AMENDED CLINICAL TRIAL PROTOCOL NO. 04

COMPOUND: HMR1726 (teriflunomide)

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

STUDY NUMBER: EFC11759 (TERIKIDS)

VERSION DATE / STATUS: 11 September 2019 / Approved

CLINICAL STUDY DIRECTOR: [redacted]

Version Number:	1	EudraCT	2011-005249-12
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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document history

Document	Country-specificity if applicable	Date, version
Amended protocol 04	All	11-Sep-2019, Version number: 1 (electronic 5.0)
Amended protocol 03	All	02-Aug-2018, Version number: 1 (electronic 4.0)
Amendment 4	Russian Federation only	26-Jul-2016, Version number 1 (electronic 1.0)
Amendment 3	Russian Federation only	18-Dec-2014, Version number 1 (electronic 1.0)
Amended protocol 2	All	26-Jun 2014, Version number: 1 (electronic 3.0)
Amendment 2	All	11-Jun-2014, Version number: 1 (electronic 1.0)
Amended protocol 1	All	18-Dec-2013, Version number: 1 (electronic 1.0)
Amendment 1	All	18-Dec-2013, Version number: 1 (electronic 1.0)
Original Protocol		30-May-2013, Version number: 1 (electronic 1.0)

Amended protocol 04 (11 Sep 2019)

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

Overall rationale for the amendment

The protocol is being amended to add an Additional Research of the effect of teriflunomide on biomarkers in plasma, such as the neurofilament light chain (NfL) and potentially other biomarkers (not yet identified) related to MS disease. The biomarkers will be measured from leftover plasma PK samples (when available) collected during the study. No additional blood samples will be required to be drawn from study patients for this exploratory research.

Neurofilament light chain has been shown to be a biomarker of the disease activity and tissue damage in relapsing remitting multiple sclerosis in the adult (1, 2). There is little literature in pediatric MS (3). Of note, this research will not involve genetic testing.

NfL could potentially be a marker of ongoing axonal damage. It can be measured in the blood, and may be earlier and more sensitive than MRI scan measures such as brain volume. Development of NfL in pediatric MS may contribute to optimize future MS therapies in children. NfL levels will also be analyzed in relation to clinical parameters.

Participation will be optional. The Investigator or authorized designee will explain to each participant/parents the objectives of the exploratory research, and participants/parents will provide a separate consent to participate in this exploratory analysis if they agree to participate. It will be made clear their refusal will not impact their participation in the study.

For the patients consenting to this additional research, samples will be stored in accordance to local regulations following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to teriflunomide.

With Amendment 4, leftover plasma PK samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to the disease process, pathways associated with the disease state.

The time points considered include W2, W12, W24, W36 and W96 from the double-blind period. The selection of time points may be adjusted, with potential additions from the double-blind and the open-label periods. It is anticipated to use a highly sensitive single molecule array (SIMOA) immunoassay which has recently been developed to measure NfL in plasma/serum.

Results of these exploratory biomarker analyses will be summarized in an ad hoc report separate from the main clinical study reports (CSR) of the double-blind and open-label periods.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 8.3 Biomarkers	Neurofilament light chain and other biomarkers may be evaluated from leftover plasma PK samples, which were drawn from study patients during the study and after patient/parents consent. This process is described in Appendix E.	Section to be added since decision was taken to assess biomarkers such as Neurofilament light chain in pediatric MS patients.
Section 12.3.2 Assent for optional neurofilament assessment	A dedicated informed consent form (ICF) will be prepared for the use of leftover mandatory PK samples for optional exploratory research and will be submitted to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion. The Investigator or authorized designee will explain to each participant/parents the objectives and conditions of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research.	Section to be updated since new analysis is planned
Section 16 Bibliographic references	Addition of 3 articles	
Appendix E Neurofilament light chain and non-	Participation in the exploration of the effect of teriflunomide on biomarkers in plasma such as Neurofilament light (NfL) chain and potentially other non-	To keep this amendment as simple as possible since it concerns only exploratory analyses of the Neurofilament light chain

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Section # and Name	Description of Change	Brief Rationale
genetic biomarkers processing	genetic biomarkers related to MS disease is optional and does not involve genetic testing. No additional blood samples will be required to be drawn from study patients for this exploratory research. The Investigator or authorized designee will explain to each participant/parents the objectives of the exploratory research, and participants/parents will have to provide a separate consent to participate in this exploratory analysis if they agree to participate. It will be made clear their refusal will not impact their participation in the study NfL and other non-genetic biomarkers will be assessed from leftover plasma PK samples (when available), collected during the study for all the patients who consented, at the following time points: W2, W12, W24, W36 and W96 for the double-blind period. Additional time points of the double-blind and the open-label may be potentially included. A highly sensitive single molecule array (SIMOA) immunoassay which has recently been developed to measure NfL in plasma/serum will be used. For the patients consenting to this research, samples will be stored in accordance with local regulations at a facility selected by the Sponsor to enable further analysis of biomarker responses to teriflunomide. Results of these exploratory biomarker analyses will be summarized in an ad hoc report separate from the main CSRs of the double-blind and open-label periods.	biomarker and potentially others without any impact on the patient safety, decision was taken to describe this additional research in an appendix.
Appendix G Protocol amendment history	Inclusion of reason for amended protocol 3 (02 August 2018)	

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CLINICAL TRIAL SUMMARY

COMPOUND: HMR1726 STUDY No:EFC11759 STUDY NAME: TERIKIDS	
TITLE	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
INVESTIGATOR/TRIAL LOCATION	Multinational
PHASE OF DEVELOPMENT	Phase III
STUDY OBJECTIVE(S)	**Primary Objective:** 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 **Secondary Objective(s):** • 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.
STUDY DESIGN	Multicenter, multinational, randomized, double-blind, placebo control, parallel group. **The study will consists of:** • A screening period up to 4 weeks. • A double-blind treatment period of up to 96 weeks for each patient, including a double-blind period and potentially an open label period. • An open-label period including the remainder of the initial 96 weeks, 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. **Double-blind treatment period of up to 96 weeks per patient:** • Patients are randomized to either teriflunomide or placebo at 2:1 ratio (110 patients on teriflunomide vs. 55 patients on placebo). • Blinded treatment phase begins at randomization and continues to Week 96 or when patient experiences a first relapse or high MRI activity. • It includes a blinded PK run-in phase (8 weeks) consisting of 4 weeks with PK sample collection plus 4 weeks of analysis (corresponding to the first 8 weeks after randomization). The PK run-in (8 weeks) phase is intended to provide individual PK parameters to allow the dose adjustment to the 14mg adult-equivalent dose for the rest of the study.
	• Patients experiencing a relapse after the PK run-in period (8 weeks)

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	and if confirmed by the Relapse Adjudication Panel (RAP) or high MRI activity as defined below or completing the 96-week period will have the option to continue in the open label period. • Evaluation of high MRI activity 1) If 5 or more new/enlarged T2 lesions at Week 24, an additional MRI will be performed at Week 36. 2) Criteria for high MRI activity to qualify for switch to open label treatment: • At least 9 new/enlarged T2 lesions at Week 36 or • At least 5 new/enlarged T2 lesions on each of 2 consecutive MRI scans at Week 36 and Week 48, or at Week 48 and Week 72. (Note: new/enlarged since previous scan) **Open-label period:** The open-label period will follow the double-blind period and last until 192 weeks after randomization. Its duration for a given patient will depend on when the patient enters this period. The duration of the open-label period will be 96 weeks for patients completing the 96-week double-blind period on treatment, and longer for patients switching to open-label during the initial 96 week double-blind period at the occurrence of a confirmed relapse or in case of high MRI activity. It includes a blinded PK run-in phase (8 weeks, similarly to the double-blind period). **Optional additional extension period for young patients:** A treatment extension period with teriflunomide will be proposed to patients too young to access commercialized teriflunomide as per authorized indication when completing the 192-week treatment period, until they become adult or until they are able to switch to commercial product, whichever comes first. **Follow up period for patients who discontinue:** Upon discontinuation of the study treatment (either by early termination or not), patients who will not be treated with teriflunomide post-study will be required to perform an accelerated elimination procedure within a 4 week follow up period. Two Clinical Study Reports (CSR) will be issued: • The first CSR will report the final analysis of the double-blind treatment period.The study methods described in this document primarily relate to this treatment period and analysis. • The second CSR will report the analysis of the open-label data at the conclusion of the extension period for all included patients. The data for the optional additional extension period for young patients will be reported separately.

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STUDY POPULATION **Main selection criteria**	**Inclusion Criteria:** • Patients with diagnosis of relapsing MS based on McDonald criteria of 2010 and International Pediatric Multiple Sclerosis Study Group criteria for pediatric MS and have: - At least one relapse (or attack) in the 12 months preceding screening, or, - At least 2 relapses (or attacks) in the 24 months preceding screening. • <18 years of age and ≥10 years of age at randomization Specific for the Russian Federation from 18 December 2014 to 26 July 2016, ≤17 years of age and ≥13 years of age at randomization. • Signed informed consent/assent obtained from patient and patient's legal representative (parents or guardians) according to local regulations. **Exclusion Criteria:** • EDSS score >5.5 at screening or randomization visits. • Relapse within 30 days prior to randomization. • Treated with: - Glatiramer acetate, interferons, or dimethyl fumarate within 1 month prior to randomization, - Fingolimod, or intravenous immunoglobulins within 3 months prior to randomization, - Natalizumab, other immunosuppressant or immunomodulatory agents such as cyclophosphamide, azathioprine, cyclosporine, methotrexate, mycophenolate, within 6 months prior to randomization, - Cladribine or mitoxantrone within 2 years prior to randomization. • Treated with alemtuzumab at any time. • History of HIV infection. • Contraindication for MRI. • Pregnant or breast-feeding females or those who plan to become pregnant during the study. • Female patients of child-bearing potential not using highly effective contraceptive method (contraception in both female and male is required).
Total expected number of patients **Expected number of sites:**	165 children and adolescents of either gender <18 years of age and ≥10 years of age (including approximately 20% pre-pubertal patients or 10% of patients under the age of 13 years at the time of inclusion into the study and at least 25% male patients): • 55 patients on placebo. • 110 patients on teriflunomide. Approximately 100 sites.

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STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation**	**Teriflunomide:** Matching film-coated tablets containing either • 3.5 mg of teriflunomide or, • 7 mg of teriflunomide or, • 14 mg of teriflunomide. **Placebo:** Matching placebo tablets During the PK run–in period including the 4 weeks analysis (corresponding to the first 8 weeks of the study): 7mg adult equivalent, QD: • For patients 30 ± 10 kg: - 1 teriflunomide tablet (3.5 mg) per day (QD). • For patients >40 kg: - 1 teriflunomide tablet (7 mg) per day (QD). After the end of the PK run-in (8 weeks) phase:14mg adult equivalent, QD: If individual predicted PK parameters are equal to or less than the 95th percentile of adult range of predicted PK parameters (repeated doses of 7 mg): • For patients 30 kg ± 10 kg - 1 teriflunomide tablet (7 mg) per day (QD). • For patients >40 kg - 1 teriflunomide tablet (14 mg) per day (QD). If individual predicted PK parameters are higher than the 95th percentile of the adult range of predicted PK parameters (repeated doses of 7 mg): • For patients 30 kg ± 10 kg - 1 teriflunomide tablet (3.5 mg) per day (QD). • For patients >40 kg - 1 teriflunomide tablet (7 mg) per day (QD). Adult range (5th - 95th percentile) of predicted PK parameters: 7 mg dose range for C_{max} is 8.03 to 49.1 μg/mL and for AUC_{0-24} is 184 to 1160 μg.h/mL (POH0339) **Optional additional extension period for young patients:** 1 teriflunomide tablet (14 mg) per day (QD). Based on Investigator's judgment, for patients less than 40 kg, dose could be adjusted to 14 mg every other day.
Route(s) of administration	Oral
Dose regimen	One per day with or without food preferably at the same time each day.
Noninvestigational medicinal product(s) (if applicable)	Cholestyramine or Activated charcoal (only for patients undergoing accelerated elimination procedure after last dose who will not be treated with teriflunomide anymore).
Route(s) of administration	Oral

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ENDPOINT(S)	**Primary Endpoint:** • Time to first clinical relapse after randomization. **Secondary Endpoints:** • Proportion of relapse free patients at 24, 48, 72 and 96 weeks. • MRI endpoints: - Number of new/newly enlarged T2 lesions, - Number of T1 Gd-enhancing T1 lesions, - Change in volume of T2 lesions, - Change in volume of T1 hypointense lesions, - Number of new T1 hypointense lesions, - Proportion of patients free of new or enlarged MRI T2-lesions at 48 weeks and 96 weeks, - Brain atrophy. • The number of new/newly enlarged T2 lesions and the number of T1 Gd-enhancing T1 lesions will be considered the key secondary imaging endpoints. • Cognitive outcome measured by SDMT and a Cognitive Battery Test which will include TMT-A and B, SRT, Beery VMI, D-KEFS Fluencies (Letter and Category); BVMTR and WASI Vocabulary as available. • Teriflunomide PK. • Exploratory endpoint: proportion of disease-free patients.
ASSESSMENT SCHEDULE	**Efficacy: referring to the 96-week double-blind period** • Clinical relapses. • EDSS: screening, randomization, after relapse, every 24 weeks and at EOT. • Cognitive battery: randomization and EOT. • SDMT: randomization, every 24 weeks and at EOT. • MRI: baseline (a previous MRI performed in the 6 weeks preceding randomization could be acceptable if performed according to the specifications for this study), 24, 36 (if criteria is met at Week 24), 48, 72 and 96 weeks. **Safety and tolerability: referring to the 96-week double-blind period** • AE reporting at each visit. • Physical examinations: screening, randomization, Weeks 12, 24, and every 12 weeks, EOT or early treatment discontinuation and at EOT +2W. • Vital signs: screening, randomization Weeks 4, 8, 12, 24, and every 12 weeks while on treatment, at EOT or early treatment discontinuation, at EOT+2W and at EOT+4W, and after relapse. • Tanner stage: at baseline, every 24 weeks and EOT (until complete sexual maturity defined by Tanner Stage 5). • Clinical laboratories: screening, randomization, Weeks 4, 8, 12, 16, 20, 24, then every 6 weeks up to EOT or early treatment discontinuation, at EOT + 2W and at EOT + 4W.

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	• Serum immunoglobulin (IgG, IgM and IgA) measurements at randomization and every 24 weeks. In addition if a patient has a vaccination, antibody titers will be assessed before and after vaccination (only inactivated vaccines are allowed during study). • TSH: at randomization and every 24 weeks. • Peripheral neuropathy: neurological symptoms suggestive of a peripheral neuropathy (confirmed with electrophysiological diagnosis including nerve conduction). • ECG: baseline, and at EOT or early treatment discontinuation • In case of suspected infection, all efforts must be made to determine an etiology using the best medical judgment (clinical signs and symptoms, laboratory data, imaging findings). **Pharmacokinetics:** • Blood sample collected to determine teriflunomide plasma concentrations: - During the 4-week PK run-in (8 weeks) period, at least 3 PK samples will be collected (at Weeks 2, 3 and 4). • Patients entering the open label period will have to re-do the PK run-in (8 weeks) which requires additional PK samples, if needed corresponding to Weeks 2, 3 and 4 of open-label treatment. • After PK run-in (8 weeks) period in the 96-week double-blind treatment phase, PK samples will be taken at Weeks 8, 12, 24, 36 and EOT. • A sample will be collected at both follow up visits (EOT+2W and EOT+4W) to check if accelerated elimination procedure was successful. Both samples will be used to verify that teriflunomide plasma concentration is less or equal to 0.02 µg/mL. Additional samples may be required to ensure that teriflunomide plasma concentration has reached a level of ≤0.02 µg/mL.
STATISTICAL CONSIDERATIONS	**Sample size determination:** In the combined, completed Phase 3 monotherapy adult studies (EFC6049/TEMSO and EFC10531/TOWER), 58.7% of placebo patients aged ≤30 (n=167) experienced at least 1 relapse versus 38.7% in the teriflunomide 14 mg group (n=163) in a 2-year treatment period. For the current study, assuming 60% of placebo patients will experience a relapse by 2 years, given a 2:1 teriflunomide to placebo randomization ratio, 165 patients (110 teriflunomide and 55 placebo) would be 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 and power are calculated using nQuery Advisor 7. The sample size is adjusted assuming 20% of patients discontinue the study in 2 years due to reasons other than relapse. **Randomization:** Patients will be randomly assigned to receive either teriflunomide or placebo in a 2:1 randomization ratio. Randomization will be stratified by the country in which the patient is being treated and patient's pubertal status.

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	Analysis dataset: The data from the placebo-controlled and the open label teriflunomide treatment phases will be the focus of the two respective CSRs. The following statistical methods/considerations relate to the analysis of the data from the placebo-controlled period. The data from the open label teriflunomide treatment arm are non-controlled and supportive in nature; summary statistics will be provided for each of the efficacy variables and safety data **Analysis population:** The analysis population for efficacy endpoints will be the intent-to-treat (ITT) population, defined as all randomized patients who received at least 1 dose of study medication. All patients will be analyzed according to the treatment to which they are randomized. The analysis population for safety endpoints will be the safety population, defined as all randomized patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment patients actually received. **Analysis of the primary endpoint:** Time to first confirmed relapse from randomization (including relapses during the PK run-in (8 weeks) phase) to last study drug administration will be analyzed using a log-rank test with time to first relapse as the dependent variable, treatment group as a test variable, and region and pubertal status as covariates. Treatment effect as measured by the hazard ratio and its associated 95% confidence interval will be estimated using a Cox proportional-hazards model with adjustment for treatment group, region, pubertal status, age, and number of relapses in the year prior to randomization. The following sensitivity analyses for the primary endpoint will be performed using the similar log-rank test and Cox proportional-hazards model as described above. • Time to first confirmed relapse occurring after the PK run-in (8 weeks) phase but before the treatment discontinuation. The patients who have a relapse during the PK run-in (8 weeks) phase will be included in the analysis with the time to first relapse right censored at the time of treatment discontinuation. • Time to first relapse (confirmed or not) after randomization during the study treatment. • Time to first confirmed relapse including relapses during the PK run-in (8 weeks) phase and relapses reported after the study drug discontinuation and up to 96 weeks after randomization. • Time to first confirmed relapse including high MRI activity (ie, meeting criteria for switching into open-label period) as equivalent to a confirmed relapse event. **Analysis of secondary endpoints:** The proportion of patients relapse-free at Weeks 24, 48, 72 and 96 will be estimated based on Kaplan-Meier methods. Interval estimates will be calculated using 95% point wise confidence intervals. The number of new or enlarged T2-lesions per MRI scan will be analyzed using a negative binomial regression model. 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 estimated

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	number of lesions per scan and associated 2-sided 95% confidence interval (CI) will be provided for each treatment group. The relative risk, 2-sided 95% CI and p-value will be provided for comparing teriflunomide to placebo. The number of T1 Gd-enhancing lesions per MRI scan and the number of new T1 hypointense lesions per MRI scan will be analyzed using a similar negative binomial regression model as described above for T2 lesions. To reduce the impact of potential outliers, ordinal logistic regression model including treatment group, region, pubertal status and age will also be used to analyze these endpoints. The following categories for the number of lesions, 0, 1, 2, 3-4 and ≥5 are considered and will be further defined in the SAP. Change from baseline in volume of T2 lesions, T1 hypointense lesions and brain atrophy will be analyzed using a mixed-effect model with repeated measures (MMRM) approach with appropriate transformation if necessary. The proportion of patients free of new or enlarged T2 lesions at Weeks 48 and 96 will be summarized based on all patients having an MRI at these time points. The change from baseline in cognitive outcomes will be analyzed descriptively. **Multiplicity adjustment procedure:** • Statistical significance will be claimed for the primary efficacy endpoint if the computed p-value from the primary analysis is ≤0.05. No multiplicity adjustment is considered for secondary efficacy outcomes for this study. **Missing data handling:** Given the time to event analysis methodology, there is no impact on the analysis of the primary endpoint for patients experiencing a first relapse and moving to open label teriflunomide treatment. Patients discontinuing double-blind treatment due to high MRI activity will be censored at discontinuation. Patients who prematurely discontinue the study drug will be encouraged to continue study follow-up as planned according to the study flowchart. Missing data due to patient's discontinuation from the study drug, therefore, should be greatly reduced. The main analysis for time to first relapse will include relapses during the study treatment. The relapses reported after the study drug discontinuation will be included for supportive analyses. **Safety analyses:** The incidence of treatment emergent adverse events (TEAEs), deaths, serious adverse events (SAE), AEs leading to treatment discontinuation, and adverse event of special interest (AESI), will be summarized by treatment group using counts and percentages. Analyses of laboratory data, vital signs and ECG will focus on descriptive statistics and summaries of pediatric potentially clinically significant abnormality (PCSA) values. Patients with peripheral neuropathy finding or abdominal findings compatible with pancreatitis will be summarized by treatment group using counts and percentages. For the optional additional extension period for young patients, the efficacy and safety data will be summarized by descriptive statistics.

