Clinical Study Protocol with Global Amendment 02

A Multinational, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Once Daily Oral Administration of Laquinimod (0.6 or 1.5 mg) in Patients with Primary Progressive Multiple Sclerosis (PPMS)

Study TV5600-CNS-20006

(ARPEGGIO - A Randomized Placebo-controlled trial Evaluating laquinimod in PPMS, Gauging Gradations In MRI and clinical Outcomes)

NCT02284568

Protocol Amendment 02 Approval Date: 01 February 2016

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Phase 2

Study TV5600-CNS-20006 (ARPEGGIO - A Randomized Placebo-controlled trial Evaluating laquinimod in PPMS, Gauging Gradations In MRI and clinical Outcomes)

IND number: 71,287 EudraCT number: 2014-001579-30

Protocol Amendment 02 Approval Date: 01 February 2016

Sponsor
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Confidentiality Statement

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Conference on Harmonization (ICH); United States (US) Code of Federal Regulations (CFR) and European Union (EU) Directives (as applicable in the region of the study); local country regulations; and the sponsor's Standard Operating Procedures (SOPs).

This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Pharmaceutical Industries Ltd., and/or its affiliate. The recipient agrees that no information contained herein may be published or disclosed without written approval from the Sponsor.

AMENDMENT HISTORY

The protocol for study TV5600-CNS-20006 (ARPEGGIO) (original protocol dated 21 July 2014) has been amended and reissued as follows:

Global Amendment 02	01 February 2016 301 patients enrolled to date
Global Amendment 01	01 July 2015 49 patients enrolled to date

Details about the changes and rationale for each change are provided in Section 17.

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Global Amendment 02

Original protocol dated 21 July 2014

IND number: 71,287 EudraCT number: 2014-001579-30

A Multinational, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Once Daily Oral Administration of Laquinimod (0.6 or 1.5 mg) in Patients with Primary Progressive Multiple Sclerosis (PPMS)

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Global Amendment 02 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience and training to and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the drug that were furnished to me by the sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the drug and the conduct of the study. I agree to keep records on all patient information, study drug shipment and return forms, and all other information collected during the study, in accordance with local and national Good Clinical Practice (GCP) regulations.

Principal Investigator	**Signature**	**Date**

Protocol Approval

Sponsor's Authorized Representative [redacted]	**Signature** [redacted]	**Protocol with Global Amendment 02 Final Date** FEB 1, 2016
Coordinating Investigator [redacted]	**Signatu** [redacted]	**Date** 01 Feb 2016

CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS

Clinical Research Organization (CRO)

PPD Development, LP
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Wilmington, North Carolina 28401
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1081 HV Amsterdam
The Netherlands

Central Optical Coherence Tomography (OCT)

[redacted]
Heinrich Heine University
Moorenstr. 5 40225, Duesseldorf
Germany

Other Vendors

This study employs the services of multiple third-party vendors (central clinical laboratory, bioanalytical laboratory, pharmacogenomics laboratory, electronic data capture, etc). The names and addresses of the vendors are provided in the Study Laboratory Manual and/or manuals from the various vendors. These manuals will be in the Trial Master File.

CLINICAL STUDY PERSONNEL CONTACT INFORMATION

For medical issues, contact the study Medical Monitor listed below:

North America

[redacted]

EMEA/APAC

[redacted]

For operational issues, contact the operational lead listed below:

[redacted]

Teva Pharmaceuticals Industries, Ltd

12 Hatrufa St., Sapir Industrial Zone

Netanya 42504, Israel

[redacted]

For serious adverse events:

Send by e-mail/facsimile to local safety officer/contract research organization (LSO/CRO). E-mail address and fax number will be provided in the serious adverse event case report form (CRF). In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.

CLINICAL STUDY PROTOCOL SYNOPSIS

Sponsor: Teva Pharmaceutical Industries Ltd

Title of Study: A Multinational, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Once Daily Oral Administration of Laquinimod (0.6 or 1.5 mg) in Patients with Primary Progressive Multiple Sclerosis (PPMS)

Study Number: TV5600-CNS-20006 (ARPEGGIO - A Randomized Placebo-controlled trial Evaluating laquinimod in PPMS, Gauging Gradations In MRI and clinical Outcomes)

EudraCT/IND Number(s): EudraCT Number 2014-001579-30; IND 71,287

Name of Active Ingredient: sodium 5-chloro-3-(ethyl(phenyl)carbamoyl)-1-methyl-2-oxo-1,2-dihydroquinolin-4-olate

Name of Investigational Product: Laquinimod

Phase of Clinical Development: 2

Number of Investigational Centers Planned: Approximately 120

Countries Planned: Approximately 10

Number of Patients Planned: Approximately 375

Study Population: Patients with Primary Progressive Multiple Sclerosis (PPMS)

Planned Study Period: Q4 2014 to Q3 2017

Objectives: The objectives of this study are to assess the efficacy, safety, and tolerability of a once daily oral dose of laquinimod (0.6 or 1.5 mg) compared to placebo in PPMS patients.

Diagnosis and Criteria for Inclusion: Patients may be included in the study only if they meet all of the following criteria:

1. Patients must have a confirmed and documented PPMS diagnosis as defined by the 2010 Revised McDonald criteria.[a]
2. Baseline magnetic resonance imaging (MRI) showing lesions consistent with PPMS in either or both brain and spinal cord.
3. Patients must have an Expanded Disability Status Scale (EDSS) score of 3 to 6.5, inclusive, at both screening and baseline visits.[b]
4. Documented evidence of clinical disability progression in the 2 years prior to screening.
5. Functional System Score (FSS) of ≥2 for the pyramidal system or gait impairment due to lower extremity dysfunction.
6. Patients must be between 25 to 55 years of age, inclusive.
7. Women of child-bearing potential (for example women who are not postmenopausal or surgically sterilized) must practice an acceptable method of birth control for 30 days before taking the study drug, and 2 acceptable methods of birth control during all study duration and until 30 days after the last dose of treatment is administered. Acceptable methods of birth control in this study include: intrauterine devices, barrier methods (condom or diaphragm with spermicide), and hormonal methods of birth control (eg, oral contraceptive, contraceptive patch, long-acting injectable contraceptive).
8. Patients must sign and date a written informed consent prior to entering the study.
9. Patients must be willing and able to comply with the protocol requirements for the duration of the study.

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[a] Polman CH, Reingold SC, Banwell B., et al. Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the "McDonald Criteria" Ann Neurol 2011; 69:292-302.

[b] A capped randomization procedure will be employed to ensure that the number of EDSS 6.0 and 6.5 patients will be no more than 20% of all enrolled patients.

Criteria for Exclusion: Patients will be excluded from participating in this study if they meet any of the following criteria:

1. Patients with history of any multiple sclerosis (MS) exacerbations or relapses, including any episodes of optic neuritis.
2. Progressive neurological disorder other than PPMS.
3. Any MRI record showing presence of cervical cord compression.
4. Baseline MRI showing other findings (including lesions that are atypical for PPMS) that may explain the clinical signs and symptoms.
5. Relevant history of vitamin B12 deficiency.
6. Positive human T-lymphotropic virus Type I and II (HTLV-I/II) serology.
7. Use of experimental or investigational drugs in a clinical study within 24 weeks prior to baseline. Use of a currently marketed drug in a clinical study within 24 weeks prior to baseline would not be exclusionary, provided no other exclusion criteria are met.
8. Use of immunosuppressive agents, or cytotoxic agents, including cyclophosphamide and azathioprine within 48 weeks prior to baseline.
9. Previous treatment with fingolimod (GILENYA®, Novartis), dimethyl fumarate (TECFIDERA®, Biogen Idec Inc), glatiramer acetate (COPAXONE®, Teva), interferon-β (either 1a or 1b), intravenous immunoglobulin, or plasmapheresis within 8 weeks prior to baseline.
10. Use of teriflunomide (AUBAGIO®, Sanofi) within 2 years prior to baseline, except if active washout (with either cholestyramine or activated charcoal) was done 2 months or more prior to baseline.
11. Prior use of monoclonal antibodies ever, except for:
    a. natalizumab (TYSABRI®, Biogen Idec Inc), if given more than 24 weeks prior to baseline AND the patient is John Cunningham (JC) virus antibody test negative (as per medical history)
    b. rituximab, ocrelizumab, or ofatumumab, if B cell count (CD19, as per medical history) is higher than 80 cells/μL
12. Use of mitoxantrone (NOVANTRONE®, Immunex) within 5 years prior to screening. Use of mitoxantrone >5 years before screening is allowed in patients with normal ejection fraction and who did not exceed the total lifetime maximal dose.
13. Previous use of laquinimod.
14. Chronic (eg, more than 30 consecutive days or monthly dosing, with the intent of MS disease modification) systemic (intravenous, intramuscular or oral) corticosteroid treatment within 8 weeks prior to baseline.
15. Previous use of cladribine or alemtuzumab (LEMTRADA®, Sanofi).
16. Previous total body irradiation or total lymphoid irradiation.
17. Previous stem cell treatment, cell-based treatment, or bone marrow transplantation of any kind.
18. Patients who underwent endovascular treatment for chronic cerebrospinal venous insufficiency (CCSVI) within 12 weeks prior to baseline.
19. Use of moderate/strong inhibitors of cytochrome P450 (CYP) 3A4 within 2 weeks prior to baseline.
20. Use of inducers of CYP3A4 within 2 weeks prior to baseline.
21. Pregnancy or breastfeeding.
22. Serum levels ≥3× upper limit of the normal range (ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at screening.
23. Serum direct bilirubin which is ≥2×ULN at screening.
24. Patients with a clinically significant or unstable medical or surgical condition that (in the opinion of the Investigator) would preclude safe and complete study participation, as determined by medical history, physical examinations, electrocardiogram (ECG), laboratory tests or chest X-ray. Such conditions may include:
    a. A major cardiovascular event (eg, myocardial infarction, acute coronary syndrome, decompensated congestive heart failure, pulmonary embolism, coronary revascularization) that occurred during the past 24 weeks prior to baseline.
    b. Any acute pulmonary disorder.
    c. A central nervous system (CNS) disorder other than MS that may jeopardize the patient's participation in the study, including such disorders that are demonstrated on the baseline MRI.

d. A gastrointestinal disorder that may affect the absorption of study medication.
e. Renal disease.
f. Any form of acute or chronic liver disease.
g. Known human immunodeficiency virus positive status.
h. A history of drug and/or alcohol abuse.
i. Unstable psychiatric disorder.
j. Any malignancies, excluding basal cell carcinoma, in the 5 years prior to baseline.

25. A known history of hypersensitivity to gadolinium (Gd).
26. Glomerular filtration rate (GFR) ≤60 mL/min/1.73 m^2 at screening visit.
27. Inability to successfully undergo MRI scanning, including claustrophobia.
28. Known drug hypersensitivity that would preclude administration of laquinimod, such as hypersensitivity to mannitol, meglumine or sodium stearyl fumarate.

Special cases may need a central review by an eligibility evaluation committee prior to baseline.

Study Drug Dose, Mode of Administration, and Administration Rate:

- 0.6 mg arm: 1 capsule containing 0.6 mg laquinimod and the other 2 containing placebo, to be administered orally once daily.
- 1.5 mg arm: 3 capsules containing 0.5 mg laquinimod to be administered orally once daily (Note: this arm was discontinued as of 01 January 2016).
- Placebo arm: 3 capsules containing placebo to be administered orally once daily.

Duration of Participation: The study will include screening up to 6 weeks and 2 parts: Part A (core study) and Part B (data analysis).

Part A will last at least 48 weeks, and individual patients will experience variable treatment durations, depending on the order of enrollment.

Once the last ongoing patient completes the week 48 visit, the sponsor will declare end of Part A and begin performing study analyses.

In Part B, patients will continue their randomly-assigned blinded treatments with visits every 12 weeks until the completion visit. After up to approximately 24 weeks of Part B, or once data analysis has been completed and the design of a potential extension study has been finalized (including blinded or open-label treatment allocation), patients will be invited to the clinic for the completion visit and will be offered the opportunity to continue into an extension study.

General Design and Methodology: This is a multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled study, to evaluate the efficacy, safety, and tolerability of daily oral administration of laquinimod (0.6 or 1.5 mg) in PPMS patients.

Prior to 01 January 2016, eligible patients were randomized in a 1:1:1 ratio into one of the following treatment arms:

- Laquinimod 0.6 mg daily
- Laquinimod 1.5 mg daily
- Daily placebo

As of 01 January 2016, following a decision to discontinue the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1 ratio into one of the following treatment arms:

- Laquinimod 0.6 mg daily
- Daily placebo

A capped randomization procedure will be employed to ensure that the number of EDSS 6.0 and 6.5 patients will be no more than 20% of all enrolled patients.

Patients will have the following study visits: screening visit (-6 weeks), baseline visit (week 0), weeks 4, 8, 12, 24, 36, 48, and every 12 weeks until study completion or early termination (ET).

The following assessments will be performed at the specified time points:

- Vital signs (temperature, pulse, blood pressure) and weight at all visits.
- Physical examination at all visits until study completion/ET, if applicable.
- ECG at screening, week 0 (3 recordings, 10 minutes apart), weeks 4, 8, 12, 24, and every 24 weeks thereafter until completion/ET, if applicable.
- Chest X-ray at screening (can be omitted if the report of a chest X-ray performed within 24 weeks of screening is obtained, or if a screening chest X-ray is considered unacceptable per local regulations).
- Review concomitant medications at all visits.
- Record adverse events at all visits.
- Cardiovascular risk assessment and management at screening, week 96, week 144, and as soon as possible for patients already in the study, following approval of Global Amendment 2.
- Safety laboratory tests:
  - Serum chemistry (including electrolytes, fibrinogen, glucose, urea, creatinine, ALT, AST, gamma-glutamyl transpeptidase [GGT], alkaline phosphatase, creatine phosphokinase [CPK], C-reactive protein [CRP], pancreatic amylase, total protein, albumin, direct and total bilirubin) at all visits.
  - Estimation of GFR at all visits
  - Fasting lipid profile at weeks 0 and 48 and every 48 weeks until completion/ET, if applicable.
  - Serum thyroid stimulating hormone (TSH), triiodothyronine (T3), and free thyroxine (T4) at weeks 0 and 24 and every 24 weeks until completion/ET, if applicable.
  - Coagulation profile (prothrombin time [PT], activated partial thromboplastin time [aPTT] and international normalized ratio [INR]), to be tested only if required according to Guidance on Safety Monitoring).
  - HTLV-I/II at screening.
  - Complete blood count (CBC) with differential at all visits.
  - B12 at screening
  - Anemia panel (blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, interleukin [IL]-1, IL-6, interferon [IFN]-γ, tumor necrosis factor [TNF]-α, and hepcidin) at baseline.
  - In case of hemoglobin decrease of >1 g/dL from the patient's hemoglobin level at baseline:
    - patient will be re-tested to confirm decrease
    - if decrease confirmed, a thorough anemia work-up will be done including:
      - directed medical history and physical examination
      - anemia panel (blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, IFN-γ, TNF-α, and hepcidin) and B12
      - additional investigations and follow-up per the investigator's discretion or sponsor's request
  - Urinalysis at screening.
  - Serum pregnancy test (beta human chorionic gonadotropin [β-hCG]) for women of child-bearing potential within 7 days prior to randomization and at all visits.
  - Urine pregnancy test (β-hCG) for women of child-bearing potential at all visits. In case of positive result, study drug should not be dispensed, until results of serum β-hCG test are available. The rest of the visit activities should be performed.
  - Starting from week 12 visit, between study visits, women of child-bearing potential will be provided with home pregnancy urine β-hCG test kits and will be instructed how to perform the test. The site staff will schedule the home test to be performed every 28 ±2 days. To verify whether the test has been performed and to record the result of the test, a mandatory phone call will be performed by the Treating Neurologist or by the site's nurse/study coordinator within 72 hours after the test was scheduled to be performed and the patient will be asked specific questions regarding the test. In case of a suspected pregnancy (positive urine β-hCG test result, delay of menstruation or any other reason suggesting pregnancy), the caller will ensure that the study drug has been stopped and the patient will be instructed to arrive to the study site as soon as possible (within 10 days) for further evaluations with the remaining study medications.
- Blood samples for evaluation of potential biomarkers will be collected at weeks 0, 24, and 48.

- Pharmacokinetic study: blood samples for analysis of laquinimod plasma concentrations will be collected at weeks 4, 8, 12, 24 and 48.
- A pharmacogenomic sample will be collected at baseline (week 0) as permitted by local regulations; if the sample is not obtained at baseline for any reason, it should be collected at the next possible visit.
- All patients will undergo brain and cervical spinal cord MRI scans at week 0 (without and with Gd), week 24 (without Gd), and week 48 (without Gd). ET visit will include MRI for patients who prematurely terminate treatment subsequent to the week 36 visit and prior to week 48.
- EDSS and FSS will be performed at screening, week 0, and every 12 weeks until completion/ET, if applicable.
- Timed 25-foot walk (T25FW), 9-Hole Peg test (9HPT), and symbol digit modalities test (SDMT) will be performed at week 0, and every 12 weeks until completion/ET, if applicable. At weeks 0, 48, and every 48 weeks thereafter, SDMT will be performed as part of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) assessment.
- BICAMS, including SDMT, will be evaluated at weeks 0, 48, and every 48 weeks thereafter.
- Low contrast visual acuity (LCVA) will be assessed at weeks 0 and 24 and every 24 weeks until completion/ET, if applicable.
- Walking ability will be assessed by the 12-Item Multiple Sclerosis Walking Scale (MSWS-12) at weeks 0 and 12 and every 12 weeks until completion/ET.
- Ancillary studies:
  - Cerebrospinal fluid (CSF) (to be performed in selected sites) will be collected from all patients who signed an appropriate, Ethic Committee (EC) approved informed consent form, at week 48.
  - Optical coherence tomography (OCT) evaluation (to be performed in selected sites) will be performed in all patients who signed an appropriate, EC approved informed consent form, at weeks 0, 48, and 96 to assess retinal thickness.

Primary Efficacy Endpoint:

Brain atrophy (BA), as defined by Percentage in Brain Volume Change (PBVC) from baseline to week 48.

Secondary Efficacy Endpoints:

- Time to confirmed disability progression (CDP), defined as increase in EDSS of ≥1 point from baseline EDSS if EDSS at entry is ≤5.0, or increase of ≥0.5 points if EDSS at entry is ≥5.5. This increase should be confirmed after at least 12 weeks. Progression cannot be confirmed during a relapse, although relapses are rare in PPMS.
- Time to CDP as measured by 2 types of events for each individual (progression cannot be confirmed during a relapse):
  - An increase from baseline in EDSS score (≥1 point from baseline EDSS if EDSS at entry is ≤5.0, or increase of ≥0.5 point if EDSS at entry is ≥5.5), confirmed after at least 12 weeks, **or**
  - An increase of at least 20% from baseline in T25FW score, confirmed after at least 12 weeks.
- Change from baseline to week 48 in the T25FW score.
- The number of new T2 brain lesions at week 48.

Exploratory Endpoints:

- Change from baseline to week 48 in the BICAMS score (California Verbal Learning Test–II [CVLT-II], Brief Visuospatial Memory Test – Revised [BVMT-R], and SDMT).
- Time to CDP as measured by at least 1 of 4 types of events for each individual (progression cannot be confirmed during a relapse):
  - An increase from baseline in EDSS score (≥1 point from baseline EDSS if EDSS at entry is ≤5.0, or increase of ≥0.5 point if EDSS at entry is ≥5.5), confirmed after at least 12 weeks **or**
  - An increase of at least 20% from baseline in T25FW score, confirmed after at least 12 weeks **or**
  - An increase of at least 30% from baseline in the 9HPT score, confirmed after at least 12 weeks **or**
  - A decrease of at least 20% from baseline in the SDMT score, confirmed after at least 12 weeks.
- Time to CDP confirmed after at least 24 weeks.

- New T1-hypointense lesions, changes in T1-hypointense lesion volume, and changes in T2 lesion volume.
- Other MRI parameters, including thalamic, cortical, white matter, and cervical cord atrophy, number of cervical cord T2 lesions, and normal-appearing brain tissue average magnetization transfer ratio (MTR).
- Modified Rankin scale (mRS) (at week 72, visit 8).
- T25FW.
- 9HPT.
- LCVA.
- MSWS-12.

Other Endpoints:

- relapses
- pharmacokinetic measures (determination of plasma concentration of laquinimod)
- pharmacogenomic measures
- potential biomarker measures
- ancillary studies measures

Safety Endpoints:

- **Safety:**
  - adverse events
  - vital signs
  - ECG findings
  - clinical laboratory parameters
  - concomitant medication usage
- **Tolerability:**
  - proportion of patients (%) who prematurely discontinue treatment, reasons for discontinuation, and time to ET
  - proportion of patients (%) who prematurely discontinue treatment due to adverse events and time to ET due to adverse events

Statistical Considerations:

Sample size calculations were based on the following assumptions:

- 2-sided alpha level of 5%
- treatment difference (delta) of 0.3 in PBVC
- standard deviation of 0.8

Under the above assumptions 252 patients enrolled for 0.6 mg and placebo (126 per arm) will provide 84% power to detect a statistically significant result for the 0.6 mg laquinimod arm comparison to placebo. To adjust for the anticipated 10% dropouts, the sample size was increased to 280 patients. Adding 95 patients on 1.5 mg yields a total of 375 patients.

Due to the decision from 01 January 2016 to discontinue the laquinimod 1.5 mg dose arm, and a low study exposure at this time, the laquinimod 1.5 mg dose arm will be presented descriptively only, and will not be included in any inferential analyses.

In addition, all efficacy analyses will be performed based on the measurements recorded during the study treatment period, ie, data captured following an early termination visit will be excluded from the analyses. The data captured after an early termination visit will be used for the sensitivity analyses of the primary and secondary endpoints.

Based on that, the following analyses will be performed using data collected during Part A (Core Study):

1. Primary Endpoint Analysis:

The primary efficacy endpoint for this study is BA as measured by the PBVC from baseline to week 48. This endpoint will be analyzed using the modified intent-to-treat 1 (mITT1) population with at least 1 post-baseline PBVC value, and will include assessments taken up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis). BA will be analyzed using baseline-adjusted repeated measures analysis of covariance (ANCOVA- SAS® PROC MIXED) in which 1 contrast will be constructed in order to compare between laquinimod 0.6 mg and placebo. The model will be comprised from the treatment group as a class variable (2 levels). In addition to the treatment group, week (categorical), week by treatment group, normalized brain volume at baseline, natural logarithm of T2 lesion volume at baseline, and Country/Geographical Region (CGR) will be used as covariates. Additionally, week (categorical) will be specified as a repeated effect and unstructured (UN) correlation matrix will be used to model intra-subject correlation. In case a convergence issue will arise using the UN correlation matrix, (1) AR1 or (2) Compound Symmetry (CS) will be used to enable model convergence (in this order).

2. Secondary Endpoints Analysis:

    a. Time to CDP as measured by EDSS confirmed after at least 12 weeks will be analyzed using the intent-to-treat (ITT) population and data from all the study assessments up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis). This analysis will be performed using baseline adjusted Cox's proportional hazards regression model (SAS® PROC PHREG) in which 1 contrast for comparing laquinimod 0.6 mg to placebo will be constructed. In addition to treatment group, categorical EDSS at baseline (≤4.5 or >4.5), age at baseline, natural logarithm of T2 lesion volume at baseline, and CGR will be used as covariates.
    b. Time to CDP, confirmed after at least 12 weeks as measured by EDSS or T25FW will be analyzed using the ITT population and data from all the study assessments up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis). This analysis will be performed using baseline adjusted Cox's proportional hazards regression model (SAS® PROC PHREG) in which 1 contrast for comparing laquinimod 0.6 mg to placebo will be constructed. In addition to treatment group, categorical EDSS at baseline (≤4.5 or >4.5), age at baseline, T25FW at baseline, natural logarithm of T2 lesion volume at baseline, and CGR will be used as covariates.
    c. Change from baseline in the T25FW score at week 48 will be analyzed on the mITT2 population and will include assessments taken up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis). Since this variable might not follow normal distribution, the ranked values of this measurement will be defined and analyzed using baseline-adjusted repeated measures ANCOVA (SAS® PROC MIXED) in which 1 contrast will be constructed in order to compare between laquinimod 0.6 mg and placebo. In addition to treatment group, T25FW score at baseline and CGR will be used as covariates. Due to the fact that the ANCOVA model will use ranked values and not the actual changes in the T25FW, Hodges-Lehmann estimates will be used in order to present the magnitude of the treatment effect and the corresponding two-sided 95% confidence limit.
    d. The number of new brain T2 lesions at week 48 will be analyzed using the mITT1 population with at least 1 post-baseline T2 scan available if it was performed at least 36 weeks under treatment and will include assessments taken up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis). This analysis will be performed using baseline adjusted negative binomial regression model (SAS® PROC GENMOD) in which 1 contrast for comparing laquinimod 0.6 mg to placebo will be constructed. In addition to the treatment group, the natural logarithm of T2 lesion volume at baseline, age at baseline, and CGR will be used as covariates.

All the secondary analyses mentioned in this section will be repeated while including observations that were recorded following an early termination visit.

Detailed statistical modeling of exploratory endpoints, as well as combined part A and B data, will be described in the Statistical Analysis Plan (SAP). Similarly, descriptive statistics for safety and tolerability measures will also be described in the SAP.

