applicable	1282 - 1323	Not applicable
192	OL Visit 35	1303 - end of open-label period[c]	1324 - end of open-label period[c]	1303 - end of open-label 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 open-label period is defined as later of the last open-label visit date or before 1st dose date in the optional additional extension period.

d If remote visits, only weight will be collected for vital signs. Assessment date should be collected separately for weight and other assessments.

2.5.4 Unscheduled visits

Unscheduled MRI scans and SDMT will be assigned to the appropriate analysis window (defined in Table 4 and Table 5, Section 2.5.3). 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 6 and Table 7, Section 2.5.3) 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

An interim analysis for open label CSR is planned at core DBL (ie, approximately 28 days after last patient last visit in the double-blind period of this study).

Only data collected up to the date of core DBL will be used for this interim analysis. Analysis results will be summarized in an interim CSR for this open-label period.

Summary of patient disposition, demographics and key baseline characteristics, concomitant medications, extent of IMP exposure and compliance will be provided, as described in Section 2.2, Section 2.4.1, Section 2.4.2, and Section 2.4.3, respectively, in the interim analysis report.

For efficacy endpoints, the interim analysis will be performed for the following efficacy endpoints in which details are provided in Section 2.4.4.

- Time to first clinical relapse after randomization up to the end the open-label treatment period
- Time to first clinical relapse after enrollment of open-label period up to the end of open-label period
- Proportion of clinical relapse-free patients
- Magnetic resonance imaging (MRI) variables
  - 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, 96, 144 and 192 weeks
  - Percentage change in brain volume
- Cognitive outcome measured by the SDMT and Cognitive Battery Tests
- Annualized relapse rate
- Sustained disability progression (using EDSS).

Summary of teriflunomide PK levels at each visit will also be provided with descriptive statistics.

For safety endpoints, key safety results including TEAE, SAE, AESI, death, AEs leading to treatment discontinuation along with related laboratory values, vital signs, and Tanner scales, in which details are provided in Section 2.4.4.4 will be provided in the interim analysis report. Long-term safety data reported in the double-blind and the open-label treatment period s will also be performed for this interim CSR.

4 DATABASE LOCK

The interim database is planned to be locked approximately 28 days after last patient last visit in the double-blind period. The final database is planned to be locked approximately 28 days after last patient last visit in the open-label period of the study. This final database lock will not include patient data collected in the optional additional extension period beyond the final DBL of the study.

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. J Am Stat Assoc.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: Flow chart for open label extension 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	
	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	

Criteria for potentially clinically significant abnormalities
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Parameter	Age range	PCSA	Comments
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

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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)
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

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Parameter	Age range	PCSA	Comments
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 1.1mg/dL	
	12 years to 16/18 years old (Adolescents)	>132 µmol/L or 1.5mg/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
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

Criteria for potentially clinically significant abnormalities
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Parameter	Age range	PCSA	Comments
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)
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 to32 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
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Parameter	Age range	PCSA	Comments
Hematology			Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 2006 ; Division of Microbiology and Infectious 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 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)
	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	
	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/mm3 (1 month-2 years), 1500 to 9 500/mm^3 (2-6 years), 1500 to 8000/mm^3 (6-10 years), 1200 to 5200/mm^3 (10-18 years)
	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	
	6 to <12 years old (Children)	<1.0 GIGA/L or 1000/mm^3 >8.0 GIGA/L or 8000/mm^3	

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Parameter	Age range	PCSA	Comments
	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 >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 >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 >0.31 mmol/L or 2 g/dL	

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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	>1+	Semi-quantitative methods
Proteinuria	All age ranges	>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.

Criteria for potentially clinically significant abnormalities
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Parameter	PCSA	Comments
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.
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/1.73m^2) (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	

Criteria for potentially clinically significant abnormalities for Phase 2/3 studies (oncology excepted) (Version 3.0 May 2014)

Parameter	PCSA	Comments
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.
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	

Criteria for potentially clinically significant abnormalities
for Phase 2/3 studies (oncology excepted)
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Parameter	PCSA	Comments
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.
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.

Criteria for potentially clinically significant abnormalities
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Parameter	PCSA	Comments
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥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.
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	Categories are cumulative
	>90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative

Criteria for potentially clinically significant abnormalities
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Parameter	PCSA	Comments
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	
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 OPEN-LABEL PERIOD

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoint					
Time to first clinical relapse after randomization in double-blind period up to the end the open-label treatment period	Efficacy	Cox proportional hazard model	Kaplan-Meier methods, log-rank test	No	No
Secondary endpoints					
Time to first clinical relapse since enrollment into the open-label period up to the exit of the open-label treatment period	Efficacy	Cox proportional hazard model	Kaplan-Meier methods. Log-rank test	No	No
The proportion of clinical relapse-free patients at Weeks 24, 48, 72 and 96,	Efficacy	Kaplan-Meier methods	No	No	No
The number of new or enlarged T2 lesions, T1 Gd-enhancing lesions and new T1 hypointense lesions	Efficacy	Negative binomial regression model	No	No	No
Change from baseline in volume of T2 lesions, T1 hypointense lesions, the percentage change of brain volume;	Efficacy	Descriptive summary	No	No	No
The proportion of patients free of new or enlarged T2 lesions at Weeks 48 and 96	Efficacy	Kaplan-Meier methods	No	No	No

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Cognitive outcomes and EDSS	Efficacy	Descriptive summary	No	No	No
Disease free patient	Efficacy	Kaplan-Meier methods	No	No	No
Additional efficacy endpoints					
Annualized relapse rate	Efficacy	Poisson regression model	No	No	No
Time to sustained disability progression	Efficacy	Cox proportional hazard model	Kaplan-Meier methods	No	No