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DURATION OF STUDY PERIOD (per patient)	Screening: up to 4 weeks. Double-Blind Treatment Period: up to 96 weeks total. Open-Label period: after completion/discontinuation of double-blind period for the remainder of 192 weeks. Optional additional extension period for young patients: after the open-label period until the patients are 18 years and/or able to switch to commercial product, whichever comes first. It will be implemented in France and possibly other countries where local solutions are not possible within a reasonable time frame. Follow-up period: 4 weeks. Further follow-up may be required to ensure that teriflunomide plasma concentration has reached a level of ≤0.02 µg/mL.
STUDY COMMITTEES	**Data Monitoring Committee**: Yes A Data Monitoring Committee (DMC), independent from the Sponsor and Investigators, will monitor and review all relevant data on a regular basis for the assessment of benefit versus risk and provide recommendations about further conduct of the trial. **Adjudication Committee**: Yes A Relapse Adjudication Panel will review all relapses reported during the double-blind period in a blinded fashion in order to confirm whether a subject has experienced a protocol-defined relapse.

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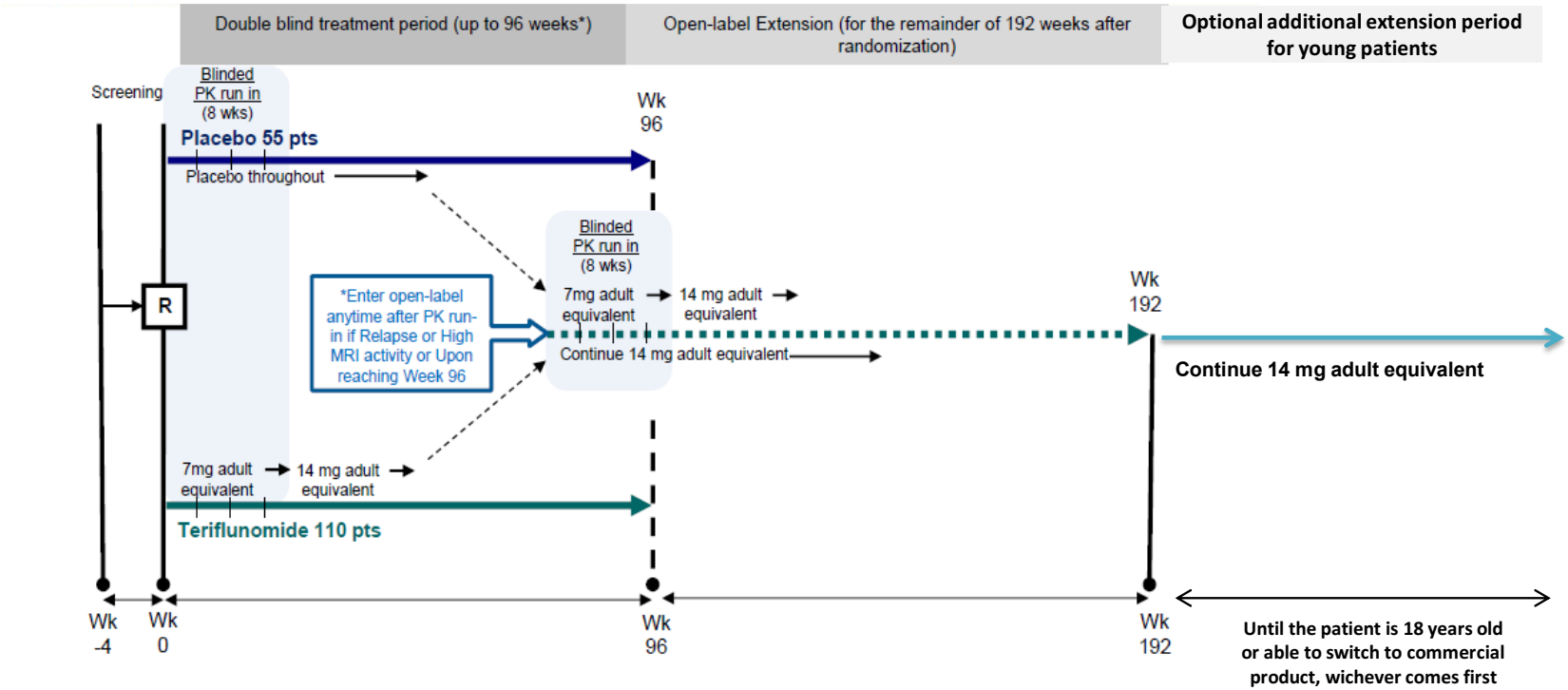
1.1



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.

1.2 STUDY FLOW CHART FOR THE DOUBLE BLIND TREATMENT PERIOD

	Baseline		Treatment period																		Post drug elimination follow up		Unscheduled
Week (W)[a]	W-4	Rand[b]	W4	W8	W12	W16	W20	W24	W30	W36	W42	W48	W54	W60	W66	W72	W78	W84	W90	W96/ EOT	EOT +2W	EOT +4W	Relapse visit [v]
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20[c]	21[d]	22[d]	
Entry procedures																							
Informed consents[e] and assent	X																						X[e]
Review inc/excl criteria	X	X																					
Demographics	X																						
Medical/surgical history	X																						
Tuberculosis test[s]	X																						
Prior medications	X	X																					
Randomization		X																					
Efficacy																							
EDSS	X	X						X				X				X				X			X[p]
SDMT		X						X				X				X				X			
Cognitive Battery Test[u]		X																		X			
Brain MRI [q]	X[f]							X				X				X				X			

	Baseline		Treatment period																		Post drug elimination follow up		Unscheduled
Week (W)[a]	W-4	Rand[b]	W4	W8	W12	W16	W20	W24	W30	W36	W42	W48	W54	W60	W66	W72	W78	W84	W90	W96/ EOT	EOT +2W	EOT +4W	Relapse visit [v]
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20[c]	21[d]	22[d]	
Safety																							
Adverse event reporting[g]		<- - - -

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

t The date of first menarche should be captured if applicable

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

v IVRS only if treatment is stopped

Please refer to Section 10 for details.

1.3 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]	<- - - -

1.4 FLOW CHART FOR OPEN LABEL 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	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]	<- - - -

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.

1.5 FLOW CHART FOR OPTIONAL ADDITIONAL EXTENSION PERIOD FOR YOUNG PATIENTS

	Optional additional extention period for young patients											Post drug elimination follow-up		Unscheduled
Week (W) [a]	**Transition visit W192/EW1**	**EW24**	**EW48**	**EW72**	**EW96**	**EW120**	**EW144**	**EW168**	**EW192**	**EW216**	**EOT**[b]	**EOT +2W**	**EOT +4W**	**Relapse visit**
Visit number	**EV1**	**EV2**	**EV3**	**EV4**	**EV5**	**EV6**	**EV7**	**EV8**	**EV9**	**EV10**	**EV11**	**EV12**[c]	**EV13**[c]	
Entry procedures														
Informed consents [d] and assent	X													
Efficacy														
Routine neurologic exams	X	X	X	X	X	X	X	X	X	X	X			X
Brain MRI[e]	X		X		X		X		X		X			
Safety														
Adverse event reporting[f]	<- - - -

c For patients prematurely 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.

d Re-consent before starting optional additional extension period for young patients.

e If patient is treated with steroids the MRI should be performed after 14 days discontinuation of the steroids. No central reading for MRI is planned in the optional additional extension period.

f 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).

g 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.

h Standard liver function test and hematology tests to be performed every 6 weeks (specific panel to be decided by Investigator). These tests will be performed in local laboratories. Clinical relevant abnormalities should be reported as TEAEs (Refer to Section 9.10.2.1). Other data will not be entered in eCRF.

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

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2 LIST OF ABBREVIATIONS

ACTH:	adrenocorticotrophic hormone
ADEM:	acute disseminated encephalomyelitis
AE:	adverse event
AEPM:	adverse event of pre-specified monitoring
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ARR:	annualized relapse rate
BP:	blood pressure
BVMI:	beery visual-motor integration
BVMTR:	brief visuospatial memory test revised
CBT:	cognitive battery tests
CI:	confidence interval
CSR:	clinical study report
D-KEFS:	Delis-Kaplan executive function system
DMC:	data monitoring committee
ECG:	electrocardiogram
EDSS:	expanded disability status scale
EOT:	end of treatment
EPTD:	early permanent treatment discontinuation
FS:	functional system
GCP:	Good Clinical Practice
GMP:	good manufacturing practice
HIV:	human immunodeficiency virus
HLGT:	high-level group term
HLT:	high level term
HR:	heart rate
ICH:	International Conference on Harmonization
IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
INR:	international normalized ratio
IPMSSG:	international pediatric multiple sclerosis study group
IRB:	institutional review board
ISG:	independent statistical group
ITT:	intent-to-treat
IVRS/IWRS:	interactive voice/web response system
JRA:	juvenile rheumatoid arthritis
LLOQ:	lower limit of quantification
MedDRA:	Medical Dictionary for Regulatory Activities
MRI:	magnetic resonance imaging or magnetic resonance image
MS:	multiple sclerosis

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NfL:	neurofilament light
NSAID:	non-steroidal anti-inflammatory drugs
PCSA:	potentially clinically significant abnormalities
PK:	pharmacokinetic
PT:	preferred term
RAP:	relapse adjudication panel
RMS:	relapsing multiple sclerosis
SAE:	serious adverse event
SAP:	statistical analysis plan
SDMT:	symbol digit modalities test
SGPT:	serum glutamate pyruvate transaminase
SOC:	system organ class
SRT:	selective reminding test
T2:	T2-weighted hyperintense lesions
TEAE:	treatment emergent adverse event
TID:	three times a day
TMT-A and B:	trail-making test A and B
ULN:	upper limit of normal
WASI:	Wechsler abbreviated scale of intelligence vocabulary
WBC:	white blood cell
WOCBP:	woman of child bearing potential

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3 INTRODUCTION AND RATIONALE

3.1 INTRODUCTION

3.1.1 Pediatric Multiple Sclerosis

Multiple sclerosis (MS) is typically considered to be a disease of young adults. However, pediatric MS, defined as onset of MS before the age of 16, is increasingly recognized and accounts for approximately 5 percent of cases, (4, 5, 6). This disorder was previously known as early onset MS and juvenile MS.

Multiple sclerosis in children and differences from the common adult MS form to a large extent are understudied. There is no approved disease modifying therapy indicated for the treatment of pediatric MS and the effects of drugs in children have not been formally evaluated in clinical trials. The current treatment and prognosis of pediatric MS are based on that of adult patients, because data are limited in pediatric MS and it is assumed that the disease response in children is likely to be similar (7, 8, 9, 10). Considering the multiple toxicities that characterize the currently used treatment for MS in children, development of an effective and well-tolerated therapy for the indication continues to be a major challenge.

In children, MS needs to be distinguished from other demyelinating disorders of childhood, including in particular acute disseminated encephalomyelitis (ADEM). Consensus definitions for pediatric MS have been proposed by multidisciplinary panels (8, 9, 10, 11, 12, 13).

In general, clinical features are not different from those of the adult form, but some are more frequent in comparison with adult MS:

- Onset with cerebellar and brainstem dysfunction (6, 10).
- Polysymptomatic presentation, with fever, headache, lethargy, meningism, seizures (acute disseminated encephalomyelitis-like onset), especially in very young patients (6).
- Evolution with a high number of relapses, specially in the first years of the disease, and an annualized relapse rate of 1–1.9, which is higher than in adult MS (6, 13, 14, 15).
- Evolution, with a predominance of the relapsing–remitting course, in more than 90% of cases, and the very low frequency of the primary progressive course (6).
- Development of progression, over a longer interval but a lower age to reach both mild and severe disability (14).

Despite slow accrual of motor disability relatively to adult patients, cognitive impairment has been found after 2 years in 70% of children with MS (16). Consequently a great need exists for early and accurate diagnosis of MS in this population, so that effective therapies can be initiated promptly.

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Specificities of MS in children also lie in their environment. The onset of MS in childhood typically occurs during the key formative years. It might restrict school attendance and has the potential to negatively affect the developing neural connections implicated in learning and higher-order information processing. Fatigue may also have a great impact on activities and development.

3.1.2 Teriflunomide

Teriflunomide inhibits dihydroorotate dehydrogenase, the fourth enzyme in the de novo synthesis pathway of pyrimidines. Activated T-lymphocytes utilize both the de novo pyrimidine and salvage pathways of pyrimidine ribonucleotide synthesis. After mitogen stimulation, teriflunomide inhibits in vitro T cell proliferation, DNA and RNA synthesis and expression of cell surface and nuclear antigens that are directly involved in T cell activation and proliferation. Teriflunomide is the primary metabolite of leflunomide (Arava®), which is marketed worldwide for the treatment of rheumatoid arthritis.

Please refer to the current Investigator Brochure for detailed information.

3.1.2.1 Clinical efficacy in adult MS patients

The main development program for teriflunomide in adult patients aims at evaluating the benefits and risks of teriflunomide, administered orally at 7 mg or 14 mg once a day, as monotherapy in the treatment of relapsing forms of MS (RMS).

The teriflunomide monotherapy program included one Phase 2 study, 2001, and four Phase 3 studies.

In the first pivotal Phase 3 study, EFC6049/TEMSO in RMS patients, both doses of teriflunomide (7 and 14 mg) significantly reduced annualized relapse rate (ARR; primary study endpoint) by 31% vs. placebo ($p \leq 0.0005$). Teriflunomide 14 mg significantly reduced the risk of disability progression (sustained for 12 weeks) by 30% ($p=0.03$). Teriflunomide was well tolerated at both doses.

In the second confirmatory Phase 3 study, EFC10531/TOWER, the ARR was reduced by 36.3% in teriflunomide 14 mg ($p=0.0001$) dose and by 22.3% ($p=0.02$) in teriflunomide 7 mg dose compared to placebo. Teriflunomide 14 mg significantly reduced the risk of disability progression sustained for 12 weeks by 31.5% ($p=0.0442$). Teriflunomide was well tolerated with a manageable safety profile on both doses and no new or unexpected safety signal was identified in this study.

Teriflunomide is approved for adult indication in RMS or RRMS in several countries (including the USA and the European Union), and is under review in other countries world-wide.

3.1.2.2 Clinical safety in adult MS patients

In the teriflunomide development program, the cumulative exposure to the product in the monotherapy trials was over 6200 patient-years.

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In the Phase 2/3 monotherapy completed placebo-controlled trials, 2430 patients with RMS were treated with either teriflunomide 7 mg (838 patients) or 14 mg (786 patients) compared to 806 patients who were exposed to placebo. The median treatment exposure was approximately 680 days across treatment groups.

A total of 2284 patients were exposed to teriflunomide 7 mg and 14 mg with a maximum exposure of up to 11.1 years either during the placebo-controlled phase or the extension phase with a median duration of 2.1 years.

Safety data from the ongoing studies were consistent with the findings from the monotherapy trials and support the overall safety conclusions.

Fatal outcome was reported in a total of 13 patients during the entire development program to date: 5 deaths occurred in placebo-controlled studies, 8 additional deaths were reported in long term extension studies.

The causes of death were pulmonary infection, and completed suicide in the placebo group, road traffic accident, myocardial infarction, death of unknown cause probably due to MS, and sudden death of unknown cause in the 7 mg teriflunomide group, and carbon monoxide poisoning (completed suicide), septicemia due to Gram-negative organism complicated with disseminated intravascular coagulation disorder, sudden cardiac disorder, acute heart failure, pulmonary embolism, and 2 completed suicides in the 14 teriflunomide group.

All of the cases have a plausible explanation. There was no evidence that teriflunomide was a causative factor in the events leading to deaths.

During the placebo-controlled phase, treatment-emergent adverse event (TEAE)s were balanced across treatment groups while the percentages of patients with TEAE leading to treatment discontinuation were reported with a slightly higher incidence in the teriflunomide groups. The most frequently reported TEAEs with an increased incidence with teriflunomide as compared to placebo were: alopecia, nausea, diarrhea, and alanine aminotransferase (ALT) increased. Most cases of alopecia were reported as hair thinning, decreased hair density, hair loss, associated or not with hair texture change with a dose-effect. There was no complete hair loss reported in the entire clinical program. Most cases were mild to moderate, reported during the first 6 months, lasting for about 4 months, and resolving without corrective therapy, while the patients continued the study treatment.

Events of nausea and diarrhea were reported with a higher frequency in both teriflunomide groups than in the placebo with a dose effect. They appeared early after initiation of treatment. They were rarely considered as serious and led to treatment discontinuation in only a few patients.

There was no signal for hepatic toxicity in pre-clinical studies. Mild increases in transaminases, ALT below or equal to 3 x upper limit of normal (ULN), were more frequently seen in teriflunomide-treated groups as compared to placebo. The frequency of elevations above 3 x ULN and higher was balanced across treatment groups.

Overall, the clinical trial data does not provide evidence for an increased risk of clinically relevant drug induced liver injury with teriflunomide.

Pancreatic disorders were reported with low incidences, were balanced across treatment groups and led to treatment discontinuation in few patients.

A mean decrease in white blood cell (WBC) counts was observed (mainly neutrophil and lymphocyte count decrease) with a small dose response. The mean decrease occurred during the first 6 weeks, followed by stabilization over time on-treatment, with a magnitude not exceeding 15%. The mean decrease was less pronounced in hemoglobin (≤3%) and platelets (<10%) as compared to baseline.

Infections were the most frequently reported TEAEs in placebo-controlled studies. A low and similar incidence of serious infections was reported across groups (2.5%, 2.4% and 2.5% in the placebo, 7 mg, and 14 mg groups, respectively). The incidence of infections leading to treatment discontinuation was similar across all groups.

The clinical data collected to date do not suggest an increased risk of severe allergic reactions with the use of teriflunomide

In placebo-controlled studies, BP elevations were more frequent on teriflunomide as compared to placebo. The analysis of BP measurements over the 2-year treatment period in placebo-controlled studies showed a higher mean change from baseline with teriflunomide as compared to placebo Patients who developed hypertension on teriflunomide treatment were usually well controlled with the introduction of or modification of antihypertensive treatment. This was also true for the experience in the long term extension studies.

There was no clinical evidence for pulmonary toxicity in the available clinical data Events potentially related to peripheral neuropathy were reported in all treatment groups A modest increase in uric acid elimination, resulting in a 20% to 30% decrease in mean plasma levels of uric acid, was observed. The uricosuric effect was considered to be most probably due to an increase in renal tubular uric acid elimination. There was no evidence for an increased risk of urolithiasis or any other clinically relevant consequence of this effect.

Non clinical studies conducted with teriflunomide showed embryofetal toxic effects in rats and rabbits.

In clinical studies no structural defects were observed in 30 delivered healthy babies (17 from patients and 13 from female partners of male patients treated with teriflunomide).

Overall, the available safety data suggested that both doses of teriflunomide 7 mg and 14 mg administered in clinical studies in patients with RMS were generally well tolerated with a manageable safety profile.

3.1.2.3 Non-clinical juvenile toxicity program

Two studies in juvenile animals were performed in juvenile rats to support dosing in children in this study: a 2-week range-finding toxicity study in juvenile rats, followed by 7-week toxicity study in juvenile rats. When teriflunomide was administered to juvenile rats for 7 weeks, no new toxicities were identified that were not previously seen in adult animals. There were no adverse effects on growth, physical or neurological development, learning and memory, locomotor activity, sexual development, or fertility. Changes in hematology and clinical chemistry included minimal effects on erythron parameters, minimal decreases in total protein and globulin concentrations, minimal increases in total cholesterol concentrations, and increased triglyceride concentrations. Microscopic changes were observed in the spleen (increased incidence and/or severity of hemopoiesis and a very minor reduction of lymphoid hyperplasia), mesenteric and mandibular lymph nodes and gut-associated lymphoid tissue (minor reduction in germinal follicles). Marked changes in immune function included failure to mount an appropriate immune response after 2 challenges with Keyhole Limpet Hemocyanin (KLH) immunization, greatly reduced concentrations of total IgM and IgG, and markedly increased B lymphocyte counts. At the end of the recovery period, all teriflunomide-related findings showed partial or complete recovery. Further details can be found in the current Investigator Brochure.

3.1.2.4 Proposed pediatric study

None of the currently approved treatments for adult relapsing MS have been formally studied for the treatment of pediatric MS. Once a day tablet of teriflunomide may offer several advantages over parenteral medicinal products currently used in treatment for MS in children. Orally administered teriflunomide may avoid the stress on children and their caregivers that is associated with repeated injections as well as flu-like symptoms following each injection (fever, chills, headache, muscle aches and pains) which occur with all interferons, and the injection site reactions observed with glatiramer acetate.