All statistical tests will be performed at 5% nominal significance level to further define the effects estimates of laquinimod but not for strict statistical inferences.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
βHCG	beta human chorionic gonadotropin
9HPT	9-Hole Peg test
AhR	aryl hydrocarbon receptor
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
ARR	annualized relapse rate
ASMA	anti smooth muscle antibodies
AST	aspartate aminotransferase (SGOT)
AUC	area under the concentration by time curve
BA	brain atrophy
BBB	blood brain barrier
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BP	blood pressure
BVMT-R	Brief Visuospatial Memory Test – Revised
CBC	complete blood count
CCSVI	chronic cerebrospinal venous insufficiency
CDMS	clinical data management system
CDP	confirmed disability progression
CFR	Code of Federal Regulations
CGR	Country/Geographical Region
CIOMS	Council for International Organizations of Medical Sciences
CK-MB	creatine kinase MB isoenzyme
C_{max}	maximum plasma concentration
CNS	central nervous system
CPK	creatine phosphokinase
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CRP	C-reactive protein
CSC	Clinical Supply Chain

Abbreviation	Term
CSF	cerebrospinal fluid
CVLT-II	California Verbal Learning Test–II
CYP	cytochrome P450
DLC	dioxin-like compound
DMC	Data Monitoring Committee
EAE	experimental autoimmune encephalomyelitis
EC	Ethics Committee
ECG	electrocardiogram
EDSS	Expanded Disability Status Scale
ET	early termination
EU	European Union
FSS	Functional System Score
GCP	Good Clinical Practice
Gd	gadolinium
GdE	Gadolinium enhancing
GFR	glomerular filtration rate
GGT	gamma-glutamyl transpeptidase
HDL	high density lipoprotein
HTLV-I/II	human T lymphotropic virus Type I and II
I3C	indole-3-carbinol
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IL	interleukin
IMP	investigational medicinal product
INN	international non-proprietary name
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IUPAC	International Union of Pure Applied Chemistry

Abbreviation	Term
IVIG	intravenous immunoglobulin
IVRS	interactive voice response system
IWRS	interactive web response system
JC	John Cunningham
LCVA	low contrast visual acuity
LDL	low density lipoprotein
LKM	liver kidney microsomal
LSO	local safety officer
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MoA	mechanism of action
MRI	magnetic resonance imaging
mRS	modified Rankin scale
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSWS-12	12-Item Multiple Sclerosis Walking Scale
MTD	maximum tolerated dose
MTR	magnetization transfer ratio
NF	nuclear factor
OCT	optical coherence tomography
OTC	over-the-counter
PBVC	Percentage in Brain Volume Change
PGx	pharmacogenomic(s)
PP	per-protocol
PPK	population pharmacokinetic
PPMS	primary progressive multiple sclerosis
PT	prothrombin time
QC	quality control
RBC	red blood cell
RNFL	retinal nerve fiber layer
RRMS	relapsing remitting multiple sclerosis

Abbreviation	Term
SAP	statistical analysis plan
SDMT	symbol digit modalities test
SDV	source document verification
SOC	system organ class
SOP	standard operating procedure
SPMS	secondary progressive multiple sclerosis
ST	Safety (population)
SUSAR	suspected unexpected serious adverse reaction
T25FW	timed 25-foot walk
T3	triiodothyronine
T4	thyroxine
TCDD	2,3,7,8-tetrachloro-p-dibenzodioxin
t_{max}	time to maximum observed drug concentration
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
ULN	upper limit of the normal range
US	United States (of America)

1. BACKGROUND INFORMATION

1.1. Introduction

Multiple sclerosis (MS) is a chronic, autoimmune and neurodegenerative disorder of the central nervous system (CNS), characterized by inflammation and demyelination, as well as oligodendrocyte and neuron dysfunction. The prevalence varies considerably, from regions with low prevalence (<5 cases per 100000) across much of central Asia, to areas with high prevalence (greater than 30 cases per 100000) across the United States (US), Canada, Australia and large parts of Europe and northern Asia ranging from 50 to 100 per 100000.

Approximately 15% of MS patients develop a sustained deterioration of neurological function without distinct exacerbations from the onset; this MS phenotype is known as primary progressive multiple sclerosis (PPMS) (Lassmann and van Horssen 2012, Lublin et al 2014). At diagnosis, approximately 85% of patients have relapsing remitting multiple sclerosis (RRMS), characterized by recurrent acute exacerbations of neurological dysfunction (relapses), followed by recovery. Over time, the majority of patients with RRMS will develop secondary progressive multiple sclerosis (SPMS), in which a less acute inflammatory and more neurodegenerative course of the disease takes over. SPMS develops with progression in disability independent of relapses which usually have subsided. The diagnosis of the transition into this SPMS phase of the disease is usually made retrospectively.

Progressive MS subtypes, such as PPMS and SPMS, typically feature gait dysfunction due to steadily worsening spastic paraparesis, progressive urinary symptoms, and gradual cognitive decline (Koch 2013). The disease mechanisms driving progressive MS remain unresolved, and there is currently no animal model available that accurately reproduces this phenomenon. Therapeutic options for progressive MS are currently limited to symptomatic treatments and physiotherapy (Koch 2013); in this context, a therapy which is effective in limiting the neurodegenerative process and associated disability accumulation would address a major unmet medical need in the treatment of MS. Recently, positive results have been reported in a PPMS trial with the monoclonal antibody ocrelizumab.

The investigational medicinal product (IMP), laquinimod (international non-proprietary name [INN]), also known by the laboratory code TV-5600 or ABR-215062 sodium salt, is a quinoline-3-carboxamide derivative. It is a novel chemical compound with the International Union of Pure and Applied Chemistry (IUPAC) name sodium 5-chloro-3-(ethyl(phenyl)carbamoyl)-1-methyl-2-oxo-1,2-dihydroquinolin-4-olate.

Laquinimod, an innovative oral immunomodulator, is currently undergoing a third Phase 3 study of its development for RRMS (see Section 1.3.2). Its emerging clinical and magnetic resonance imaging (MRI) efficacy profile, supported by extensive pre-clinical evidence, suggests a direct protective effect in the CNS, largely independent of its peripheral anti-inflammatory effects, supporting the evaluation of laquinimod's efficacy in progressive MS.

1.1.1. Study Rationale

Several disease modifying treatments have been registered to treat RRMS, mostly targeting relapse activity and MRI parameters of inflammation, however their effects on brain tissue damage and progressive disability are limited.

Some of the neurodegenerative process in the MS brain are due to inflammation transmigrating from the peripheral blood and lymphatic system and some are independent (Lassmann and van Horssen 2011, Luessi 2012). Importantly, degeneration starts at the earliest stages of the disease and may be responsible for the slow accrual of disability observed in progressive MS subtypes (Trapp 1998).

While none of the tested drugs which work in RRMS have been efficacious in progressive MS, some key learnings have emerged. Given what is known about the pathophysiology of progressive MS, it is reasonable to assume that beneficial drugs would ideally enter the CNS, target microglial and astrocytic activation (Prineas et al 2001), mitigate axonal degeneration (Fitzner and Simons 2010), or block glutamate excitotoxicity (Gonsette 2008), as well as promote remyelination (Irvine and Blakemore 2008). Laquinimod is a small molecule that passively crosses the blood brain barrier (BBB) and is detectable in CNS tissues. It has been shown to modulate several significant pathways common to key neurodegenerative diseases. More specifically, laquinimod modulates the immune cell lineages in the periphery and in the CNS. In the periphery, laquinimod down-regulates monocytic activation and pro-inflammatory cytokine secretion. In the CNS, laquinimod reduces tissue damage by down regulating microglial and astrocytic activation, which is a major cause for tissue destruction, myelin, axonal and neuronal loss.

In the toxic cuprizone rodent model, a well-known model of demyelination and secondary neurodegenerative BBB damage, laquinimod penetrated the intact BBB (Brück and Wegner 2011) and prevented demyelination, microglia activation, axonal transections, reactive gliosis and oligodendroglial apoptosis (Brück et al 2012, Matsushima and Morell 2001).

In addition, 2 recent separate experimental autoimmune encephalomyelitis (EAE) studies revealed that laquinimod can regulate synaptic transmission by increasing inhibitory GABAergic post-synaptic currents and reducing glutamatergic excitatory post-synaptic currents (Ruffini et al 2013), and improve axonal remyelination and integrity (Moore et al 2013), thus supporting its functional neuroprotective and neurorestorative effects.

Importantly, the clinical efficacy profile of laquinimod derived from the 2 completed pivotal RRMS studies, ALLEGRO and BRAVO, is distinctive and different from other disease modifying treatments in MS because the reduction in disease progression is consistently larger than expected based on the relapse based outcomes.

In the pooled analysis, laquinimod demonstrated a 34% reduction in disability progression confirmed after 3 months and a 45% to 47% reduction in disability confirmed at 6, 9, and 12 months. By using the Sormani meta-analysis, it was found that the predicted reduction in 3-month confirmed disability progression (CDP) with laquinimod, given the observed effect on relapses, should be only 5%, whereas the observed reduction in 3-month CDP using the relative risk was 29% (p=0.007), suggesting a pronounced dissociation between the effect on relapses and the effect on disability.

The central action is further supported by laquinimod's consistent effect on reduction of brain atrophy (BA) (30%) as well as other MRI markers of neurodegeneration including thalamic atrophy, preservation of magnetization transfer ratio (MTR) in whole brain and in normal-appearing white matter, and reduction in the evolution of permanent T1 hypointense lesions (Filippi 2013). While the effects on brain volume change occur early following treatment initiation, this effect is evidence for central CNS target organ engagement and will be utilized as the primary endpoint in this study.

Further assessment of the large RRMS clinical study dataset was performed in order to assess patient subgroups which may be more informative with respect to a progressive MS population.

Post-hoc analyses were performed on subgroups defined by baseline Expanded Disability Status Scale (EDSS) and presence of relapses during study. These subgroup analyses showed that in those with baseline EDSS >3, laquinimod treatment led to a 40% reduction in 3-month CDP, and a 53% reduction in 6-month CDP compared to placebo. Patients in the EDSS >3 group who received placebo declined by 2.79 seconds more on the timed 25-foot walk (T25FW) after 24 months compared to patients who were treated with laquinimod (p=0.0035; relative difference=59%). Also, although the number of events was low, laquinimod treatment reduced 3-month CDP by 38.9% in patients who were relapse-free throughout the studies.

Taken together, pre-clinical and clinical data support testing of the hypothesis that laquinimod exerts its effect by a direct protective effect in the CNS largely independent of its peripheral anti-inflammatory effects. This preclinical and clinical profile meets the requirements for clinical testing of laquinimod as a candidate drug in progressive MS.

The rationale for including exclusively PPMS patients in this study is to allow testing of laquinimod in a relatively homogenous patient population.

1.1.1.1. Rationale for Laquinimod 0.6 mg Dose

The selection of the 0.6 mg as the therapeutic dose for pivotal RRMS studies was based on results from two Phase 2 clinical studies (01506203 and LAQ/5062) and an ascending-dose study (99506202).

In the Phase 2 Study 01506203, which evaluated daily doses of laquinimod 0.1 and 0.3 mg, only the 0.3 mg dose reduced the cumulative number of active lesions at week 24. In the Phase 2b Study LAQ/5062, which evaluated daily doses of laquinimod 0.3 and 0.6 mg, only the 0.6 mg dose achieved a statistically significant (p=0.0048) 40% reduction in the mean cumulative number of gadolinium enhancing (GdE) T1 lesions at weeks 24, 28, 32, and 36 (the primary endpoint of the study). However, unlike in Study 01506203, statistical significance was not achieved on this primary endpoint for laquinimod 0.3 mg versus placebo. The lack of effect for the 0.3 mg dose is attributed to the fact that study LAQ/5062 used a standard gadolinium (Gd) dose for detection of enhancing MS lesions, whereas Study 01506203 used a triple Gd dose.

The data from the two Phase 3 studies were obtained with the 0.6 mg dose, here the clinical hypothesis was generated, including data from subgroups with aspects of progressive disease or more advanced RRMS. This extensive safety and efficacy database derived from RRMS makes the use of 0.6 mg as a reference dose useful, as it will allow comparison to these data. The current study includes laquinimod 0.6 mg as the minimal effective dose noted in previous RRMS studies with laquinimod.

1.1.1.2. Rationale for Laquinimod 1.5 mg Dose

The Phase 2 studies (01506203 and LAQ/5062) suggest a dose response up to 0.6 mg based on MRI parameters. In addition, in the rodent cuprizone model laquinimod reduces callosal demyelination in a dose-dependent manner supportive of a linear dose response.

In light of the dose-dependent effects, evaluation of a higher dose of laquinimod in the current Phase 2 study is appropriate and to test whether a further dose response on the pronounced effect on brain volume preservation is noted and whether this 1.5 mg dose is associated with greater efficacy on other endpoints, while preserving an adequate safety and tolerability profile. Notably, an ongoing Phase 3 study in RRMS included a laquinimod dose of 1.2 mg (CONCERTO).

Two studies to evaluate the maximum tolerated dose (MTD) of laquinimod in healthy volunteers and MS patients have been performed. A multiple ascending dose study in MS patients (Study MS-LAQ-101), in which a safety committee recommended dose escalation following data availability for each dosing cohort, did not reveal dose-dependent adverse events, laboratory or electrocardiogram (ECG) findings up to and including the dose of 2.7 mg/day. The results of Study MS-LAQ-101 did not reproduce the results from an earlier multiple ascending-dose study in healthy volunteers and MS patients (Study 99506202), which had established a dose of 1.2 mg/day as the MTD in MS patients, based solely on laboratory findings that were predefined in the protocol as dose limiting toxicity (increased levels of C-reactive protein [CRP]) and fibrinogen). The sample size, treatment duration (4 weeks) and overall exposure were greater in Study MS-LAQ-101 compared to Study 99506202, and assessment of tolerability of dose was based on a combination of clinical evaluation and laboratory parameters. Hence, study MS-LAQ-101 is considered to more accurately represent the safety profile of higher doses of laquinimod, justifying the use of the 1.5 mg dose. The last cohort of patients received 2.7 mg laquinimod with no dose limiting adverse events or laboratory findings. An MTD has not been established as the dose escalation beyond 2.7 mg which had no dose limiting effects was not performed. Therefore, laquinimod 1.5 mg was selected as the maximal dose to be tested for the current study.

While laquinimod at the 0.6 mg dose has been extensively studied in RRMS, this is the first study assessing laquinimod in PPMS patients, bridging the 0.6 mg dose experience and assessing a higher dose of 1.5 mg versus placebo.

Note: On 30 December 2015 the Data Monitoring Committee (DMC) for the CONCERTO and ARPEGGIO studies held an unscheduled meeting to review cardiovascular events. The DMC found an imbalance in serious cardiovascular events in the high dose treatment arms (1.2 mg in CONCERTO, 1.5 mg in ARPEGGIO): in CONCERTO there were 6 such cases in the 1.2 mg arm but none in the 0.6 mg or placebo arms, along with a myocardial infarction in the ARPEGGIO 1.5 mg dose group and a cerebral infarction in a 31-year old patient in the 1.2 mg arm of CONCERTO. Due to these events and the DMC recommendation to stop all laquinimod treatment arms above 0.6 mg in the MS trials, the 1.5 mg treatment arm in the ARPEGGIO study was discontinued as of 01 January 2016. The risk/benefit balance of this dose was considered negative at that point.

The DMC did not identify any overt cardiovascular risk in the 0.6 mg treatment arm, but felt that long term monitoring for emergence of any signal is necessary. Therefore, the 0.6 mg treatment arm will be continued while the sponsor closely monitors cardiovascular events in all laquinimod

studies. Additional measures implemented in this protocol amendment include an emphasis on disallowed medications and stopping rules for organ impairment (ie, factors which may increase laquinimod exposure), as well as regular evaluation and management of major modifiable cardiovascular risk factors.

1.1.1.3. Rationale for Primary Endpoint

MRI-measured BA is a quantitative measure of the irreversible tissue loss observed in MS (Miller et al 2002). Accordingly, significant associations were found between cerebral atrophy and worsening of disability (Barkhof et al 2001, Fisher et al 2000, Kalkers et al 2001, Losseff et al 1996, Pagani et al 2005), as well as with decline in cognitive functions (Christodoulou et al 2003). In the first large study in untreated patients with MS with different disease subtypes it was shown that BA proceeds relentlessly throughout the course of MS, with a rate that seems largely independent of the MS subtype, when adjusting for baseline brain volume (De Stefano 2010).

Reduced brain volume loss (measured by Percentage in Brain Volume Change [PBVC] from baseline to month 24) was consistently demonstrated in laquinimod studies: ALLEGRO 32.8% reduction compared to placebo ($p<0.0001$); BRAVO 28% reduction compared to placebo ($p=0.0001$).

Several longitudinal studies have reported that BA predicts disability progression and cognitive impairment over the longer term. Even if correlation between BA and disability has been difficult to establish within the time frame of clinical studies, a recent meta-analysis of randomized controlled studies demonstrated a correlation between the effect of treatments on BA and the effect of treatments on disability progression (Sormani et al 2013a). The time course of the PBVC effect of laquinimod has not been clearly defined, however, preliminary data (Teva on file) suggest that there is a potential for the effect to occur early following treatment initiation. Therefore, PBVC measures at 24 and 48 weeks may serve as a biomarker for laquinimod's CNS target organ engagement and allow for the assessment of a potential dose response.

1.2. Name and Description of Investigational Product

The IMP, laquinimod (INN), also known by the laboratory code TV-5600 or ABR-215062 sodium salt, is a quinoline-3-carboxamide derivative. It is a novel chemical compound with the IUPAC name sodium 5-chloro-3-(ethyl(phenyl)carbamoyl)-1-methyl-2-oxo-1,2-dihydroquinolin-4-olate.

Laquinimod is supplied as white opaque cap and body hard gelatin capsules filled with white to off-white granulate. The capsules contain laquinimod sodium and are available in doses equivalent to 0.5 or 0.6 mg laquinimod. Placebo capsules are also supplied.

The capsules are packed in aluminium blister cards and should be stored at room temperature (+15°C to +25°C). A more detailed description of the product is given in Section 3.4.

1.3. Findings from Nonclinical and Clinical Studies

1.3.1. Nonclinical Studies

1.3.1.1. Pharmacology

In models of MS (EAE and cuprizone), the mechanism of action (MoA) of laquinimod includes modulation of the peripheral inflammation and CNS-resident inflammatory response resulting in down regulation of myelin and axonal damage. These effects are compatible with interference of nuclear factor (NF)-κB activation and may represent a novel protective mechanism which down regulates peripheral and central inflammation, tissue damage and neurodegeneration in CNS demyelinating diseases.

1.3.1.2. Metabolism and Pharmacokinetics

Laquinimod is rapidly absorbed resulting with high oral bioavailability of 80% to 90% in all animal species tested and its exposure was shown to increase proportionally without major sex differences. Low or no accumulation of parent drug and/or metabolites in tissues was observed. Laquinimod does not preferentially distribute to skin and eyes, and no uptake of radioactivity was registered in melanin-containing structures in either skin or eye. Laquinimod-related radioactivity was shown to be covalently bound to plasma and liver proteins in vitro however no adduct was found in human in-vivo.

Laquinimod metabolism is mostly cytochrome P450 (CYP) 3A4-mediated biotransformation, resulting in a few hydroxylated and dealkylated minor metabolites which could undergo further glucuronidation. All circulating plasma human metabolites were formed in animal test species at adequate exposure levels. Laquinimod was shown to cause a decrease of CYP3A4 activity and is a strong inducer of CYP1A enzymes. CYP1A induction is a biomarker of activation of the aryl hydrocarbon receptor (AhR) transcription factor: activation of this pathway by laquinimod has been demonstrated.

For a complete overview of the ADME-PK program of laquinimod, please refer to the laquinimod Investigator's Brochure (IB).

1.3.1.3. Toxicology

The nonclinical safety program of laquinimod has encompassed separate investigations on vital organ systems, single and repeat dose toxicity in mice (duration up to 13 weeks), rats (duration up to 26 weeks), and dogs (duration up to 52 weeks), genotoxicity, carcinogenicity studies in p53+/- transgenic mice and in rats, toxicity to reproduction, photosafety testing, immunotoxicity evaluation, and local tolerance.

Safety pharmacology studies in the rat and dog did not demonstrate significant effects of laquinimod on the function of cardiovascular, respiratory, central nervous, renal and gastrointestinal systems providing safety margins in the range of 32- to 257-fold above the originally intended clinical dose of 1.5 mg/day based on maximal plasma concentrations.

Overall, the non clinical safety program identified several safety issues. Specifically, the toxicities identified are pro-inflammatory effects (including thyroiditis), mild liver toxicity, and mild reductions of red blood cell (RBC) indices. In general, the severity of these effects was

dose-related and toxicity was mostly reversible upon drug discontinuation. The nature of these toxic events allows adequate monitoring in the clinical setting (for details please refer to the laquinimod IB).

Laquinimod was neither mutagenic nor clastogenic in in vitro and in vivo assays. Laquinimod treatment resulted in the formation of micronuclei in vitro and in vivo through an aneugenic mechanism, with broad safety margin (>32) above the originally intended clinical dose of 1.5 mg/day.

The carcinogenicity program consisted of a 26-week study in transgenic p53+/- mice and a 2-year rat study. The study in transgenic p53+/- mice did not show an increase in treatment-related neoplastic findings at any tested dose. In the 2-year rat carcinogenicity study, increased incidence of uterine adenocarcinomas was observed in high dose female rats. It is the sponsor's position that this finding is likely due to a decrease in the incidence of prolactin secreting pituitary adenomas that was observed in this study. In contrast to rodents, in humans prolactin is not a luteinizing hormone and does not affect the estrogen:progesterone ratio; therefore the mechanism proposed by the sponsor is not considered relevant to humans. A higher incidence of thyroid follicular cell adenomas was observed in high dose male rats. This lesion is considered to be related to laquinimod's induction of liver enzymes and consequently enhanced clearance of thyroid hormones in rats, a well-characterized rat-specific mechanism proposed by the sponsor, that is not considered relevant to humans. In addition, an increase in the incidence of oral cavity tumors was noted in mid and high dose female rats (2/60 in each group). The oral effects may relate to the AhR activation properties of laquinimod since similar lesions were seen following lifelong exposure of rats to other AhR activators. However, the incidence of oral cavity tumors in rats treated with laquinimod was lower than that seen with industrial chemicals such as 2,3,7,8-tetrachloro-p-dibenzodioxin (TCDD) (NTP TR-521) and dioxin-like compounds (DLCs), and was more similar to the incidence seen with the dietary ingredient indole-3-carbinol (I3C) found in cruciferous vegetables. Of note, the oral tumors seen with I3C were considered by the US National Toxicology Program as irrelevant for I3C risk assessment (NTP TR-584). No increased incidence of oral tumors was seen in humans exposed to TCDD, indicating a species specific response in rats. Therefore, oral cavity tumors induced by laquinimod in rats after a lifelong exposure do not imply an elevated carcinogenicity risk in humans. Humans, in general, also seem to be less sensitive to AhR activation by laquinimod than rats, as shown by the differential gene expression profiles discussed in the IB.

A standard pre- and post-natal toxicity study and a follow-up investigational study in rats demonstrated urogenital malformations in female rat offspring exposed in utero to laquinimod at doses similar to the clinical dose of 0.6 mg/day based on exposure. A slight delay in puberty and reduction in fertility were noted in offspring exposed in utero to laquinimod at doses slightly higher than the originally intended clinical dose of 1.5 mg/day in humans. The mechanism leading to the malformations in rats is unknown. Induction of urogenital malformations in rodents has been reported for a variety of agents including sex hormones and the AhR agonist TCDD. Several studies were performed to investigate the potential hormonal modulating activity of laquinimod, but no such effects were demonstrated at clinically relevant levels. An AhR mediated effect cannot be excluded since it plays a distinct role in developmental processes in many experimental animals. However, the relevance to humans of the teratogenic effects seen in rodents is unknown. In a pre- and post-natal toxicity study in monkeys, the high dose level was associated with higher incidence of prenatal loss which limited the number of monkeys that

could be evaluated, but there were no treatment-related malformations at doses up to 9-fold the expected plasma exposure at the originally intended clinical dose of 1.5 mg/day. Based on the above, humans should not be exposed to laquinimod during pregnancy.

Based on calculations from a study to determine laquinimod levels in monkey semen, in which the semen:plasma ratio of laquinimod was 0.32, the estimated exposure to a female partner of laquinimod-treated male patient via semen is approximately 600-fold lower than the exposure after oral administration of laquinimod at a dose of 1.5 mg, indicating that the risk of male-mediated embryo-fetal toxicity through laquinimod treatment is negligible.

A complete overview of the safety pharmacology and non clinical safety program of laquinimod is presented in the laquinimod IB.

In the planned clinical study, potential risks will be mitigated by careful screening of patients, frequent and proactive monitoring of patients and appropriate stopping rules. Furthermore, an independent DMC will be assigned to assess the data (see Section 7).

1.3.2. Clinical Studies

Fifteen Phase 1 studies in healthy volunteers and MS patients were completed. A placebo-controlled pharmacokinetic bridging study in Japanese and Caucasian patients was completed.