SAFETY ANALYSES IN THE OPEN-LABEL PERIOD

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

Appendix C Flow chart for open label extension period

FLOW CHART FOR OPEN LABEL EXTENSION PERIOD, FIRST 96 WEEKS

	Transition to open label	Open label treatment period																
Week (W)[a]	**Transition**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W30**	**W36**	**W42**	**W48**	**W54**	**W60**	**W66**	**W72**	**W78**	**W84**	**W90**	**W96**
Visit number[r]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Entry procedures																			
Informed consents[d] and assent	X																		
Efficacy																			
EDSS/FS							X				X				X				X
SDMT							X				X				X				X
Cognitive tests[q]																			X
Brain MRI[o]											X								X
Safety																			
Adverse event reporting[e]	<---------->																		
Vital signs[f]	X	X	X	X			X		X		X		X		X		X		X
Physical examination[s]				X			X				X				X				X
ECG 12-leads																			
Tanner[g]							X				X				X				X
Clinical routine laboratories[h, i]	X	X		X			X		X		X		X		X		X		X
Clinical safety laboratories[h, j, m]			X		X	X		X		X		X		X		X		X	
Immunoglobulins/TSH																			X
Treatments																			
Concomitant medications	X	X		X			X		X		X		X		X		X		X
Dispense study drugs/IVRS call	X		X	X			X		X		X		X		X		X		X
Accountability/compliance			X	X			X		X		X		X		X		X		X
Teriflunomide PK sampling[k]		XXX	X	X			X		X										

FLOW CHART FOR OPEN LABEL EXTENSION PERIOD, CONTINUED

	Open label treatment period																Post drug elimination follow up		Unscheduled
Week (W)[a]	**W102**	**W108**	**W114**	**W120**	**W126**	**W132**	**W138**	**W144**	**W150**	**W156**	**W162**	**W168**	**W174**	**W180**	**W186**	**W192/ EOT[b, u]**	**EOT +2W**	**EOT +4W**	**Relapse visit**
Visit number[r]	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36[c]**	**37[c]**	
Entry procedures																			
Informed consents[d] and assent																			X
Efficacy																			
EDSS/FS				X				X				X				X			X[n]
SDMT				X				X				X				X			
Cognitive tests[q]																X			
Brain MRI[o]								X								X			
Safety																			
Adverse event reporting[e]	<----------															---------->			
Vital signs[f]		X		X		X		X		X		X		X		X	X	X	X
Physical examination[s]				X				X				X				X	X		
ECG 12-leads																X	X[p]	X[p]	
Tanner[g]				X				X				X				X			
Clinical routine laboratories[h, i]		X		X		X		X		X		X		X		X			
Clinical safety laboratories[h, j, m]	X		X		X		X		X		X		X		X		X	X	
Immunoglobulins/ TSH																X			

	Open label treatment period																Post drug elimination follow up		Unscheduled
Week (W)[a]	**W102**	**W108**	**W114**	**W120**	**W126**	**W132**	**W138**	**W144**	**W150**	**W156**	**W162**	**W168**	**W174**	**W180**	**W186**	**W192/ EOT[b, u]**	**EOT +2W**	**EOT +4W**	**Relapse visit**
Visit number[r]	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36[c]**	**37[c]**	
Treatments																			
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drugs/IVRS call		X		X		X		X		X		X		X		X[t]			
Accountability/compliance		X		X		X		X		X		X		X		X			
Teriflunomide PK sampling[k]																X	X[l]	X[l]	

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 The open label period starts by the transition visit. It is recommended that there is no time gap between the 2 periods, or as short as possible and if possible less than 2 weeks. In case of start of the open label period at the end of the 96 weeks of the double-blind period, the transition visit will generally coincide with the EOT visit of the double-blind period. 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 transition visit. Post drug elimination follow-up visits should be ±7 days of scheduled visit relative to end of treatment.

b End-of-treatment and premature discontinuation visit.

c For patients 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. When applicable patients who prematurely and permanently discontinue study medication will be asked to continue until the planned end of double-blind period (ie, 96 weeks after randomization).

d Re-consent before starting open-label period and after confirmed MS relapse and when patients turn adults as per local regulations.

e 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).

f Including systolic and diastolic blood pressure, heart rate, body temperature, weight and height; 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.

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

h 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.

i The following routine parameters will be measured at transition visit if previous laboratory assessment was performed more than 4 weeks before, at 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 every 12 weeks.

j 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 treatment (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.

k 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.

l Post drug elimination procedure: samples to be collected for verification of plasma teriflunomide concentrations ≤0.02 µg/mL.

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

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

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

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

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

r The number of visits is linked to the time in the previous double blind phase as the maximum period in the study is 192 weeks. The maximum potential duration is therefore 184 weeks.

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

t IVRS only if treatment is stopped.

u An optional additional extension period with teriflunomide is offered to young patients, to provide them treatment until they are 18 years old and/or can switch to commercial product, whichever comes first.

Appendix D List of search terms for COVID-19 (MedDRA v24.0)

PT	PT codes
Asymptomatic COVID-19	10084459
Coronavirus infection	10051905
Coronavirus test	10084353
Coronavirus test positive	10070255
COVID-19	10084268
COVID-19 immunisation	10084457
COVID-19 pneumonia	10084380
COVID-19 prophylaxis	10084458
COVID-19 treatment	10084460
Exposure to SARS-CoV-2	10084456
Occupational exposure to SARS-CoV-2	10084394
SARS-CoV-2 carrier	10084461
SARS-CoV-2 test	10084354
SARS-CoV-2 test false negative	10084480
SARS-CoV-2 test positive	10084271
Suspected COVID-19	10084451
SARS-CoV-2 antibody test positive	10084491
SARS-CoV-2 sepsis	10084639
SARS-CoV-2 viraemia	10084640

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