The high number of relapses in the first years of the disease, and the high frequency of patients with the relapsing-remitting course suggest that the inflammatory process is more pronounced in children with MS compared to adults. This pattern is also suggested by the frequent pleocytosis in the cerebrospinal fluid (CSF) (17), and by MRI (18, 7). It seems reasonable to expect that drugs targeting the inflammatory process could have a positive beneficial effect in pediatric patients with MS similar to adult patients with MS. Further, with profound effects seen on MRI lesions in adults, effects on relapses and disease progression are also expected to be similar in a pediatric population.

In summary, the benefit risk profile of teriflunomide has already been shown to be favorable in an adult population in the Phase 3 placebo-controlled studies of the monotherapy program. Teriflunomide has demonstrated advantages in adult relapsing forms of MS patients in reducing frequency of relapse rate, disease progression, and MRI activity.

The objectives of the proposed clinical pediatric development program are to assess the efficacy, safety/tolerability, and pharmacokinetics (PK) of teriflunomide in children and adolescents 10 to below 18 years of age with relapsing forms of multiple sclerosis (RMS). This study will have a

double blind placebo control period. Patients who experience a confirmed relapse after 8 weeks in the double blind period or high MRI activity as defined in protocol may continue in an open label teriflunomide treatment arm. 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. It will be implemented in France, and possibly other countries, where local solutions for continued teriflunomide treatment are not possible within a reasonable time frame. Details of the study design are described in Section 1.1.

3.2 RATIONALE

3.2.1 Population rationale

In adults, the prevalence of MS is close to 50/100,000 on average.

The frequency of MS onset before the age of 16 years is estimated at 2-5 % of all cases, and onset during infancy and early childhood was observed in 0.2-0.7 % of all cases (6, 13). Chitnis et al (11) recently described the disease characteristics of pediatric MS patients in the United States. Physician records of all MS patients seen at the Partners Multiple Sclerosis Center, Brigham and Women's Hospital (Boston, MA), from 2002 to 2008 were recorded in an electronic database and included in this study. It was found that 3.06% (135 / 4399) of their patients experienced first symptoms before the age of 18. Of those, 10% (ie, 0.3% of all cases) experienced onset between 10 and 12 years of age (compared with 87% with onset between 13 and 17).

The last updated survey administered in March 2012 among 76 IPMSSG respondents from 64 sites in 25 countries identified a minimum prevalence of 4000 cases seen over the past 5 years amongst respondents and a minimum incident frequency of 415 new cases seen in 2011 amongst respondents (IPMSSG communication July 2012).

Only 2-5% of patients diagnosed with MS present before age 18 and the majority of these cases occur at or after the age of 10. For this reason, neonates and pediatric patients less than 10 years of age will not be studied.

3.2.2 Rationale for study design

Study design with controlled comparison based on a superiority hypothesis using a clinical endpoint has been historically required and/or preferred by most national health authorities in order to evaluate a treatment for potential market authorization. Alternative designs which may offer advantages in terms of smaller sample size (superiority on an MRI outcome), or avoidance of placebo (eg non-inferiority evaluation versus active comparators) are generally not accepted for this purpose, although there can be regional differences in this regard. However, given the rarity of the pediatric population, it is important to design and conduct a trial that will provide globally acceptable evidence for evaluation of the benefits and risks of teriflunomide in pediatric MS patients.

Current consensus is to treat children with MS, although the efficacy of MS therapies has not been formally demonstrated in children (Chitnis et al, 2013). Therefore, the International Pediatric MS Study Group (IPMSSG) has indicated that placebo-controlled trials in children with MS may be acceptable, provided there are stringent escape criteria such as offering active treatment in the event of new disease activity (Chitnis et al, 2013).

The current design includes such stringent escape criteria and minimizes the potential exposure to placebo by specifying time to relapse as the primary endpoint. In this setting a patient may exit the placebo-controlled phase and will be offered active teriflunomide treatment in case of clinical relapse occurring after 8 weeks of treatment. In addition, the protocol includes specific criteria to allow for a patient to exit the placebo-controlled phase and be eligible for active treatment in case~~s~~ of a high level of sub-clinical activity (eg, MRI lesions) in absence of a relapse (Verhey et al, 2013).

3.2.3 Teriflunomide choice of dose and PK run-in (8 weeks) rationale

At the beginning of the study, a PK run-in (8 weeks) phase will be conducted with limited PK sampling for a duration of 4 weeks, when the concentrations are expected to be at 64% of the steady state based on adult data (95% of the steady-state is reached at approximately 12 weeks in adults after repeated 7 mg doses). Then an assessment of the adequacy of dosing will be done (4 weeks after the 4-week run in). Teriflunomide individual predicted steady-state PK parameters for each pediatric patient will be compared to the range of individual predicted steady-state PK parameters derived from population PK (PopPK) adult model after repeated doses of 7 mg. The dose will be then adjusted if necessary, so the patient has an adult equivalent of 14mg QD.

In this initial PK run-in (8 weeks) phase, the starting dose (3.5 mg per day for patients with body weight of 30 ± 10 kg OR 7 mg per day for patients with body weight >40 kg) is expected to correspond to the adult dose of 7 mg QD as per the following rationale.

- The pharmacodynamic effects in children and adults are expected to be similar.
- It is predicted that the absorption, distribution, metabolism and excretion of teriflunomide will be similar in the children (> 10 years of age) and adults (19, 20, 21, 22, 23, 24, 25), (26, 17). Based on data from juvenile rheumatoid arthritis pediatric (JRA) patients after leflunomide administration, the doses in pediatric patients can be extrapolated from the adult dose according to body weight. The body weight correlated strongly with apparent distribution volume (V/F) and it correlated weakly with apparent total clearance (CL/F) in the pediatric PopPK analysis and, therefore, the doses in pediatric patients were extrapolated from the adult dose according to body weight. This was confirmed as body weight was found to be a significant covariate on the V/F in the first PopPK analysis using teriflunomide data from adult healthy subjects and MS patients (POH0290). The V/F was increased by ~ 25% in a typical patient of 79.8 kg (75th percentile of patient's weight) as compared to a patient weighing 59.5 kg (25th percentile).
- The PK run-in (8 weeks) phase is intended to provide exposure in the range of what is observed in adult patients receiving 7 mg per day; consequently individual PK parameters (C_{max} and AUC_{0-24}) will be assessed to allow the dose adjustment at the end of the first 8 weeks of the core study to the adult-equivalent dose.

During the PK run–in period including the 4weeks analysis (corresponding to the first 8 weeks of the core study): 7mg adult equivalent, QD:

- For patients 30 ±10 kg:
  - 1 teriflunomide tablet (3.5 mg) per day (QD).
- For patients >40 kg:
  - 1 teriflunomide tablet (7 mg) per day (QD).

Individual predicted PK parameters will be assessed at the end of the PK run-in (8 weeks) phase (with no interruption of dosing) using a PopPK model adapted to the pediatric population (POH0401) and compared to the adult 7 mg PK predicted parameter range derived from the second PopPK adult model (POH0339). Adult range (5th - 95th percentile) of predicted PK parameters: 7 mg dose range for C_{max} is 8.03 to 49.10 µg/mL and for AUC_{0-24} is 184 to 1160 µg.h/mL.

After the end of the initial PK run-in (8 weeks) phase (14mg adult equivalent, QD):

If individual predicted PK parameters are equal to or less than the 95th percentile of adult range of predicted PK parameters (repeated doses of 7 mg):

- For patients 30 kg ± 10 kg
  - 1 teriflunomide tablet (7 mg) per day (QD).
- For patients >40 kg
  - 1 teriflunomide tablet (14 mg) per day (QD).

If individual predicted PK parameters are higher than the 95th percentile of the adult range of predicted PK parameters (repeated doses of 7 mg):

- For patients 30 kg ± 10 kg
  - 1 teriflunomide tablet (3.5 mg) per day (QD).
- For patients >40 kg
  - 1 teriflunomide tablet (7 mg) per day (QD).

Dose adjustment will be performed 4 weeks after the end of the 4-week PK run-in (8 weeks) phase for the patients based upon PK availability of parameters (see Table 1). During the rest of the study (after the PK run-in (8 weeks)), the dose may be adjusted when patient weight goes from ≤40 kg to >40kg and vice versa from one visit to the other.

Optional additional extension period for young patients:

One teriflunomide tablet (14 mg) per day (QD). Based on Investigator's judgment, for patients less to 40 kg, dose could be adjusted by the Investigator to 14 mg every other day.

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Table 1 - Chart for dose adjustment

8 week PK-run in Period		Therapeutic : maintenance doses period
4 weeks sample collection	4 weeks analysis	Treated phase/Open Label Phase
Dose given = 7 mg adults equivalent		**Dose given = 14 mg adults equivalent**
30 +/- 10 kg = 3.5 mg / day	≤ range	7 mg / day
	> range	3.5 mg / day
> 40 kg = 7.0 mg / day	≤ range	14 mg / day
	> range	7 mg / day

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4 STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVE

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

4.2 SECONDARY OBJECTIVE(S)

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.

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5 STUDY DESIGN

5.1 DESCRIPTION OF THE PROTOCOL

EFC11759 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. It consists of:

- A screening period up to 4 weeks, designed to evaluate suitability to participate in the trial, in terms of MS diagnosis, MS treatment(s), and safety screening evaluations. No investigational medicinal product (IMP) is administered in this period.
- A double-blind treatment period of up to 96 weeks total duration for each patient
  - Patients are randomized to either teriflunomide or placebo at 2:1 ratio (110 patients on teriflunomide vs. 55 patients on placebo),
  - It includes a blinded PK run-in (8 weeks) phase consisting of 4 weeks of PK sample collection plus 4 weeks of analysis (corresponding to the first 8 weeks after randomization). The PK run-in (8 weeks) phase is intended to provide individual PK parameters to allow the dose adjustment to the 14mg adult-equivalent dose for the rest of the study from Week 8,
  - Patients experiencing a relapse after the PK run-in (8 weeks) and if confirmed by the Relapse Adjudication Panel (RAP) will have the option to continue in an open label period. If RAP does not confirm the relapse, the patient can continue in the double blind phase or prematurely discontinue the treatment. Similarly, patients with high MRI activity (defined in Section 8.1) or completing the 96-week double-blind period will have the option to continue in the open label period.
- An open-label period for the remainder of 192 weeks after randomization

The open-label period will follow the double-blind period and last until 192 weeks after randomization. Its duration for a given patient will depend on when the patient enters this period. The duration of the open-label period will be 96 weeks for patients completing the 96-week double-blind period on treatment, and longer for patients switching to open-label during the initial 96 week double-blind period at the occurrence of a confirmed relapse or in case of high MRI activity.

It includes a blinded PK run-in phase (8 weeks, similarly to the double-blind period).

NOTE: patients, investigators and the study team will remain blinded for the duration of the study. All patients entering the open label period from the placebo arm or teriflunomide arm, will repeat a second PK run-in phase one sample per week over 4 weeks and 4 weeks of analysis) and will be followed until completion of the planned 192 weeks-from randomization. Placebo patients will start with teriflunomide 7 mg adult equivalent dose QD, while teriflunomide patients will continue with the same previous adjusted dose.

- 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.

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- Follow up period with accelerated elimination of teriflunomide.
  - Patients discontinuing study treatment will have a procedure to accelerate the elimination of teriflunomide with either cholestyramine or activated charcoal. However if they will continue to have teriflunomide after the study, this procedure will not take place,
  - Post drug elimination procedure samples to be collected for verification of clearance of plasma teriflunomide concentrations.
- Two Clinical Study Reports (CSR) will be issued:
  - The first CSR will report the final analysis of the 96-week double-blind treatment period, including data after treatment discontinuation, as applicable and defined in the methods. The methods described in this document primarily relate to this treatment period and analysis,
  - The second CSR will report the analysis of the open-label data at the conclusion of the extension period for all included patients.

The data for the optional additional extension period for young patients will be reported separately.

5.1.1 Duration of study participation for each patient

Each patient will have a screening period up to 4 weeks then a Double-Blind Treatment Period for up to 96 weeks (or until a confirmed relapse or high MRI activity as defined in the protocol), and an Open-Label Period for the remainder of 192 weeks. The complete treatment duration, from randomization to end of open-label extension, will be 192 weeks. The duration of the extension will be 96 weeks for patients completing the 96-week double-blind period on treatment, and longer for patients switching at a confirmed relapse or in case of high MRI activity. Patients discontinuing study treatment will have a post-drug elimination follow-up period of 4 weeks which may need to be extended until teriflunomide level is ≤0.02 µg/mL.

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.

Upon completion of the study the Sponsor may evaluate options for further treatment under a separate mechanism.

5.1.2 Determination of end of clinical trial

The end of the clinical trial occurs on the day of the last visit of the last patient (or last contact with the last patient, in the case of no last visit).

5.2 STUDY COMMITTEES

5.2.1 Data monitoring committee (DMC)

An independent Data Monitoring Committee (DMC), operating independently from the Sponsor and clinical investigators is commissioned for this clinical trial. This committee is comprised of externally-based individuals with expertise in the disease under study. The primary responsibilities of the DMC are to review and evaluate the benefit versus risk and provide appropriate recommendations regarding trial continuation to the Sponsor.

Details of the responsibilities of the DMC will be described in the DMC charter that will be provided at study start. The Sponsor is responsible for promptly reviewing and for taking into account in a timely manner the recommendations of the DMC in terms of trial continuation with or without alterations or of potential trial termination.

5.2.2 Adjudication Committee (AC)

To ensure objectivity in the primary endpoint, a Relapse Adjudication Panel (RAP) will be convened to evaluate all relapses reported during the 96-week double-blind period. The RAP will consist of independent neurologists with expertise in MS clinical research. The RAP members will be trained on study procedures by the Sponsor (or delegate ie, CRO). Relapses, as adjudicated by the RAP, need to meet strict criteria including the presence of objective signs and symptoms that persisted for at least 24 hours.

RAP assessments will use blinded data and will be performed in real time. Details of the responsibilities of the RAP will be described in the RAP charter that will be provided prior to study start.

6 SELECTION OF PATIENTS

6.1 NUMBER OF PATIENTS PLANNED

It is planned that a total of approximately 165 children and adolescents of either gender 10 to below 18 years of age will be randomized into the core study to receive either teriflunomide (110 patients) or placebo (55 patients).

6.2 INCLUSION CRITERIA

I 01. Patients with relapsing multiple sclerosis are eligible. Patients should meet the criteria of MS based on McDonald criteria 2010 and International Pediatric Multiple Sclerosis Study Group (IPMSSG) criteria for pediatric MS, version of 2012 (8) and have:

- At least one relapse (or attack) in the 12 months preceding screening or,
- At least two relapses (or attack) in the 24 months preceding screening.

<18 years of age and ≥10 years of age at randomization

Specific for the Russian Federation from 18 December 2014 to 26 July 2016, ≤17 years of age and ≥13 years of age at randomization (see Appendix F).

Signed informed consent/assent obtained from patient and patient's legal representative (parents or guardians) according to local regulations.

6.3 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria will be screened for the following exclusion criteria which are sorted and numbered in the following sub-sections:

6.3.1 Exclusion criteria related to study methodology

E 01. Expanded Disability Status Scale score >5.5 at screening or randomization visits.

E 02. A relapse within 30 days prior to randomization.

E 03. Body weight <20 kg.

E 04. Mental condition rendering the patient or parent/guardian unable to understand the nature, scope, and possible consequences of the study.

E 05. Patient or parent/guardian unlikely to comply with the protocol as determined by Investigator, eg, uncooperative attitude, inability to return for follow-up visits.

E 06. Clinically relevant cardiovascular, hepatic, neurological, endocrine, or other major systemic disease making implementation or interpretation of the study results difficult or that would put the patient at risk by participating in the study.

E 07. Persistent significant or severe infection.

E 08. History of drug or alcohol abuse.

E 09. Patient or parent/legal guardian is the Investigator or any Sub investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof, directly involved in the conduct of the study. Any technical/administrative reason that makes it impossible to randomize the patient in the study.

E 10. Contraindication for MRI, ie, presence of pacemaker, metallic implants in high-risk areas (ie, artificial heart valves, aneurysm/vessel clips), presence of metallic material (ie, shrapnel) in high-risk areas, known history of allergy to any contrast medium

6.3.2 Exclusion criteria related to treatments, which may interfere with the study

E 11. Patients must not have used adrenocorticotrophic hormone or systemic corticosteroids for 2 weeks prior to MRI assessment

E 12. Treated with :

- Glatiramer acetate, interferons or dimethyl fumarate within 1 month prior to randomization.
- Fingolimod or intravenous immunoglobulins within 3 months prior to randomization.
- Natalizumab, other immunosuppressant or immunomodulatory agents such as cyclophosphamide, azathioprine, cyclosporine, methotrexate, mycophenolate, within 6 months prior to randomization.
- Cladribine or mitoxantrone within 2 years prior to randomization.

E 13. Treated with alemtuzumab at any time.

E 14. Treated with any investigational drug within 6 months prior to randomization.

6.3.3 Exclusion criteria related to study treatment at screening

E 15. Liver function impairment or persisting elevations (confirmed by retest) of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or direct bilirubin greater than 2 x the upper limit of normal range (ULN) based on screening lab values.

E 15. Active hepatitis or hepatobiliary disease or known history of severe hepatitis.

E 16. Pregnant or breast-feeding female patients.

E 17. Female patients of child-bearing potential or male patient not using highly effective (double barrier) contraceptive and /or female patients of childbearing potential who are unwilling to or unable to be tested for pregnancy.

E 18. Patients wishing to parent children (be a partner in the conception of a child) during the course of the trial.

E 19. Patients with significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia:

- Hemoglobin<10g/dL,
- Absolute white blood cell count <3000 cells/mm3 (µL) and/or,
- Platelet count <150 000 cells/mm3 (µL) and/or,
- Absolute neutrophil ≤1500 cells/mm3 (µL)

E 20. Persisting elevations (confirmed by retest) of serum amylase or lipase greater than 3-fold the upper limit of normal.

E 21. Active pancreatitis or known history of chronic pancreatic disease.

E 22. Patients with a congenital or acquired severe immunodeficiency, a history of cancer (except for basal or squamous cell skin lesions which have been surgically excised, with no evidence of metastasis), lymphoproliferative disease, or any patient who has received lymphoid irradiation.

E 23. History of HIV infection.

E 24. Positive tuberculin test leading to suspicion of tuberculosis (eg, unless known to have been treated for tuberculosis in the past, or interpreted in light of vaccination; if in doubt, chest X-ray is recommended).

E 25. Hypoproteinemia (eg, in case of severe liver disease or nephrotic syndrome) with serum albumin <3.0 g/dL.

E 26. Moderate to severe impairment of renal function, as shown by serum creatinine >133 µmol/L (or >1.5 mg/dL).

E 27. Concomitant use of cholestyramine or prior use within 4 weeks preceding randomization.

E 28. Known hypersensitivity to teriflunomide, leflunomide or any excipients in the formulation of IMP (note: teriflunomide tablets contain lactose therefore investigators should consider whether history of lactose intolerance, in particular Lapp lactase deficiency could affect treatment tolerability).

6.3.4 Criteria to reduce reproductive risk

The effect of teriflunomide on human fetal development is not known, and may be potentially harmful based on results from animal studies. Therefore, all patients must be fully informed as to this risk and provide written consent /assent to not become pregnant or father a child during their participation in this study. If during the study, a female patient becomes pregnant or decides to attempt to become pregnant or if a male patient decides to attempt to father a child, then she or he must stop the study medication and undergo the accelerated elimination procedure.

Female patients must not be breast feeding or pregnant (as confirmed by serum pregnancy test) at the time of study entry and must agree to undergo serum pregnancy testing throughout the study at each 12-week clinic visit. In addition, pregnancy test should be conducted in case of an unexpected delay of menorrhea.

Definition of "woman not of child bearing potential":

- Be sterilized (eg, hysterectomy, bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation).

A woman of child bearing potential (WOCBP) is any female who has experienced menarche and does not meet the criteria for "woman not of child bearing potential".

Women of child bearing potential and male subjects must agree that they will take means to reduce reproductive risk by agreeing to use a double method of contraception (ie, an acceptable method in both female and male) until successful plasma elimination has been confirmed (refer to Section 9.9). Acceptable methods of contraception are defined for this protocol as:

- For male:
  - True abstinence: when this is in line with the preferred and usual lifestyle of the subject (Periodic abstinence [eg, calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception),
  - Male sterilization (with the appropriate post vasectomy documentation of the absence of sperm in the ejaculate),
  - Use of condoms throughout the study, in addition to spermicides is recommended.
- For women of child bearing potential:
  - True abstinence: when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [eg, calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception),
  - Highly effective oral contraceptives, such as biphasic and triphasic oral contraceptives are considered adequate. Progestogene only pills or "mini pills" which have demonstrated high efficacy will be acceptable,
  - Injectable hormones (ie, Depo-Provera), hormonal implants, transdermal patches or intrauterine device (IUD) or intrauterine systems (IUS) or intravaginal ring (NuvaRing) which have demonstrated efficacy comparable to high efficacy oral contraceptives are adequate.