Two Phase 2 studies (1 placebo-controlled [01506203] and 1 open-label [03506207]) in MS patients were completed. Two Phase 2b studies, LAQ/5062 (a randomized, double-blind, parallel-group, placebo-controlled study) and its double-blind active extension study (LAQ/5063) with 2 laquinimod doses (0.3 and 0.6 mg/day) were also completed. Based on the efficacy and safety results of LAQ/5062, an amendment to the protocol of LAQ/5063 study was submitted to change it into an open-label study (LAQ/5063OL) with the 0.6 mg/day dose as a single active arm; this study is still ongoing.

Two Phase 3 studies, MS-LAQ-301 (ALLEGRO) and MS-LAQ-302 (BRAVO) were completed. Open-label extension studies MS-LAQ-301E and MS-LAQ-302E are currently ongoing.

A Phase 3 study, LAQ–MS-305 (CONCERTO), is ongoing with laquinimod doses of 0.6 mg/day. As of 01 January 2016, and based on DMC recommendations, the 1.2 mg/day arm was discontinued .

For further details refer to the laquinimod IB.

1.3.2.1. Clinical Pharmacology Studies

Laquinimod is considered to have high oral bioavailability with linear, time independent and predictable pharmacokinetics, characterized by high plasma protein binding (>98%), high oral bioavailability (~90%), low oral clearance (~0.09 L/h), low apparent volume of distribution (~10 L), and long half-life (~80 h). Absorption under fasting conditions is rapid and maximal plasma levels attained generally within 1 hour after laquinimod administration. Concomitant administration with a high-fat high-calorie meal results in reduction of the absorption rate reflected by prolongation of the time to maximum plasma drug concentration (t_{max}) to approximately 5 hours and reduction of the maximum plasma concentration (C_{max}) by 30%. Food

however did not significantly affect the overall extent of absorption area under the concentration by time curve (AUC).

Laquinimod is extensively metabolized, predominantly by CYP3A4. Laquinimod metabolites levels in plasma are very low and parent laquinimod is the main systemically circulating entity. Laquinimod pharmacokinetics are affected by moderate and strong CYP3A4 inhibitors (2.5- and 3.1-fold increase in laquinimod systemic exposure, respectively) and strong CYP3A4 inducers. At doses of 0.6 and 1.2 mg, laquinimod is a weak inhibitor of CYP3A4 and a strong inducer of CYP1A2; therefore, laquinimod may affect the systemic exposure of other drugs metabolized by CYP3A4 and CYP1A2. For additional information on concomitant use of laquinimod with CYP1A2 and CYP3A4 substrates, please refer to the IB.

Studies in subjects with mild and moderate hepatic impairment resulted in an increase of laquinimod exposure by approximately 1.3- and 2.3-fold, respectively. In subjects with moderate renal impairment laquinimod exposure was increased by 1.4-fold. A physiologically based pharmacokinetic model was further used to predict the effect of hepatic impairment and renal impairment on the pharmacokinetics of laquinimod after a single and multiple doses of 0.6 to 1.5 mg in comparison to healthy subjects (Study DP-2015-017). The model predictions indicated that mild hepatic impairment and moderate renal impairment would result in further modest increases in exposure to laquinimod following multiple 0.6 mg dose administration based on unbound drug concentration (1.71-fold and 1.65-fold respectively). More significant increases in laquinimod exposure, in particular in terms of unbound drug fraction, are predicted in patients with moderate and severe hepatic impairment (3.41- and 6.51-fold respectively) and severe renal impairment (1.86-fold). The model predictions indicated similar increases in systemic laquinimod exposure with a given stage of organ impairment across the 0.6 to 1.5 mg dose range following single or multiple dose administration, demonstrating that the dose proportional pharmacokinetics of laquinimod is maintained in subjects with hepatic impairment (mild to severe) and renal impairment (moderate to severe) across this dose range.

1.3.2.2. Clinical Safety and Efficacy Studies

Results of Phase 2 clinical studies led to the definition of 0.6 mg as the minimal effective dose in MS.

The Phase 3 of the clinical development of laquinimod for MS comprised of 2 pivotal studies, ALLEGRO and BRAVO. ALLEGRO met its primary end point for reduction of annualized relapse rate (ARR; 23% reduction, p=0.0024) and 3 key secondary endpoints (EDSS, cumulative GdE T1 lesions and cumulative new T2 lesions) were met (Table 1).

Table 1: ALLEGRO: Summary of Efficacy Results

Endpoints	% reduction (p-value)
ARR	23% (0.0024)
EDSS progression (3m confirmation)	36% (0.0122)
EDSS progression (6m confirmation)[a]	48% (0.0023)
Cumulative number of GdE T1 lesions	37% (0.0003)
Cumulative number of new T2 lesions	30% (0.0002)
Brain Atrophy[a]	32.8%[a] (< 0.0001)
MSFC z-score	51% (0.59)

[a] Post Hoc analysis
ARR = annualized relapse rate, EDSS = Expanded Disability Status Scale, GdE = gadolinium enhancing, MSFC = Multiple Sclerosis Functional Composite

Overall, the BRAVO study did not meet its primary endpoint (ARR; 17.7% reduction, p=0.0746), and some explanations for this result are proposed based on lack of power to detect the observed effect and post-hoc analyses showing baseline MRI imbalance in favor of the placebo group. It is Teva's assessment that the results obtained after a covariate analysis correcting for these baseline imbalances (ARR; 21.3%, p=0.0264) represent the true effect of laquinimod 0.6 mg in this patient population (Table 2).

Table 2: BRAVO: Summary of Efficacy Results

Endpoints	Laquinimod 0.6 mg		Interferon Beta-1a (AVONEX®, Biogen Idec Inc)	
	Original	Corrected	Original	Corrected
	% reduction (p-value)	% reduction (p-value)	% reduction (p-value)	% reduction (p-value)
ARR	17.7% (0.0746)	21.3% (0.0264)	25.9% (0.0067)	28.7% (0.0021)
Brain atrophy	27.6% (0.0001)	27.4% (<0.0001)	-10% (0.14)	-9% (0.14)
EDSS progression (3 m confirmation)	31.3% (0.06)	33.5% (0.04)	25.8% (0.13)	28.7% (0.09)
EDSS progression (6 m confirmation)[a]	39% (0.0423) [b]	40.6% (0.0423[b])	26.6% (0.1686)	28.3% (0.1426)
MSFC z-score	77% (0.15)	77% (0.15)	66% (0.2)	66% (0.2)
Cumulative number of GdE T1 lesions[c]	21.5% (0.07)	21.7% (0.062)	61.5% (<0.0001)	60% (<0.0001)
Cumulative number of new T2 lesions[c]	16.5% (0.08)	18.7% (0.037)	51.1% (<0.0001)	52.3% (<0.0001)

[a] Post hoc analysis
[b] p-value calculated based on log rank test
c Exploratory endpoint
ARR = annualized relapse rate, EDSS = Expanded Disability Status Scale, MSFC = Multiple Sclerosis Functional Composite, GdE = gadolinium enhancing

The observed clinical benefits of laquinimod indicate a distinctive efficacy profile with a pronounced effect on disability which appears to be larger than that predicted by the common

relationship between relapse rate and disability observed for other disease modifying therapies (Sormani et al 2010). This effect was consistent between the 2 studies (EDSS; ALLEGRO: 35.9% [p=0.0122], BRAVO: 33.5% [p=0.04[a]]. In addition, treatment with laquinimod demonstrated reduction in BA: ALLEGRO: 32.8% [p<0.0001], BRAVOa : 27.4% [p<0.0001]).

The safety profile of laquinimod is detailed in Section 1.4.

1.4. Known and Potential Risks and Benefits to Human Patients

1.4.1. Known and Potential Risks and Benefits for Laquinimod

Unless noted otherwise, characterization of the safety profile (important risks and adverse drug reactions) of laquinimod is based on the pivotal MS studies, in which laquinimod was administered to a total of 983 MS patients at a dose of 0.6 mg/day for up to 2 years. Very common or important adverse reactions include headache, abdominal pain, back and neck pain and appendicitis. Mild liver enzyme elevations (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and gamma-glutamyl transpeptidase [GGT]) have been reported commonly, but Hy's law criteria have not been met and there have been no cases of liver failure. Treatment with laquinimod may be associated with some additional laboratory abnormalities, including hematological changes (hemoglobin decreased/anemia, white blood cell count increased, platelets decreased) and elevation of blood CRP or fibrinogen levels; these laboratory changes are generally mild and asymptomatic.

The safety profile of laquinimod is provided in detail below:

Table 3 presents the list of possible adverse drug reactions.

The following definitions apply to the frequency terminology used hereafter:

Very common (≥ 1/10)

Common (≥ 1/100 to < 1/10)

Uncommon (≥ 1/1000 to < 1/100)

Rare (≥ 1/10000 to < 1/1000)

Very rare (< 1/10000)

Not known (cannot be estimated from the available data)

Note: the table has been updated in line with the updated Reference Safety Information; myocardial infarction and cerebrovascular accident are now included.

[a] Results corrected for two MRI parameters found to imbalanced at baseline. Original results were: EDSS: 31.3%, p=0.0628; Brain Atrophy: 27.6%, P=0.0001

Table 3: Tabulated List of Adverse Reactions

Cardiac disorders	
Uncommon:	Myocardial infarction
Infections and infestations	
Common:	Urinary tract infection, skin infections
Uncommon:	Appendicitis, furuncle
Blood and lymphatic system disorders	
Very Common:	Decreased platelets, increased white blood cells
Common:	Anemia[a]
Psychiatric disorders	
Common:	Anxiety
Nervous system disorders	
Very Common:	Headache
Rare	Cerebrovascular accident
Respiratory, thoracic and mediastinal disorders	
Common:	Cough, bronchospasm
Uncommon:	Asthma
Gastrointestinal disorders	
Very Common:	Abdominal pain
Common:	Constipation, toothache, abdominal distension , nausea, and vomiting
Uncommon:	Dry mouth
Hepatobiliary disorders	
Common:	Liver enzymes increased[a] (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase [GGT])
Musculoskeletal and connective tissue disorders	
Very Common:	Back and neck pain
Common:	Arthralgia
Uncommon:	Bursitis
Reproductive system and breast disorders	
Common:	Menstruation disorders and uterine bleeding
General disorders and administration site conditions	
Common:	Peripheral edema
Investigations	
Common:	Blood fibrinogen increased, blood amylase increased, creatinine decreased, blood C-reactive protein increased[b]
Renal and urinary disorders	
Uncommon:	Micturition urgency

[a] For liver enzyme elevations and anemia - see below.
[b] Blood C‑reactive protein increased was observed at doses higher than 0.6 mg.

1.4.1.1. Details of Important Adverse Drug Reactions

1.4.1.1.1. Liver Enzyme Elevations

Treatment with laquinimod has been associated with mostly mild, asymptomatic, and reversible liver enzyme elevations (Table 4) that generally occurred within 6 months after initiation of treatment.

In clinical trials, laquinimod was discontinued if elevation of liver enzymes exceeded 5 times the upper limit of the normal range (ULN) for more than 2 weeks in the absence of a clear alternative explanation; if the elevation exceeded 8 times the ULN, laquinimod was discontinued without further delay.

Table 4: ALLEGRO and BRAVO: Shift from Normal Test at Baseline to Highest Value for Alanine Aminotransferase, Aspartate Aminotransferase, and Gamma-Glutamyl Transpeptidase Tests

Test	Range of Increase	Placebo	Laquinimod 0.6 mg
AST (IU/L)		Patients with Normal Test at Baseline: N = 977	Patients with Normal Test at Baseline: N = 950
	> 1 and ≤ 3 x ULN	83 (8.5%)	159 (16.7%)
	> 3 and ≤ 5 x ULN	6 (0.6%)	9 (0.9%)
	> 5 and ≤ 8 x ULN	4 (0.4%)	1 (0.1%)
	> 8 x ULN	2 (0.2%)	0 (0.0%)
ALT (IU/L)		Patients with Normal Test at Baseline: N = 930	Patients with Normal Test at Baseline: N = 888
	> 1 and ≤ 3 x ULN	165 (17.7%)	262 (29.5%)
	> 3 and ≤ 5 x ULN	5 (0.5%)	30 (3.4%)
	> 5 and ≤ 8 x ULN	6 (0.6%)	5 (0.6%)
	> 8 x ULN	7 (0.8%)	5 (0.6%)
GGT (IU/L)		Patients with Normal Test at Baseline: N = 930	Patients with Normal Test at Baseline: N = 906
	> 1 and ≤ 3 x ULN	90 (9.7%)	147 (16.2%)
	> 3 and ≤ 5 x ULN	11 (1.2%)	22 (2.4%)
	> 5 and ≤ 8 x ULN	1 (0.1%)	6 (0.7%)

The percentages listed in the table refer to all patients with normal values at baseline.
ULN = Upper limit of normal range; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma-glutamyl transpeptidase; IU/L = international units/L

1.4.1.1.2. Elevated Blood Fibrinogen Level

Treatment with laquinimod has been associated with an increased incidence (43% versus 34%; laquinimod versus placebo) of shifts of blood fibrinogen to levels that are above normal, without clinical manifestations. Maximal fibrinogen level did not exceed 2.5×>ULN; maximal fibrinogen level was 9.0 g/L in the laquinimod group and 8.4 g/L in the placebo group until month 24 of the pivotal MS studies.

1.4.1.1.3. Elevated Blood C-Reactive Protein Level

An increase in blood CRP level has not been found in clinical studies in patients treated with laquinimod at a dose of 0.6 mg/day. In the pivotal trials, until month 15, the proportion of patients with elevations in CRP was slightly higher in the laquinimod group compared to placebo. In the MS-LAQ-101 dose-escalation study, a higher proportion of patients with elevations in CRP was seen in the laquinimod groups compared to placebo.

1.4.1.1.4. Back and Neck Pain

Treatment with laquinimod has been associated with an increased incidence of back and neck pain. Back and neck pains usually occurred during the first 3 months of treatment, were generally of mild severity, but occasionally occurred at a later time point, were of longer duration, or required symptomatic treatment.

1.4.1.1.5. Appendicitis

Treatment with laquinimod has been associated with an increased incidence of appendicitis. There was no characteristic pattern for this risk in terms of duration of treatment and no predisposing factors were identified. This diagnosis should be considered in patients with typical symptoms.

1.4.1.1.6. Hematological Changes

- Hemoglobin decrease/anemia:

Treatment with laquinimod has been associated with a mild, asymptomatic, non-progressive decrease of the hemoglobin level, which occurred early after initiation of treatment and was usually transient without cessation of therapy or need for anti-anemic therapy.

- Decreased platelets:

Treatment with laquinimod has been associated with a generally mild decrease of the platelet count, without clinical manifestations.

- Increased white blood cells:

Treatment with laquinimod has been associated with a generally mild increase of the total white blood cell count that was consistent across white blood cell subtypes, without clinical manifestations.

1.4.1.1.7. Cardiovascular Events (on Doses Above Laquinimod 0.6 mg)

On 30 December 2015, a DMC review of 8 unblinded cases from the ARPEGGIO and CONCERTO studies found an imbalance in serious cardiovascular events in the high dose

treatment arms in the study: 6 cases of myocardial infarction in the CONCERTO 1.2 mg treatment arm, compared to no events in the 0.6 mg or placebo treatment arms, along with a cerebral infarction in a 31-year old man on the 1.2 mg treatment arm. In the ARPEGGIO study, 1 myocardial infarction event was identified in the laquinimod 1.5 mg treatment arm. The decisions were largely based on data from 15 November 2015 when total exposure in CONCERTO was 3070 patient-years in 2199 individuals and total exposure in ARPEGGIO was 35 patient-years in 191 individuals.

Due to these events, the DMC recommended stopping all laquinimod treatment arms above 0.6 mg in the laquinimod MS trials. The DMC did not identify any overt cardiovascular risk in the 0.6 mg treatment arm, but felt that long term monitoring for emergence of any signal was necessary. The DMC also recommend that study subjects continuing on laquinimod 0.6 mg be reconsented with information about the cardiovascular risk seen in higher doses.

Currently the mechanism of the cardiovascular events remains unknown. Although no specific time-to-event patterns have been identified, cardiovascular risk factors and demographics may play a role. Different pre-existing risk factors were noted, including hypertension, high cholesterol, and/or smoking history. While all cases exhibited signs of myocardial tissue injury, the cardiac work-up in these cases revealed heterogeneous etiologies. Of note, the cases all had some established cardiovascular risk factors, including patients with probable myocarditis or with probable familial hypercholesterolemia. Further investigation into potential predictors and the potential causality are ongoing.

1.4.1.2. Potential Safety Issues with Laquinimod

1.4.1.2.1. Pregnancy

Studies in rats have shown reproductive toxicity including teratogenicity (urogenital malformations) at doses similar to the clinical dose of 0.6 mg/day in humans. Delay in puberty and reduced fertility were noted in rat offspring exposed to laquinimod in utero at doses slightly higher than the originally intended clinical dose of 1.5 mg/day in humans (Section 1.3.1.3). The relevance to humans of these findings is not known, but cannot be excluded.

Exposure to laquinimod during pregnancy should be avoided.

To prevent such exposure, women who are of child-bearing potential (for example women who are not postmenopausal or surgically sterilized) must practice an acceptable method of birth control (Section 4.1) for 30 days before initiation of treatment, and 2 acceptable methods of birth control throughout treatment duration and for 30 days after cessation of treatment. Acceptable methods of birth control in this study include: intrauterine devices, barrier methods (condom or diaphragm with spermicide), and hormonal methods of birth control (eg, oral contraceptive, contraceptive patch, long-acting injectable contraceptive). Use of acceptable contraception should be ascertained at every study visit.

In addition, regular pregnancy testing is required during the study. Women of child-bearing potential must have a negative serum pregnancy test within 7 days prior to initiation of treatment. During treatment, if pregnancy is suspected despite all recommended precautions (based on a positive pregnancy test, delay in menstruation or any other reason to suspect pregnancy), treatment should be discontinued immediately. The patient should be reminded of the potential risk to the fetus, and all options, including termination of pregnancy, should be discussed.

All patients should be counseled by the investigator about the potential teratogenicity and delayed risks for a child exposed in uterus to laquinimod and the need to use acceptable contraception and avoid pregnancy throughout treatment with laquinimod and for 30 days after the last dose of treatment was administered.

1.4.1.2.2. Cancer

The 2-year carcinogenicity studies in rats demonstrated an increase in uterine and oral cancers (Section 1.3.1.3). These findings are likely related to species-specific mechanisms, regardless, a relevance of these cancers to humans cannot be definitively excluded. Available Phase 3 and extension clinical trial data show no association of 0.6 mg/day with an increased risk of cancer.

1.4.1.2.3. Cardiotoxicity and Systemic Inflammation

In clinical studies performed with laquinimod's predecessor molecule, roquinimex, pericarditis/pleuritis and ischemic heart disorders were identified as important safety concerns. Serious toxicities that occurred during Phase 3 trials led to discontinuation of these trials. Roquinimex demonstrated serious toxicities including increased rates of myocardial infarction, pericarditis, and pleuritis that were observed in three Phase 3, placebo-controlled studies in MS patients. The mechanism by which roquinimex caused these events was not identified, but they were considered to be possible manifestations of a systemic inflammatory response, an assessment which was also supported by roquinimex nonclinical findings. A thorough analysis was done on the laquinimod safety data (which is mostly reflective of the 0.6 mg/day dose) to evaluate similar potential safety issues. Based on 2347 patients exposed to laquinimod 0.6 mg for over 10,000 patient-years. as well as the patients exposed to 0.6 mg in the CONCERTO and ARPEGGIO studies, analyses showed that these safety issues do not constitute a clear signal for laquinimod in doses up to 0.6 mg/day. However, at doses of 1.2 and 1.5 mg, laquinimod manifested clinical evidence of myocardial infarction.

1.4.2. Overall Risk Benefit Statement

This is the first study to evaluate laquinimod treatment in patients with PPMS.

The effects of laquinimod in the 2 pivotal studies in RRMS describe a robust and consistent effect on 3, 6, and 12 months CDP. This effect is larger than expected based on the outcomes projected from the relapse and suggests an effect on disability progression independent from inflammation (Sormani et al 2013b). This effect has also been demonstrated in subgroups indicative of transition to progressive stages.

The effect of laquinimod on PBVC in RRMS patients is also consistent between studies and substantiated by an effect on other MRI markers of neurodegeneration.

The clinical and preclinical aspects of the known MoA support testing of the hypothesis whether treatment with laquinimod changes MRI and potentially clinical outcomes in patients with PPMS in a dose responsive manner. The extensively assessed clinically observed safety profile of laquinimod 0.6 mg is favorable.

The 4-week MTD study with doses up to 2.7 mg QD (Study MS-LAQ-101) did not show an increase in total adverse events with increased dose. Higher incidence of post baseline shifts to abnormally high levels of laboratory parameters compared to the pooled placebo included liver

enzymes, P-amylase, CRP, and fibrinogen, but most shifts were not to potentially clinically significant levels, and no dose response was observed.

Due to cardiovascular events and a DMC recommendation to stop all laquinimod treatment arms above 0.6 mg in the MS trials, the 1.5 mg treatment arm was discontinued as of 01 January 2016. The risk/benefit balance of this dose was considered negative at that point.

The DMC did not identify any overt cardiovascular risk in the 0.6 mg treatment arm, but felt that long term monitoring for emergence of any signal was necessary. As of 29 September 2015, 2347 patients had been exposed to laquinimod 0.6 mg for 10,417 patient-years. It is estimated that the rate for myocardial infarction and cardiovascular death for patients treated with laquinimod 0.6 mg is about 0.16 per 100 person-years which is within range of the expected cardiovascular event incidence in the underlying population. Therefore, while no increased risk was seen with laquinimod 0.6 mg, because of the findings with higher doses, there is a potential risk that some individuals may be at increased risk of cardiovascular events while taking laquinimod 0.6 mg. Appropriate risk mitigation procedures have been implemented via a protocol amendment to restrict excess drug exposure due to disallowed medications or organ impairment, as well as to assure evaluation and management of cardiovascular risk factors.

Given the unmet need for treatments of progressive MS, the data supportive of a potential effect of laquinimod in this population, and the identified safety profile of laquinimod, it is judged that the administration of laquinimod to patients with PPMS has the potential to yield clinical benefits which may outweigh the potential risks, supporting investigation of its role in this patient population for which there is equipoise.

1.5. Selection of Drugs and Dosages

The rationale for the selection of doses is presented in Sections 1.1.1.1 and 1.1.1.2.

A more detailed description of study drug administration is presented in Section 5.1.

1.6. Compliance Statement

This study will be conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, European Union [EU] Directive 20/EC and 28/EC). Any episode of noncompliance will be documented.

The investigators are responsible for performing the study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of each investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the sponsor and other forms as required by national authorities.

Each investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. Each investigator and the applicable study staff must be familiar with the background to, and requirements of, the study and with the properties of the study drug(s) as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the study at that center and for contacts with study management, with the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with local authorities.

1.7. Population To Be Studied

The current study is a Phase 2 dose ranging study in PPMS patients.

1.8. Relevant Literature and Data

Relevant literature is cited above. Further literature and data may be found in the current IB.

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

This is a Phase 2 study and is intended to serve as a proof of concept for potential treatment with laquinimod in patients with PPMS. The study is also aimed at evaluating 2 doses of laquinimod in this population.

2.2. Study Objectives

The objectives of this study are to assess the efficacy, safety, and tolerability of a once daily oral dose of laquinimod (0.6 or 1.5 mg) compared to placebo in PPMS patients.

Study endpoints are detailed in Section 3.2.

3. STUDY DESIGN

3.1. General Design and Study Schema

This is a multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled study, to evaluate the efficacy, safety and tolerability of daily oral administration of laquinimod (0.6 or 1.5 mg) in patients with PPMS.

Prior to 01 January 2016, eligible patients were randomized in a 1:1:1 ratio into 1 of the following treatment arms (a total of 286 patients were randomized 1:1:1 prior to 01 January 2016):

- Laquinimod 0.6 mg daily
- Laquinimod 1.5 mg daily
- Daily placebo

As of 01 January 2016, following a decision to discontinue the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1 ratio into one of the following treatment arms:

- Laquinimod 0.6 mg daily
- Daily placebo

A capped randomization procedure will be employed to ensure that the proportion of EDSS 6.0 and 6.5 patients will not exceed more than 20% of all enrolled patients.

The study will include screening up to 6 weeks and 2 parts: Part A (core study) and Part B (data analysis).

Part A will last at least 48 weeks, and individual patients will experience variable treatment durations, depending on the order of enrollment.