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Therefore:

For female patients participating to the study:

If the patient is a "woman not of child bearing potential", then no method is required.

If the patient is a WOCBP and meets criteria for "true abstinence" (as defined above) then no method is required. These patients must agree that they will use acceptable double methods of contraception before becoming sexually active.

If the patient is a WOCBP and sexually active with a male partner who is sterilized (as defined above), then an additional method of contraception is recommended but not required. These patients must agree that they will use acceptable double methods of contraception before becoming sexually active with another male partner.

Otherwise both the female patient participating to the study and the male partner must use an acceptable method of contraception as defined above.

For male patients participating to the study:

If the patient is sterilized (as defined above) then no method is required.

If the patient meets criteria for "true abstinence" (as defined above) then no method is required. These patients must agree that they will use acceptable double methods of contraception before becoming sexually active.

If the patient is sexually active with a female partner who is a "woman not of child bearing potential", then no other method is required. These patients must agree that they will use acceptable double methods of contraception before becoming sexually active with another female partner.

Otherwise both the male patient participating to the study and the female partner must use an acceptable method of contraception as defined above.

Local additional requirements are to be followed, eg spermicidal foam / gel / film / cream / suppository is to be associated with condoms in UK, as per MHRA rules.

6.4 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s).

All treatments being taken by the patients on entry to the study or at any time during the study in addition to the IMP are regarded as concomitant treatments and must be documented on the Case Report Form (CRF). A history of all prior medications needs to be documented in the eCRF:

- MS treatments taken within the past 2 years
- Non MS treatment taken within 4 weeks prior to screening.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the IMPs, they may be given at the discretion of the Investigator and recorded in the CRF.

Medications that are permitted during the study may be used as clinically indicated, at the physician's discretion. However, medication with a low therapeutic index such as digoxin should be carefully monitored. All efforts should be made to adhere to the same dosing regimen during conduct of the study. The combined use of teriflunomide with nonsteroidal anti-inflammatory drugs (NSAID) may be associated with an increased incidence of hypertension. Blood pressure (BP) must be monitored carefully before treatment with teriflunomide and at the regular visits during study medication administration.

In adult, repeated doses of teriflunomide had no effect on the pharmacokinetics of S-warfarin. However, a 25% decrease in peak international normalized ratio (INR) was observed when teriflunomide was coadministered with warfarin as compared with warfarin alone. Therefore, when warfarin is coadministered with teriflunomide, close INR follow-up and monitoring is recommended.

In adult, there was an increase in mean repaglinide C_{max} and AUC (1.7- and 2.4-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of CYP2C8 in vivo. Therefore, drugs metabolized by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, should be used with caution during the treatment with teriflunomide.

In adult, there was an increase in mean ethinylestradiol C_{max} and AUC_{0-24} (1.58- and 1.54-fold, respectively) and levonorgestrel C_{max} and AUC_{0-24} (1.33- and 1.41-fold, respectively) following repeated doses of teriflunomide. While this interaction of teriflunomide is not expected to adversely impact the efficacy of oral contraceptives, consideration should be given to the type of oral contraceptives used in combination with teriflunomide.

In adult, there was an increase in mean cefaclor C_{max} and AUC (1.43- and 1.54-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of OAT3. Therefore, when teriflunomide is coadministered with substrates of OAT3, such as cefaclor, penicillin G, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution should be observed**.**

In adult, there was an increase in mean rosuvastatin C_{max} and AUC (2.65- and 2.51-fold, respectively), following repeated doses of teriflunomide. However there was no apparent impact of this increase in plasma rosuvastatin exposure on the HMG-CoA reductase activity. If used with teriflunomide, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (eg, methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-CoA reductase inhibitors (eg, simvastatin, atorvastatin pravastatin, methotrexate, nateglinide, repaglinide, rifampin) concomitant administration of teriflunomide should also be undertaken with caution. Patients should be monitored closely for signs and symptoms of excessive exposure to the drugs and consider reduction of the dose of these drugs.

The following concomitant treatments are not permitted due to potential effects on the immune system:

- Cladribine or mitoxantrone.
- Azathioprine, cyclophosphamide, cyclosporine, methotrexate or mycophenylate.
- Natalizumab.
- Leflunomide.
- Fingolimod.
- Interferons.
- Glatiramer acetate.
- Dimethyl fumarate.
- Alemtuzumab.
- Intravenous immunoglobulins.
- Attenuated live vaccines.

The following concomitant treatments are not permitted during this study and for a minimum of 4 weeks prior to randomization:

- Cholestyramine or activated charcoal, which accelerate elimination of teriflunomide (except during the elimination procedure).

The above therapy exclusions are not exhaustive. If the Investigator has used or intends to use similar drugs not specified above, he/she should contact the local site monitor. In addition, increased side effects may occur in case of recent or concomitant use of hepatotoxic (including alcohol), hematotoxic, or immunosuppressive substances in combination with teriflunomide.

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

Concomitant use of systemic corticosteroids for the treatment of MS relapse is allowed during the study (see below).

6.4.1 Standardization of acute therapy for relapses during the study

Relapses may be treated with systemic corticosteroids if clinically necessary and as per investigator judgment in doses appropriate for pediatric population.

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7 STUDY TREATMENTS

7.1 INVESTIGATIONAL MEDICINAL PRODUCT

Both teriflunomide (HMR1726) and placebo are defined as the investigational medicinal products (IMP) for this study.

7.1.1 HMR1726 (teriflunomide)

Film-coated tablets containing 3.5 mg, 7 mg, and 14 mg teriflunomide will be supplied by the Sponsor. Teriflunomide tablet (s) will be taken orally as a single dose each day of the treatment period. Teriflunomide tablet (s) will be taken with water and may be taken with or without food. Patients should be encouraged to take their study medication in the morning at the same time each day of the core study period, except on the days in which PK sampling is planned - patients will take the study medication at the study site after pre-dose PK sample collection (see Section 9.11.1).

<u>During 4-week PK run-in (8 weeks) phase (7 mg adult equivalent, QD):</u>

- For patients 30 ± 10 kg:
  - 1 Teriflunomide tablet (3.5 mg) per day (QD).
- For patients > 40 kg:
  - 1 Teriflunomide tablet (7 mg) per day (QD).

<u>After the end of the PK run-in (8 weeks) phase (Week 8):</u>

If individual predicted PK parameters are equal to or less than the adult range of predicted PK parameters (repeated doses of 7 mg):

- For patients 30 kg ± 10 kg
  - 1 Teriflunomide tablet (7 mg) per day (QD).
- For patients > 40 kg
  - 1 Teriflunomide tablet (14 mg) per day (QD).

If individual predicted PK parameters are higher than the 95th percentile of the adult range of predicted PK parameters (repeated doses of 7 mg):

- For patients 30 kg ± 10 kg
  - 1 Teriflunomide tablet (3.5 mg) per day (QD).
- For patients > 40 kg
  - 1 Teriflunomide tablet (7 mg) per day (QD).

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Adult range (5th - 95th percentile) of predicted PK parameters: 7 mg dose range for C_{max} is 8.03 to 49.10 µg/mL and for AUC0-24 is 184 to 1160 µg.h/mL.

Optional additional extension period for young patients:

One teriflunomide tablet (14 mg) per day (QD). Based on Investigator's judgment, for patients less to 40 kg, dose could be adjusted by the Investigator to 14 mg every other day.

7.2 NON-INVESTIGATIONAL MEDICINAL PRODUCT(S)

Cholestyramine or activated charcoal is used as non IMP in this study during the 4-week post elimination period to accelerate teriflunomide elimination process (see Section 9.9).

7.3 BLINDING PROCEDURES

Patients will be randomized to teriflunomide or matching placebo at randomization visit (Visit 2). All study medication will be identical film-coated tablets sealed in child resistant-blister packs. The study treatment of the double-blind period will be kept blinded to the sites and patients until the final database lock.

7.3.1 Measures to protect blinding of this trial

Please also refer to Section 7.3.2 randomization code breaking during the study. In the case of an SAE, the Investigator may only break the code in exceptional circumstances when knowledge of the IMP is essential for treating the patient. The treatment codes will be unblinded by the Pharmacovigilance Department for reporting of any unexpected SAE that is reasonably associated with the use of IMP. A list of expected events commonly associated (and therefore not unexpected) for teriflunomide can be found in the current Investigator Brochure (IB).

The DMC will review unblinded data. An independent statistical group (ISG), completely independent from the Sponsor and Investigators, is responsible for performing the interim data analyses and preparing the interim report for the DMC.

The laboratory responsible for the pharmacokinetic sample bioanalysis will be unblinded as well as the pharmacometrician who will calculate the individual predicted PK parameters during the PK run-in. They will, however, agree to follow the procedures defined in the Sanofi SOP/Quality documents to maintain the blind and not to disclose the randomization schedule or the individual unblinded analytical results before the database lock.

Post accelerated elimination PK samples, collected at the post accelerated elimination follow up visits (EOT+2 and EOT+4) to verify plasma teriflunomide concentrations of ≤0.02 µg/mL, could potentially unblind the investigational site to a patient's treatment after study medication discontinuation. Site notification is required to inform the Investigator if the accelerated elimination procedure needs to be repeated after EOT+4 if the teriflunomide plasma concentration at EOT+2 is still above threshold. The risk of unblinding (of discontinued or completed patients) is low, since greater than 97% of the patients treated with teriflunomide are expected to have adequately low plasma teriflunomide concentrations following the recommended accelerated elimination procedure.

7.3.2 Randomization code breaking during the study

In case of a SAE, the code must be broken only in exceptional circumstances when knowledge of the IMP is essential for treating the patient.

Code breaking can be performed at any time by using the proper module of the IVR/IWR (Interactive Voice/Web Response) system and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day, and reason for code breaking.

7.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Patients will be randomly assigned to one of the two groups in a 1:2 ratio, and will receive either placebo or teriflunomide. The randomization will be stratified by the country in which the patient is being treated and the patient pubertal status. The randomization code list is generated by the interactive web response system and interactive voice response system (IWRS/IVRS) service provider.

Patients filling all inclusion and exclusion criteria at the Visit 1 (Day-28) and Visit 2 (Day 0) are qualified for randomization.

Randomization occurs at Visit 2. The first dose of randomized IMP (either teriflunomide or placebo) will be taken the same day or the following day.

A patient is considered randomized when allocated to treatment regardless whether the treatment kit was used or not.

The study medication will be administered only to patients included in this study following the procedures described in this protocol.

The randomization treatment kit number list is generated centrally by the sponsor. Investigational Products (IMPs) are packaged according to this list.

The clinical site coordinator will document the medication kit number in the electronic Case Report Form (eCRF) and in the patient's source documents, and the site/patient number on the study medication label prior to dispensing to the patient.

At the randomization visit, at Week 8 (after PK run-in period), Week 12 and then every 12 weeks during the course of the study, the investigational site will contact the IWRS/IVRS to allocate a new medication kit number to the patient. The IWRS/IVRS will allocate medication kits containing the same study medication as the one designated at randomization. A patient will be considered randomized once a medication kit number has been assigned by the IWRS/IVRS. Therefore, it is important that all inclusion/exclusion criteria are confirmed and baseline procedures are completed prior to the randomization call to the IWRS/IVRS.

If a screened patient is not eligible, the Investigator will call IWRS/IVRS to enter the patient as screen failure.

If a patient was deemed a screen failure, he or she may be re-screened for this study after waiting at least 4 weeks following the date of screen failure. However, if the screen failure is due to non-safety reasons, the patient can be re-screened earlier. If a patient who had previously failed screening for any reason is re-screened, the patient must sign a new informed consent form and be assigned a new patient number by IWRS/IVRS (the next sequential patient number at the site).

Patients withdrawn from the study retain their patient number. New patients will always be allocated a new patient number.

7.5 PACKAGING AND LABELING

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

7.5.1 Teriflunomide/placebo

During the double-blind treatment period and the open-label period for the remainder of 192 weeks, teriflunomide/placebo will be supplied as 3-Month kit. A 3-Month kit is a box containing 3 child resistant wallets of 35 tablets of 3.5 mg or 7 mg or 14 mg teriflunomide. Each box contains sufficient medication for 12 weeks plus 21 extra-days (=105 tablets). Each box contains 3 wallets of the same strength.

A 2-panel label is affixed to the box. At the time of dispensing, the tear-off label of the 2-panel label will be removed and adhered to the patient's treatment log form. Each wallet has a 1-panel label affixed.

During the optional additional extension period 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, two 3-Month kit teriflunomide 14 mg will be supplied in open-labelled conditions. It is required that these treatments will not be used after the patient is able to switch to commercial product and come back to the last visit with remaining kits, in order to prevent any IMP intake once patients have switched to the commercial product.

7.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) will be responsible for storing all investigational product supplies in a secure and safe room in accordance with local regulations, labeling specifications, policies and procedures.

Teriflunomide storage conditions are specified on the IMP medication kit boxes and their wallets.

7.7 RESPONSIBILITIES

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

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

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

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

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

7.8 TREATMENT ACCOUNTABILITY AND COMPLIANCE

At the end of Visit 2, patient will receive IMP for the following 8 weeks.

At Visit 4 (W8), a new kit will be then dispensed.

From V5 (W12), patients will receive subsequent IMP every 12 weeks until the end of the study.

The patient will receive subsequent IMP every 24 weeks, when participating in the optional additional extension period.

It is the responsibility of the Investigator to check the patients' compliance to study treatment administered. Compliance is tracked by counting dispensed and unused tablets at W8, W12 and then from W12 every 12 weeks corresponding to mandatory on site visits until EOT visit. The investigator (or authorized delegate) completes the appropriate page of the case report form and IMP source document logs by recording the number and dates of doses taken (or not) by the patient.

Temporary study treatment discontinuation should generally not exceed 2 consecutive weeks.

The monitor in charge of the clinical trial checks the case report form data by comparing the recorded data with the retrieved IMP kit and data recorded on the IMP source document logs.

7.9 RETURN AND/OR DESTRUCTION OF TREATMENTS

Whenever possible all unused investigational product will be destroyed on site according to the standard practices of the site. A detailed treatment log of the destroyed investigational product will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy any investigational product unless the Sponsor provides written authorization. When destruction at site cannot be performed, all investigational products will be retrieved by the Sponsor. A detailed treatment log of the returned investigational product will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

8 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

The assessments will be performed according to the schedule presented in the Study Flowchart.

8.1 EFFICACY

In order to assure proper evaluation of the efficacy, at each study center the staff will consist of a minimum of 2 neurologists. One neurologist will be the treating neurologist and one will be the examining neurologist for a given subject throughout the study. One of the neurologists may be the Principal Investigator. This delineation assures that AEs or other health issues for any patient do not influence the neurological assessment.

Treating neurologist:

The treating neurologist will be responsible for subject eligibility evaluation, supervision of study medication administration, recording and treating of AEs and assessing relapses, and monitoring of safety assessments, including routine laboratory results and concomitant medications. The same physician should, as best as possible, maintain the role of treating neurologist for a given subject throughout the study.

Examining neurologist:

The examining neurologist will be responsible for conducting all Functional System (FS) score and Expanded Disability Status Scale (EDSS) score assessments. The examining neurologist should be certified for EDSS rating prior any involvement in the study. The Investigator can delegate the role of examining neurologist to a highly qualified health professional who meets a predetermined level of experience in evaluating MS patients including experience in examining MS patients and scoring the EDSS/FS. Such a delegation is only allowed when permitted by local laws, health authority rules, and ethics committee requirements. Throughout the study, the examining neurologist is to remain unaware of the patient's treatment assignment and the safety profile of the patient (AEs, concomitant medications, and laboratory results). All efforts should be made to maintain the same person at the role of examining neurologist for a given subject throughout the study. All other investigational site staff and the subject must refrain from discussing treatment assignment and safety issues with the examining neurologist.

MRI

All brain scans will be reviewed and interpreted by one or more neuroradiologists at an independent, central facility with no access (ie, blinded) to treatment assignment thereby avoiding bias.

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

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MRI should not be conducted within 2 weeks of steroid administration due to potential interference.

In case of at least 5 new/enlarged T2 lesions at the MRI of Week 24, an additional MRI will be performed at Week 36.

Then, in case of:

- At least 9 new/enlarged T2 lesions at Week 36, or,
- At least 5 new/enlarged T2 lesions on each of the 2 consecutive MRI scans of Week 36 and Week 48, or,
- At least 5 new/enlarged T2 lesions on each of the 2 consecutive MRI scans of Week 48 and Week 72.

Patients will have the option to continue in an open label teriflunomide treatment arm.

(Note: new/enlarged refer to previous scan)

8.1.1 Primary efficacy

The primary efficacy endpoint for the 96-week double blind treatment period is the time to first clinical relapse after randomization

Subjects/parents/guardians will be instructed to contact their investigator immediately should any symptoms suggestive of an MS relapse appear. The subject must be examined as soon as possible, within 7 days.

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). The subject must have objective signs on the Examining Neurologist's examination confirming the event and must then be reviewed and confirmed by an independent Relapse Adjudication Panel (RAP). The RAP will assess the relapse in real time.

New or recurrent symptoms that occur less than 30 days following the onset of a relapse should be considered part of the same relapse.

The investigator can, at his/her discretion, treat the patient with corticosteroids but the switch to the open label can only occur if the RAP assesses the event as a relapse.

8.1.2 Secondary efficacy

The secondary efficacy endpoints for the 96-week double-blind treatment period are the following:

- Proportion of relapse free patients at 24, 48, 72 and 96 weeks.
- MRI endpoints:

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- Number of new/newly enlarged T2 lesions,
- Number of T1 Gd-enhancing T1 lesions,
- Change in volume of T2 lesions,
- Change in volume of T1 hypointense lesions,
- Number of new hypointense T1,
- Proportion of patients free of new or enlarged MRI T2-lesions at 48 weeks and 96 weeks,
- Brain atrophy.

The number of new/newly enlarged T2 lesions and the number of T1 Gd-enhancing T1 lesions will be considered the key secondary imaging endpoints.

- Cognitive outcome measured by the SDMT and Cognitive Battery Tests (18, 7), when available.
- Teriflunomide PK.

Exploratory endpoint: proportion of disease-free patients.

8.2 SAFETY

The clinical trial-specific and general safety criteria include:

- Pre-specified potential risks which will require specific monitoring, management and follow-up procedures.
- Physical examinations: screening, randomization, Weeks 12, 24, and every 12 weeks.
- Vital signs: screening, randomization, Weeks 4, 8, 12, 24, and every 12 weeks.
- Laboratory: screening, randomization, every 4 weeks up to 24 weeks and then every 6 weeks up to the end of treatment (EOT). Patients who enter the open-label period will restart the laboratory visit schedule of every 4 weeks up to 24 weeks and then every 6 weeks up to the EOT.
- Abdominal ultrasound visits: for patients with signs or symptoms of pancreatitis.
- ECG randomization, EOT and after EOT if abnormality.
- Tuberculosis test (skin test or blood testing are allowed), to be performed at screening. An additional test should be performed during the study if deemed clinically indicated. Skin test or blood testing are allowed.
- AE reporting throughout the duration of the study. A priori, efficacy endpoints as specified in the protocol will not be considered as AEs except if, because of the course or severity or any other features of such events, the Investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition. Therefore, MS relapses will be captured as efficacy events and are excluded from the definition of AE and SAE. However, for all associated symptoms or events or if an event that was initially considered a possible MS relapse but upon evaluation is found to be any other type of

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event (some example but not limited to: fever, injury, musculoskeletal event, systemic illness, mood disorder, etc) the event must be captured as an AE/SAE.

- In case of suspected infection, tests (eg, appropriate cultures, erythrocyte sedimentation rate and/or C reactive protein, chest and/or sinus imaging) must be performed in addition to general laboratory testing as clinically indicated.
- In case of an increase in frequency or severity of infectious illness or due to the nature of the infections and suspected immune deficiency, more advanced immunologic testing will be required. The measurements of specific antibody titers in response to intentional immunization will be performed as well.
- Peripheral neuropathy confirmed by nerve conduction study: all neurological symptoms suggestive of a peripheral neuropathy will be followed up with nerve conduction studies. The Peripheral neuropathies reporting form has to be completed.
- Avoidance of attenuated live vaccinations during study.

8.3 BIOMARKERS

Neurofilament light chain and other biomarkers may be evaluated from leftover plasma PK samples, which were drawn from study patients during the study and after patient/parents consent. This process is described in Appendix E.

9 SAFETY ENDPOINTS ASSESSED IN THIS TRIAL

Safety and tolerability will be evaluated using the assessments described below. During the optional additional extension period, safety parameters will be evaluated as per investigator's judgement.

9.1 SPONTANEOUSLY REPORTED ADVERSE EVENTS

Collection of adverse events (AEs) spontaneously reported by the patient or observed by the investigator extends from the signing of the informed consent form until post drug elimination follow up. All patients who prematurely and permanently discontinue double-blind study medication will be asked to enter an early permanent treatment discontinuation (EPTD) follow-up period, which involves returning to the clinic approximately every 3 months to evaluate adverse events until the planned end of the double-blind treatment period (96 weeks). All reported AEs will be recorded in the patient's records and in the case report form at all visits, including the unscheduled relapse visit, if necessary.

Adverse events will be graded by CTCAE version 4.0.

9.2 VITAL SIGNS

Vital signs include systolic and diastolic blood pressure, radial heart rate (HR), and body temperature. Vital signs will be obtained at screening, randomization, Weeks 4, 8, 12, 24 and every 12 weeks, at EOT, or early treatment discontinuation, and washout period EOT +2W and EOT +4W (except height only measured at randomization and EOT), and after relapse. Height and weight is to be documented in the growth charts.

Blood pressure and heart rate are measured after the patient has been supine for 3 minutes. The patient then stands. Standing blood pressure and heart rate are obtained 3 minutes later. A sphygmomanometer with a blood pressure cuff appropriate to the patient's arm girth is used.

9.3 PHYSICAL EXAMINATION

Physical examinations are performed at screening, baseline, every 12 weeks thereafter and at EOT. In addition, one examination is also performed at the first post drug elimination follow up visit. Physical examinations should be performed for patients who prematurely discontinued the study treatment.

The Tanner scale (also known as the Tanner stages I-V) is a scale of physical development in children, adolescents and adults (Marshall and Tanner, 1969; Marshall and Tanner, 1970). The scale defines physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitalia, and development of pubic hair.

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Tanner scale is performed either at the study site by the pediatric neurologist or pediatrician or at a designated site arranged by the investigator. Tanner scale is encouraged to be performed at scheduled visits. However, it is acceptable if the assessments are performed shortly after the scheduled visits due to logistical reasons.

The treating neurologist must assess for neurological signs and symptoms suggestive of a peripheral neuropathy (defined as bilateral sensory and/or motor involvement with stocking glove distribution) at each visit involving a physical examination. If the treating neurologist suspects a peripheral neuropathy then electrophysiological nerve conduction studies must be performed. If the overall assessment of the patient is consistent with a diagnosis of peripheral neuropathy or the worsening of a pre-existing peripheral neuropathy, that event will be reported as AE. If a drug-related peripheral neuropathy is suspected treatment should be discontinued.

9.4 12-LEAD ECG

A standard 12-lead ECG will be performed at baseline and at EOT and will be evaluated centrally. For ECG, the variables analyzed will be heart rate, PR interval, QRS interval, QT, QTcB (QTc interval calculated by Bazett's method), and QTcF (QTc interval calculated by Fridericia's method).

In the case of an abnormal ECG (ie, QTcB/QTcF ≥500 msec) transmitted to the centralized ECG system and manually interpreted by the cardiologist in the centralized ECG facility, a cardiology consultation should be performed, and consideration is should be given to placing the patient under supervision in a specialized setting.

A confirmed prolonged QTc interval (QTcB/QTcF ≥500 msec) should be reported in an expedited fashion by the centralized ECG system. An expedited notification of the finding of QTc interval prolongation is communicated to the investigator and to the Sponsor.

9.5 ULTRA SOUND OF THE PANCREAS

An ultrasound will be performed for patients with confirmed pancreatic enzymes elevation ≥3 x ULN and/or symptoms suggestive of pancreatitis.

The ultrasound examination will be performed according to local standards. A gastroenterologist will review the report and provide clinical conclusion. Abnormal findings should be reported as AEs.

All ultrasounds with abnormal pancreatic findings must be followed by a CT scan with contrast or MRI of the pancreas and report added to the CRF

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9.6 CLINICAL LABORATORY PARAMETERS

The Central Laboratory performs clinical laboratory assessments. This includes two-parts: for scheduled study center visits, laboratory samples will be drawn at the site and samples will be shipped to the Central Laboratory to be analyzed; for safety laboratory samples collected locally in between site visits, blood samples are drawn locally but are shipped to the Central Laboratory for analyses. Fasting is not required, but the information on fasting/non fasting conditions will be collected. Local anaesthetic must be offered for blood draws to minimize pain and discomfort. A specific written manual regarding the mechanisms and procedures related to the centralized laboratory process is provided to each investigator.

9.6.1 Routine clinical laboratory parameters

The following routine parameters will be measured at screening, randomization, Weeks 4, 12 and 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, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total bilirubin, direct/indirect bilirubin, alkaline phosphatase, calcium, 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) (NOTE: This test is performed at baseline and every 12 weeks and at EOT or premature treatment discontinuation).

9.6.2 Safety clinical laboratory parameters

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

Note: Any abnormal laboratory value will be immediately rechecked for confirmation before making a decision of permanent discontinuation of Investigational Product for the concerned patient.

Threshold values for laboratory parameters of special concern (ie, liver enzymes, pancreatic enzymes and neutrophil counts) are defined for monitoring purposes as AEPMs with expedited reporting when thresholds are met; (ie, Neutrophils< 1000/mm3, ALT>3 x ULN and Bilirubin >2 x ULN for liver function according to see Appendix D), and AEPMs (see Section 9.8.1).

9.6.3 Additional laboratory parameters

TSH: at baseline, every 24 weeks and EOT.

9.6.4 Optional additional extension period for young patients

After the patient has entered the optional additional extension period, laboratory tests will be performed upon investigator discretion based on signs/symptoms of adverse reactions.

9.7 IMMUNOGLOBULINS

Serum immunoglobulins concentration (IgG, IgM and IgA) at randomization and every 24 weeks.

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

9.8 SAFETY INSTRUCTIONS

9.8.1 Pre-defined adverse events and laboratory abnormalities for specific reporting (AEPM)

For the following events, the Investigator should follow the procedures for specific expedited reporting in order to assure Sponsor monitoring and DMC review, even if the criteria for seriousness are not fulfilled. The Investigator is required to completely document the evaluations and treatments and provide them to the Sponsor. For all of these events the “Safety complementary form” has to be completed in the eCRF. For some of the listed events specific CRF pages have to be completed in addition to that.

All the following adverse events must be monitored until symptom resolution or until the condition stabilizes

Instructions for reporting and Follow-Up:

- Confirmed ALT >2 x ULN by a retest done as soon as possible (in 7 days if ALT ≤3 x ULN). See Appendix D for guidance of reporting and Follow-Up (note that only ALT is to be taken into account in the aminotransferase figure).

- Any occurrence of ALT >3 x ULN with total bilirubin value >2 x ULN. See Appendix D for guidance of reporting and Follow-Up.
- Any occurrence of ALT >8 x ULN. This should be reported as SAE with the criteria of medical importance. See Appendix D for guidance of reporting and Follow-Up.
- Depressive disorder that is considered clinically important by the investigator;
- Any occurrence of confirmed (by a retest) neutrophil count of less than 1000 cells/µL. See Appendix D for guidance of reporting and Follow-Up.
- Confirmed serum amylase or lipase >2 x ULN by a retest done as soon as possible (up to 14 days).
  (Amylase or lipase values greater than 2 x ULN and less than 3 x ULN must be repeated within 7 days and weekly thereafter until it is less than 2 x ULN. Amylase or lipase values greater than 3 x ULN must be repeated within 48 hours and every 48 hours until it is less than 3 x ULN and weekly until it is less than 2 x ULN. Study medication must be discontinued if serum amylase or lipase values are greater than 2 x ULN and associated with signs or symptoms consistent with pancreatitis. Study medication must also be discontinued if serum amylase or lipase values are greater than 5 x ULN, confirmed within 48 hours, and without signs or symptoms of acute pancreatitis. In this case, a thorough evaluation for the basis of these elevations must be performed.)
- Abdominal CT or MRI scan with findings with pancreatic abnormalities;
- Pulmonary symptoms such as onset or worsening of cough or dyspnea requiring pulmonary evaluation and consistent with a pulmonary toxicity.
- Peripheral neuropathy confirmed by nerve conduction study.
  All neurological symptoms suggestive of a peripheral neuropathy will be followed up with nerve conduction studies.
- Any sign, symptom, laboratory data suggestive or evocative of renal dysfunction with acute renal failure, as defined by a rapid increase in serum creatinine over 150 µmol/L or rapid decrease in creatinine clearance below 50ml/min (See Appendix D for guidance of reporting and Follow-Up).
- Severe skin reaction such as toxic epidermal necrolysis or Stevens Johnson syndrome.
- Sustained increase in blood pressure: SBP ≥160 mmHg, DBP ≥100 mmHg on at least 2 consecutive visits.
- Other reasons for expedited reporting:
  - Overdose (see Section 9.8.4). An overdose (symptomatic or not) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the intended dose (ie, 2 tablets) on a given calendar day. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE form,
  - Any pregnancy diagnosed in a female subject or in the female partner of a male subject during treatment with the IMP must be reported to the Sponsor immediately. The treatment should be withdrawn and the accelerated elimination procedure performed.

Information related to the pregnancy must be provided to the Sponsor. Information related to the birth of a child of an exposed patient must be provided to the Sponsor. The "Drug exposure via parent" form must be completed.

9.8.2 Laboratory test monitoring

In the case of elevated aminotransferases, neutropenia, thrombocytopenia, acute renal failure, or suspicion of rhabodomyolysis, the specific follow-up actions for this abnormality should be initiated according to the appended decision chart (Appendix D – General guidance for the follow-up of laboratory abnormalities).

9.8.3 Monitoring electrocardiogram

The ECG of any clinical trial patient with a clearly prolonged QTc interval (QTcB/QTcF ≥500 msec) will be reported in an expedited fashion by the centralized ECG system to the investigator and to the Sponsor.

Appropriate medical diligence by the investigator, in such an instance, includes an investigation of the cause of the QTc interval prolongation. This investigation includes clinical laboratories to determine serum potassium, calcium, and magnesium levels, as well as to obtain a PK sample at the time of discovery of the QTc interval prolongation.

9.8.4 Overdose information

An overdose with the IMP is an event suspected by the investigator or spontaneously notified by the patient (not based on systematic pill count) and defined as any dose above the recommended maximal dose administered within the Clinical Trial:

- Overdose is defined as 2 or more tablets of IMP in one day (a 24-hour period)

NOTE: The circumstance (ie, accidental or intentional), amount, and time period should be clearly specified in the verbatim terminology.

9.8.5 General guidance for relapses (refer to Section 10.1.3.5 for detailed instructions)

Subjects/parents/guardians will be instructed to contact their investigator immediately should any neurological symptom appear. The subject must be examined as soon as possible, but within 7 days of contact as follows:

Patient should have a physical exam and a complete neurological examination with FSS/EDSS by the blinded rater.

The relevant information will be sent to the RAP for confirmation of relapse.

The RAP will determine whether a subject has experienced a protocol-defined relapse. The RAP will review, in an expedited fashion, the records of all subjects who develop new or worsening neurological symptoms. All reviews will be done based on subject examination records from the

Treating Neurologist and Examining Neurologist, but without knowledge of the subject's treatment assignment.

9.8.6 Re-consent process

Patients/parents/guardian may decide to discontinue study treatment or to discontinue from participation in the trial at any time. In addition, to continue study participation, patients must undergo a repeat informed consent process when they enter the open label period or when they enter the optional additional extension period for young patients. They must also re-consent each time they have a RAP-confirmed relapse in the PK run-in, and each time they have a confirmed relapse in the open-label period.

The re-consent/assent process must include discussion with the patient/parents/guardians about the alternative approaches to therapy, such as all approved therapies, that are available to him or her.

Additional re-consents may be needed as per local regulations, eg, when patients turn 18.

9.9 ACCELERATED ELIMINATION PROCESS

Oral intake of cholestyramine or activated charcoal significantly accelerates the elimination of teriflunomide. The preferred washout medication is cholestyramine. Without using the accelerated elimination procedure, it may take years for teriflunomide plasma concentrations to reach acceptable low levels (≤0.02 µg/mL) due to the long elimination half-life. All patients who complete or discontinue the study drug must undergo one of the accelerated elimination procedures described below. These procedures must be carried out at the study site by the Investigator. For patients who will continue to the commercially available drug, no accelerated elimination procedure is required.

Accelerated elimination procedure

The accelerated elimination procedure must be initiated in all patients who have definitively discontinued the study medication and will not continue teriflunomide treatment after completion of the study. The recommended procedure is cholestyramine with a dose adjusted for children's weight (240 mg/kg/day (80 mg TID)). Alternatively 50 g oral activated charcoal powder administered every 12 hours for 11 days may be used.

Table 2 - Washout medications and dosage

	Cholestyramine	Activated Charcoal
Washout (11 days)	240mg/kg/day TID	2 x 50 g = 100 g daily

After treatment with either cholestyramine or activated charcoal taken for 11 days, the teriflunomide plasma concentration has to be verified as <0.02 µg/mL prior to withdrawal from/completion of the study. A post-washout PK sample will be collected immediately following administration of washout medication and at both post-drug elimination follow up visits

(EOT+2W and EOT+4W). The PK samples after washout will be labeled separately from the regular pharmacokinetic samples (using labels and tubes provided in the Washout lab kit) and will be analyzed using a more sensitive bioanalytical assay (see Section 9.11.3). Feed-back on plasma levels above 0.02 µg/mL will be provided only when requested by the Investigator, eg, in case of desired pregnancy. This is applicable for women or men wishing to parent a child, or in specific situations, including planned prescription of fingolimod, natalizumab or mitoxantrone. If the sample collected at EOT+2 weeks has blood plasma levels of teriflunomide >0.02 µg/mL, the site will be notified at EOT+4 weeks and the cholestyramine/charcoal treatment should be repeated. The level should continue to be followed every two weeks until it is equal or below 0.02 µg/mL.

Both cholestyramine and activated charcoal may influence the absorption of estrogens and progestogens and reduce the effectiveness of oral contraceptives; therefore, the use of alternative contraceptive methods for women is recommended during the accelerated elimination procedure.

9.10 ADVERSE EVENTS MONITORING

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

9.10.1 Definitions of Adverse Event(s)

9.10.1.1 Adverse Event

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

9.10.1.2 Serious Adverse Event

A **Serious Adverse Event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death or,
- Is life-threatening or,

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization or,
- Results in persistent or significant disability/incapacity or,
- Is a congenital anomaly/birth defect or,
- Is a medically important event.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately

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life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following medically important events intend to serve as a guideline for determining which condition has to be considered as a medically important event. It is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm,
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia…),
  - Convulsions (seizures, epilepsy, epileptic fit, absence…)
  - Development of drug dependency or drug abuse,
  - ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN,
  - Suicide attempt or any event suggestive of suicidality,
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
  - Bullous cutaneous eruptions,
  - Cancers diagnosed during the study or aggravated during the study,
  - Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged as unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

9.10.2 Obligation of the Investigator regarding safety reporting

9.10.2.1 Adverse events

All AEs regardless of seriousness or relationship to IMP, spanning from the signature of the Informed Consent Form, until the end of the clinical trial as are recorded on the corresponding page(s) included in the case report form.

Whenever possible, a diagnosis or single syndrome is reported instead of symptoms. The investigator specifies the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP. Intensity will be graded based on CTCAE Version 4.0.

Laboratory, vital signs, or ECG abnormalities are recorded as AEs only if they are clinically significant or defined as AEPM (see Section 9.8.1):

- Symptomatic, or,

- Requiring either corrective treatment or consultation, or,
- Leading to IMP discontinuation or modification of dosing, or,
- Fulfilling a seriousness criterion.

A priori, efficacy endpoints as specified in the protocol will not be considered as AEs except if, because of the course or severity or any other features of such events, the Investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition.

9.10.2.2 Serious adverse events

In the case of occurrence of an SAE, the investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate pages screens of the electronic case report form; the system automatically sends the notification to the Monitoring Team after approval of the investigator within the electronic case report form or after a standard delay.
- SEND (preferably by fax or email) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the Monitoring Team. Care is taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges with the report.
- PROVIDE all further data updates that should be reported in the electronic case report form. Further documentation as well as additional information (for lab data, concomitant medication, patient status) is sent (by fax or email) to the Monitoring Team within 1 working day of knowledge. In addition, every effort should be made to further document each SAE that is fatal or life threatening within the week (7 days) following initial notification.
- UTILIZE a back-up plan (using paper flow) when the electronic case report form system does not work.

9.10.2.3 Safety observations (follow-up)

- The investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of SAE and AEs of special interest until clinical recovery is complete and laboratory results have returned to normal or until progression has been stabilized or until death. In all cases, this may imply that observations will continue beyond the last planned visit of the patient, and that additional investigations may be requested by the Monitoring Team.
- When treatment is prematurely discontinued, the patient’s observations will continue until the end of the study (except for patients discontinuing during the optional additional treatment extension period).

- At any time after the end of the study for the patient, if a SAE/AEPM is brought to the attention of the investigator and considered by him/her to be caused by the IMP with a reasonable possibility, the investigator should report the event with immediate notification to the Monitoring Team.

9.10.3 Obligations of the Sponsor

During the course of the study, the Sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the Health Authorities, Institutional Review Boards (IRBs), Independent Ethics Committees (IEC) as appropriate and to the investigators.

9.11 PHARMACOKINETICS (PK)

9.11.1 Sampling time

Blood samples will be collected at the following times for the evaluation of teriflunomide PK in pediatric patients. Local anaesthetic must be offered for blood draws to minimize pain and discomfort.

Table 3 - PK sampling times for teriflunomide concentrations during double-blind treatment period and open-label period

Visit	Dosing status	Sampling Time
Week 2, 3, 4, 8, 12, 24, 36 and EOT and overdose	Pre-dose	One PK sample: approximately 5 minutes before IMP intake Time and date of the PK sample collection and time of last IMP intake recorded
Post drug elimination (both visits)	No dosing	One PK sample is taken per visit to verify that plasma teriflunomide concentration is less or equal to 0.02 µg/mL. Date and time of the PK sample collection will be recorded

EOT: End of treatment; IMP = investigational medicinal product; PK = pharmacokinetics.

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 or safety lab visit (W2, W3 or in the event the 4th sample is needed).

9.11.2 PK handling procedure

Special procedures for collection, storage, and shipping of teriflunomide PK samples are described in the operational manual for handling samples to be sent by the Central Laboratory. An overview of PK handling procedures for teriflunomide PK samples is provided in Table 4.

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Table 4 - Pharmacokinetics handling for teriflunomide

Sample type	Teriflunomide
Blood sample volume	2 mL
Anticoagulant	Sodium heparin
Blood handling procedures	Keep whole blood on ice until harvest (must be within 30 minutes of sampling time) by centrifugation at approximately 1500-2000 g for approximately 10 minutes. Separate the plasma into a storage tube.
Plasma storage conditions	In 5 mL Sarstedt polypropylene, screw cap, flat base tube (Product Code No. 60.558 PP) (www.sarstedt.com) at -20°C.

9.11.3 Bioanalytical method

Teriflunomide PK samples will be assayed using a validated liquid chromatography method coupled with tandem mass spectrometry (LC-MS/MS) with a lower limit of quantification of 0.01 µg/mL under the responsibility of Covance Bioanalytical Services, LLC, Indianapolis, IN, USA.

9.11.4 Pharmacokinetic parameters

An assessment of the adequacy of dosing will be done at the end of the PK run-in (8 weeks) phase. For each pediatric patient, teriflunomide C_{trough} from Weeks 4, 8 and 12 will be used to calculate individual post hoc steady-state predicted PK parameters (C_{max} and AUC_{0-24}) using the PopPK model adapted to the pediatric population (POH0401). These predicted parameters will then be compared to the range (5th - 95th percentile) of the individual predicted PK parameters in adult patients after repeated doses of 7 mg. Adult range (5th - 95th percentile) of predicted PK parameters: 7 mg dose range for C_{max} is 8.03 to 49.10 µg/mL and for AUC0-24 is 184 to 1160 µg.h/mL. (POH0339; including data from studies TDR10892, 2001 EFC6049/TEMSO, EFC10891/TENERE and EFC10531/TOWER).

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10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

It is preferred that all study visits take place in the morning. Visits can be performed on 2 consecutive days when convenient. If a patient is prematurely discontinued from the study treatment, all EOT visit procedures should be performed.