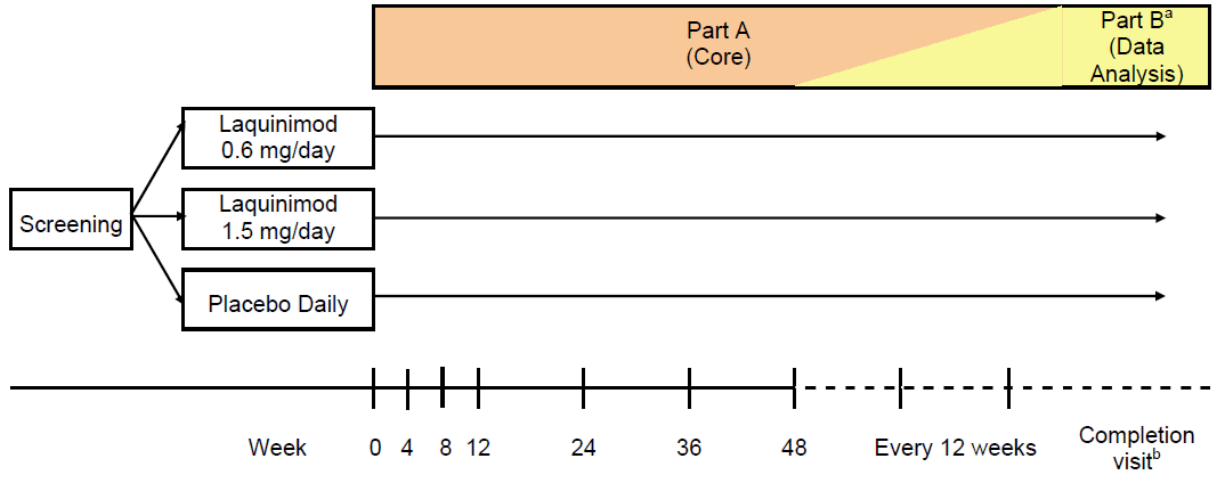
Once the last ongoing patient completes the week 48 visit, the sponsor will declare end of Part A and begin performing study analyses.

In Part B, patients will continue their randomly-assigned blinded treatments with visits every 12 weeks until the completion visit. After up to approximately 24 weeks of Part B, or once data analysis has been completed and the design of a potential extension study has been finalized (including blinded or open-label treatment allocation), patients will be invited to the clinic for the completion visit and will be offered the opportunity to continue into an extension study, if applicable.

Patients will have the following study visits: screening visit (-6 weeks), baseline visit (week 0), weeks 4, 8, 12, 24, 36, 48, and every 12 weeks until study completion or early termination (ET).

The study schema is presented in Figure 1 (prior to 01 January 2016) and Figure 2 (from 01 January 2016).

Figure 1: Overall Study Schema (prior to 01 January 2016)

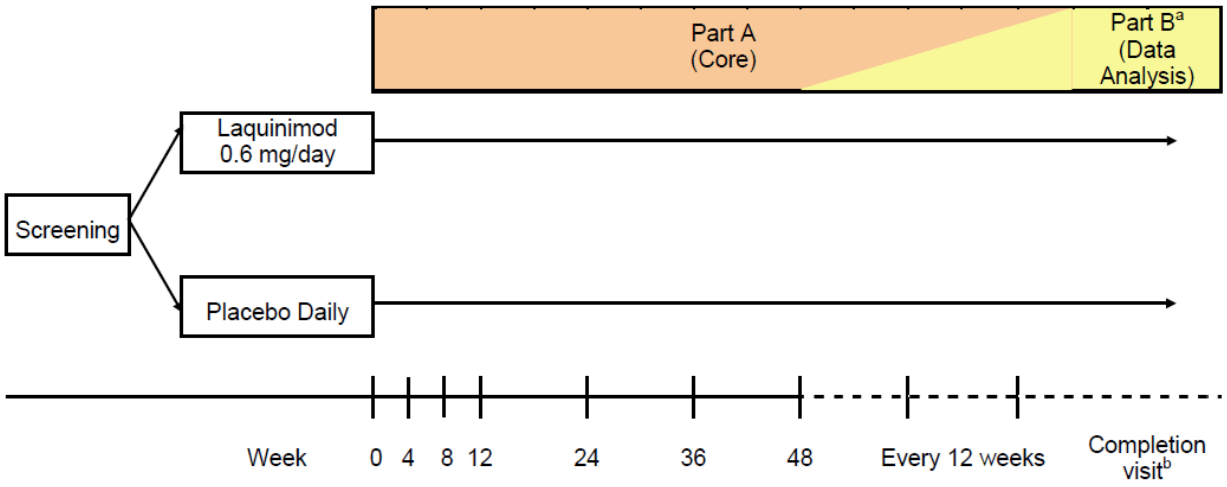


Screening should occur up to 6 weeks prior to the baseline (week 0) visit

[a] Part B commences once the last ongoing patient completes week 48; consequently, individual patients will experience variable treatment durations, depending on the order of enrollment. As of 01 January 2016, treatment was discontinued for patients enrolled to the 1.5 mg arm.

[b] Patients will be invited for a completion visit once data analysis is complete and the design of a potential extension study has been finalized

Figure 2: Overall Study Schema (from 01 January 2016)



Screening should occur up to 6 weeks prior to the baseline (week 0) visit

[a] Part B commences once the last ongoing patient completes week 48; consequently, individual patients will experience variable treatment durations, depending on the order of enrollment

[b] Patients will be invited for a completion visit once data analysis is complete and the design of a potential extension study has been finalized

Study assessments are detailed (by time point) in Sections 3.11.1 to 3.11.6.

In the event of neurological symptoms suggestive of a relapse, the definitions and procedures in 0 apply. Confirmed relapses must be recorded in the case report form (CRF). Patients with a relapse may continue in the study. The suggested treatment for a relapse will be intravenous methylprednisolone 500 to 1000 mg/day for 3 to 5 consecutive days.

Pharmacogenomic (PGx) assessments will be performed in all patients, however this can be omitted if considered unacceptable per local regulations.

Ancillary studies include assessments of cerebrospinal fluid (CSF) and optical coherence tomography (OCT) to assess retinal thickness.

3.2. Primary and Secondary Measures and Endpoints

3.2.1. Primary Efficacy Measures and Endpoints

The primary endpoint for this study will be BA as defined by the PBVC from baseline to week 48.

3.2.2. Secondary Efficacy Measures and Endpoints

- Time to CDP, defined as increase in EDSS of ≥1 point from baseline EDSS if EDSS at entry is ≤5.0, or increase of ≥0.5 point if EDSS at entry is ≥5.5. This increase should be confirmed after at least 12 weeks. Progression cannot be confirmed during a relapse, although relapses are rare in PPMS.
- Time to CDP as measured by 2 types of events for each individual (progression cannot be confirmed during a relapse):
  - An increase from baseline in EDSS score (≥1 point from baseline EDSS if EDSS at entry is ≤5.0, or increase of ≥0.5 point if EDSS at entry is ≤5.5), confirmed after at least 12 weeks, **or**
  - An increase of at least 20% from baseline in the T25FW score, confirmed after at least 12 weeks.
- Change from baseline to week 48 in the T25FW score.
- The number of new T2 brain lesions at week 48.

3.2.3. Exploratory Efficacy Measures and Endpoints

- Change from baseline to week 48 in the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) score (California Verbal Learning Test–II [CVLT-II], Brief Visuospatial Memory Test – Revised [BVMT-R], and symbol digit modalities test [SDMT]).
- Time to CDP as measured by at least 1 of 4 types of events for each individual (progression cannot be confirmed during a relapse):
  - An increase from baseline in EDSS score (≥1 point from baseline EDSS if EDSS at entry is ≤5.0, or increase of ≥0.5 point if EDSS at entry is ≥5.5), confirmed after at least 12 weeks **or**
  - An increase of at least 20% from baseline in T25FW score, confirmed after at least 12 weeks **or**
  - An increase of at least 30% from baseline in the 9-Hole Peg test (9HPT) score, confirmed after at least 12 weeks **or**

  - A decrease of at least 20% from baseline in the SDMT score, confirmed after at least 12 weeks.

- Time to CDP confirmed after at least 24 weeks.
- New T1-hypointense lesions, changes in T1-hypointense lesion volume, and changes in T2 lesion volume.
- Other MRI parameters, including thalamic, cortical, white matter, and cervical cord atrophy, number of cervical cord T2 lesions, and normal-appearing brain tissue average MTR.
- Modified Rankin scale (mRS) (at week 72, visit 8).
- T25FW.
- 9HPT.
- Low contrast visual acuity (LCVA).
- 12-Item Multiple Sclerosis Walking Scale (MSWS-12).

3.2.4. Other Measures and Endpoints

- relapses
- pharmacokinetic measures (determination of plasma concentration of laquinimod)
- PGx measures
- potential biomarker measures
- ancillary studies measures

3.2.5. Safety Measures and Endpoints

The safety of laquinimod will be assessed throughout the study by evaluating adverse events, vital signs, ECG findings, clinical laboratory parameters, and concomitant medication usage.

3.2.6. Tolerability Measures and Endpoints

- Proportion of patients (%) who prematurely discontinue treatment, reasons for discontinuation, and time to ET.
- Proportion of patients (%) who prematurely discontinue treatment due to adverse events, and time to ET due to adverse events.

3.2.7. Pharmacokinetic Measures and Endpoints

Blood samples for determination of plasma concentration of laquinimod will be collected at weeks 4, 8, 12, 24 and 48. The patient should be instructed to take the daily oral dose at the same time each day. The date and time of the blood sample, as well as the date and time of the last study drug dose prior to the sample will be recorded in the source document and on the CRF.

Pharmacokinetics of laquinimod will be evaluated in this study using a population pharmacokinetics (PPK) approach. The PPK model may also include any unscheduled

pharmacokinetic samples collected to assist with further investigations of cardiovascular events or other clinical event of interest (see Section 8.1). Details of sample collection and processing are provided in the Laboratory Manual.

3.3. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Patients will be randomly assigned to receive treatment with laquinimod at a dosage of 0.6 or 1.5 mg/day, or placebo in a 1:1:1 ratio (prior to 01 January 2016) or randomly assigned to receive treatment with laquinimod at a dosage of 0.6 mg/day, or placebo in a 1:1 ratio (from 01 January 2016). Patients, investigators, and study site personnel will remain blinded to treatment assignment during the study. Laquinimod and placebo will be packaged and administered in a blinded manner. All patients that discontinued the 1.5 mg dose have been unblinded.

The randomization number will be generated by the sponsor or a vendor following specifications from the sponsor's biostatistics department. A statistician not assigned to the study will be responsible for reviewing the randomization number.

The sponsor's clinical personnel involved in the study will be blinded to the study drug identity until the database is locked for analysis (end of Part A) and the treatment assignment revealed.

Patients will be randomly assigned to treatment through a qualified randomization service provider (eg, interactive response technology [IRT]).

This system is used to ensure a balance across treatment groups. A capped randomization procedure will be employed to ensure that the number of EDSS 6.0 and 6.5 patients will be no more than 20% of all enrolled patients.

The patient number assigned during the screening visit through the interactive voice response system (IVRS)/interactive web response system (IWRS) will be used to identify patients during the whole course of the study regardless of the randomization number assigned during the randomization visit. The randomization number assigned is solely for treatment group allocation. In addition to the randomization number, the IVRS/IWRS will assign a pack number. The patient will be supplied and treated throughout the study with IMP labeled with the pack number/s assigned by IVRS/IWRS at each visit.

3.3.1. Emergency Code Breaking

In case of a serious adverse event, pregnancy, or in cases when knowledge of the study drug assignment is needed to make treatment decisions, the investigator may unblind the patient's drug assignment as deemed necessary, mainly in emergency situations. Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) at the study center via the IRT, via the internet.

If possible, the sponsor should be notified of the event prior to breaking of the code. If this is not possible, the sponsor should be notified immediately afterwards, and the patient's drug code assignment should not be revealed. Breaking of the treatment code can always be performed by the site without prior approval by the sponsor.

In case of pregnancy, if deemed necessary by the investigator, the patient's drug assignment may be unblinded; however, the sponsor should not be notified of the treatment assignment.

The circumstances leading to the breaking of the code should be fully documented, in the investigator's study files and in the patient's source documentation. Treatment assignment should not be recorded in any study documents or source document.

For adverse events that are defined as: Suspected, Unexpected, Serious, Adverse Reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance may independently request that the treatment code be revealed (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct, analysis, and reporting of the data.

3.3.2. Reducing Assessment Bias

To maintain reliable evaluation and reduce the potential for bias, the following actions will be undertaken:

- Site clinicians may serve as either Examining Neurologist or Treating Neurologist.
- Both Examining Neurologist and Treating Neurologist will remain blinded to study drug assignment.
- Only an Examining Neurologist will administer the EDSS and Functional System Scores (FSS).
- The Examining Neurologist will not have access to the patient's medical records or source documents, including previous EDSS/FSS forms or adverse events.
- Safety evaluations and other clinical considerations will be the sole responsibility of the Treating Neurologist. The Treating Neurologist will be responsible for patient eligibility evaluation, the supervision of the study drug administration, clinical assessment and treatment, the recording and treating of adverse events, the monitoring of safety assessments, including routine laboratory parameters, and coordinating MRI performance.
- The Treating Neurologist and the Examining Neurologist will be instructed not to discuss the patients with each other. In particular, the Treating Neurologist and Examining Neurologist will not discuss the performance or scoring of the EDSS/FSS.
- Patients will be instructed not to discuss their general health condition and adverse events with the Examining Neurologist.
- Only a trained, blinded rater will administer the T25FW, 9HPT, BICAMS, and SDMT. The blinded rater need not be a physician or nurse. The blinded rater will not have access to the patient's medical records or source documents, including previous T25FW, 9HPT, BICAMS, or SDMT forms.

3.4. Study Drugs and Dosage

3.4.1. Investigational Product and Dosage

- 0.6 mg arm: 1 capsule containing 0.6 mg laquinimod and the other 2 containing placebo, to be administered orally once daily.

- 1.5 mg arm: 3 capsules containing 0.5 mg laquinimod to be administered orally once daily (Note: this arm was discontinued as of 01 January 2016).

3.4.2. Other Study Drugs and Dosage

- Placebo arm: 3 capsules containing placebo to be administered orally once daily.

3.4.3. Manufacturing and Packaging

Laquinimod capsules and placebo capsules are manufactured and packaged in compliance with current good manufacturing practice (GMP) standards and guidelines applicable to study drugs by Teva Pharmaceutical Industries, Ltd.

3.4.4. Packaging and Labeling

The secondary packaging and labeling for patients is under the responsibility of the Clinical Supply Chain (CSC) of Teva Pharmaceutical Industries Ltd and is according to EU regulations and ICH guidelines as adopted by the FDA – GCP (E6). Patients will receive weekly packs each containing 3 distinct labeled blisters in accordance with the associated treatment arm. The blisters will be used to accomplish the dosing of 1 of the 3 treatment arms. One capsule from each blister should be taken daily. Both blisters and outer pack will be labeled with a unique pack number.

3.4.5. Distribution, Storage, Dispensing and Return

Distribution of study drugs will be performed under sponsor's responsibility. If the study drug supplies appear to be damaged/missing upon arrival at the investigational site, the sponsor should be contacted immediately. Study drug supplies will be kept in a secure, limited-access, temperature-controlled storage area. Only authorized personnel will have access to the study drug. The study site personnel at each site will be responsible for correct storage and handling of the study drug. All study drug packs must be stored at room temperature 15°C to 25°C/59°F to 77°F. Study drug packs will be dispensed to the patient at the study site at each dispensing visit through the IRT. Patients will be instructed to return all used blisters and unused study drug at each visit. The Site Investigator/site coordinator is responsible for performing study drug accountability at the site. The Monitor is responsible for the accountability of the returned study drugs.

3.5. Duration of Patient Participation

For each patient, the study will consist of a screening phase of up to 6 weeks, Part A (core study) of at least 48 weeks, and Part B (data analysis) of up to approximately 24 weeks or until data analysis is completed and the design of a potential extension study has been finalized. Following the completion visit, patients will be offered the opportunity to continue into an extension study.

3.6. Safety Guidelines and Stopping Rules

3.6.1. Pregnancy

Exposure to laquinimod during pregnancy must be avoided. Therefore, women of childbearing potential (for example women who are not postmenopausal or surgically sterilized) must practice

an acceptable method of birth control for 30 days before taking the study treatment and have a negative serum pregnancy test within 7 days prior to initiation of treatment.

To further emphasize the importance of use of acceptable contraception and avoidance of pregnancy under laquinimod exposure, and to reduce as much as possible the exposure to laquinimod if a pregnancy occur despite all recommended measures, all patients who are women of child-bearing potential (for example women who are not postmenopausal or surgically sterilized) will be instructed about the teratogenicity and potential delayed risks for a child exposed in utero to laquinimod. These patients will also be counseled about the importance of using 2 methods of acceptable contraception throughout treatment duration, and until 30 days after the last dose of treatment is administered, and about the need to stop treatment immediately if pregnancy is suspected.

Acceptable methods of birth control include intrauterine devices, barrier methods (condom or diaphragm with spermicide) and hormonal methods of birth control (oral contraceptive, contraceptive patch, long-acting injectable contraceptive).

In case of suspected pregnancy (positive urine beta human chorionic gonadotropin [β-hCG] test result, delay of menstruation or any other reason suggesting pregnancy), the study drug will be suspended, and follow-up will be done as detailed in Appendix B.

3.6.2. Liver Enzymes

For any increase of ALT or AST to ≥2×ULN, the "Guidance on Safety Monitoring" in Appendix B should be thoroughly followed.

In the following circumstances, the patient's participation in the study will be discontinued immediately and liver enzymes will be monitored until normalization or stabilization, according to the guidance in Appendix B:

- Any increase in ALT or AST to ≥3×ULN, combined with international normalized ratio (INR) >1.5 or total bilirubin >2×ULN.
- Any increase in ALT or AST to ≥3×ULN, which is accompanied by nausea, vomiting, fever, rash, or eosinophilia.
- Any increase in ALT or AST to levels ≥5× but <8×ULN, which is persistent for ≥2 weeks of repeated measurements.
- Any increase in ALT or AST to levels ≥8×ULN.
- In any case where monitoring of liver enzymes cannot be performed according to the protocol guidance (see Appendix B).

3.6.3. Cancer

Patients who are diagnosed with a malignant solid or liquid tumor while participating in the study should stop study medication.

3.6.4. Liver Impairment

To avoid exposures to higher levels of laquinimod (see Section 1.3.2.1), a stopping role related to liver impairment has been introduced. Patients who develop any chronic liver disease

associated with hepatic function impairment while participating in the study should stop study medication.

3.6.5. Renal Impairment

To avoid exposures to higher levels of laquinimod (see Section 1.3.2.1), a stopping role related to renal impairment has been introduced. Patients who develop renal disease associated with moderate or severe functional impairment, defined as glomerular filtration rate (GFR) ≤60 mL/min/1.73 m^2, while participating in the study should stop study medication temporarily and the GFR assessment should be repeated. If the renal impairment is confirmed (GFR ≤60 mL/min/1.73 m^2), the patient should stop study medication permanently.

3.6.6. Temporary Discontinuation of Study Drug Treatment

Temporary discontinuation is defined as missing of more than 3 consecutive doses of the study drug. Skipping 14 or more consecutive doses of study drug will be considered a major protocol violation.

In the event of temporary study drug discontinuation, the local clinical management should be notified. The patient will report any temporary discontinuation to the investigator and will be instructed by the investigator regarding continuation of treatment based on the reason and duration of discontinuation.

3.6.7. Early Termination (ET)

An ET visit should be completed for all patients who prematurely terminate treatment or who become pregnant (see Section 3.11.4 for details of procedures).

In all cases of ET due to ongoing adverse event, manifestation of a severe degree of intolerance to study drug and/or ongoing MS relapse, the patient should remain under medical observation and followed until the medical condition returns to baseline or is considered stable or chronic.

Early termination refers to the study drug termination and not termination of the patient from the study. Patients will be encouraged to continue all scheduled visits and procedures after study drug discontinuation (with the exception of drug dispensing and accountability, pregnancy testing, and pharmacokinetic sampling).

Women of child bearing potential should continue using 2 acceptable contraception methods up to 30 days after the last dose of treatment was administered.

Moderate/strong CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered. For information on the use of CYP1A2 substrates following laquinimod cessation, please refer to the laquinimod IB.

3.7. Study Drug Supply and Accountability

3.7.1. Study Drug Storage and Security

Study drug (laquinimod and placebo) must be stored at room temperature (15°C to 25°C), in a dry, temperature-controlled, securely locked, substantially-constructed cabinet or enclosure. The study site personnel at each site will be responsible for correct storage and handling of the study drug.

3.7.2. Study Drug Accountability

Each study drug shipment will include a packing slip, listing the contents of the shipment. The return instructions and the applicable forms will be provided to the site. The investigator is responsible for ensuring that deliveries of study drug and other study materials from the sponsor are correctly received and recorded, handled and stored safely and properly in accordance with the local regulations, and used in accordance with this protocol.

A record of study drug accountability (ie, study drug and other materials received, used, retained, returned) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Reconciled study drug will be returned to the sponsor or its designee.

During the study, all unused study drugs and the corresponding accountability forms must be returned by the monitor to the sponsor or sponsor's designee on an on-going basis for reconciliation and destruction. A photocopy of these records must be kept at the study sites.

The accountability of the returned study drugs should be performed and recorded by the sponsor's assigned monitor. The Patient Number, the date, batch code/batch number, pack number and quantity of study drugs returned by the patient will be checked for correctness and recorded on the appropriate accountability forms, to be provided by the CSC via IWRS and/or IVRS. The monitor will use the IRT to record the returns.

3.8. Maintenance of Randomization and Blinding

The relevant SOPs regarding the maintenance of randomization and blinding will be followed by sponsor's/vendor's personnel.

Staff responsible for bioanalysis and pharmacokinetic data analysis will not have access to any clinical data and will provide concentration data to other staff members in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to an individual patient's concentration data).

For a SUSAR, the sponsor's Global Patient Safety and Pharmacovigilance Department may independently request that the treatment code be revealed if needed (on a case-by-case basis). If this occurs, the investigator will remain blinded to treatment.

All patients that discontinued the 1.5 mg dose have been unblinded.

3.9. Source Data Recorded on the Case Report Form

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed onto the CRF. Data may not be recorded directly onto the CRF and considered as source data unless the investigational center obtains written documentation from the sponsor, before the beginning of the study, indicating which data are permitted to be recorded directly onto the CRF.

Source data, including test results and/or assessments (eg, clinical laboratory test results, ECG data, safety and efficacy measurements) collected by institutions outside of the study center are sent to the study center, where they are retained but not entered into the CRF. These results may be sent directly to the sponsor for entry into the clinical database (see Section 13.1).

The CRFs are filed in the sponsor's central file.

3.10. Time Schedule

The study is expected to start in Q4 2014 and be completed in Q3 2017. Approximately 375 patients from approximately 120 investigational centers in approximately 10 countries are planned to be enrolled in the study.

3.11. Study Procedures

Study procedures and assessments with their timing are summarized in Table 5 (up to week 48) and Table 6 (from week 60).

Table 5: Study Procedures and Assessments (up to Week 48)

Visit	Screening	Baseline	1	2	3	4	5	6	ET	Unscheduled Visit[a]
Study week[b]	**up to -6**	**0**	**4**	**8**	**12**	**24**	**36**	**48**		
Informed consent	X									
Eligibility criteria	X	X								
Medical and MS history	X									
Cardiovascular risk factor assessment and management[c]	X									
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X
Randomization		X								
First dose at site		X								
Adverse event	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	
Vital signs[d]	X	X[d]	X	X	X	X	X	X	X	X
ECG	X	X[e]	X	X	X	X		X	X	
Chest X-ray[f]	X									
Anemia panel[g]		X	Anemia panel is performed if there is a confirmed hemoglobin decrease of >1 g/dL from baseline							
B12	X		B12 is analyzed if there is a confirmed hemoglobin decrease of >1 g/dL from baseline							
Safety laboratory tests[h]	X	X	X	X	X	X	X	X	X	X[i]
Fasting lipid profile[j]		X						X	X	
Thyroid function tests		X				X		X	X	
GFR[k]	X	X	X	X	X	X	X	X	X	X[i]
HTLV- I/II	X									
Urinalysis	X									
β-hCG[l]	X	X	X	X	X	X	X	X	X	
Home urine β-hCG test[m]					Every 28±2 days between visits; telephone confirmation within 72 hours of the scheduled home pregnancy test					
Ascertain use of acceptable contraception	X	X	X	X	X	X	X	X	X	X
Call IVRS/IWRS	X	X	X	X	X	X	X	X	X	

Visit	Screening	Baseline	1	2	3	4	5	6	ET	Unscheduled Visit[a]
Study week[b]	**up to -6**	**0**	**4**	**8**	**12**	**24**	**36**	**48**		
Study drug dispensing		X	X	X	X	X	X	X		
Study drug accountability			X	X	X	X	X	X	X	
MRI[n]		X				X		X	X[n]	
EDSS/FSS[o]	X	X			X	X	X	X	X	
T25FW[p]		X			X	X	X	X	X	
9HPT[p]		X			X	X	X	X	X	
SDMT[p,q,]		X[q]			X	X	X	X[q]	X	
BICAMS[p,q]		X						X	X[r]	
LCVA		X				X		X	X	
MSWS-12		X			X	X	X	X	X	
Pharmacokinetic samples			X	X	X	X		X		X[i]
Potential biomarker samples		X				X		X		X[i]
Pharmacogenomic sample[s]		X								
Ancillary studies										
CSF assessment[t]								X		
OCT evaluation		X[u]						X	X[v]	

Patients who are discontinued from study treatment will be encouraged to continue all scheduled visits and procedures after study drug discontinuation (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, and pharmacokinetic sampling).

[a] An unscheduled visit may be performed at any time at the patient's request or per investigator's discretion. Only mandatory procedures are specified; additional assessments per clinical discretion. In addition, unscheduled urgent safety laboratory samples, pharmacokinetic blood samples, and/or samples for potential biomarker analyses may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.

[b] For the purpose of scheduling study visits, a week is defined as 7±2 days.

[c] In addition, an evaluation should take place as soon as possible for patients already in the study, following approval of Global Amendment 2.