The visit schedule consists of the following visits:

- Screening (Visit 1/Week -4) up to 4 weeks prior to the randomization visit (Visit 2).
  - No IMP is administered in this period.
- Double-Blind Treatment period
  - Randomization (to either teriflunomide or placebo) at randomization (Visit 2),
  - Patients will be on the treatment period of the study for 96 weeks unless prematurely discontinued or switching to the open-label extension period,
  - Patients experiencing a relapse after the PK run-in period (8 weeks) and if confirmed by the Relapse Adjudication Panel (RAP) will have the option to continue in an open label teriflunomide treatment arm. If RAP does not confirm the relapse, the patient may continue in the double-blind treatment period or prematurely discontinue treatment,
  - Visit 3 (W4) to Visit 20 (W96/EOT),
  - For patients prematurely discontinued from treatment, Visit 20 (W96/EOT) procedures should be performed,
  - Clinical laboratories are performed in both routine study site visits and safety laboratory visits that are performed locally (see Section 1.2; two separate lines in the flowchart to indicate the different schedules),
  - In case of at least 5 new/enlarged T2 lesions at the MRI of Week 24, an additional MRI will be performed at Week 36. Then, in case of -at least 9 new/enlarged T2 lesions at Week 36 or -at least 5 new/enlarged T2 lesions on each of the 2 consecutive MRI scans of Week 36 and Week 48, or at least 5 new/enlarged T2 lesions on each of the 2 consecutive MRI scans of Week 48 and Week 72, patients will have the option to continue in the open label period.
- Post drug elimination follow up period (4 weeks)
  - No IMP is administered in this period,
  - Patients who complete the treatment period as well as patients who discontinue prematurely should be scheduled for 2 follow-up visits (Visit 21 and Visit 22),
  - Patients will be taking non-IMP (either cholestyramine or activated charcoal) to accelerate the drug elimination process, starting immediately after IMP discontinuation (ie, the same day or the day after).

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10.1.1 Screening (Visit 1, Week-4)

This visit is to be conducted up to 4 weeks prior to randomization (Visit 2).

The following items will be checked/performed and recorded:

- Informed consent/assent to be signed prior to all screening assessments
  - Patient must sign the assent form,
  - Patient's legal guardian must sign the informed consent.
- Eligibility by review of Inclusion/Exclusion criteria.
- Demographic data.
- Medical and surgical history, including:
  - Concurrent illnesses,
  - Detailed neurological history,
  - Detailed vaccination history.
- Prior medications.
- EDSS assessment.
- Adverse event reporting.
- Vital signs (BP, HR, body temperature and weight).
- Physical examination.
- Clinical laboratories
  - Hematology and differential panel,
  - Coagulation group panel,
  - Liver function panel,
  - Chemistry panel,
  - Pancreatic enzyme tests,
  - Urinalysis panel,
  - Pregnancy testing (β-HCG),
  - Tuberculosis test.

10.1.2 Randomization Visit (Visit 2) (to be randomly assigned either to teriflunomide or to placebo

The following items will be checked/performed and recorded and then patients are randomized to either teriflunomide or placebo group:

- Verification of eligibility by review of Inclusion/Exclusion criteria.

- Prior medications.
- Randomization via IVRS.
- EDSS.
- Symbol Digit Modalities Test (SDMT) and Cognitive battery test.
- Brain MRI (can be performed anytime between Visit 1 and Visit 2) A previous MRI performed in the 6 weeks preceding randomization could be acceptable if performed according to the specifications for this study.
- Adverse event reporting.
- Vital signs (BP, HR, body temperature, height and weight).
- Physical examination, including Tanner assessment.

NOTE: Tanner can be performed either at the study site or by pediatricians independent of the study clinic. This examination can be done at Visit 2 or shortly after Visit 2 and it is independent of criteria for randomization.

- 12-lead ECG.
- Pregnancy testing (β-HCG).
- Clinical laboratories (including immunoglobulins and TSH).
- Concomitant medications.
- Dispensing study medication.

10.1.3 Visits during the double-blind treatment period

10.1.3.1 Assessments performed for all clinic visits

- Adverse event reporting.
- Concomitant medications.
- Vital signs (BP, HR, body temperature and weight); height only at the Visit 2 and EOT visit.
- Accountability/compliance.

10.1.3.2 Assessments performed on the clinic visits specified

- Dispense study medication: Week 8, 12 and every 12 weeks.
- EDSS: Every 24 weeks.
- SDMT: Every 24 weeks.
- Laboratory routine parameters at Weeks 4, 12, 24, 36, 48 then every 12 weeks.
- B-HCG every 12 weeks.
- Immunoglobulins and TSH every 24 weeks.

- Physical examinations: Week 12, then every 12 weeks.
- Tanner Staging at Week 24, 48, 72 (until complete sexual maturity defined by Tanner Stage 5).
- Pre- and post- dose plasma PK sampling: Weeks 2, 3, 4, 8, 12, 24, 36.
- Brain MRI: Weeks 24, 48, 72 and 36 if necessary.
- 12-lead ECG: Baseline and at EOT or premature treatment discontinuation.

10.1.3.3 Safety laboratories performed in between clinic visits

Safety laboratory visits will be scheduled in between clinic visits. At Weeks 8, 16, 20, 30 and then every 12 weeks until the end of the treatment (EOT), 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).
- Pancreatic enzymes (serum amylase and lipase).

Study nurse visit at patient's home can be provided (except at Week 8).

Safety laboratory visits, with prior documented study site approval, may be collected at a qualified blood testing center more convenient to the patient's travel needs. The samples will be sent by the test center to the Central laboratory. Safety blood samples may only be analyzed at the test center (ie, local laboratory) in exceptional cases where a patient requires emergency treatment involving the need of immediate laboratory results or where centralized analysis is not possible.

10.1.3.4 Assessments performed on the EOT or premature treatment discontinuation

Patients who complete the treatment period or who prematurely discontinue should complete EOT procedures including both safety and efficacy assessments. This visit does not need to be performed when the patient switches to the open label period after a confirmed relapse or high MRI activity (as per protocol criteria). Prematurely discontinued patients are encouraged to participate in an early permanent treatment discontinuation (EPTD): they will be followed for safety until they complete 96 weeks from randomization. This includes discontinuation from the open label period, when it occurs within 96 weeks of randomization.

- EDSS.
- SDMT.
- Cognitive Battery Test.
- Brain MRI.
- Adverse event reporting.
- Vital signs.

- Physical examination.
- ECG 12-leads.
- Tanner staging.
- Clinical routine laboratories (including immunoglobulins and TSH).
- Concomitant medication.
- Accountability / compliance.
- Teriflunomide PK sampling.

Post drug elimination process (ie, prescribing Cholestyramine or Activated charcoal and scheduling for two follow up visits) should be initiated.

10.1.3.5 Assessments performed on the unscheduled relapse visits

At each evaluation of a potential relapse, the following procedures will be performed. The procedures should be performed in the order in which they appear:

1. Patients or parents/guardians must call the study site within 48 hours of symptom onset to report any symptoms that suggest a possible relapse and present for evaluation. All calls to the site reporting a possible relapse should be recorded in a call log maintained at the site as part of source documentation.

2. Patient should be evaluated at the site within 7 days of onset of neurological symptoms.

3. Blinded rater performs examination to document the Functional System Scores (FSS) and EDSS, with no reference to previous scores. Conversation between the rater and patient should elicit only the minimum historical information needed to complete these tasks.

4. Treating Neurologist or designee obtains vital signs, and takes a history of recent symptoms. A blinded rater may NOT serve as designee for the Treating Neurologist.

5. Supportive laboratory testing, as indicated, is performed.

6. Treating Neurologist completes Clinical Event source documents. Treating Neurologist also determines whether there is a fever or other disqualifying event.

7. If the Treating Neurologist determines treatment for relapse or other clinical event is warranted, treatment can be initiated after the blinded rater's assessment is complete, regardless of whether the event is RAP-confirmed.

Information on all suspected relapses occurring during the double-blind period will be also assessed by a Relapse Adjudication Panel (RAP) in real time.

Treating neurologists do not need to wait for RAP-confirmation to initiate treatment that he or she deems necessary, including corticosteroid treatment for suspected relapses.

The following will also be checked/ performed and recorded:

- Adverse events.
- Concomitant medications.
- Vital signs (BP, HR, body temperature and weight).
- Time and date of last dose prior to the visit.
- If the patient has had a RAP confirmed relapse: signing the informed consent/assent form in order to continue in the study.
- The appointment for the next scheduled clinic visit and safety laboratory visit, if appropriate, will be confirmed.

10.1.4 Post drug elimination follow up visits

Two post-washout follow up visits should be scheduled 2 weeks and 4 weeks after study medication discontinuation and initiation of the washout procedure. These visits are not required in case the patient receives commercial product immediately after the study end.

The following items will be checked/performed and recorded at Visit 21 (EOT+2W) and Visit 22 (EOT+4W):

- Adverse events reporting.
- Concomitant medications.
- Vital signs (BP, HR, body temperature and weight).
- Physical examination at EOT + 2 Weeks only.
- ECG should be performed only for patients who had new abnormalities on the EOT ECG.
- Clinical safety laboratories
  - Hematology and differential panel,
  - Liver function panel,
  - Pancreatic enzyme tests,
  - Uric acid and inorganic phosphorus.
- Post-washout PK sampling (note that the EOT+4W PK sample should be taken even if the EOT+2W PK sample is under 0.02 µg/mL, to document stability level as per EU SmPC).

In case of adverse events AE/abnormal laboratory values, or teriflunomide level > 0.02 µg/mL after the elimination treatment, follow up until resolution should be planned.

10.1.5 Open Label Period

Procedures are described in the specific flow chart Section 1.3.

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10.1.6 Optional additional extension period for young patients

During the optional additional extension period for young patients, the study visits will be performed every 24 weeks and will include the followings:

- AE reporting.
- Concomitant medications.
- Brain MRI (every year). No central reading for MRI is planned in the optional additional extension period.
- Routine neurological exams, vital signs, and physical examinations as per local practice.
- Clinical laboratories: standard liver function tests and hematology tests to be performed every 6 weeks (specific panel to be decided by Investigator). These tests will be performed in local laboratories. Clinically relevant abnormalities should be reported as TEAEs (see Section 9.10.2.1). Other data will not be entered in CRFs.

In addition, all centralized activities will be suspended. Laboratory tests will no longer be performed except at the end of treatment visit (EOT). Safety laboratory test may be performed at any time during the study based on signs and symptoms. These tests will be performed at a local facility. Potential additional local requirements for laboratory monitoring should be taken into account.

10.2 DEFINITION OF SOURCE DATA

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

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

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined if it could be temporarily or permanent.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Re-initiation of treatment with the Investigational Product will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the Investigational Product(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met.

All temporary treatment discontinuation and date of treatment re-initiation should be recorded by the Investigator in the appropriate pages when considered as confirmed.

10.3.2 Definitive treatment discontinuation with investigational medicinal product(s)

All patients who prematurely and permanently discontinue study medication will be asked to continue until the planned end of the double-blind treatment period EPTD. After completion of the premature discontinuation visit (EOT) and the post drug elimination follow-up visits, the patients continue to have study visits approximately every 12 weeks for clinical follow-up including EDSS, relapse reporting, AE reporting and Concomitant Medications recording.

10.3.2.1 List of criteria for definitive treatment discontinuation

The patients discontinue from study treatment if the patients/parents/guardians decide to do so, at any time and irrespective of the reason or the investigator may decide that it is best for the patient to stop treatment.

Study medication will be discontinued and the washout procedure will be performed after any of the following events:

Safety

- If acute, potentially life-threatening cytopenias develop.
- If severe bullous skin reactions develop. As soon as skin or mucosal reactions are observed which raise the suspicion of such severe reactions.
- A SGPT/ALT >3-fold ULN must be repeated within 48 hours. In the event of a confirmed value of >3- fold ULN, study medication should be discontinued and subject monitored until the value normalizes.
- A SGPT/ALT between 2 and 3-fold ULN associated with any of the following signs and symptoms including fever, rash, abdominal pain, dark urine, light stools.
- A serum amylase and/or lipase >2-fold ULN associated with symptoms consistent with pancreatitis (eg, abdominal pain, back pain, nausea and vomiting, fever, sweating) or serum amylase and/or lipase >5-fold ULN with or without associated symptoms.
- Abdominal CT scan or MRI findings consistent with chronic pancreatitis. A washout procedure will be initiated following discontinuation.
- If a drug-related peripheral neuropathy is diagnosed.
- If pulmonary toxicity is diagnosed.
- If a patient is found to be HIV positive.

Other

- If a female patient becomes pregnant or wishes to become pregnant during the study (if a female patient confirms plans to continue the pregnancy).

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- If a male patient wishes to father a child during the study.

10.3.2.2 Handling of patients after definitive treatment discontinuation

Patients will be followed up according to the study procedures up to the scheduled date of study completion (96 weeks from randomization), or up to recovery or stabilization of a followed-up AE, whichever comes last.

If possible, all patients who prematurely and permanently discontinue study medication will be asked to perform EOT visit procedures and will be scheduled for post drug elimination visits. Wash-out medications should be prescribed (Cholestyramine or Activated charcoal, see Section 9.9). All definitive treatment discontinuation should be recorded by the Investigator in the appropriate eCRF pages when considered as confirmed.

10.3.3 Procedure for withdrawal of patients from study follow-up schedule

The patients may withdraw from the study if they decide to do so, at any time and irrespective of the reason.

All study withdrawals should be recorded by the Investigator in the appropriate eCRF pages when considered as confirmed;

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

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.

11 STATISTICAL CONSIDERATIONS

The data from the placebo-controlled and the open label teriflunomide treatment phases will be the focus of the CSR of their respective phase. The following statistical methods/considerations relate to the analysis of the data from the placebo-controlled period. The data from the open label teriflunomide treatment arm are non-controlled and supportive in nature; summary statistics will be provided for each of the efficacy variables and safety data. For the optional additional extension period for young patients, the efficacy and safety data will be summarized by descriptive statistics and reported separately.

11.1 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the primary efficacy endpoint, time to first confirmed relapse after randomization. Assuming 60% of placebo patients will experience a relapse by 2 years, 165 children aged 10 to <18 years (110 teriflunomide and 55 placebo; including approximately 20% pre-pubertal patients or 10% of patients under the age of 13 years at time of inclusion into the study and at least 25% male patients) 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.

11.2 DISPOSITION OF PATIENTS

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

Randomized patients consist of all patients, who have been allocated a treatment kit through the study randomization process, ie, with a treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population. Their safety experience will be reported separately, and these patients will not be in the safety population.

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

11.3 ANALYSIS POPULATIONS

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used or not.

11.3.1 Efficacy populations

11.3.1.1 Intent-to-treat (ITT) population

The analysis population for efficacy endpoints will be the ITT population, defined as all randomized patients who receive at least 1 dose of study medication, analyzed according to the treatment allocated by randomization.

11.3.2 Safety population

The analysis population for safety endpoints will be the safety population, defined as all randomized patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment patients actually received.

In addition:

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

11.3.3 Pharmacokinetic population

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

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11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

11.4.2 Extent of investigational medicinal product exposure

Duration of IMP exposure is defined as: last dose date – first dose date + 1 day, regardless of unplanned intermittent discontinuations. The distribution of treatment duration will be summarized by treatment group using descriptive statistics.

11.4.3 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.

Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance <80% will be summarized. In addition, the number and percentage of patients with at least 1 above-planned dosing administration will be given, as well as the number and percentage of patients with 0, (0, 20%], and >20% under-planned dosing administrations.

11.4.4 Analyses of efficacy endpoints

11.4.4.1 Analysis of primary efficacy endpoint(s)

Main statistical model and adjustment for covariates:

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

Handling of dropouts:

Given the time to event analysis methodology, there is no impact on the analysis of the primary endpoint for patients experiencing a first relapse and moving to the open label teriflunomide treatment. Patients discontinuing double-blind treatment due to high MRI activity will be

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censored at discontinuation. Patients who prematurely discontinue the study drug will be encouraged to continue study follow-up as planned according to the study flowchart. The main analysis for time to first relapse will include relapses during the placebo-controlled study treatment period. Relapses reported after study drug discontinuation (for non-relapse reason) will be included in a supportive analysis.

Sensitivity analysis:

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

- Time to first confirmed relapse occurring after the PK run-in (8 weeks) phase but before the treatment discontinuation. The patients who have a relapse during the PK run-in (8 weeks) phase will be included in the analysis with the time to first relapse right censored at the time of treatment discontinuation.
- Time to first relapse (confirmed or not) after randomization during the study treatment.
- Time to first confirmed relapse including relapses during the PK run-in (8 weeks) phase and relapses reported after the study drug discontinuation and up to 96 weeks after randomization.
- Time to first confirmed relapse including high MRI activity meeting criteria for switching into open-label period as an equivalent to confirmed relapse event.

Subgroup analysis:

Subgroup analyses will be performed for the primary efficacy endpoint. The results will be presented for demographic (eg, pubertal status, age, sex, race) and other (eg, MS history, region) subgroups. One of these analyses will include patients with relapsing-remitting form of MS versus other forms. The detailed information will be provided in the Statistical Analysis Plan (SAP).

11.4.4.2 Analyses of secondary efficacy endpoints

The proportion of patients relapse-free at Weeks 24, 48, 72 and 96 will be estimated based on Kaplan-Meier methods. Interval estimates will be calculated using 95% point wise confidence intervals.

The number of new or enlarged T2-lesions per MRI scan will be analyzed using a negative binomial regression model. 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 estimated number of lesions per scan and associated 2-sided 95% CI will be provided for each treatment group. The relative risk, 2-sided 95% confidence interval (CI) and p-value will be provided for comparing teriflunomide to placebo.

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

To reduce the impact of potential outliers, an ordinal logistic regression model including treatment group, region, pubertal status and age will also be used to analyze these endpoints. The following categories for the number of lesions, 0, 1, 2, 3-4 and ≥5, are considered and will be further defined in the SAP.

A Poisson regression model with a robust error variance will be used in sensitivity analyses.

Change from baseline in volume of T2 lesions, T1 hypointense lesions and brain atrophy will be analyzed using a mixed-effect model with repeated measures (MMRM) approach with appropriate transformation if necessary. The proportion of patients free of new or enlarged T2-lesions at Weeks 48 and 96 will be summarized based on all patients having an MRI at these time points. More details will be provided in the SAP.

The change from baseline in cognitive outcomes at each visit will be analyzed descriptively.

11.4.4.3 Multiplicity considerations

Statistical significance will be claimed for the primary efficacy endpoint if the computed p-value from the primary analysis is ≤0.05. No multiplicity adjustment is considered for secondary efficacy outcomes for this study.

11.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group. Analysis of safety will be performed using the safety population. Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately, as appropriate.

The safety analysis will be based on the reported AEs and other safety information including clinical laboratory data, vital signs and ECG data. The baseline value is defined as the last available value before the first intake of IMP.

The observation periods for safety during the 96-week double-blind period will be as follows:

- Screening Period is from informed consent to first dose of IMP.
- Treatment-emergent adverse event (TEAE) period is defined as from first dose of IMP up to 4 weeks (28 days) after last dose of IMP or up to inclusion in open label treatment phase, whichever occurs first. The TEAE period can be divided into 2 distinct periods:
  - Treatment Period from first dose of IMP to last dose of IMP,
  - Accelerated elimination period from 1 day after treatment period up to 4 weeks (28 days) after last dose of IMP or up to inclusion in open label treatment phase, whichever occurs first.

- The post-treatment period is from the day after the TEAE period to the end of the 96-week double-blind period, where applicable.

All safety analyses will adhere to sanofi "Guideline for the Analysis and Reporting of Safety Data from Clinical Trials".

Adverse events:

Pre-treatment, treatment-emergent, and post-treatment AEs are defined as AEs that developed or worsened during the screening, TEAE, and post-treatment observation periods. TEAEs will be further differentiated as "TEAEs during treatment period" and "TEAEs during accelerated elimination period".

The analysis will focus on TEAEs. TEAEs during treatment period and TEAEs during accelerated elimination period will be analyzed separately and combined, as applicable. Proportion of patients with at least one TEAE, treatment emergent SAE, TEAE leading to discontinuation, and treatment-emergent AEs of special interest will be tabulated by treatment group. In addition TEAEs will be described according to maximum intensity and relation to the study medication. Non treatment emergent serious AE will be summarized separately.

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Patient data listings will be provided for all AEs, TEAEs, SAEs, deaths (if any) and AEs leading to treatment discontinuation.

Clinical laboratory evaluation:

The analysis of laboratory data will focus on descriptive statistics and summaries of potentially clinically significant abnormalities (PCSA) and Common Terminology Criteria for Adverse Event (CTCAE) abnormalities based on data from the treatment emergent period. For each parameter, results and changes from baseline will be summarized by treatment group for baseline and each post baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of patients, mean, standard deviation, median, Q1, Q3, minimum and maximum. The proportion of patients who had at least one incidence of PCSA/CTCAE at any time during the TEAE period, treatment period, and accelerated elimination period will be summarized by treatment group. Listings will be provided with flags indicating clinically out-of range values, as well as PCSA values.