[d] Vital signs include temperature, pulse and blood pressure. Height will be measured at screening visit. Weight will be measured at all visits. At baseline (week 0), pulse and blood pressure will be measured pre dose as well as 30 and 60 minutes after onsite drug administration.

[e] At baseline (week 0), 3 ECG recordings 10 minutes apart are required before first dose.

[f] Chest X-ray can be omitted if the report of a chest X-ray performed within 24 weeks of screening is obtained, or if a screening chest X-ray is considered unacceptable per local regulations.

[g] Anemia panel includes blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, IFN-γ, TNF-α, and hepcidin. Assessed at baseline and also at 1 subsequent time point (with B12) if hemoglobin decrease of >1 g/dL from the patient's hemoglobin level at baseline and the decrease is confirmed.

[h] Serum chemistry (including electrolytes, fibrinogen, glucose, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, creatine phosphokinase, C-reactive protein, pancreatic amylase [lipase will be tested in case of abnormal pancreatic amylase results], total protein, albumin, direct and total bilirubin) and complete blood count (CBC) with differential. Coagulation to be tested only if required according to Guidance on Safety Monitoring.

[i] Unscheduled urgent safety laboratory samples, pharmacokinetic blood samples, and/or samples for potential biomarker analysis may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.

[j] Fasting lipid profile includes total cholesterol, HDL, LDL (measured), and triglycerides.

[k] Patients who develop renal disease associated with moderate or severe functional impairment, defined as glomerular filtration rate (GFR) ≤60 mL/min/1.73 m^2, while participating in the study should stop study medication temporarily and the GFR assessment should be repeated. If the renal impairment is confirmed (GFR ≤60 mL/min/1.73 m^2), the patient should stop study medication permanently.

[l] For women of child-bearing potential serum β-hCG test will be done at each scheduled study visit. Urine β-hCG tests will be done at each study visit; in case of a positive result, study drug should not be dispensed until the serum β-hCG result is available. At baseline, serum β-hCG will be done within 7 days prior to randomization, such that the result is available prior to the first dose; urine β-hCG test will also be done on site prior to the first dose.

[m] Starting from week 12 visit, women of child-bearing potential will be provided with home pregnancy urine β-hCG test kits and will be instructed how to perform the test. The site staff will schedule the home test to be performed every 28 ±2 days between study visits.

[n] MRI scans (without and with gadolinium) will be performed at least 14 days but not more than 6 weeks before baseline. MRI (without gadolinium) will be performed within 14 days of the week 24 and week 48 visits. In case of steroid treatment, study MRI should be delayed to allow a minimum of 14 days but not more than 28 days from the completion of the steroid course. ET visit will only include MRI for patients who prematurely terminate treatment subsequent to the week 36 visit and prior to week 48. Patients who stop treatment before week 36 or after week 48 will not have MRI at ET visit.

[o] Only an Examining Neurologist will administer the EDSS/FSS. The Examining Neurologist will not have access to the patient's medical records or source documents, including previous EDSS/FSS forms or adverse events.

[p] Only a trained, blinded rater will administer the T25FW, 9HPT, BICAMS, and SDMT. The blinded rater will not have access to the patient's medical records or source documents, including previous T25FW, 9HPT, BICAMS, or SDMT forms.

[q] At baseline and at week 48, SDMT will be performed as part of the BICAMS assessment.

[r] ET visit will only include BICAMS for patients who prematurely terminate treatment subsequent to the week 24 visit and prior to week 48. Patients who stop treatment before week 24 or after week 48 will not have BICAMS at ET visit.

[s] If the pharmacogenomic sample is not obtained at baseline for any reason, it should be collected at the next possible visit. This can be omitted if mandatory pharmacogenomic sampling is considered unacceptable per local regulations.

[t] CSF collection (in selected sites) will be performed for all patients who signed an appropriate, EC approved ICF.

[u] Week 0 OCT evaluation (in selected sites) will be performed up to 42 days prior to baseline, in all patients who signed an appropriate, EC approved ICF.

[v] ET visit will only include OCT for patients who prematurely terminate treatment subsequent to the week 24 visit and prior to week 48. Patients who stop treatment before week 24 or after week 48 will not have OCT at ET visit.

ET = early termination; MS = multiple sclerosis; ECG = electrocardiogram; GFR = glomerular filtration rate; HTLV-I/II = human T lymphotropic virus Type I and II; β-hCG = beta human chorionic gonadotropin; IVRS/IWRS = interactive voice response system/interactive web response system; MRI = magnetic resonance imaging; EDSS = Expanded Disability Status Scale; FSS = Functional System Score; T25FW = timed 25 foot walk; 9HPT = 9 Hole Peg test; SDMT = symbol digit modalities test; BICAMS = Brief International Cognitive Assessment for Multiple Sclerosis; LCVA = low contrast visual acuity; MSWS-12 =

12-Item Multiple Sclerosis Walking Scale; CSF = cerebrospinal fluid; OCT = optical coherence tomography; IL = interleukin; IFN = interferon; TNF = tumor necrosis factor; HDL = high density lipoprotein; LDL = low density lipoprotein; EC = Ethics Committee; ICF = informed consent form

Table 6: Study Procedures and Assessments (from Week 60)

Visit	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**Completion[a]**	**ET**	**Unscheduled Visit[b]**
Study week[c]	**60**	**72**	**84**	**96**	**108**	**120**	**132[d]**	**144[d]**	**156[d]**	**168[d]**			
Cardiovascular risk factor assessment and management[e]				X				X					
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG		X		X		X		X		X	X	X	
Anemia panel[g]	Anemia panel is performed if there is a confirmed hemoglobin decrease of >1 g/dL from baseline												
B12	B12 is analyzed if there is a confirmed hemoglobin decrease of >1 g/dL from baseline												
Safety laboratory tests[h]	X	X	X	X	X	X	X	X	X	X	X	X	X[i]
Fasting lipid profile[j]				X				X			X	X	
Thyroid function tests		X		X		X		X		X	X	X	
GFR[k]	X	X	X	X	X	X	X	X	X	X	X	X	X[i]
β-hCG[l]	X	X	X	X	X	X	X	X	X	X	X	X	
Home urine β-hCG test[m]	Every 28±2 days between visits; telephone confirmation within 72 hours of the scheduled home pregnancy test												
Ascertain use of acceptable contraception	X	X	X	X	X	X	X	X	X	X	X	X	X
Call IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug dispensing	X	X	X	X	X	X	X	X	X	X	X[n]		
Study drug accountability	X	X	X	X	X	X	X	X	X	X	X	X	
EDSS/FSS[o]	X	X	X	X	X	X	X	X	X	X	X	X	
mRS		X											
T25FW[p]	X	X	X	X	X	X	X	X	X	X	X	X	
9HPT[p]	X	X	X	X	X	X	X	X	X	X	X	X	
SDMT[p,q,]	X	X	X	X[q]	X	X	X	X[q]	X	X	X	X	
BICAMS[p,q]				X				X					

Visit	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**Completion[a]**	**ET**	**Unscheduled Visit[b]**
Study week[c]	**60**	**72**	**84**	**96**	**108**	**120**	**132[d]**	**144[d]**	**156[d]**	**168[d]**			
LCVA		X		X		X		X		X	X	X	
MSWS-12	X	X	X	X	X	X	X	X	X	X	X	X	
Ancillary study													
OCT				X[r]									

Patients who are discontinued from study treatment will be encouraged to continue all scheduled visits and procedures after study drug discontinuation (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, and pharmacokinetic sampling).

[a] Once analyses are completed and the design of a potential extension study has been finalized, patients will be invited for a completion visit and offered the opportunity to enter into an anticipated extension study.

[b] An unscheduled visit may be performed at any time at the patient's request or per investigator's discretion. Only mandatory procedures are specified; additional assessments per clinical discretion. In addition, unscheduled urgent safety laboratory samples may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.

[c] For the purpose of scheduling study visits, a week is defined as 7±2 days.

[d] It is anticipated that few patients will require visits beyond week 120, however the number of visits required will depend on order and duration of enrollment. After week 168, further visits occur every 12 weeks until completion. If necessary, the visit at week 180 would have identical procedures to week 132, the visit at week 192 would have identical procedures to week 144. If a visit beyond week 192 is necessary, contact Sponsor for guidance.

[e] In addition, an evaluation should take place as soon as possible for patients already in the study, following approval of Global Amendment 2.

[f] Vital signs include temperature, pulse and blood pressure. Weight will be measured at all visits.

[g] Anemia panel includes blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, IFN-γ, TNF-α, and hepcidin. Assessed at baseline and also at 1 subsequent time point (with B12) if hemoglobin decrease of >1 g/dL from the patient's hemoglobin level at baseline and the decrease is confirmed.

[h] Serum chemistry (including electrolytes, fibrinogen, glucose, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, creatine phosphokinase, C-reactive protein, pancreatic amylase [lipase will be tested in case of abnormal pancreatic amylase results], total protein, albumin, direct and total bilirubin) and complete blood count (CBC) with differential. Coagulation to be tested only if required according to Guidance on Safety Monitoring.

[i] Unscheduled urgent safety laboratory samples, pharmacokinetic blood samples, and/or samples for potential biomarker analysis may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.

[j] Fasting lipid profile includes total cholesterol, HDL, LDL (measured), and triglycerides.

[k] Patients who develop renal disease associated with moderate or severe functional impairment, defined as glomerular filtration rate (GFR) ≤60 mL/min/1.73 m^2, while participating in the study should stop study medication temporarily and the GFR assessment should be repeated. If the renal impairment is confirmed (GFR ≤60 mL/min/1.73 m^2), the patient should stop study medication permanently.

[l] For women of child-bearing potential serum β-hCG test will be done at each scheduled study visit. Urine β-hCG tests will be done at each study visit; in case of a positive result, study drug should not be dispensed until the serum β-hCG result is available.

[m] Starting from week 12 visit, women of child-bearing potential will be provided with home pregnancy urine β-hCG test kits and will be instructed how to perform the test. The site staff will schedule the home test to be performed every 28 ±2 days between study visits.
[n] Study drug will be dispensed at completion visit for those patients continuing to the potential extension study.
[o] Only an Examining Neurologist will administer the EDSS/FSS. The Examining Neurologist will not have access to the patient's medical records or source documents, including previous EDSS/FSS forms or adverse events.
[p] Only a trained, blinded rater will administer the T25FW, 9HPT, BICAMS, and SDMT. The blinded rater will not have access to the patient's medical records or source documents, including previous T25FW, 9HPT, BICAMS, or SDMT forms.
[q] At week 96 and every 48 weeks thereafter, SDMT will be performed as part of the BICAMS assessment
[r] OCT evaluation (in selected sites) will be performed in all patients who signed an appropriate, EC approved ICF.

ET = early termination; ECG = electrocardiogram; β-hCG = beta human chorionic gonadotropin; IVRS/IWRS = interactive voice response system/interactive web response system; EDSS = Expanded Disability Status Scale; FSS = Functional System Score; mRS = modified Rankin scale; T25FW = timed 25 foot walk; 9HPT = 9 Hole Peg test; SDMT = symbol digit modalities test; BICAMS = Brief International Cognitive Assessment for Multiple Sclerosis; LCVA = low contrast visual acuity; MSWS-12 = 12-Item Multiple Sclerosis Walking Scale; OCT = optical coherence tomography; IL = interleukin; IFN = interferon; TNF = tumor necrosis factor; HDL = high density lipoprotein; LDL = low density lipoprotein; EC = Ethics Committee; ICF = informed consent form

3.11.1. Screening Procedures

Prior to performing any study activities/evaluations, the patient must be thoroughly informed about all aspects of the study, including scheduled study visits and activities, and must sign the informed consent. A signed copy of the informed consent should be given to the patient.

Screening should occur up to 6 weeks (42 days) prior to the baseline (week 0) visit.

The following procedures will be performed:

- The patient will be allocated a patient number by the investigator using IVRS and/or IWRS. The patient will then be assessed for eligibility criteria.

The activities will include:

- Documentation of general, non-MS related medical history (including current and past smoking habits).
- Complete history of MS including:
  - the date of the first symptom
  - the date of diagnosis of MS
  - documentation of clinical disability progression (retrospectively or prospectively determined) within the 2 years prior to screening
  - absence of relapses prior to screening.
- All MS medications taken at any time prior to baseline and all concomitant medications taken up to 6 weeks prior to baseline will be recorded in the source document as well as in the CRF. Source documents from 2 years prior to the baseline visit should be reviewed for the detection of disallowed medications, according to the exclusion criteria and the list in Sections 5.2.1 and 5.2.2.2 and Appendix C.
- Vital signs (temperature, pulse, blood pressure [BP]), including height and weight.
- Complete physical examination.
- EDSS and FSS.
- Laboratory tests, including:
  - complete blood count (CBC) with differential
  - serum chemistry (including electrolytes, fibrinogen, glucose, urea, creatinine, liver enzymes, creatine phosphokinase [CPK], CRP, pancreatic amylase, total protein, albumin, direct and total bilirubin).
  - estimated GFR (see Section 7.7)
  - human T lymphotropic virus Type I and II (HTLV-I/II)
  - urinalysis
  - serum and urine β-hCG in women of child-bearing potential

  - B12
- ECG.
- Chest X-ray (can be omitted if the report of a chest X-ray performed within 24 weeks of screening is obtained, or if a screening chest X-ray is considered unacceptable per local regulations).
- Adverse event recording (from the moment the patient signs the informed consent form).
- Ascertain use of acceptable contraception. Women of child-bearing potential who are not yet practicing at least 1 acceptable method of birth control must practice an acceptable method for at least 30 days before taking the study drug.
- Evaluation and management of major modifiable cardiac risk factors (eg, diabetes, high blood pressure, hyperlipidemia, tobacco smoking) and referral to treatment and follow-up in suitable clinic if needed.

Following completion of screening procedures by the site, special cases may need a central review by an eligibility evaluation committee prior to baseline.

3.11.1.1. Re-Screening

Re-screening will be permitted on a case by case basis. A new informed consent form should be signed in any case of re-screening. A patient may only be re-screened once. Any patient who has previously participated in the study and early terminated cannot be re-screened.

A new patient number will be assigned to the patient.

The required re-screening visit activities should be discussed on a case by case basis with the sponsor.

Mandatory re-screening visit procedures:

- vital signs and weight
- review of concomitant medications
- evaluation of adverse events
- pregnancy test
- EDSS and FSS

Optional re-screening procedures:

- ECG
- physical examination
- laboratory tests including estimated GFR
- chest X-ray
- MRI.

The baseline (week 0) visit should take place within 6 weeks (42 days) from the re-screening visit.

3.11.2. Baseline Visit Procedures (Week 0)

3.11.2.1. Between 6 weeks (42 days) and 14 days Prior to Baseline

- Brain and cervical spinal cord MRI scan without and with Gd.

3.11.2.2. Up to 42 days Prior to Baseline

For patients participating in the OCT ancillary study, to be conducted only in selected countries and sites, after signature of an additional informed consent and ethics committee (EC) approval, the following assessment will be done:

- OCT evaluation (in selected sites) will be performed in all patients who signed an appropriate, EC approved informed consent form, to assess retinal thickness.

3.11.2.3. Up to 7 days Prior to Baseline

- Serum β-hCG in women of child-bearing potential (result must be available prior to the first dose at baseline).

3.11.2.4. Pre-randomization

The following procedures will be performed:

- vital signs (temperature, pulse and BP) and weight
- physical examination
- EDSS and FSS
- T25FW and 9HPT
- BICAMS, including SDMT
- LCVA
- MSWS-12
- ECG, 3 recordings 10 minutes apart before first dose
- review of changes in concomitant medications since screening visit
- inclusion/exclusion criteria confirmation, including confirmation of local radiologist that no MRI findings other than MS-related findings are present which exclude patient's participation in the study
- adverse event recording
- laboratory tests including:
  - CBC with differential

- anemia panel (blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, interleukin [IL]-1, IL-6, interferon [IFN]-γ, tumor necrosis factor [TNF]-α, and hepcidin)
- serum chemistry (including electrolytes, fibrinogen, glucose, urea, creatinine, liver enzymes, CPK, CRP, pancreatic amylase, total protein, albumin, direct and total bilirubin)
- estimated GFR
- fasting lipid profile (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL, measured], triglycerides)
- serum thyroid stimulating hormone (TSH), triiodothyronine (T3), and free thyroxine (T4)
- urine β-hCG test will be performed in women of child-bearing potential

- Blood samples for PGx assessment. If the PGx sample is not obtained at baseline for any reason, it should be collected at the next possible visit.
- blood samples for potential biomarker measures
- ascertain use of acceptable contraception

If all inclusion/exclusion criteria have been reviewed and are met, and the patient is eligible for treatment, he/she will be randomized (see Section 3.3).

3.11.2.5. Post Randomization

The following procedures will be performed:

- First dose administration of the study drug.
- Vital signs (pulse and BP will be measured predose and 30 and 60 minutes after first drug administration).
- Adverse event recording will be performed upon any complaint following study drug administration (if relevant) or staff observation.
- Patients will be given all the necessary supplies and detailed instructions for administration of study drug, which will be reviewed with the patient during the visit. In addition, patients will be instructed to contact the study center if any questions or problems arise.

Patients will be instructed to contact the study site in the event of any change in their medical condition, the appearance of any adverse events, or any symptom suggestive of a relapse.

3.11.3. Scheduled Treatment Visits (Visits 1 to 6, Weeks 4 to 48, and Every 12 weeks Thereafter)

Following the baseline visit, patients will return to the study center at weeks 4, 8, 12, and every 12 weeks thereafter until completion. A week is defined as 7 ±2 days.

Procedures for study completion are detailed in Section 3.11.5.

The following procedures and evaluations will be performed at these visits:

- Call IVRS/IWRS.*
- Vital signs (temperature, pulse, BP)
- Weight*
- Physical examination.
- ECG (weeks 4, 8, 12, 24, and every 24 weeks thereafter)
- Review concomitant medications.
- Record adverse events.
- Patient compliance (study drug accountability) and study drug dispensing.*
- Safety laboratory tests:
  - serum pregnancy test (β-hCG) for women of child-bearing potential.*
  - Urine pregnancy test (β-hCG) for women of child-bearing potential. In case of positive result, study drug should not be dispensed, until results of serum β-hCG test are available. The rest of the visit activities should be performed.*
  - Starting from week 12 visit, between study visits, women of child-bearing potential will be provided with home pregnancy urine β-hCG test kits and will be instructed how to perform the test. The site staff will schedule the home test to be performed every 28 ±2 days. To verify whether the test has been performed and to record the result of the test, a mandatory phone call will be performed by the Treating Neurologist or by the site's nurse/study coordinator within 72 hours after the test was scheduled to be performed and the patient will be asked specific questions regarding the test. In case of a suspected pregnancy (positive urine β-hCG test result, delay of menstruation or any other reason suggesting pregnancy), the caller will ensure that the study drug has been stopped and the patient will be instructed to arrive to the study site as soon as possible (within 10 days) for further evaluations with the remaining study medications.*
  - CBC with differential.
  - In case of hemoglobin decrease of >1 g/dL from the patient's hemoglobin level at baseline:
    - patient will be re-tested to confirm decrease
    - if decrease confirmed, a thorough anemia work-up will be done including:
      - directed medical history and physical examination
      - anemia panel (blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, IFN-γ, TNF-α, and hepcidin) and B12

        - additional investigations and follow-up per the investigator's discretion or sponsor's request

    - Serum chemistry (including electrolytes, fibrinogen, glucose, urea, creatinine, liver enzymes, CPK, CRP, pancreatic amylase, total protein, albumin, direct and total bilirubin).
    - estimated GFR*
    - Fasting lipid profile at week 48 and every 48 weeks until completion/ET.
    - Serum TSH, T3, and free T4 at week 24 and every 24 weeks until completion/ET.
- Blood samples for potential biomarker measures will be collected at weeks 24 and 48.
- Pharmacokinetic study: blood samples for analysis of laquinimod plasma concentrations will be collected at weeks 4, 8, 12, 24 and 48.*
- Ascertain use of acceptable contraception.*
- All patients will undergo brain and cervical spinal cord MRI scans without Gd at weeks 24 and 48.
    - Weeks 24 and 48 MRI will be performed within 14 days of the clinical visit.
    - In case of steroid treatment, study MRI should be performed before such treatment or delayed to allow a minimum of 14 days but not more than 28 days from the completion of the steroid course.
- EDSS and FSS will be performed every 12 weeks until completion/ET visit (if applicable)
- T25FW, 9HPT, and SDMT will be performed every 12 weeks until completion/ET visit (if applicable). At week 48 and every 48 weeks thereafter, SDMT will be performed as part of the BICAMS assessment.
- mRS will be evaluated at week 72.
- BICAMS, including SDMT, will be evaluated at week 48 every 48 weeks thereafter.
- LCVA will be assessed at week 24 and every 24 weeks until completion/ET.
- MSWS-12 will be performed at week 12 and every 12 weeks until completion/ET.
- Evaluation and management of major modifiable cardiac risk factors (with referral to treatment and follow-up in suitable clinic if needed) will be performed at weeks 96 and 144.
- Ancillary studies:
    - CSF (to be performed in selected sites) will be collected from all patients who signed an appropriate, EC approved informed consent form, at week 48 (see Section 8.4.1 for further details of the assessments).

  - OCT evaluation (to be performed in selected sites) will be performed in all patients who signed an appropriate, EC approved informed consent form, at weeks 48 and 96 to assess retinal thickness.

* Patients who are discontinued from study treatment will be encouraged to continue all scheduled visits and procedures after study drug discontinuation (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, GFR testing, and pharmacokinetic sampling).

3.11.4. Early Termination (ET) Visit

The following procedures and evaluations will be performed at this visit:

- call IVRS/IWRS
- patient compliance (study drug accountability)
- vital signs (temperature, pulse, and BP) and weight
- physical examination
- ECG
- review concomitant medications
- record adverse events
- safety laboratory tests:
  - serum pregnancy test (β-hCG) for women of child-bearing potential
  - urine pregnancy test (β-hCG) for women of child-bearing potential.
  - CBC with differential.
  - serum chemistry
  - estimated GFR
  - fasting lipid profile
  - serum TSH, T3, and free T4
- Ascertain use of acceptable contraception.
- EDSS and FSS
- T25FW and 9HPT
- SDMT
- LCVA
- MSWS-12
- MRI scan (without Gd): ET visit will only include MRI for patients who prematurely terminate treatment subsequent to the week 36 visit and prior to week 48. Patients who stop treatment before week 36 or after week 48 will not have MRI at ET visit. MRI will be performed within 14 days of ET visit. In case of steroid treatment, study

MRI should be performed before such treatment or delayed to allow a minimum of 14 days but not more than 28 days from the completion of the steroid course.

- BICAMS and OCT: ET visit will only include BICAMS and OCT for patients who prematurely terminate treatment subsequent to the week 24 visit and prior to week 48. Patients who stop treatment before week 24 or after week 48 will not have BICAMS and OCT at ET visit.

All reasons for ET will be documented in the source documents and the study drug termination CRF form should be recorded with the reason (the most severe) for ET.

Women of child bearing potential that performed ET should continue using 2 acceptable contraception methods up to 30 days after the last dose of oral treatment was administered. Pregnant women will perform ET visit procedures.

Moderate/strong CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered. For information on the use of CYP1A2 substrates following laquinimod cessation, please refer to the laquinimod IB.

3.11.5. Completion Visit

The following patients will be considered to have completed the study:

- Patients who participated in the study until the sponsor declared the completion of the study.

Patients who discontinue study drug but continue to attend scheduled study visits for follow-up are not considered to have completed the study.

For patients who performed a visit within the 4 weeks prior to this visit, certain activities that had already been performed do not need to be repeated. However patient compliance/drug accountability, review of concomitant medications, vital signs, ECG, and recording of adverse events must be performed in any case.

The following procedures and evaluations will be performed at this visit:

- Call IVRS/IWRS
- Patient compliance/study drug accountability
- Vital signs (temperature, pulse and BP) and weight
- Physical examination
- ECG
- Review concomitant medications
- Record adverse events
- Safety laboratory tests:
  - serum pregnancy test (β-hCG) for women of child-bearing potential, if applicable
  - urine pregnancy test (β-hCG) for women of child-bearing potential, if applicable
  - CBC with differential

  - serum chemistry
  - estimated GFR
  - fasting lipid profile
  - serum TSH, T3, and free T4
- Ascertain use of acceptable contraception.
- EDSS and FSS
- T25FW, 9HPT, and SDMT
- LCVA
- MSWS-12

Women of child bearing potential should continue using 2 acceptable contraception methods up to 30 days after the last dose of oral treatment was administered.

Moderate/strong CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered. For information on the use of CYP1A2 substrates following laquinimod cessation, please refer to the laquinimod IB.

Study drug will be dispensed at completion visit for those patients continuing to the potential extension study.

3.11.6. Unscheduled Visit

An unscheduled visit may be performed at any time during the study at the patient's request or as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded.

The reasons for the unscheduled visit may be:

- a new adverse event or an adverse event follow-up
- change in concomitant medications
- possible relapse
- relapse follow-up
- laboratory follow-up
- study drug dispensing, accountability and/or replacement
- patient compliance
- repeat MRI scan
- other

If the visit is related to a relapse, this will be clearly indicated on the CRF and the Examining Neurologist will carry out a complete neurological evaluation (EDSS and FSS).

Mandatory unscheduled visit procedures (except for patients that perform the unscheduled visit for repeat MRI scan):

- vital signs
- evaluation of adverse events
- review of concomitant medications
- ascertain use of acceptable contraception.

Additional clinical procedures may be performed by the Treating Neurologist to assure patient safety, and must be recorded in the source documentation.

According to the judgment of the investigator or medical monitor, the following unscheduled procedures may be performed:

- urgent safety laboratory test panel (see Section 7.3.4)
- collection of unscheduled pharmacokinetic blood sample
- collection of sample for potential biomarker analysis

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Patient Inclusion Criteria

Patients may be included in the study only if they meet all of the following criteria:

1. Patients must have a confirmed and documented PPMS diagnosis as defined by the 2010 Revised McDonald criteria (see Appendix D).
2. Baseline MRI showing lesions consistent with PPMS in either or both brain and spinal cord.
3. Patients must have an EDSS score of 3 to 6.5, inclusive, at both screening and baseline visits.[a]
4. Documented evidence of clinical disability progression in the 2 years prior to screening.
5. FSS of ≥2 for the pyramidal system or gait impairment due to lower extremity dysfunction.
6. Patients must be between 25 to 55 years of age, inclusive.
7. Women of child-bearing potential (for example women who are not postmenopausal or surgically sterilized) must practice an acceptable method of birth control for 30 days before taking the study drug, and 2 acceptable methods of birth control during all study duration and until 30 days after the last dose of treatment is administered. Acceptable methods of birth control in this study include: intrauterine devices, barrier methods (condom or diaphragm with spermicide), and hormonal methods of birth control (eg, oral contraceptive, contraceptive patch, long-acting injectable contraceptive).
8. Patients must sign and date a written informed consent prior to entering the study.
9. Patients must be willing and able to comply with the protocol requirements for the duration of the study.

4.2. Patient Exclusion Criteria

Patients will be excluded from participating in this study if they meet any of the following criteria:

1. Patients with history of any MS exacerbations or relapses, including any episodes of optic neuritis.
2. Progressive neurological disorder other than PPMS.
3. Any MRI record showing presence of cervical cord compression.
4. Baseline MRI showing other findings (including lesions that are atypical for PPMS) that may explain the clinical signs and symptoms.

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[a] A capped randomization procedure will be employed to ensure that the number of EDSS 6.0 and 6.5 patients will be no more than 20% of all enrolled patients.

5. Relevant history of vitamin B12 deficiency.
6. Positive HTLV-I/II serology.
7. Use of experimental or investigational drugs in a clinical study within 24 weeks prior to baseline. Use of a currently marketed drug in a clinical study within 24 weeks prior to baseline would not be exclusionary, provided no other exclusion criteria are met.
8. Use of immunosuppressive agents, or cytotoxic agents, including cyclophosphamide and azathioprine within 48 weeks prior to baseline.
9. Previous treatment with fingolimod (GILENYA®, Novartis), dimethyl fumarate (TECFIDERA®, Biogen Idec Inc), glatiramer acetate (COPAXONE®, Teva), interferon-β (either 1a or 1b), intravenous immunoglobulin (IVIG), or plasmapheresis within 8 weeks prior to baseline.
10. Use of teriflunomide (AUBAGIO®, Sanofi) within 2 years prior to baseline, except if active washout (with either cholestyramine or activated charcoal) was done 2 months or more prior to baseline.
11. Prior use of monoclonal antibodies ever, except for:
    a. natalizumab (TYSABRI®, Biogen Idec Inc), if given more than 24 weeks prior to baseline AND the patient is John Cunningham (JC) virus antibody test negative (as per medical history)
    b. rituximab, ocrelizumab, or ofatumumab, if B cell count (CD19, as per medical history) is higher than 80 cells/µL
12. Use of mitoxantrone (NOVANTRONE®, Immunex) within 5 years prior to screening. Use of mitoxantrone >5 years before screening is allowed in patients with normal ejection fraction and who did not exceed the total lifetime maximal dose.
13. Previous use of laquinimod.
14. Chronic (eg, more than 30 consecutive days or monthly dosing, with the intent of MS disease modification) systemic (intravenous, intramuscular or oral) corticosteroid treatment within 8 weeks prior to baseline.
15. Previous use of cladribine or alemtuzumab (LEMTRADA®, Sanofi).
16. Previous total body irradiation or total lymphoid irradiation.
17. Previous stem cell treatment, cell-based treatment, or bone marrow transplantation of any kind.
18. Patients who underwent endovascular treatment for chronic cerebrospinal venous insufficiency (CCSVI) within 12 weeks prior to baseline.
19. Use of moderate/strong inhibitors of CYP3A4 within 2 weeks prior to baseline.
20. Use of inducers of CYP3A4 within 2 weeks prior to baseline.
21. Pregnancy or breastfeeding.
22. Serum levels ≥3×ULN of either ALT or AST at screening.

23. Serum direct bilirubin which is ≥2×ULN at screening.
24. Patients with a clinically significant or unstable medical or surgical condition that (in the opinion of the Investigator) would preclude safe and complete study participation, as determined by medical history, physical examinations, ECG, laboratory tests or chest X-ray. Such conditions may include:
    a. A major cardiovascular event (eg, myocardial infarction, acute coronary syndrome, decompensated congestive heart failure, pulmonary embolism, coronary revascularization) that occurred during the past 24 weeks prior to baseline.
    b. Any acute pulmonary disorder.
    c. A CNS disorder other than MS that may jeopardize the patient's participation in the study, including such disorders that are demonstrated on the baseline MRI.
    d. A gastrointestinal disorder that may affect the absorption of study medication.
    e. Renal disease.
    f. Any form of acute or chronic liver disease.
    g. Known human immunodeficiency virus positive status.
    h. A history of drug and/or alcohol abuse.
    i. Unstable psychiatric disorder.
    j. Any malignancies, excluding basal cell carcinoma, in the 5 years prior to baseline.
25. A known history of hypersensitivity to Gd.
26. GFR ≤60 mL/min/1.73 m^2 at screening visit.
27. Inability to successfully undergo MRI scanning, including claustrophobia.
28. Known drug hypersensitivity that would preclude administration of laquinimod, such as hypersensitivity to mannitol, meglumine or sodium stearyl fumarate.

Special cases may need a central review of the documentation by an eligibility evaluation committee prior to baseline.

4.3. Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient is free to withdraw from the study at any time. The investigator also has the right to withdraw a patient from the study or stop drug treatment due to any of the reasons listed in Section 4.3.1. In addition, a patient may be withdrawn from the study as described in Sections 3.6 and 5.3.

Should a patient decide to withdraw after administration of study drug(s), or should the investigator decide to withdraw the patient, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given as to why the patient is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from study drug treatment and the reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed onto the CRF. If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a clinically significant abnormal laboratory test result, monitoring will be continued at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The specific event or test result(s) must be recorded on the source documentation and transcribed onto the CRF.

All evaluations should be performed according to the protocol on the last day the patient takes study drug, or as soon as possible thereafter.

4.3.1. Patient Withdrawal Criteria

A patient may withdraw or be withdrawn from the study for the following reasons:

- death
- patient withdrew consent
- sponsor requested patient to be withdrawn
- study terminated by the sponsor
- protocol violation
- non-compliance with study drug
- lost to follow-up/failure to return
- adverse event
- lack of efficacy (according to the investigators decision)
- pregnancy

For patients in the 1.5 mg arm who were withdrawn from study treatment, the reason will be recorded as ‘sponsor requested patient to be withdrawn’.

5. TREATMENT OF PATIENTS

5.1. Study Drugs Administered

Until 01 January 2016, following the baseline visit patients were randomly assigned in a 1:1:1 ratio into 1 of the following:

- laquinimod capsules 0.6 mg (1 capsule of 0.6 mg laquinimod and 2 capsules of placebo)
- laquinimod capsules 1.5 mg (3 capsules of 0.5 mg laquinimod)
- placebo (3 capsules of placebo)

From 01 January 2016, following the baseline visit patients will be randomly assigned in a 1:1 ratio into 1 of the following:

- laquinimod capsules 0.6 mg (1 capsule of 0.6 mg laquinimod and 2 capsules of placebo)
- placebo (3 capsules of placebo)

Compliance to study drug administration will be monitored.

5.2. Prior and Concomitant Therapy or Medication

All MS medications (taken at any time prior to baseline) and all concomitant medications taken up to 6 weeks prior to baseline will be recorded in the source document as well as the CRF.

At each clinic visit after the screening visit, the investigator will ask patients whether they have taken any medications (other than study drug), including over-the-counter (OTC) medications, vitamins, or herbal or nutritional supplements, since the previous visit. Indication, dosage, and start and end dates should be entered on the CRF.

5.2.1. Disallowed Previous Medications/Therapies

- Use of experimental or investigational drugs in a clinical study within 24 weeks prior to baseline.
- Use of immunosuppressive agents, or cytotoxic agents, including cyclophosphamide and azathioprine within 48 weeks prior to baseline.
- Previous treatment with fingolimod (GILENYA®, Novartis), dimethyl fumarate (TECFIDERA®, Biogen Idec Inc), glatiramer acetate (COPAXONE®, Teva), interferon-β (either 1a or 1b), IVIG, or plasmapheresis within 8 weeks prior to baseline.
- Use of with teriflunomide (AUBAGIO®, Sanofi) within 2 years prior to baseline, except if active washout (with either cholestyramine or activated charcoal) was done 2 months or more prior to baseline.
- Prior use of monoclonal antibodies ever, except for:

  - Natalizumab (TYSABRI®, Biogen Idec Inc), if given more than 24 weeks prior to baseline AND the patient is JC virus antibody test negative at screening.
  - rituximab, ocrelizumab, or ofatumumab, if B cell count (CD19) is higher than 80 cells/μL.
- Use of mitoxantrone (NOVANTRONE®, Immunex) within 5 years prior to screening. Use of mitoxantrone >5 years before screening is allowed in patients with normal ejection fraction and who did not exceed the total lifetime maximal dose.
- Previous use of laquinimod.
- Chronic (eg, more than 30 consecutive days or monthly dosing, with the intent of MS disease modification) systemic (intravenous, intramuscular or oral) corticosteroid treatment within 8 weeks prior to baseline.
- Previous use of cladribine or alemtuzumab (LEMTRADA®, Sanofi).
- Previous total body irradiation or total lymphoid irradiation.
- Previous stem cell treatment, cell-based treatment, or bone marrow transplantation of any kind.
- Endovascular treatment for CCSVI within 12 weeks prior to baseline.
- Use of moderate/strong inhibitors of CYP3A4 within 2 weeks prior to baseline.
- Use of inducers of CYP3A4 within 2 weeks prior to baseline.

Appendix C provides a partial list of CYP3A4 inhibitors and inducers.

5.2.2. Concomitant Medications/Therapies During Study

5.2.2.1. Allowed Medications/Therapies During Study

Administration of all medications, including indication, dose, frequency, and route of administration will be recorded in the source documentation file and in the CRF.

- Symptomatic MS agents, such as anti-cholinergic and spasmolytic drugs, are permitted at clinically appropriate doses. Dose changes and initiation of symptomatic treatments during the study should be avoided if possible.
- Short-term treatment (up to 5 days) with intravenous corticosteroids will be allowed during relapses, although these are rare in PPMS. The suggested treatment for a relapse will be intravenous methylprednisolone 500 to 1000 mg/day for 3 to 5 consecutive days.
- Other medications, excluding those mentioned in Appendix C may be given concomitantly as needed for the patient's welfare.
- Topical and inhaled steroids are allowed at the discretion of the Treating Neurologist for indications other than MS.
- Clinical studies have shown laquinimod to be a strong inducer of CYP1A2. Patients taking drugs that are metabolized by CYP1A2 (examples listed in Appendix E)

should be advised that plasma levels of these drugs could decrease when combined with laquinimod. In general, as a precautionary measure, it is recommended to avoid the use of CYP1A2 substrates in clinical trials of laquinimod. Therapeutic alternatives may be considered in the appropriate clinical context. Additional information on concomitant use of laquinimod and CYP1A2 substrates is presented in the laquinimod IB.

- Drug-drug interaction studies have been performed with laquinimod doses of 0.6 and 1.2 mg. These studies showed that laquinimod, at both doses, is a weak inhibitor of CYP3A4. Patients taking drugs that are metabolized by CYP3A4 (specifically those with a narrow therapeutic index listed in Appendix E) should be advised that plasma levels of these drugs could increase when combined with laquinimod.
- Use of a currently marketed drug in a clinical study within 24 weeks prior to baseline is allowed.

5.2.2.2. Disallowed Concomitant Medications/Therapies During Study

- glatiramer acetate
- interferon β-1a
- interferon β-1b
- natalizumab
- fingolimod
- teriflunomide
- dimethyl fumarate
- alemtuzumab
- inducers of CYP3A4 such as rifampin (more examples listed in Appendix C)
- moderate/strong inhibitors of CYP3A4 such as erythromycin and ketoconazole (more examples listed in Appendix C). Laquinimod is extensively metabolized predominantly by CYP3A4, and ketoconazole and fluconazole, strong and moderate inhibitors of CYP3A4, were found to inhibit the metabolism, leading to 2.5- and 3.1-fold increases in laquinimod exposure, respectively.
- mitoxantrone
- oral steroids, except as prescribed for non-MS reasons (eg, asthma, chronic obstructive pulmonary disease)
- parenteral steroids (except if given as defined by protocol for treatment of a relapse as specified in Section 5.2.2.1)
- chemotherapeutic agents
- IVIG
- plasmapheresis

- any other experimental agents
- other immunosuppressive or immunomodulating agents
- other agents with the aim of disease modification

5.3. Procedures for Monitoring Patient Compliance

Each investigator will be responsible for monitoring patient compliance. A check of study drug compliance will be performed during each visit after the initial dispensation of study drug, and study drug accountability records will be completed. If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn. The IEC/IRB should be notified, according to local regulations.

5.4. Total Blood Volume

The total amount of blood to be drawn during the study for serum chemistry, CBC, pharmacokinetic, biomarker and PGx measurements is approximately 550 mL/patient.

6. ASSESSMENT OF EFFICACY

6.1. Primary Efficacy Variables

BA, as defined by the PBVC from baseline to week 48. See Section 6.4.1 for MRI methodology and Section 9.6.4.1 for statistical analysis of BA.

6.2. Secondary Efficacy Variables

- Time to CDP, defined as increase in EDSS of ≥1 point from baseline EDSS, if EDSS at entry is ≤5.0 or increase of ≥0.5 point, if EDSS at entry is ≥5.5. This increase should be confirmed after at least 12 weeks. Progression cannot be confirmed during a relapse. See Section 6.4.2 for EDSS methodology and Section 9.6.4.3 for statistical analysis of CDP.
- Time to CDP as measured by 2 types of events for each individual (progression cannot be confirmed during a relapse):
  - An increase from baseline in EDSS score (≥1 point from baseline EDSS if EDSS at entry is ≤5.0, or increase of ≥0.5 point if EDSS at entry is ≥5.5), confirmed after at least 12 weeks, or
  - An increase of at least 20% from baseline in the T25FW score, confirmed after at least 12 weeks.

  See Sections 6.4.2 and 6.4.3 for EDSS and T25FW methodologies, respectively, and Section 9.6.4.3 for statistical analysis of CDP.
- Change from baseline to week 48 in the T25FW score. See Section 6.4.3 for methodology and Section 9.6.4.3 for statistical analysis.
- The number of new T2 lesions at week 48. See Section 6.4.1 for MRI methodology, and Section 9.6.4.3 for statistical analysis of T2 lesion numbers.

6.3. Exploratory/Other Efficacy Variables

For a full list of exploratory/other variables see Section 9.6.3. Exploratory/other endpoints include BICAMS (see Section 6.4.5), time to CDP as measured by at least 1 of 4 types of events, 24-week CDP (see Section 6.4.2), T1 hypointense lesions, changes in T1-hypointense lesion volume, changes in T2 lesion volume, and MRI (see Section 6.4.1), T25FW (see Section 6.4.3), 9HPT (see Section 6.4.4), SDMT (see Section 6.4.6), mRS (see Section 6.4.7), LCVA (see Section 6.4.8), MSWS-12 (see Section 6.4.9), relapses (see Section 6.4.10), and potential biomarker measures (see Section 8.2). Statistical analysis for exploratory endpoints will be detailed in the statistical analysis plan (SAP).

6.4. Methods and Timing of Assessing, Recording, and Analyzing Efficacy Data

Methods and timing of assessing efficacy data are discussed in Section 3.11. Procedures for recording efficacy data are discussed in Section 13.1, and methods of analyses are discussed in Section 9.6.4.

6.4.1. MRI Evaluations

The patients will undergo up to 3 MRI scans:

- baseline (at least 14 days but not more than 6 weeks prior to baseline)
- week 24
- week 48 (or ET visit if performed after the week 36 visit and prior to week 48).

Gd will be administered at baseline MRI only. In case of steroid treatment, study MRI should be performed before or be delayed to allow a minimum of 14 days, but not more than 28 days, from the completion of the steroid course.

The following parameters will be assessed:

- normalized brain volume - at baseline
- PBVC – at week 24 as well as week 48 or ET
- T2-lesions volume – at baseline, as well as week 48 or ET
- T1 hypointense lesions volume - at baseline, as well as week 48 or ET
- number of GdE-T1 lesions – at baseline
- number of new T2 lesions - at week 48 or ET
- number of new T1 hypointense lesions - at week 48 or ET
- thalamic volume, cortical volume, and white matter volume - at baseline
- percent volume change (thalamus, cortex, white matter) - at week 48 or ET
- normalized cervical cord area based on 3D T1-w acquisition of the cervical cord - at baseline
- cervical cord area percentage volume change - at week 48 or ET
- number of T2 cervical cord lesions based on a sagittal T2 acquisition of the cervical cord - at baseline
- number of new T2 cervical cord lesions based on a sagittal T2 acquisition of the cervical cord - at week 48 or ET
- normal-appearing brain tissue average MTR, at baseline, as well as week 48 or ET

If MTR is not performed due to MRI site technical limitations, this would not be considered a protocol violation.

Additional details of MRI procedures are presented in Appendix F and in the MRI manual.

6.4.2. Neurological Evaluations (EDSS and FSS)

Neurological evaluations (EDSS and FSS) will be performed in a treatment blinded manner by the Examining Neurologist. The patient will be instructed not to discuss his/her well-being and adverse events with the Examining Neurologist. Every effort should be made to ensure that the same Examining Neurologist will perform the neurological assessment at all visits for a particular patient.

EDSS and FSS will be assessed based on the Neurostatus scoring guidelines (Appendix G), a slightly modified neurological examination than the one described by Kurtzke (Kurtzke 1983). The results will be recorded in standardized and validated examination forms (see Appendix G) as well as in the CRF. Fatigue will not contribute to the cerebral FSS and EDSS step.

6.4.3. Timed 25-Foot Walk (T25FW)

The T25FW is a quantitative measure of lower extremity function. The patient is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The task is immediately administered again by having the patient walk back the same distance. Patients may use assistive devices when doing this task.

The T25FW is administered in person by a blinded, trained rater. The rater need not be a physician or nurse.

Full instructions for the T25FW are provided in Appendix H.

6.4.4. 9-Hole Peg Test (9HPT)

The 9HPT is a brief, standardized, quantitative test of upper extremity function. It is a component of the Multiple Sclerosis Functional Composite (MSFC). Both the dominant and non-dominant hands are tested twice. The patient is seated at a table with a small, shallow container holding 9 pegs and a wood or plastic block containing 9 empty holes. A stopwatch is started and the patient picks up the 9 pegs, 1 at a time as quickly as possible, puts them in the 9 holes, and, once they are in the holes, removes them again as quickly as possible, 1 at a time, replacing them into the shallow container. The total time to complete the task is recorded. Two consecutive trials with the dominant hand are immediately followed by 2 consecutive trials with the non-dominant hand.

The 9HPT is administered in person by a blinded, trained rater. The rater need not be a physician or nurse.

Full instructions for the 9HPT are provided in Appendix I.

6.4.5. Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) Score

The BICAMS battery of tests takes 15 minutes to complete, requires no specialist equipment and no specialist expertise in cognitive assessment (Langdon 2012). BICAMS comprises:

- SDMT (see Section 6.4.6). While part of BICAMS, it will be administered as a standalone test, thus performing this as part of BICAMS is not required.

- California Verbal Learning Test–II (CVLT-II) (first 5 recall trials): this comprises a 16-item word list, with 4 items belonging to each of 4 categories, arranged randomly. The list is read aloud 5 times in the same order to the patient, at a slightly slower rate than 1 item per second. Patients are required to recall as many items as possible, in any order, after each reading of the list. The test can be completed in 5 to 10 minutes, including instructions, testing and responses.
- Brief Visuospatial Memory Test – Revised (BVMT-R) (first 3 recall trials): this requires the patient to inspect a 2 × 3 stimulus array of abstract geometric figures (Form 1 from the Recall Stimulus Booklet). There are 3 learning trials of 10 seconds. The array is removed and the patient is required to draw the array from memory, with the correct shapes in the correct position. Scoring of the BVMT-R drawings will be performed by a central expert vendor.

The BICAMS is administered in person by a treatment blinded, trained rater. The rater does not need to be a physician or nurse.

Full instructions for the BICAMS administration and scoring are provided in the BICAMS administration manual.

6.4.6. Symbol Digit Modalities Test (SDMT)

SDMT is a traditional, person-administered cognitive test that measures visual processing speed in 5 minutes. It can detect cognitional changes over time and be done orally or in writing. Despite its brevity, the SDMT is probably the most robust correlate with abnormal brain MRI findings, including brain lesion volume, BA, diffusion tensor indices of normal-appearing brain tissue, and retinal thickness. In addition, other findings suggest that compared to other well-established measures of cognitive function, it more accurately reflects the qualitative nature of self-reported cognitive impairment.

Only verbal administration of the SDMT will be permitted in this study.

Full instructions for SDMT administration and scoring are provided in the BICAMS administration manual. Although SDMT is part of BICAMS, it will be administered as a standalone test during this study.

6.4.7. Modified Rankin Scale

The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability (Rankin 1957; Farrell et al 1991). The scale runs from 0 (no symptoms) to 5 (severe disability), with a score of 6 used in the event of a death (Appendix J).

6.4.8. Low Contrast Visual Acuity (LCVA)

It has been demonstrated that LCVA, as measured using the Sloan Charts, has a substantial capacity to capture visual dysfunction in patients with MS.

LCVA will be assessed for each eye separately and then binocularly, at week 0 (baseline), week 24, and every 24 weeks until completion/ET. At each visit, the letter acuity will be captured using 100%, 2.5%, and 1.25% contrast charts, from a distance of 2 meters, with the

patient's usual distance correction. In case the patient is not familiar with the English/Roman alphabet, the Tumbling E charts will be used.

Detailed instructions for LCVA administration are provided in the operations manual.

6.4.9. 12-Item Multiple Sclerosis Walking Scale (MSWS-12)

The MSWS-12 was designed as a disease-specific, patient-based instrument, ie a patient reported outcome, for use in clinical studies and clinical practice, to capture the complex impact of MS on walking ability (Hobart et al 2003). It contains 12 questions with ordered responses, and has a recall period of 2 weeks (Appendix K). Individual items are scored on a Likert scale. The test takes less than 5 minutes to complete.

6.4.10. Relapse Evaluation

6.4.10.1. On-Study Relapse Evaluation

Relapses are rare events in PPMS. In the event of neurological symptoms suggestive of a relapse, patients will be instructed to telephone their study site within 48 hours. The Treating Neurologist will evaluate the patient once any symptom suggestive of a relapse occurs. During a scheduled or unscheduled visit, in case of a suggested relapse, the Treating Neurologist will refer the patient to the Examining Neurologist for performance of EDSS and FSS assessments. The Examining Neurologist will evaluate the patient within 7 days of symptom onset, conditional upon a symptomatic period of ≥48 hours.

6.4.10.2. The Treating Neurologist

The Treating Neurologist will determine if a patient experiences a relapse (see relapse definition, 0) and whether to treat the relapse or not. The Treating Neurologist will remain blinded to study drug assignment.

6.4.10.3. The Examining Neurologist

The Examining Neurologist will be responsible for all EDSS and FSS assessments. Throughout the study, the Examining Neurologist will remain unaware of the safety profile and will be kept blinded to all treatment assignments. For each patient, the same Examining Neurologist should be used for all neurological exams performed throughout the study.

Note: It is particularly important that the Treating Neurologist and the Examining Neurologist do not discuss safety issues or performance or scoring of the EDSS/FSS with each other. The Examining Neurologist will not ask the patient any questions regarding his/her well being.

The Treating Neurologist will inform the patient of the importance of not discussing safety issues with the Examining Neurologist.

6.4.10.4. Relapse Determination

An Examining Neurologist will administer the EDSS and FSS, unaware of patient's well-being.

The Treating Neurologist will make the decision as to whether the neurological change is considered a relapse (see relapse definition, 0). Clinical relapses must be recorded in the CRF. Patients with a relapse may continue in the study.

The Treating Neurologist will prescribe steroids or other concomitant medications as needed. The suggested treatment for a relapse will be intravenous methylprednisolone 500 to 1000 mg/day for 3 to 5 consecutive days.

Follow-up visits to monitor the course of the relapse until stabilization will be made at Treating Neurologist discretion, in addition to the assessment at the next scheduled visit.