Drug-Induced Liver Injury:

The liver function tests, namely, ALT, AST, alkaline phosphatase and total bilirubin are used to assess possible drug induced liver toxicity. The proportion of patients with PCSA/CTCAE values at any post-baseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any post baseline 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 ULN) and total bilirubin elevation (>2 x ULN) will be analyzed for each parameter using Kaplan-Meier estimates, presented by treatment group. 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.

The normalization (to ≤1 ULN) of elevated liver function tests will be summarized 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 before permanent discontinuation of study drug, and normalized after permanent discontinuation of study drug. Note that a patient will be counted only under the maximum elevation category.

The incidence of liver related TEAEs will be summarized by treatment group. The selection of preferred terms will be based on standardized MedDRA query (SMQ) Drug related hepatic disorders – comprehensive search (narrow).

Vital signs and ECG:

The analysis of vital signs and ECG will focus on descriptive statistics and summaries of PCSA and outliers based on data from the treatment emergent period. For each parameter, results and changes from baseline will be summarized by treatment group for baseline and each post baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of patients, mean, standard deviation, median, Q1, Q3, minimum and maximum.

The proportion of patients who had at least one incidence of PCSA/outlier at any time during the TEAE period, treatment period, and accelerated elimination period will be summarized by treatment group. Listings will be provided with flags indicating clinically out-of range values, as well as PCSA values.

Other safety variables:

Patients with peripheral neuropathy finding or abdominal ultrasound findings during the treatment emergent period will be summarized by treatment group using counts and percents.

11.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

Teriflunomide plasma concentrations will be summarized by mean, SD, geometric mean, coefficient of variation, median, minimum, and maximum at each visit where a PK sample is taken 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.

Teriflunomide individual post hoc predicted PK parameters (C_{max} and AUC_{0-24}) will be summarized by mean, SD, geometric mean, coefficient of variation, median, minimum, and maximum at each visit of the PK run-in (8 weeks) phase(s) for teriflunomide-treated patients.

Values will be expressed in the tables with no more than three significant figures.

11.4.7 Analyses of quality of life/health economic variables

Not applicable.

11.5 INTERIM ANALYSIS

No formal interim efficacy analysis of the double-blind treatment period is planned. A Data Monitoring Committee (DMC), independent from the Sponsor and Investigators, will monitor and review all relevant data on a regular basis for the assessment of benefit versus risk and provide recommendations about further continuation of the trial.

12 ETHICAL AND REGULATORY STANDARDS

12.1 ETHICAL PRINCIPLES

This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice (GCP).

In compliance with sanofi-aventis public disclosure commitments, this clinical trial will be recorded in the public registry website clinicaltrials.gov before the enrollment of the first patient. The registry will contain basic information about the trial sufficient to inform interested patients (and their healthcare practitioners) how to enroll in the trial.

12.2 LAWS AND REGULATIONS

This Clinical Trial will be conducted in compliance with all international guidelines, and national laws and regulations of the country(ies) in which the Clinical Trial is performed, as well as any applicable guidelines. Please cross-refer to Section 13.

12.3 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the Patient (and the parent[s] or guardian[s]) of all pertinent aspects of the Clinical Trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the Clinical Trial, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. Local law must be observed in deciding whether one or both parents/guardians consent is required. If only one parent or guardian signs the consent form, the Investigator must document the reason for only one parent or guardian's signature. A specific Informed Consent Form will be obtained before entering into the optional additional extension period for young patients.

A copy of the signed and dated written Informed Consent Form will be provided to the patient.

If informed consent is obtained under special circumstances (emergency, from a guardian, minor, etc.), the method should be specified following the ICH requirements. The first part of the section should be adapted, keeping the point as appropriate.

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The Informed Consent Form and the Assent Form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, should fully inform the patient (and the parent[s] or guardian[s]) of all pertinent aspects of the clinical trial including the written information given approval / favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.

In addition, participants will assent as detailed below or will follow the Ethics Committee (IRB/IEC) approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRB's/IEC's or be consistent with the local requirements):

Participants who can read the Assent Form will do so before writing their name and dating or signing and dating the form.

Participants who can write but cannot read will have the assent form read to them before writing their name on the form.

Participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the Assent form to confirm that assent was given.

The Informed Consent Form and the Assent Form used by the Investigator for obtaining the Patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval / favorable opinion.

In relation with the population of patients exposed in the trial ie, pediatric/minor patients, the IRB/IEC should ensure proper advice from specialist with pediatrics expertise (competent in the area of clinical, ethical and psychosocial problems in the field of pediatrics) according to national regulations. This should be documented.

12.3.1 Assent for patients

An assent is to be signed by children and adolescents 10-below 18 years of age, also for the optional additional extension period. The language for assent is age appropriate for participants to understand the clinical trial.

12.3.2 Assent for optional neurofilament assessment

A dedicated informed consent form (ICF) will be prepared for the use of leftover mandatory PK samples for optional exploratory research and will be submitted to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion. The Investigator or authorized designee will explain to each participant/parents the objectives and conditions of the exploratory research. Participants will be told that they are free to refuse to participate (without impact on study participation) and may withdraw their consent at any time and for any reason during the storage

period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research.

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

As required by local regulation, the Investigator or the Sponsor must submit this Clinical Trial to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

The Clinical Trial (study number, Clinical Trial title and version number), the documents reviewed (Clinical Trial , Informed Consent Form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

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

During the Clinical Trial, any amendment or modification to the Clinical Trial should be submitted to the Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC).

A progress report is sent to the Ethics Committee (IRB/IEC) at least annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) and delegated Investigator staff undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical Trial (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial as regards ethics, Clinical Trial compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

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

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The Informed Consent Form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

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

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

Should a correction be made, the information to be modified must not be overwritten. The corrected information will be transcribed by the authorized person next to the previous value, initialed and dated.

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

Description of the collection of the e-CRF (visit by visit or other).

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

The computerized handling of the data by the Sponsor after review of the e-CRFs may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be appended to the CRFs held by the Investigator and the Sponsor.

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

13.5 USE OF COMPUTERIZED SYSTEMS

Computerized systems used during the different steps of the study are:

- For data management activities, described in operational manual.
- For pharmacokinetic activities, NONMEM® computer program.
- For statistical activities, SAS.
- For pharmacovigilance activities, AEGIS.
- For monitoring activities, IMPACT®, POLARIS.
- For medical writing activities, DOMASYS.

External data loading is planned for this clinical trial.

14 ADMINISTRATIVE EXPECTATIONS

14.1 CURRICULUM VITAE

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

14.2 RECORD RETENTION IN STUDY SITES

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

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

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

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

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

14.3 CONFIDENTIALITY

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

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

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

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

Furthermore, the Investigator and the Sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, Investigator and its collaborators involved in the study.

14.4 PROPERTY RIGHTS

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

The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights.

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

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

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

14.5 DATA PROTECTION

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

Subject race or ethnicity will be collected in this study because these data are required by several health authorities (eg, on afro American population for FDA, on Asian population for the PMDA in Japan or S-FDA in China).

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/ risk ratio, efficacy and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

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

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

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

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

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

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

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

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

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

14.8.1 Decided by the Sponsor

Decided by the Sponsor in the following cases

- If the information on the product leads to doubt as to the benefit/risk ratio.
- If the Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.

- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the clinical trial, breach of the applicable laws and regulations or breach of the ICH guidelines on Good Clinical Practice.
- If the total number of patients are included earlier than expected.
- Conduct of the study is no longer feasible due to changes in therapeutic landscape or ability to recruit or complete the study as designed.

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

14.8.2 Decided by the Investigator

The Investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing clinical study reports and providing summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

A publication committee may be established to take the responsibility for the first international publication. Authorship will include members of the steering committee, employees of the Sponsor, and the principal Investigators at up to 3 top enrolling sites. The committee chairman will be appointed by the Sponsor who will serve as the principle Investigator for the study and lead author on the first international publication.

NOTE: If a data monitoring committee is used in the clinical trial, Sanofi is free to publish, and to communicate the recommendations made by the data monitoring committee, using all existing or future means of communication with an agreement between both parties.

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

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, first presentation or publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the study. However, if no multicenter publication has occurred within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study to the review procedure set forth herein. The Investigator shall provide the Sponsor with a

copy of any such presentation or publication derived from the study for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

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

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

15 CLINICAL TRIAL AMENDMENTS

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

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

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

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

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17 APPENDICES

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Appendix A McDonald's criteria

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TABLE 4: The 2010 McDonald Criteria for Diagnosis of MS

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

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

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

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

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

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

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

Appendix B Kurtzke Expanded Disability Status Scale and Functional System scores

The Kurtzke Expanded Disability Status Scale and Functional Systems are reproduced in this appendix.

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neurostatus scoring

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

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

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EQUIVALENCE WITH PREVIOUS VERSIONS

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

GENERAL GUIDELINES

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

FUNCTIONAL SYSTEMS (FS)

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

EXPANDED DISABILITY STATUS SCALE (EDSS)

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

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

1 VISUAL (OPTIC) FUNCTIONS

VISUAL ACUITY

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

VISUAL FIELDS

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

SCOTOMA

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

* DISC PALLOR

0 not present
1 present

NOTE

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

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

FUNCTIONAL SYSTEM SCORE

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

* = optional part of the examination.

2 BRAINSTEM FUNCTIONS

EXTRAOCULAR MOVEMENTS (EOM) IMPAIRMENT

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

NYSTAGMUS

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

TRIGEMINAL DAMAGE

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

FACIAL WEAKNESS

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

HEARING LOSS

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

DYSARTHRIA

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

DYSPHAGIA

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

OTHER CRANIAL NERVE FUNCTIONS

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

FUNCTIONAL SYSTEM SCORE

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

3 PYRAMIDAL FUNCTIONS

REFLEXES

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

Cutaneous Reflexes
0 normal
1 weak
2 absent

* Palmomental Reflex
0 absent
1 present

Plantar Response
0 flexor
1 neutral or equivocal
2 extensor

LIMB STRENGTH

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

BMRC RATING SCALE

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

FUNCTIONAL TESTS

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

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

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

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

LIMB SPASTICITY (AFTER RAPID FLEXION OF THE EXTREMITY)

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

GAIT SPASTICITY

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

OVERALL MOTOR PERFORMANCE

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

FUNCTIONAL SYSTEM SCORE

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

4 CEREBELLAR FUNCTIONS

HEAD TREMOR

0 none
1 mild
2 moderate
3 severe

TRUNCAL ATAXIA

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

LIMB ATAXIA (TREMOR/DYSMETRIA AND RAPID ALTERNATING MOVEMENTS)

0 none
1 signs only
2 mild: tremor or clumsy movements easily seen, minor interference with function
3 moderate: tremor or clumsy movements interfere with function in all spheres
4 severe: most functions are very difficult

TANDEM (STRAIGHT LINE) WALKING

0 normal
1 impaired
2 not possible

GAIT ATAXIA

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

ROMBERG TEST

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

OTHER CEREBELLAR TESTS

0 normal
1 mild abnormality
2 moderate abnormality
3 severe abnormality

NOTE

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

FUNCTIONAL SYSTEM SCORE

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

5 SENSORY FUNCTIONS

SUPERFICIAL SENSATION (LIGHT TOUCH AND PAIN)

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

VIBRATION SENSE (AT THE MOST DISTAL JOINT)

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

POSITION SENSE

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

* LHERMITTE'S SIGN

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

* PARAESTHESIAE (TINGLING)

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

FUNCTIONAL SYSTEM SCORE

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

6 BOWEL AND BLADDER FUNCTIONS

URINARY HESITANCY AND RETENTION

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

URINARY URGENCY AND INCONTINENCE

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

BLADDER CATHETERISATION

0 none
1 intermittent self-catheterisation
2 constant catheterisation

BOWEL DYSFUNCTION

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

*SEXUAL DYSFUNCTION

Male

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

Female

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

NOTE

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

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

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

FUNCTIONAL SYSTEM SCORE

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

7 CEREBRAL FUNCTIONS

° DEPRESSION AND EUPHORIA

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

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

DECREASE IN MENTATION

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

+ FATIGUE

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

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

FUNCTIONAL SYSTEM SCORE

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

8 AMBULATION

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

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

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

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

NOTE

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

DISTANCE AND TIME REPORTED BY PATIENT

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

ASSISTANCE

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

DISTANCE

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

AMBULATION SCORE

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

9 EXPANDED DISABILITY STATUS SCALE

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

neurostatus.net

Independent Internet Platform for training and certification of physicians participating in projects that use a standardized, quantified neurological examinationand Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

neurostatus training

Interactive Training DVD-ROM for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

neurostatus e-test

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

neurostatus forum

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

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Appendix C Tanner puberty stage classification

Tanner puberty stage classification

Classification of sex maturity stages in girls

Stage	Pubic hair	Stage	Breasts
P1	Preadolescent	B1	Preadolescent
P2	Sparse, lightly pigmented, straight, medial border of labia	B2	Breast and papilla elevated as small mound; areolar diameter increased
P3	Darker, beginning to curl, increased amount	B3	Breast and areola enlarged, no contour separation
P4	Coarse, curly, abundant but amount less than in adult	B4	Areola and papilla form secondary mound
P5	Adult feminine triangle, spread to medial surface of thighs	B5	Mature; nipple projects, areola part of general breast contour

Classification of sex maturity stages in boys

Stage	Pubic hair	Stage	Testes
P1	None	T1	Preadolescent
P2	Scanty, long, slightly pigmented	T2	Enlarged scrotum, pink texture altered
P3	Darker, starts to curl, small amount	T3	Larger
P4	Resembles adult type, but less in quantity; coarse, curly	T4	Larger, scrotum dark
P5	Adult distribution, spread to medial surface of thighs	T5	Adult size

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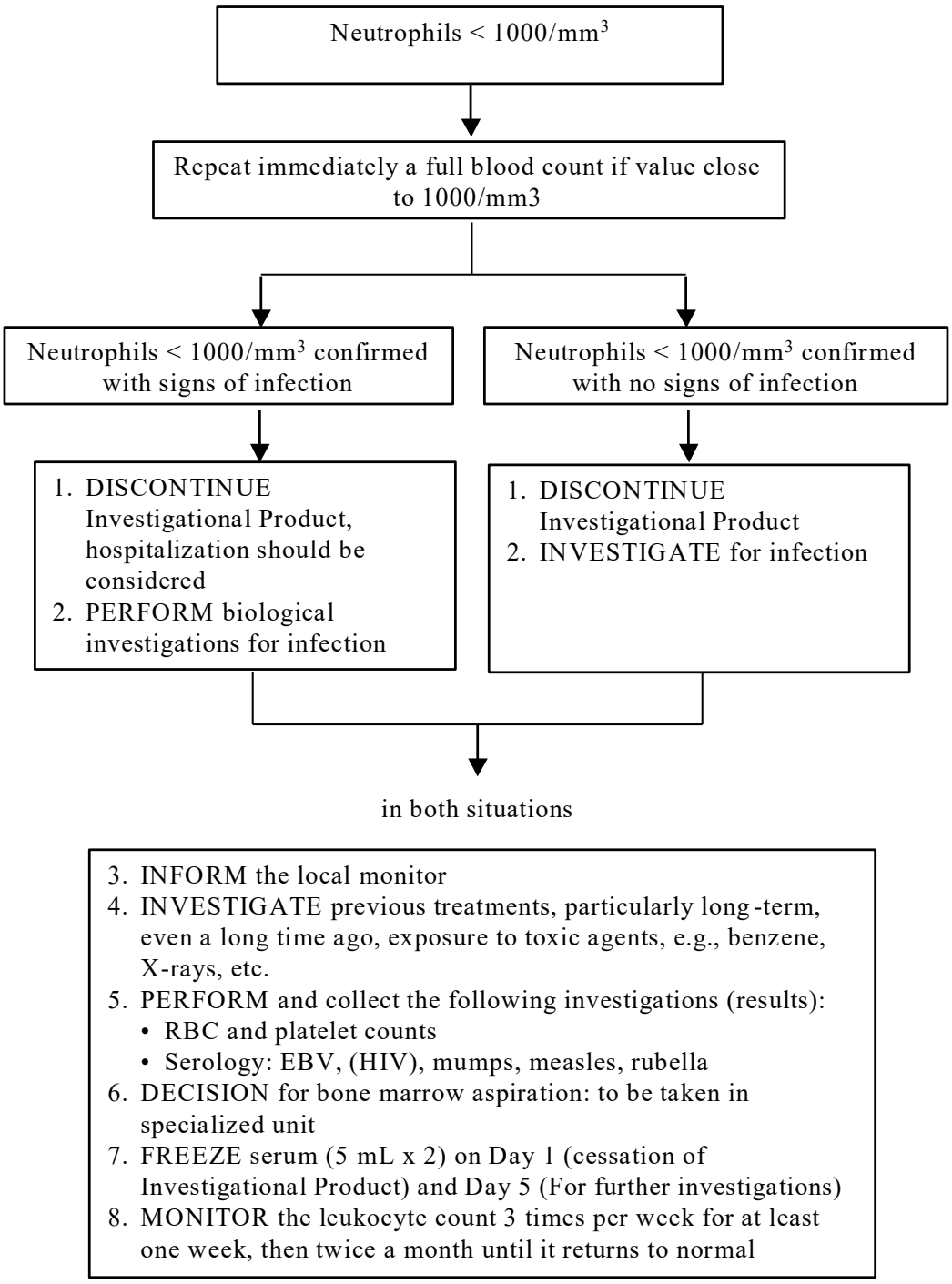
Appendix D General guidance for the follow-up of laboratory abnormalities

NEUTROPENIA



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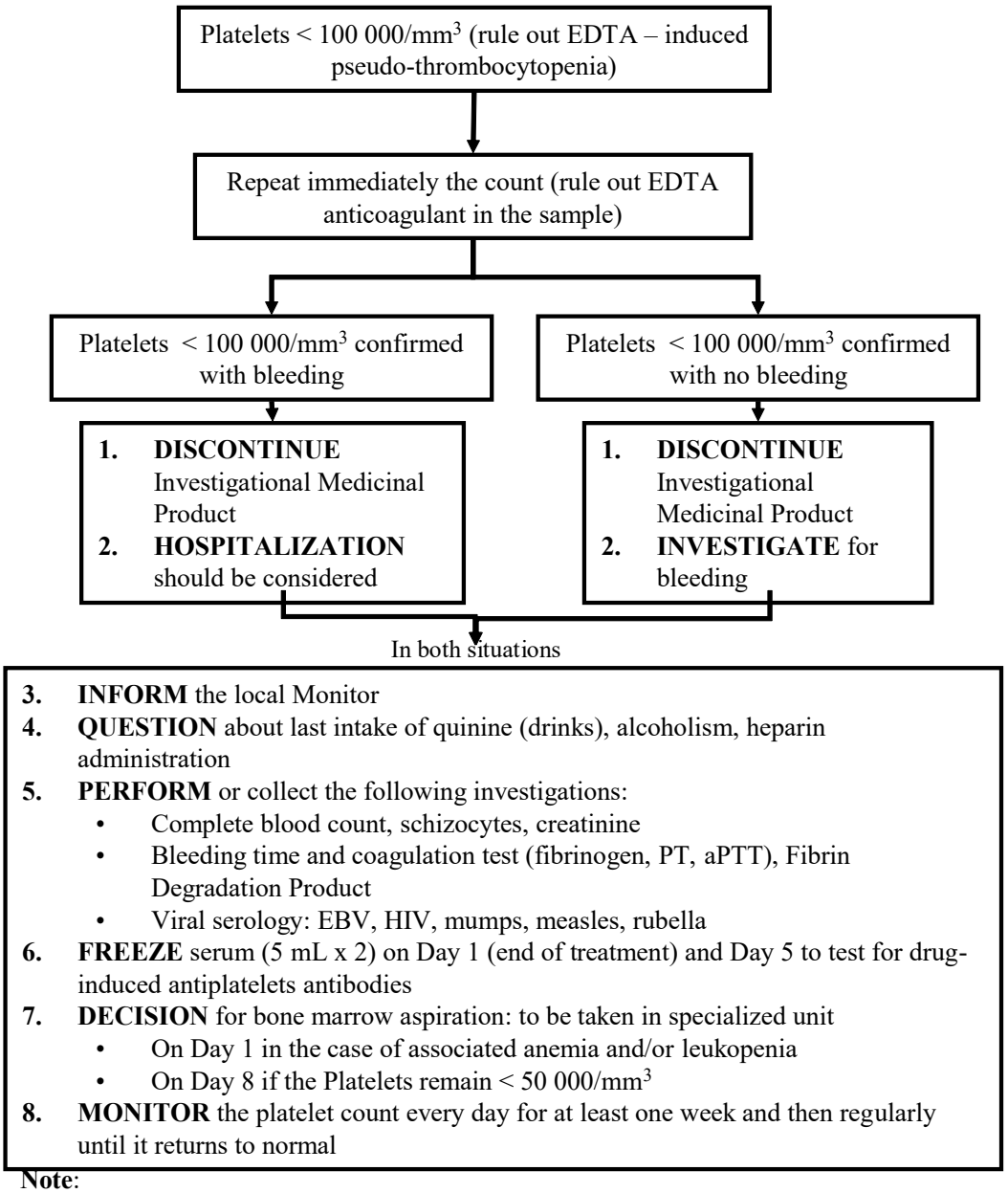
THROMBOCYTOPENIA