In the case of an ongoing relapse at the study completion/ET visit, patients will be followed up until relapse stabilization, wherever possible.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study staff by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, physical examination findings and concomitant medication usage.

During the conduct of the study, an independent DMC will review accumulating safety data on a regular basis to ensure the continuing safety of the study patients and study conduct issues.

The DMC will be composed of independent physicians with expertise in the relevant therapeutic field and other relevant experts, such as a statistician. The DMC will receive safety data periodically. They will have the right to recommend discontinuation of the study for safety reasons.

DMC sessions can be open or closed. During open sessions, representatives of the sponsor may be present and information is provided and discussed in a blinded fashion. During closed sessions, the only participants are members of the DMC and the designated unblinded statistician.

The DMC chairperson will communicate with the sponsor in regard to issues resulting from the conduct and clinical aspects of the study. The sponsor will work closely with the committee to provide the necessary data for review.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

In this study, any adverse event occurring after the clinical study patient has signed the informed consent form should be recorded and reported as an adverse event.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during the study will not be considered adverse events.

Worsening of the disease under study should be recorded as an adverse event only if the presentation and/or outcome is more severe than would normally be expected from the normal course of the disease in a particular patient.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication

- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions. (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and which occurs during the study should be recorded as an adverse event.)
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of the study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, or require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant. Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events, but will be evaluated to monitor data from patients who do not meet screening criteria
- all events of possible drug-induced liver injury with hyperbilirubinemia (defined as AST or ALT ≥3×ULN, plus either bilirubin ≥2×ULN or INR >1.5) or Hy's Law events require immediate study treatment cessation and reporting as a serious adverse event

7.1.2. Recording and Reporting Adverse Events

For adverse event recording, the study period is defined for each patient as that time period from signature of the informed consent form through the end of the follow-up period. For this study, the follow-up period is defined as 30 days after the last dose of study drug.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed onto the CRF, regardless of the severity of the event or judged relationship to the study drug. For serious adverse events, the Serious Adverse Event Form must also be completed and the serious adverse event must be reported immediately (see Section 7.1.5.3.1).

At each contact with the patient, the investigator or designee must query the patient for adverse events by asking an open-ended question such as, "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the Serious Adverse Event Form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized or returned to baseline, or until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed onto the CRF.

The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the choices on the following scale:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Study Drug

The relationship of an adverse event to the study drug is characterized as follows:

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • it does not follow a reasonable temporal sequence from the administration of the test drug. • it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • it does not follow a known pattern of response to the test drug. • it does not reappear or worsen when the drug is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty nor felt with a high degree of certainty to be related to the study drug.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • it follows a reasonable temporal sequence from administration of the drug. • it cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • it disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • it follows a known pattern of response to the test drug.

7.1.5. Serious Adverse Events

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (ie, the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered serious adverse events.
- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.1.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The reference safety information for this study is the laquinimod IB.

The sponsor's Pharmacovigilance Department will determine the expectedness for all serious adverse events.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events (as described in Section 7.1.5.1) that occur during the study period (including the protocol-defined follow-up period), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the

investigator within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the Teva local safety officer (LSO) or other designated personnel (a contract research organization [CRO] in a country without a Teva LSO) Contact information is in the Clinical Study Personnel Contact Information section; the LSO will forward the report to the sponsor's Global Patient Safety and Pharmacovigilance Department.

The following information should be provided to record the event accurately and completely:

- study number TV5600-CNS-20006 (ARPEGGIO)
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the study drug (no reasonable possibility, reasonable possibility)

Additional information may include the following:

- age and gender of patient
- date of first dose of study drug
- date and amount of last administered dose of study drug
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant therapy (including doses, routes, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death:
  - cause of death (whether or not the death was related to study drug)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigational center within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's Global Patient Safety and Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO/CRO for local submission to the regulatory authorities and IEC/IRBs and investigators, according to regulations. The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with local regulations.

The blinding will be maintained for the people who are involved directly in the study. Therefore, in case of a SUSAR, only the LSO (or CRO personnel involved with safety regulatory submissions) will receive the unblinded report for regulatory submission; the others will receive a blinded report.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 7.2).

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the study drug or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of laquinimod and the appropriate regulatory authorities/EC.

In addition to notifying the investigators and regulatory authorities/EC, other measures may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- altering the process of informed consent by modifying the existing consent form and informing current study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to laquinimod

7.1.6. Protocol-Defined Adverse Events for Expedited Reporting

Ischemic cardiac events (such as myocardial infarction, unstable angina, acute coronary syndrome etc), and cerebrovascular events (such as cerebral arterial occlusion, cerebral ischemia, etc) should be reported to the sponsor within 48 hours, including completion of the corresponding dedicated CRF.

7.1.7. Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from the study at any time at the discretion of the investigator. If a patient is withdrawn wholly or in part because of an adverse event, both the adverse event page and termination page of the CRF will be completed at that time.

The patient will be monitored at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The investigator must inform the sponsor as soon as possible of all patients who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be need to take a prohibited medication, not the adverse event.

7.1.8. Medical Emergencies

Medical emergencies must be reported to the individual identified in the clinical study personnel contact information section of this protocol.

Equipment, supplies, and properly skilled medical personnel must be accessible for an adverse event requiring immediate treatment. Any dose of study drug (whether the investigational product, reference therapy, or a placebo), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor. When the identification of the study drug must be known, the investigator must follow the procedures outlined in Section 3.8.

7.1.9. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, departures from the protocol may be allowed on a case-by-case basis. After stabilization and/or treatment has been administered to ensure patient safety, the investigator or other physician in attendance must contact the individual identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study. Any departures from the protocol because of adverse events must be noted on the CRF and in source documents, along with the reason for such departures.

7.2. Pregnancy

Patients who are women of child-bearing potential (for example women who are not postmenopausal or surgically sterilized) must practice an acceptable method of birth control for 30 days before taking the study drug, and use 2 acceptable methods of contraception throughout treatment duration and until 30 days after the last dose of treatment.

Acceptable methods of birth control include intrauterine devices, barrier methods (condom or diaphragm with spermicide), and hormonal methods of birth control (eg, oral contraceptive, contraceptive patch, long-acting injectable contraceptive).

The patients' understanding of the importance of preventive pregnancy measures and their ability to follow the required instructions will be ensured by the investigator and documented in source documents.

Additionally, pregnancy tests (urine dipstick and/or serum pregnancy β-hCG test, as applicable per the relevant time point) will be performed.

All pregnancies of women participating in study that occur during the study, or within 30 days after the last dose of treatment was administered, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the LSO/CRO with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event (see Section 7.1.5.3).

Any woman who becomes pregnant during the study will discontinue treatment. Patients who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), details of birth, and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after termination from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

7.3. Clinical Laboratory Tests

Clinical laboratory tests will be measured as detailed in the sections below.

7.3.1. Serum Chemistry

The following serum chemistry tests will be performed at all study visits (except where stated):

- electrolytes
- fibrinogen
- glucose
- urea
- creatinine (Note: GFR will be estimated at all visits)
- ALT
- AST
- GGT
- alkaline phosphatase
- CPK

  - in case of CPK results >ULN, creatine kinase MB isoenzyme (CK-MB) and troponin will be tested by the central laboratory.
  - in case of CPK >10×ULN, an unscheduled visit to assess urine myoglobin will be required. The following blood tests will be repeated at the unscheduled visit: CPK, blood urea nitrogen, creatinine, electrolytes including potassium, calcium, phosphate.
- CRP
- pancreatic amylase
  - lipase will be tested in case of abnormal pancreatic amylase results
- total protein
- albumin
- direct and total bilirubin
- fasting lipid profile at weeks 0 and 48 and every 48 weeks until completion/ET.
- TSH, T3, and T4 at weeks 0 and 24 and every 24 weeks until completion/ET.
- Coagulation profile (prothrombin time [PT], activated partial thromboplastin time [aPTT] and INR),to be tested only if required according to Guidance on Safety Monitoring (see Appendix B).

7.3.2. Complete Blood Count

CBC (with differential) will be performed at all study visits (except where stated) and will comprise the following tests:

- Absolute neutrophil count
- hemoglobin
- hematocrit
- platelet count
- RBC count
- mean corpuscular hemoglobin (MCH)
- mean corpuscular hemoglobin concentration (MCHC)
- mean corpuscular volume (MCV)
- white blood cell (WBC) count and differential count
  - polymorphonuclear leukocytes (neutrophils)
  - lymphocytes
  - eosinophils
  - monocytes

- basophils

7.3.3. Anemia Panel

The anemia panel is assessed at baseline and also at 1 subsequent time point (with B12) if hemoglobin decrease of >1 g/dL from the patient's hemoglobin level at baseline and the decrease is confirmed.

- At baseline: blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, interferon IFN-γ, TNF-α, and hepcidin.
- In case of hemoglobin decrease of >1 g/dL from the patient's hemoglobin level at baseline:
  - patient will be re-tested to confirm decrease
  - if decrease confirmed, a thorough anemia work-up will be done including:
    - directed medical history and physical examination
    - anemia panel (blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, IFN-γ, TNF-α, and hepcidin) and B12
    - additional investigations and follow-up per the investigator's discretion or sponsor's request

7.3.4. Urgent Safety Laboratory Panel

Unscheduled urgent safety laboratory samples may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.

The following tests will be performed on these samples:

- serum chemistry panel (see Section 7.3.1)
- CBC panel (see Section 7.3.2)
- CK-MB
- troponin

7.3.5. Serology

- Serology for hepatitis A, B and C viruses (to be performed in a central laboratory, only if required according to Guidance on Safety Monitoring, see Appendix B)
- Serology for autoimmune hepatitis: anti-nuclear antibodies, anti smooth muscle antibodies (ASMA), anti-liver kidney microsomal (LKM) antibodies (to be performed in a central laboratory, only if required according to the Guidance on Safety Monitoring, see Appendix B)

7.3.6. Urinalysis

Urinalysis, performed at the screening visit, will include the following:

- protein
- glucose
- ketones
- erythrocytes
- leukocytes
- pH

7.3.7. Other Clinical Laboratory Tests

- Serum pregnancy test (β-hCG) for women of child-bearing potential at all visits; at baseline, this will be done within 7 days prior to the initiation of treatment, such that the result is available prior to the first dose.
- Urine pregnancy test (β-hCG) for women of child-bearing potential at all visits. In case of positive result, study drug should not be dispensed, until results of serum β-hCG test are available. The rest of the visit activities should be performed.
- Starting from week 12 visit, between study visits, women of child-bearing potential will be provided with home pregnancy urine β-hCG test kits and will be instructed how to perform the test. The site staff will schedule the home test to be performed every 28 ±2 days. To verify whether the test has been performed and to record the result of the test, a mandatory phone call will be performed by the Treating Neurologist or by the site's nurse/study coordinator within 72 hours after the test was scheduled to be performed. In case of a suspected pregnancy (positive urine β-hCG test result, delay of menstruation or any other reason suggesting pregnancy), the caller will ensure that the study drug has been stopped and the patient will be instructed to arrive to the study site as soon as possible (within 10 days) for further evaluations with the remaining study medications.

7.4. Vital Signs and Weight

Vital signs will be measured as detailed in Section 3.11. Weight will be measured at all visits.

7.5. Electrocardiography

Central ECG reading is used in this study and ECGs should be performed according to central ECG reading instructions.

The patient should rest for at least 10 minutes before measurement is taken. Twelve-lead ECGs should be performed following the patient being in a supine position for 5 minutes. Three recordings will be performed before first dose during the baseline visit.

The ECG will be evaluated by the investigator at time of performance (signed and dated) and the printout should be kept in the source documentation file. When potentially clinically significant findings are detected by the site investigator, a cardiologist should be consulted for a definitive

interpretation. All communications and diagnoses should be filed in the source documentation file.

Objective alerts are pre-defined as described in the central ECG reading manual. In these cases the site and the sponsor will be informed immediately.

The final decision whether the ECG findings are of clinical significance is under investigator/local cardiologist responsibility.

All unscheduled ECGs must be performed through central ECG reading.

7.6. Physical Examinations

Any abnormal findings assessed by the investigator as clinically significant should be recorded in the relevant CRF modules (eg, adverse event, medical history).

7.7. Glomerular Filtration Rate Estimation

Significant changes in laquinimod exposure, in particular in terms of unbound drug fraction, are predicted in patients with moderate and severe renal impairment (see Section 1.3.2.1). Consequently, GFR will be estimated at all visits to monitor renal function in the study in order to identify patients with potentially impaired laquinimod clearance. Patients with a confirmed GFR ≤60 mL/min/1.73 m^2 should stop study medication temporarily and the GFR assessment should be repeated. If the renal impairment is confirmed (GFR ≤60 mL/min/1.73 m^2), the patient should stop study medication permanently (see Section 3.6.5).

Following recent findings connecting Gd-based contrast agents and nephrogenic systemic sclerosis, the GFR result should be available prior to the baseline MRI scan. GFR estimation will be done in accordance with the central laboratory creatinine value measurement performed at the screening visit. The central laboratory will report estimated GFR; however, if the result is not available prior to the baseline MRI scan, the CKD-EPI Creatinine Equation (2009) from the following online GFR calculator should be used by the investigator:

http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm

7.8. Cardiovascular Risk Assessment and Management

Evaluation and management of major modifiable cardiac risk factors (eg, diabetes, high blood pressure, hyperlipidemia, tobacco smoking) will be performed at the time points indicated in Table 5 and Table 6. In addition, an evaluation should take place as soon as possible for patients already in the study, following approval of Global Amendment 2.

Cardiovascular risk management should be conducted according to evidence-based, local standard-of-care procedures. Patients will undergo referral to a suitable clinic if needed.

7.9. Other Safety Measures and Variables: Concomitant Therapy or Medication

Concomitant therapy or medication usage will be monitored throughout the study. Details of prohibited medications are found in Section 5.2.

8. ASSESSMENT OF PHARMACOKINETICS/ PHARMACOGENOMICS/OTHER ANCILLARY STUDIES

8.1. Pharmacokinetic Variables

Samples will be analyzed for laquinimod using an appropriate validated method. Incurred sample reanalysis may be performed.

Blood samples (approximately 4 mL) will be collected from all patients at weeks 4, 8, 12, 24, and 48 for plasma concentration measurements of laquinimod.

Unscheduled pharmacokinetic blood samples may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.

The dates and times of study drug administration and the date and time of each pharmacokinetic sample will be recorded on the source documentation and transcribed onto the CRF.

Pharmacokinetics of laquinimod will be evaluated in this study using a PPK approach. Details of blood sampling collection and processing are provided in the Laboratory Manual.

8.2. Potential Biomarker Measures

Potential biomarker assessments to better understand laquinimod MoA, as well as to explore response predictive markers for efficacy or safety, may include 1) cytokines and other soluble marker levels; 2) gene and RNA expression; 3) proteomic profile; and/or 4) other relevant biomarkers.

Details of sample collection and processing are provided in the Laboratory Manual.

Analysis will be performed if and when required. Since new biomarker techniques continue to be developed, the method and laboratory that will be recommended cannot be anticipated.

Unscheduled samples for potential biomarker assessments may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.

8.3. Pharmacogenomic Variables

PGx studies investigate the association between genetic sequence polymorphisms and/or gene expression signatures and clinical response to a certain therapeutic intervention. It may help explaining inter-individual variability and subsequently identify population subgroups that respond differently to the drug. Furthermore, regulatory guidance and white papers indicate that PGx analyses employing DNA collected from all study participants may support investigation of unexpected adverse events.

In order to allow any subsequent analyses, appropriate samples will be requested from all patients in the study; however this can be omitted if considered unacceptable per local

regulations. PGx assessment might include DNA variations potentially associated with clinical treatment responses to laquinimod (eg, clinical effect, pharmacokinetics, tolerability, and safety features or disease susceptibility and severity features). The final list of genes that might be investigated will be selected at a later stage before the analysis so as to allow updating with new scientific information. Genomic analysis could also include a sequencing of the whole genome if required.

The PGx sample should be collected at baseline; if the sample is not obtained at baseline for any reason, it should be collected at the next possible visit.

8.4. Other Ancillary Studies

8.4.1. Cerebrospinal Fluid (CSF) Assessment

Putative neuroprotective effects of laquinimod will be explored in a subset of patients (only selected sites will participate) by analyzing CSF levels of axonal, neuronal, and/or inflammatory markers. CSF will be collected via lumbar puncture according to standard or local practice, using atraumatic needles. Additional detail can be found in the CSF Ancillary Study Manual.

CSF (to be performed in selected sites) will be collected from all patients who signed an appropriate, EC approved informed consent form, at week 48.

8.4.2. Optical Coherence Tomography (OCT) Evaluation

OCT is a fast, non-invasive, interferometric technique that allows imaging of the retina, including the retinal nerve fiber layer (RNFL), which is principally composed of the axons of the ganglion cells that form the optic nerves. Since these axons are nonmyelinated until they penetrate the lamina cribrosa, the RNFL is an ideal structure for visualizing subtle processes of axonal degeneration.

Retinal degeneration in MS not only reflects a morphological correlate of the functional visual deficits in MS patients, but also mirrors the overall disability assessed by the EDSS and the BA measured by MRI. Therefore, OCT is an ideal tool for visualizing the processes of neurodegeneration, neuroprotection, and neurorepair in MS.

Additional detail can be found in Appendix L and the OCT Ancillary Study manual.

OCT (to be performed in selected sites) will be performed in all patients who signed an appropriate, EC approved informed consent form, at week 0 (can be performed up to 42 days prior to baseline), week 48 (or ET visit if performed after the week 24 visit and prior to week 48), and week 96 to assess retinal thickness.

9. STATISTICS

9.1. Study Design and Randomization

This study is a multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled study, to evaluate the efficacy, safety and tolerability of daily oral administration of laquinimod (0.6 or [until 01 January 2016] 1.5 mg) in patients with PPMS. Randomization will be as described in Section 3.3. The analyses described in Sections 9.6 and 9.8 will be performed using data collected during Part A (Core Study). Data collected during Part B may be used for additional exploratory analyses as will be described in a SAP, to be approved and signed prior to unblinding the Part A data.

9.2. Sample Size and Power Considerations

Sample size calculations were based on the following assumptions:

- 2-sided alpha level of 5%
- treatment difference (delta) of 0.3 in PBVC
- standard deviation of 0.8

Under the above assumptions 252 patients enrolled for 0.6 mg and placebo (126 per arm) will provide 84% power to detect a statistically significant result for 0.6 mg laquinimod arm comparison to placebo. To adjust for the anticipated 10% dropouts, the sample size was increased to 280 patients. Adding 95 patients on 1.5 mg yields a total of 375 patients.

9.3. Populations

9.3.1. Intent-to-Treat (ITT) Population

The intent-to-treat (ITT) population will include all randomized patients. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

9.3.2. Modified ITT 1 (mITT1) Population

The modified ITT 1 (mITT1) population is a subset of the ITT set. It will include all patients in the ITT population with at least 1 post baseline PBVC assessment.

9.3.3. Modified ITT 2 (mITT2) Population

The modified ITT 2 (mITT2) population is a subset of the ITT set. It will include all patients in the ITT population with at least 1 post baseline efficacy assessment.

9.3.4. Safety (ST) Population

The safety (ST) population will include all randomized patients who receive at least 1 dose of study drug. In this population, treatment will be assigned based upon the treatment patients actually receive, regardless of the treatment to which they were randomized.

9.3.5. Per-Protocol (PP) Population

The Per Protocol (PP) population is a subset of the mITT1 population and will consist of all patients with no major protocol violations.

9.4. Data Handling Conventions

Only the observed data from the patients will be used in the statistical analyses. There is no plan to estimate missing data.

The censoring rules for time to event analysis will be as described in Section 9.6.2.

9.5. Study Population

The ITT population (see Section 9.3) will be used for all study population summaries unless otherwise noted. Summaries will be presented by treatment group and for all patients.

9.5.1. Patient Disposition

Data from patients screened, patients screened but not randomized (and reason not randomized), patients who are randomized (ITT), patients randomized but not treated (and reason not treated), patients in the safety, mITT1, mITT2, and PP populations, patients who complete the study, and patients who perform ET will be summarized using descriptive statistics. Data from patients who perform ET will also be summarized by reason for discontinuation using descriptive statistics.

9.5.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including MS history, medical history, prior medications, ECG findings, and baseline MRI will be examined to assess the comparability of the treatment groups and will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

Treatment groups will be compared for all baseline variables, using an appropriate methodology. Further details will be specified in the SAP.

9.6. Efficacy Analysis

Due to the decision from 01 January 2016 to discontinue the laquinimod 1.5 mg dose arm, and a low study exposure at this time, the laquinimod 1.5 mg dose arm will be presented descriptively only, and will not be included in any inferential analyses.

In addition, all efficacy analyses will be performed based on the measurements recorded during the study treatment period, ie, data captured following an early termination visit as described in Section 3.6.7 will be excluded from the analyses. The data captured after an early termination visit will be used for the sensitivity analyses of the primary and secondary endpoints.

9.6.1. Primary Variable

The primary variable for this study will be BA as defined by the PBVC from baseline to week 48.

9.6.2. Secondary Variables

1. Time to CDP.

Time to CDP will be defined as increase in EDSS of ≥1 point from baseline EDSS, if EDSS at entry is ≤5.0 or increase of ≥0.5 point, if EDSS at entry is ≥5.5. This increase should be confirmed after at least 12 weeks. Progression cannot be confirmed during a relapse.

To calculate the time of CDP, the following algorithm will be used:

Let E_t be an EDSS measurement of the patient under consideration observed at time (measured by weeks from the patient's baseline date).

Let E_0 be the baseline EDSS measurement for that patient.

Let $s = t + 12$.

The time to CDP for the patient under consideration is defined as t if all the following conditions hold:

1. If $0 \le E_0 \le 5$ then let $\Delta = 1$. Otherwise, let $\Delta = 0.5$.
2. $E_t \ge E_0 + \Delta$.
3. For any $t < q_1 < s$, if the patient's EDSS was evaluated at time q_1, then $E_{q1} \ge E_0 + \Delta$
4. $E_{q2} \ge E_0 + \Delta$ for some $q_2 \ge s$, and at time q_2, the patient was not experiencing a relapse.
5. t is the earliest time point during the study in which conditions 2-4 hold.

If no such *t* exists, then the time to confirmed progression will be right censored by the patient's last EDSS evaluation date from Part A of the study. In case time t exists without fulfilling conditions 3 and 4 because time *q2* is after the patient completed Part A of the study (or performed ET), and therefore cannot be seen, then the right censored will be on time t and not in the last EDSS evaluation.

If a patient died due to MS disease progression, then this patient will be analyzed as having CDP and the time to CDP will be calculated using the onset date of progression.

If a patient died due to MS before having progression, then the time to disability progression will be censored using the date of death.

2. Time to CDP event defined by reaching at least 1 of the following 2 types of event for each individual:
   - An increase from baseline in EDSS score (≥1 point from baseline EDSS, if EDSS at entry is ≤5.0 or increase of ≥0.5 point, if EDSS at entry is ≥5.5), confirmed after at least 12 weeks, **or**
   - An increase of at least 20% from baseline in the T25FW score, confirmed after at least 12 weeks

Similar algorithm to that described for CDP as measured by EDSS confirmed after at least 12 weeks will be used for definition and censoring rules of this variable.

3. Change from baseline to week 48 in the T25FW score.

4. The number of new T2 lesions at week 48.

9.6.3. Exploratory/Other Variables

- Change from baseline to week 48 in the BICAMS score (CVLT-II, BVMT-R, and SDMT)
- Time to CDP as measured by at least 1 of 4 types of events for each individual (progression cannot be confirmed during a relapse):
  - An increase from baseline in EDSS score (≥1 point from baseline EDSS if EDSS at entry is ≤5.0, or increase of ≥0.5 point if EDSS at entry is ≥5.5), confirmed after at least 12 weeks **or**
  - An increase of at least 20% from baseline in T25FW score, confirmed after at least 12 weeks **or**
  - An increase of at least 30% from baseline in the 9HPT score, confirmed after at least 12 weeks **or**
  - A decrease of at least 20% from baseline in the SDMT score, confirmed after at least 12 weeks
- Time to CDP confirmed after at least 24 weeks.
- New T1-hypointense lesions, changes in T1-hypointense lesion volume, and changes in T2 lesion volume.
- MRI, including thalamic, cortical, white matter, and cervical cord atrophy, number of cervical cord T2 lesions, and normal-appearing brain tissue average MTR.
- mRS (at week 72, visit 8).
- T25FW.
- 9HPT.
- LCVA.
- MSWS-12
- Relapses.
- Pharmacokinetic measures (determination of plasma concentration of laquinimod)
- PGx measures.
- Potential biomarker measures.
- Ancillary studies measures.

9.6.4. Planned Method of Analysis

The mITT1 and mITT2 populations (see Section 9.3) will be used for all efficacy analyses, unless otherwise noted. Summaries will be presented by treatment group.

9.6.4.1. Primary Efficacy Analysis

The primary efficacy variable for this study is BA as measured by the PBVC from baseline to week 48. This endpoint will be analyzed using the mITT1 population with at least 1 post-baseline PBVC value and will include assessments taken up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis). BA will be analyzed using baseline-adjusted repeated measures analysis of covariance (ANCOVA- SAS® PROC MIXED) in which 1 contrast will be constructed in order to compare between laquinimod 0.6 mg and placebo.