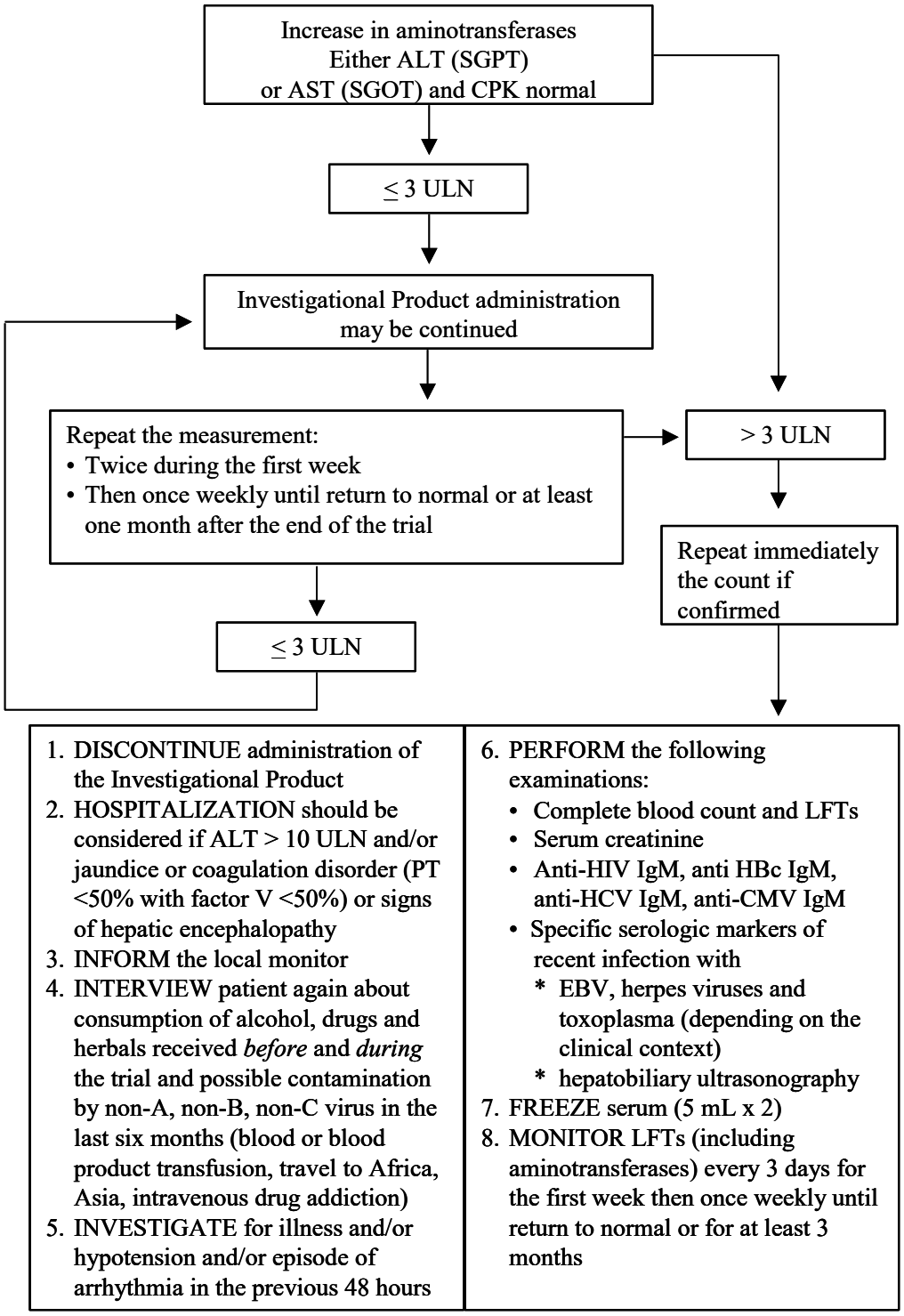


Note:
the procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia are to be recorded as AE only if they are:
- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion [in that case, the event (SAE) should be notified within 1 working day to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI)

INCREASE IN AMINOTRANSFERASES

(Expressed as a multiple of the upper limit of normal (ULN) for the laboratory performing the assay)



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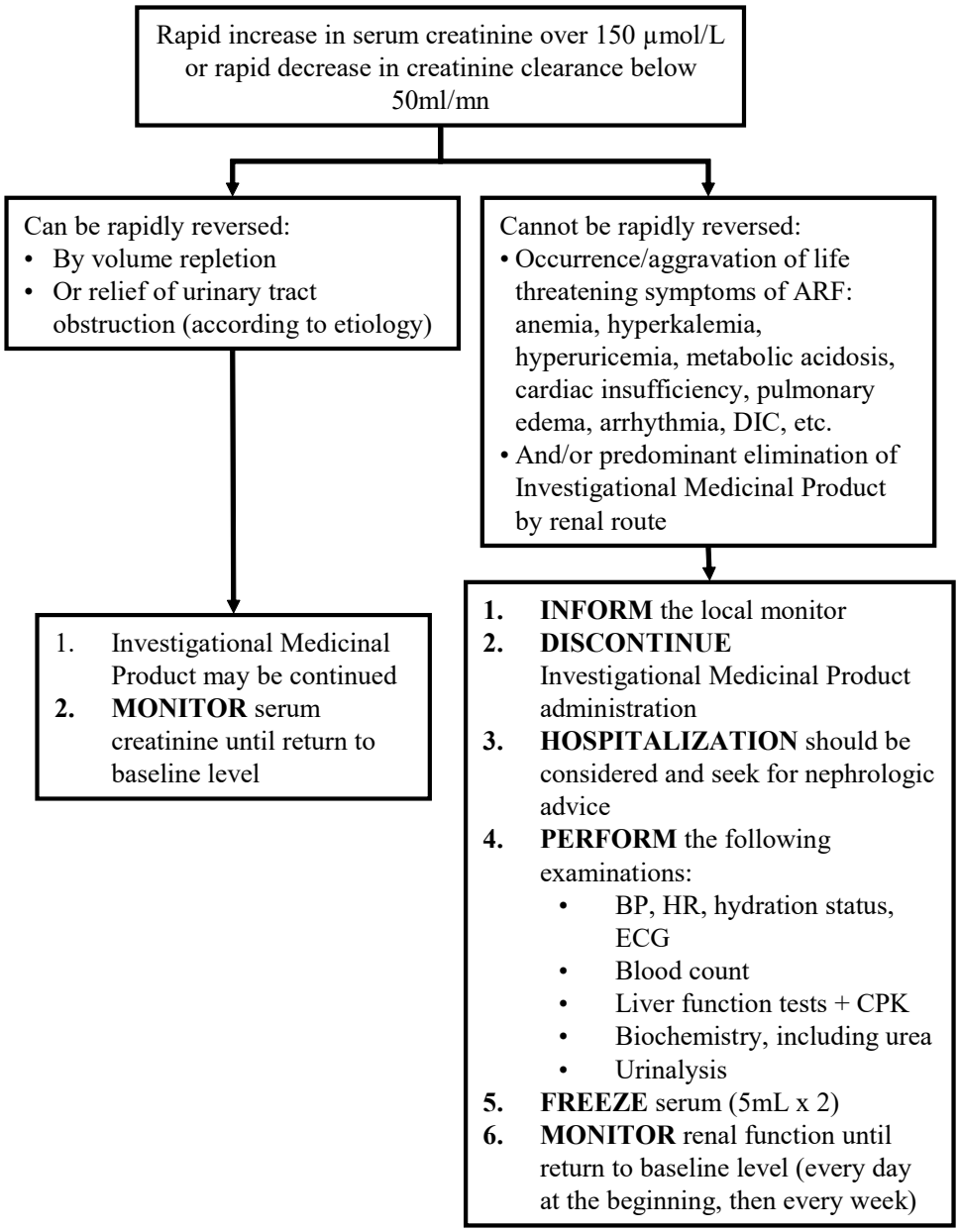
ACUTE RENAL FAILURE



Acute renal failure is to be recorded as AE only if it is :

- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion [in that case, the event (SAE) should be notified within 1 working day to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI)

SUSPICION OF RHABDOMYOLYSIS

Muscular symptoms (myalgia, pain , weakness, dark urines)

Systematic CPK assessment as per protocol

↓

Perform CPK

↓

If Increase in CPK (expressed in ULN)

↓

> 3 ULN

↓

Repeat immediately the count.
If confirmed, inform the local monitor and

↓

INVESTIGATE for the origin:
- **PERFORM**:
  - ECG
  - CPK-MB -MM
  - Troponin
  - Creatinine
  - Iono (k+, Ca^{2}+)
  - Transaminases + Total and conjugated bilirubin
  - Myoglobin (serum and urines)
- **FREEZE** SERUM (5mlx2) for PK
- **INTERVIEW** the patient about a recent intensive muscular effort, trauma, convulsions, electrical injury, injury or stress to the skeletal muscle, multiple intramuscular injections, recent surgery, concomitant medications, consumption of alcohol, morphine, cocaine.
- **SEARCH** for alternative causes to cardiac or muscular toxicity, ie, stroke, pulmonary infarction, dermatomyositis or polymyositis, convulsions, hypothyroidism, delirium tremens, muscular dystrophies.

↓

If either the cardiac origin or the rhabdomyolysis is confirmed or if CPK > 10 ULN:
1. **DISCONTINUE** Investigational Medicinal Product administration
2. **MONITOR** CPK every 3 days for the first week then once weekly until return to normal or for at least 3 months
3. **HOSPITALIZATION** should be considered

If the cardiac origin or the rhabdomyolysis is ruled out and if CPK ≤ 10 ULN:
MONITOR CPK every 3 days for the first week then once weekly until return to normal or for at least 3 months

Suspicion of rhabdomyolysis is to be recorded as AE only if it is:
- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion [in that case, the event (SAE) should be notified within 1 working day to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI)

Appendix E Neurofilament light chain and non-genetic biomarkers processing

1. Participation in the exploration of the effect of teriflunomide on biomarkers in plasma such as Neurofilament light (NfL) chain and potentially other non-genetic biomarkers related to MS disease is optional and does not involve genetic testing. No additional blood samples will be required to be drawn from study patients for this exploratory research. The Investigator or authorized designee will explain to each participant/parents the objectives of the exploratory research, and participants/parents will have to provide a separate consent to participate in this exploratory analysis if they agree to participate. It will be made clear their refusal will not impact their participation in the study
2. NfL and other non-genetic biomarkers will be assessed from leftover plasma PK samples (when available) collected during the study, for all the patients who consented, at the following time points: W2, W12, W24, W36 and W96 for the double-blind period.
3. Additional time points of the double-blind and the open-label may be potentially included.
4. A highly sensitive single molecule array (SIMOA) immunoassay which has recently been developed to measure NfL in plasma/serum will be used.
5. For the patients consenting to this research, samples will be stored in accordance with local regulations at a facility selected by the Sponsor to enable further analysis of biomarker responses to teriflunomide.
6. Results of these exploratory biomarker analyses will be summarized in an ad hoc report separate from the main CSRs of the double-blind and open-label periods.

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Appendix F Country specific requirements

Amendments for the Russian Federation

- As per **Amendment 3 dated 18 December 2014**, at the request of the Ministry of Health of the Russian Federation, the age range was restricted, for the Russian Federation only, to include patients aged from 13 to 17 rather than 10 to 17 years old.
  - Section clinical trial summary - Study population – Main selection criteria – Inclusion criteria:

    ≤17 years of age and ≥13 years of age at randomization
  - Section 6.2 – Inclusion criteria

    ≤17 years of age and ≥13 years of age at randomization
- As per **Amendment 4 dated 26 July 2016**, the previous age range for the recruitment in the Russian Federation that was restricted to patients aged 13 to ≤17, rather than 10 to ≤17, was amended again to allow the recruitment of children 10 to ≤12 years of age, based on the availability of blinded safety data from the global study that show no age specific safety concerns. Therefore, this amendment harmonized the study entry criteria in the Russian Federation related to the age of the patients at enrollment with the age range in the global protocol.
  - Section clinical trial summary - Study population – Main selection criteria – Inclusion criteria:

    ≤17 years of age and ≥10 years of age at randomization
  - Section 6.2 – Inclusion criteria

    ≤17 years of age and ≥10 years of age at randomization

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Appendix G Protocol amendment history

REASON FOR AMENDMENT 1 AND AMENDED PROTOCOL 1 (18 December 2013):

One MRI is added, at Week 24, in addition to the scans at baseline, Week 48 and Week 96, in order to strengthen MRI data which are important in the study. It will provide information on early effect of teriflunomide on MRI endpoints, and increase the power on these endpoints, by being included in statistical modeling. This higher frequency is commonly used in clinical practice. In addition, an MRI will be performed in case of confirmed relapse after PK run-in, to provide additional data before switching to open-label treatment, in particular if the relapse occurs before the Week 24 MRI.

In addition, it is specified that in case of at least 5 new/enlarged T2 lesions at the MRI of Week 24, an additional MRI will be performed at Week 36. Then, in case of -at least 9 new/enlarged T2 lesions at Week 36 (new since Week 24), or -at least 5 new/enlarged T2 lesions at both Week 36 and Week 48 (10 total on these 2 MRIs, new since Week 24), patients will have the option to continue in an open label teriflunomide treatment arm. It is expected that the number of patients meeting these stringent criteria will be low. It is considered that in case of a high number of new/enlarged MRI lesions, investigators will generally be willing to end the study treatment which potentially is a placebo, and that standardization of rules is appropriate under these circumstances.

In the initial protocol, only the two main MRI endpoints are listed, ie, number of new/enlarged T2 lesions and number of Gd-enhancing T1 lesions. The following have been added: change in volume of T2 lesions, change in volume of T1 hypointense lesions, number of new T1 hypointense lesions and brain atrophy. The MRI endpoints have been grouped together.

Immunoglobulin (IgG, IgM and IgA) measurements have been added at baseline and every 24 weeks, in the aim of providing additional information on a potential, although not expected, effect of teriflunomide on the immune system in this age group.

The Poisson regression model with a robust error variance is changed to a negative binomial model for the analysis of the number of new or enlarged T2-lesions per MRI scan and the number of T1 Gd-enhancing lesions per MRI scan MRI. While the Poisson regression model with robust error variance accommodates the overdispersed MRI lesion count data, simulations generally show the negative binomial provides a better fit. Furthermore the negative binomial model is commonly used for analysis of this type of count data in clinical trials. To reduce the impact of potential outliers, ordinal logistic regression model including treatment group, region, pubertal status and age will also be used to analyze these endpoints. The following categories for the number of lesions, 0, 1, 2, 3-4 and ≥5, are considered and will be further defined in the Statistical Analysis Plan. The Poisson regression model with a robust error variance will be used in sensitivity analyses.

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In addition, numerous clarifications and text corrections are made throughout the protocol. These include corrections of the level of title, as the description of assessments appeared inappropriately as subsections of the Section 7 Study Treatment. All subsequent numbering is modified.

REASON FOR AMENDMENT 2 (11 June 2014) AND AMENDED PROTOCOL 2 (26 June 2014):

Extension of open-label period

The open-label period is extended up to 192 weeks after randomization, instead of 96 weeks previously. This change provides patients with the option to enter open-label period for patients completing the 96-week double-blind period.

The duration of the open-label period for a given patient will depend on when he/she enters this period. The duration of the open-label period will be 96 weeks for patients completing the 96-week double-blind period on treatment, and longer for patients switching to open-label during the initial 96 week double-blind period at the occurrence of a confirmed relapse or in case of high MRI activity.

The flow-chart of the open-label period is prolonged and adjusted to extend up to 192 weeks (maximum).

Addition of one MRI timepoint

One MRI is added, at Week 72, in addition to the scans at baseline, Week 24, Week 48 and Week 96, in order to strengthen MRI data which are important in the study. The frequency of MRI will thus be one MRI every 24 weeks.

In addition, a criterion for switch into open-label period taking this additional MRI scan into account is added as follows: at least 5 new/enlarged T2 lesions on each of the 2 consecutive MRI scans of Week 48 and Week 72.

Exclusion criteria

The required minimum washout period duration for previous MS treatment is modified. It is broken down into the following categories:

- 1 month prior to randomization: glatiramer acetate, interferons, dimethyl fumarate.
- 3 month prior to randomization: fingolimod, or intravenous immunoglobulins.
- 6 months prior to randomization: natalizumab, or other immunosuppressant or immunomodulatory agents such as cyclophosphamide, azathioprine, cyclosporine, methotrexate, mycophenolate.
- 2 years prior to randomization: cladribine or mitoxantrone.

Previous treatment with alemtuzumab is added to the list of exclusion criteria.

A note is added that teriflunomide tablets contain lactose and that therefore, investigators should consider whether history of lactose intolerance, in particular Lapp lactase deficiency could affect treatment tolerability.

Regarding contraception, a note is added that local additional requirements are to be followed, eg, spermicidal foam / gel / film / cream / suppository is to be associated with condoms in UK, as per MHRA rules.

Endpoints

Proportion of patients free of new or enlarged MRI T2-lesions at 48 weeks and 96 weeks is added as an additional endpoint. It is specified that the main MRI endpoints will be the number of new/newly enlarged T2 lesions and the number of T1 Gd-enhancing T1 lesions. Proportion of disease-free patients is added as an exploratory endpoint.

Miscellaneous

Added text to the introduction on rationale for placebo-controlled design (Section 3.2.2 Rationale for study design).

Added endocrine function evaluation consisting of measurement of TSH every 24 weeks and at EOT.

Added text that local anaesthetic must be offered for blood draws to minimize pain and discomfort.

Corrected text in Section 9.8.1Pre-defined adverse events and laboratory abnormalities for specific reporting (AEPM) to restore the instructions that were included in the initial protocol but had been inadvertently taken out in amended protocol 1.

In addition, numerous minor clarifications and text corrections are made throughout the protocol.

REASON FOR AMENDED PROTOCOL 3 (02 August 2018):

The efficacy and safety of teriflunomide are evaluated in children with pediatric multiple sclerosis (MS) in Study EFC11759/Terikids, which is ongoing. The enrolment in the study is completed. Teriflunomide is currently approved in countries participating in this study for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS). At the end of their participation in the study, some patients will be too young to access commercial teriflunomide as per authorized indication. This open-label optional additional extension period may be considered for such patients. The optional additional extension period will assess the continued safety and efficacy of teriflunomide in patients until they are 18 years old and/or are able to switch to commercial teriflunomide in their country, whichever comes first. It will be implemented in France, and possibly other countries, where local solutions for continued teriflunomide treatment are not possible within a reasonable time frame.

The optional additional extension period will be performed in conditions approaching clinical practice. In this perspective, the dose will be decided by the Investigator without knowledge of the

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dose in the study. This is necessary to ensure blinding and integrity of the core study, and it is similar to what is done for young patients who receive marketed Aubagio at the end of the study in the context of local country specific solutions. The recommended dose will be teriflunomide 14 mg for patients >40 kg, in continuation to the open-label period of the study, in which the maintenance dose is 14 mg adult equivalent and is expected to be usually 14 mg. This is supported by the good safety of teriflunomide in the study up to now. If the investigator considers that a lower dose would be more appropriate, in particular for patients <40 kg (which is expected to be infrequent, as patients' age will be ≥14 years old), it is possible to administer teriflunomide 14 mg with a lower frequency, eg, every other day for an equivalent of 7 mg.

The safety of teriflunomide is being continuously monitored in the Study EFC11759/Terikids. Regular safety reviews have been performed by an independent external Data Monitoring Committee (DMC). No major safety issues have been identified since the beginning of the study.

Teriflunomide Clinical Investigators' Brochure and SmPC/USPI should be taken into account for patients entering the optional additional extension period.

In addition, Sanofi uses this opportunity to edit other sections of the protocol as listed below, to correct some minor discrepancies and to clarify some sentences.

Inconsistencies, typographical, and spelling errors throughout the document were also corrected.

Signature Page for VV-CLIN-0269458 v5.0
efc11759-16-1-1-amended-protocol04

Approve & eSign	[redacted]

Approve & eSign	[redacted]