The model will be comprised from the treatment group as a class variable (2 levels). In addition to the treatment group, week (categorical), treatment by week interaction, normalized brain volume at baseline, natural logarithm of T2 lesion volume at baseline, and Country/Geographical Region (CGR) will be used as covariates. Additionally, week (categorical) will be specified as a repeated effect and unstructured (UN) correlation matrix will be used to model intra-subject correlation. In case a convergence issue will arise using the UN correlation matrix, (1) AR1 or (2) Compound Symmetry (CS) will be used to enable model convergence (in this order).

Mean values of the PBVC from baseline to weeks 24 and 48 will be summarized using descriptive statistics.

The assumption of a no treatment-by-covariate interaction will be evaluated by a separate repeated measures ANCOVA model (SAS® PROC MIXED) with the items treatment, week (categorical), week by treatment interaction, CGR, baseline, and treatment-by-baseline covariate interaction included in the model. If there is evidence of treatment-by-covariate interaction ($p \leq 0.10$), further exploration of this interaction will be done graphically/descriptively and the treatment p-values will still be reported from the main effects model (repeated measures ANCOVA from above).

The consistency of treatment effects among different CGR will be evaluated by a separate repeated measures ANCOVA model (SAS® PROC MIXED) with treatment, week (categorical), week by treatment interaction, CGR, and treatment-by-CGR interaction in the model. If there is evidence of a treatment-by-CGR interaction ($p \leq 0.10$), a descriptive summary of treatment differences for each CGR will be used to identify the Country (or Countries) for which the treatment effects are consistent with the remaining countries. This will be an exploratory analysis and the treatment p-values will still be reported from the main effects model (repeated measures ANCOVA from above).

9.6.4.2. Sensitivity Analyses

The robustness of the primary analysis results will be explored by applying it, as described in the previous section, to the PP population as well. In addition the, following sensitivity analysis will be performed:

- Repeat the primary analysis without introduction of covariates except for the treatment group, week, and treatment by week interaction.
- Repeat the primary analysis when introducing additional baseline covariates variables that differ appreciably between the treatment groups, if any. The list of baseline measurements will be provided in the SAP.

- Repeat the primary analysis while including observations that were recorded following an early termination visit.

9.6.4.3. Secondary Efficacy Analysis

a. Time to CDP as measured by EDSS confirmed after at least 12 weeks will be analyzed using the ITT population and data from all the study assessments up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis). This analysis will be performed using a baseline adjusted Cox's proportional hazards regression model (SAS® PROC PHREG) in which 1 contrast for comparing laquinimod 0.6 mg to placebo will be constructed. In addition to treatment group, categorical EDSS at baseline (≤4.5 or >4.5), age at baseline, natural logarithm of T2 lesion volume at baseline, and CGR will be used as covariates.

   The adequacy of the proportional hazards assumption will be confirmed by including 1 time-dependent covariate of dose (as dummy variable) by log (time) interactions in the analysis model and testing each of them at the 5% level. In case the proportional hazards assumption will be rejected, the log rank test (SAS® PROC LIFTEST) will be used for statistical inference.

b. Time to CDP, confirmed after at least 12 weeks as measured by EDSS or T25FW will be analyzed using the ITT population and data from all the study assessments up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis). This analysis will be performed using baseline adjusted Cox's proportional hazards regression model (SAS® PROC PHREG) in which 1 contrast for comparing laquinimod 0.6 mg to placebo will be constructed. In addition to treatment group, categorical EDSS at baseline (≤4.5 or >4.5), age at baseline, T25FW at baseline, natural logarithm of T2 lesion volume at baseline, and CGR will be used as covariates.

   The adequacy of the proportional hazards assumption will be confirmed by including 1 time-dependent covariate of dose (as dummy variables) by log (time) interactions in the analysis model and testing each of them at the 5% level. If the proportional hazards assumption will be rejected, the log rank test (SAS® PROC LIFTEST) will be used for statistical inference.

c. Change from baseline in the T25FW score at week 48 will be analyzed on the mITT2 population and will include assessments taken up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis). Since this variable might not follow normal distribution, the ranked values of this measurement will be defined and analyzed using baseline adjusted repeated measures ANCOVA (SAS® PROC MIXED) in which 1 contrast will be constructed in order to compare between laquinimod 0.6 mg and placebo. In addition to treatment group, T25FW score at baseline and CGR will be used as covariates. Due to the fact that the ANCOVA model will use ranked values and not the actual changes in the T25FW, Hodges-Lehmann estimates will be used in order to present the magnitude of the treatment effect and the corresponding two-sided 95% confidence.

d. The number of new brain T2 lesions at week 48 will be analyzed using the mITT1 population with at least 1 post-baseline T2 scan available if it was performed at least 36 weeks under treatment and will include assessments taken up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis).. This analysis will be performed using baseline adjusted negative binomial regression model (SAS® PROC GENMOD) in which 1 contrast for comparing laquinimod 0.6 mg to placebo will be constructed. In addition to the treatment group, the natural logarithm of T2 lesion volume at baseline, age at baseline, and CGR will be used as covariates.

All the secondary analyses mentioned in this section will be repeated while including observations that were recorded following an early termination visit.

9.6.4.4. Exploratory Efficacy Analysis

Detailed methodology for analyses of exploratory efficacy and other variables will be specified in the SAP signed and approved before treatment unblinding.

9.7. Multiple Comparisons and Multiplicity

All statistical tests will be performed at 5% nominal significance level to further define the effects estimates of laquinimod but not for strict statistical inferences. Therefore, no adjustments will be made for the preplanned multiple comparisons.

9.8. Safety Variables and Analysis

9.8.1. Safety Variables

All safety analysis will be performed for ST population. Summaries will be presented by treatment group and for all patients unless otherwise noted.

The overall safety and tolerability of laquinimod treatment will be assessed throughout the study by evaluating adverse events and the following additional safety variables:

- clinical laboratory tests
- vital signs
- 12-lead ECG
- concomitant medications use throughout the study

9.8.2. Safety Analysis

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class (SOC) category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to study treatment (ie, reasonable possibility; see Section 7.1.4) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing ET. Patient listings of serious adverse events and adverse events leading to discontinuation will be presented.

Changes in laboratory and vital signs measurement data will be summarized descriptively. All values will be compared with prespecified boundaries to identify potentially clinically significant changes or values, and such values will be listed. Additionally, descriptive summaries of potentially clinically significant abnormal values (clinical laboratory or vital signs) will be provided.

The use of concomitant medications will be summarized by preferred term and therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while patient participated in the study.

For continuous variables, descriptive statistics (n, mean, standard deviation, standard error, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided.

If any patient dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the patient narrative included in the clinical study report.

9.9. Pharmacokinetic Analysis

A single blood sample will be collected from all patients at weeks 4, 8, 12, 24 and 48. Unscheduled pharmacokinetic blood samples may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.

Pharmacokinetics of laquinimod will be evaluated using a PPK approach. The PPK model may also include any unscheduled pharmacokinetic samples collected to assist with further investigations of cardiovascular events or other clinical event of interest (see Section 8.1).The effect of covariates on the pharmacokinetics of laquinimod will be evaluated. Possible covariates will include demographic variables (eg, age, gender, body weight and ethnicity), clinical variables, concomitant medications, blood and urine chemistry variables and markers of renal function (creatinine clearance and serum creatinine).

The date and time of the blood sample, as well as the date and time of the last study drug dose prior to the sample will be recorded on the CRF.

9.10. Planned Interim Analysis

No interim analysis is planned for this study.

9.11. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the complete statistical plan, the clinical study report, or any combination of these, as appropriate.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The medical experts, study monitors, auditors, IEC/IRB, and health authority inspectors (or their agents) will be given direct access to source data and documentation (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, protocol required worksheets, and CRFs that are used as the source (see Section 3.9).

The investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. All study-related documents must be kept until notification by the sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Protocol Amendments and Protocol Deviations and Violations

11.1.1. Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB, except when necessary to address immediate safety concerns to the patients or when the change involves only logistics or administration. The principal investigator and the sponsor will sign the protocol amendment.

11.1.2. Protocol Deviations

Any significant deviation from the protocol will be considered a protocol violation. Protocol violations include nonadherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to study drug administration; use of prohibited medications; or any other deviations that may have an impact on the processes put in place for the care and safety of the patients. Protocol violations will be identified and recorded by investigational center personnel on the CRF. All protocol violations will be reported to the responsible IEC/IRB, as required.

When a protocol violation is reported, the sponsor will determine whether to discontinue the patient from the study or permit the patient to continue in the study, with documentation from the medical representative. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Deviations from the inclusion/exclusion criteria of the protocol are not prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol eligibility criteria was entered into a study, they must immediately inform the sponsor of the protocol violation. If such patient has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded.

11.2. Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the investigational center authorization form, which includes a clear description of each staff member’s responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring they comply with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

11.3. Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the informed consent form and the study is conducted according to applicable standard operating procedures (SOPs), the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and each investigator. The main responsibilities of the study monitors are to visit each investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitors will contact each investigator and visit the investigational center at regular intervals throughout the study. The study monitor will be permitted to check and verify the various records (CRFs and other pertinent source data records, to include specific electronic source documentation [see Section 3.9]) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. If electronic CRFs are used for the study, the study monitor will indicate verification by electronically applying source document verification (SDV) flags to the CRF and will ensure that all required electronic signatures are being implemented accordingly.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. Each investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits and/or provided in follow-up written communication.

11.4. Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies and/or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to the following:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc.)
- defective components
- missing or extra units (eg, primary container is received at the site with more or less than the designated number of units inside)
- incorrect packaging or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the Product Complaint Form provided by Teva and emailing it to [redacted] within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving a drug product, all relevant samples (eg, the remainder of the patient's drug supply) should be sent back to the sponsor for investigative testing whenever possible.

11.4.1. Product Complaint Information Needed from the Investigational Center

In the event that the Product Complaint Form cannot be completed, the investigator will obtain the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No
- description or nature of complaint
- associated serious adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a complaint must not be delayed because not all the required information can be immediately obtained. Known information must be immediately reported. The sponsor will collaborate with the investigator to obtain any outstanding information.

11.4.2. Handling the Study Drug at the Investigational Center

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the study drug.

If it is determined that the investigational center must return all of the study drug, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality

problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

11.4.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an adverse event or serious adverse event, the protocol should be followed.

11.4.4. Documenting a Product Complaint

The investigator will record a description of the product complaint in the source documentation as well as any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

11.5. Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCPs, and applicable regulatory requirements. The sponsor Global Clinical Quality Assurance department, independent of the Global Clinical Development department, is responsible for determining the need for (and timing of) an investigational center audit.

Each investigator must accept that regulatory authorities and sponsor representatives may conduct inspections to verify compliance with GCP guidelines.

12. ETHICS

12.1. Informed Consent

The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the IEC/IRB. Written informed consent will be obtained from each patient before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, according to the IEC/IRB requirements.

Overall, this study includes: (I) an informed consent for the clinical study (main study),(II) informed consent forms for the ancillary studies (CSF and OCT), and (III) informed consent forms for dummy run scans (MRI and OCT) required prior to initiation of the study and ancillary study respectively.

The patient's willingness to participate in the study will be documented in writing in a consent form, which will be signed and personally dated by the patient. The investigator will keep the original consent forms, and copies will be given to the patients. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Written and/or oral information about the study in a language understood by the patient will be given to all patients.

12.2. Health Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national/local health authorities and to each IEC/IRB for review. As required, the study will not start at a given investigational center before the IEC/IRB and health authority (where applicable) for the center give written approval or a favorable opinion.

12.3. Confidentiality Regarding Study Patients

The investigator must assure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification code (eg, initials and identification number).

Personal medical information may be reviewed for the purpose of patient safety and/or verifying data in the source and transcribed onto the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, the quality assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

12.4. Declaration of the End of the Clinical Study

For clinical investigational centers located in the EU, a declaration of the end of the clinical study will be made according to the procedures outlined in Directive 2001/20/ED, Article 10(c); for other countries, local regulations will be followed.

12.5. Registration of the Clinical Study

This clinical study will be registered on clinical trials registry websites according to Teva standard procedures.

13. DATA HANDLING, DATA QUALITY ASSURANCE, AND RECORD KEEPING

13.1. Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21 CFR part 11. Before being used to capture data from this study, the CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study. Before using the CDMS, all users will receive training on the system and any study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient screened according to the data source. Patient identity should not be discernible from the data provided on the CRF. Data will be verified using the data source by the study monitor, and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center), the results will be sent to the investigational center, where they will be retained but not entered into the CRF. These results may also be sent electronically to the sponsor (or organization performing data management) for direct entry into the clinical database (see Section 3.9). Laboratory test results will not be entered into the CRF unless otherwise noted in the protocol.

For patients who enter a study but do not meet screening criteria, at a minimum, data for screen failure reason, demography, and adverse events from the time of informed consent will be entered into the CRF.

13.2. Data Quality Assurance

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality assurance, will comply with international regulatory guidelines (eg, ICH GCP). Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality assurance, will be described in a data management plan.

CRFs received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS. Discrepancies found will be queried.

Data corrections in the CDMS will be made using the CDMS update function. For each instance of data modifications, the system requires a reason for the change and keeps a complete audit trail of the data values, dates and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

13.3. Archiving of Case Report Forms and Source Documents

13.3.1. Investigator Responsibilities

All records related to the study (ie, source data, source documents, CRFs [see Section 3.9], data results from other sources [see Section 13.1], copies of protocols and protocol amendments, drug accountability forms, correspondence, patient identification lists, signed informed consent forms, and other essential documents) must be retained until the sponsor notifies the institution, in writing, that records may be destroyed.

If the sponsor has not provided written notification of records destruction after 10 years from study completion (or earlier in the event of an institution closing), and the institution determines the study record retention is unduly burdensome, the institution may submit a written request to the sponsor at least 60 days before the planned disposition of the study records. No study document or image (eg, scan, radiograph, ECG tracing) should be destroyed without prior written agreement between the sponsor and each investigator. Should an investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to the sponsor.

13.3.2. Sponsor Responsibilities

The sponsor will be responsible for the processing and quality control (QC) of the data. Data management and filing will be carried out as described in the sponsor's SOPs for clinical studies.

If data management and filing of documents for this study are delegated to a contract organization, these functions will be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management and filing activities. The original CRFs will be archived by the sponsor. Center-specific CRFs will be provided to the respective investigational centers for archiving.

14. FINANCING AND INSURANCE

A separate financial agreement will be made between the principal investigator and the sponsor before the study drug is delivered.

This clinical study is insured in accordance with the corresponding local legal provisions.

The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions.

Excluded from the insurance cover are, inter alia, damages to health and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete Form FDA 3454. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

15. REPORTING AND PUBLICATION OF RESULTS

The sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to local and regional requirements for registration and posting of results.

The sponsor is responsible for preparing a clinical study report, in cooperation with the coordinating investigator. The final report is signed by the sponsor and, if applicable, by the coordinating investigator.

When the sponsor generates reports from the data collected in this study for presentation to regulatory authorities, drafts may be circulated to the coordinating investigator for comments and suggestions. An endorsement of the final report will be sought from the coordinating investigator.

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor. The primary publication from this study will report the results of the study in accordance with the current "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as established by the International Committee of Medical Journal Editors (www.ICMJE.org). Authorship will be restricted to parties who have editorial or conceptual input to protocol design, collection of data and/or analysis, interpretation of data, and manuscript preparation. The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent application(s) based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

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17. SUMMARY OF CHANGES TO PROTOCOL

17.1. Amendment 02 Dated 01 February 2016

The primary reason for this global amendment was to discontinue treatment for patients receiving 1.5 mg laquinimod, and to implement additional safety measures to help ensure the safety of subjects (both ongoing subjects and those still to be enrolled) receiving 0.6 mg laquinimod. To avoid increased exposure to laquinimod at the 0.6 mg dose, stopping rules have been introduced for renal impairment and hepatic impairment, with additional assessments of GFR introduced for increased monitoring of renal function.

Table 5 and Table 6 (Study Procedures and Assessments) have been revised to reflect changes described below. An additional study schema (Figure 2) has been included to reflect the amended study design.

The revisions listed below have been made to the protocol (and protocol synopsis, as appropriate). A determination of which changes are considered to be substantial will be dependent on the region, and will be indicated in the covering letter or application form that accompanies the amendment in that region.

Where appropriate, the informed consent form will be amended to reflect the changes introduced into the protocol.

Table 7: Changes to the Protocol (Global Amendment 02)

Original text with changes shown	New wording	Reason/Justification for change
TITLE PAGE		
Sponsor's Safety Officer [redacted] Teva Pharmaceutical Industries, Ltd. [redacted]	Sponsor's Safety Officer [redacted] Teva Pharmaceutical Industries, Ltd. [redacted]	Change of personnel
1.1. Introduction		
Therapeutic options for progressive MS are currently limited to symptomatic treatments and physiotherapy (Koch 2013); in this context, a therapy which is effective in limiting the neurodegenerative process and associated disability accumulation would address a major unmet medical need in the treatment of MS. Recently, positive results have been reported in a PPMS trial with the monoclonal antibody ocrelizumab.	Therapeutic options for progressive MS are currently limited to symptomatic treatments and physiotherapy (Koch 2013); in this context, a therapy which is effective in limiting the neurodegenerative process and associated disability accumulation would address a major unmet medical need in the treatment of MS. Recently, positive results have been reported in a PPMS trial with the monoclonal antibody ocrelizumab.	New information available.
1.1.1.2. Rationale for Laquinimod 1.5 mg Dose		
(new text)	Note: On 30 December 2015 the Data Monitoring Committee (DMC) for the CONCERTO and ARPEGGIO studies held an unscheduled meeting to review cardiovascular events. The DMC found an imbalance in serious cardiovascular events in the high dose treatment arms (1.2 mg in CONCERTO, 1.5 mg in ARPEGGIO): in CONCERTO there were 6 such cases in the 1.2 mg arm but none in the 0.6 mg or placebo arms, along with a myocardial infarction in the ARPEGGIO 1.5 mg dose group and a cerebral infarction in a 31 year old patient in the 1.2 mg arm of CONCERTO. Due to these events and the DMC recommendation to stop all laquinimod treatment arms above 0.6 mg in the MS trials, the 1.5 mg treatment arm in the ARPEGGIO study was discontinued as of 01 January 2016. The risk/benefit balance of this dose was considered negative at that point. The DMC did not identify any overt cardiovascular risk in the 0.6 mg treatment arm, but felt that long term monitoring for emergence of any signal is necessary. Therefore, the 0.6 mg treatment arm will be continued while the sponsor closely	Text added to reflect cardiovascular findings at doses higher than 0.6 mg laquinimod

Original text with changes shown	New wording	Reason/Justification for change
	monitors cardiovascular events in all laquinimod studies. Additional measures implemented in this protocol amendment include an emphasis on disallowed medications and stopping rules for organ impairment (ie, factors which may increase laquinimod exposure), as well as regular evaluation and management of major modifiable cardiovascular risk factors.	
1.3.1.3. Toxicology		
Safety pharmacology studies in the rat and dog did not demonstrate significant effects of laquinimod on the function of cardiovascular, respiratory, central nervous, renal and gastrointestinal systems providing safety margins in the range of 32- to 257-fold above the originally intended clinical dose of 1.5 mg/day based on maximal plasma concentrations.	Safety pharmacology studies in the rat and dog did not demonstrate significant effects of laquinimod on the function of cardiovascular, respiratory, central nervous, renal and gastrointestinal systems providing safety margins in the range of 32- to 257-fold above the originally intended clinical dose of 1.5 mg/day based on maximal plasma concentrations.	Reflecting that 1.5 mg is no longer an intended clinical dose (changed several other times in this section)
It is the sponsor's position that t~~T~~his finding is likely due to a decrease in the incidence of prolactin secreting pituitary adenomas that was observed in this study. In contrast to rodents, in humans prolactin is not a luteinizing hormone and does not affect the estrogen:progesterone ratio; therefore the mechanism proposed by the sponsor is not considered relevant to humans. A higher incidence of thyroid follicular cell adenomas was observed in high dose male rats. This lesion is considered to be related to laquinimod's induction of liver enzymes and consequently enhanced clearance of thyroid hormones in rats, a well-characterized rat-specific mechanism proposed by the sponsor, that is not considered relevant to humans. In addition, ~~a small~~an increase in the incidence of oral cavity ~~squamous cell carcinomas~~tumors was noted in mid and high dose female rats (2/60 in each group). The oral effects may relate to the AhR activation properties of laquinimod since similar lesions were seen following lifelong exposure of rats to other AhR activators. However, the incidence of oral cavity tumors in rats treated with laquinimod was lower than that seen with industrial chemicals such as 2,3,7,8-tetrachloro-p-dibenzodioxin (TCDD) (NTP TR-521) and dioxin-like compounds (DLCs), and was more similar to the incidence seen with the dietary ingredient indole-3-carbinol (I3C) found in cruciferous vegetables. Of note, the oral tumors seen with I3C were considered by the US National Toxicology Program as irrelevant	It is the sponsor's position that this finding is likely due to a decrease in the incidence of prolactin secreting pituitary adenomas that was observed in this study. In contrast to rodents, in humans prolactin is not a luteinizing hormone and does not affect the estrogen:progesterone ratio; therefore the mechanism proposed by the sponsor is not considered relevant to humans. A higher incidence of thyroid follicular cell adenomas was observed in high dose male rats. This lesion is considered to be related to laquinimod's induction of liver enzymes and consequently enhanced clearance of thyroid hormones in rats, a well-characterized rat-specific mechanism proposed by the sponsor, that is not considered relevant to humans. In addition, an increase in the incidence of oral cavity tumors was noted in mid and high dose female rats (2/60 in each group). The oral effects may relate to the AhR activation properties of laquinimod since similar lesions were seen following lifelong exposure of rats to other AhR activators. However, the incidence of oral cavity tumors in rats treated with laquinimod was lower than that seen with industrial chemicals such as 2,3,7,8-tetrachloro-p-dibenzodioxin (TCDD) (NTP TR-521) and dioxin-like compounds (DLCs), and was more similar to the incidence seen with the dietary ingredient indole-3-carbinol (I3C) found in cruciferous vegetables. Of note, the oral tumors seen with I3C were considered by the US National Toxicology Program as irrelevant	Text updated to reflect current version of IB

Original text with changes shown	New wording	Reason/Justification for change
for I3C risk assessment (NTP TR-584). No increased incidence of oral tumors was seen in humans exposed to TCDD, indicating a species specific response in rats. Therefore, oral cavity tumors induced by laquinimod in rats after a lifelong exposure do not imply an elevated carcinogenicity risk in humans. Humans, in general, also seem to be less sensitive to AhR activation by laquinimod than rats, as shown by the differential gene expression profiles discussed in the IB~~with other AhR activators, including industrial chemicals (such as 2,3,7,8-tetrachloro-p-dibenzodioxin [TCDD] and dioxin-like compounds [DLCs]) and the dietary ingredient indole-3-carbinol (I3C) found in cruciferous vegetables. However, the incidence of oral cavity tumors in rats treated with laquinimod was lower than that seen with TCDD and DLCs, and was more similar to the incidence seen with I3C. Importantly, the oral cavity tumors seen with TCDD in rats did not translate into increased incidence of oral tumors in exposed humans, indicating a species difference in this response between rats and humans. It should be noted that several lines of evidence suggest that the oral lesions seen in rats are mediated by direct contact of the rat oral mucosa with high concentrations of laquinimod in the dosing solution during the gavage procedure. An effect on the oral mucosa in rats is not considered relevant to humans, who take laquinimod as a capsule that dissolves in the stomach. Based on sponsor's calculations, in the human stomach, the local concentration of laquinimod is expected to be low, and the type of epithelium exposed is not considered sensitive to the effects of laquinimod, with safety margins greater than 13 (dogs), 20 (rats) and 1000 (mice) for exposure in the stomach~~.	for I3C risk assessment (NTP TR-584). No increased incidence of oral tumors was seen in humans exposed to TCDD, indicating a species specific response in rats. Therefore, oral cavity tumors induced by laquinimod in rats after a lifelong exposure do not imply an elevated carcinogenicity risk in humans. Humans, in general, also seem to be less sensitive to AhR activation by laquinimod than rats, as shown by the differential gene expression profiles discussed in the IB.	
1.3.2. Clinical Studies		
A Phase 3 study, LAQ–MS-305 (CONCERTO), is ongoing with laquinimod doses of 0.6 mg/day ~~and 1.2 mg/day, is ongoing~~. As of 01 January 2016, and based on DMC recommendations, the 1.2 mg/day arm was discontinued	A Phase 3 study, LAQ–MS-305 (CONCERTO), is ongoing with laquinimod doses of 0.6 mg/day. As of 01 January 2016, and based on DMC recommendations, the 1.2 mg/day arm was discontinued	High dose level has now been discontinued in CONCERTO.
1.3.2.1. Clinical Pharmacology Studies		
Laquinimod is extensively metabolized, predominantly by CYP3A4. Laquinimod metabolites levels in plasma are very low	Laquinimod is extensively metabolized, predominantly by CYP3A4. Laquinimod metabolites levels in plasma are very low	Added text on hepatic and renal impairment as

Original text with changes shown	New wording	Reason/Justification for change
and parent laquinimod is the main systemically circulating entity. Laquinimod pharmacokinetics are affected by moderate and strong CYP3A4 inhibitors (2.5- and 3.1-fold increase in laquinimod systemic exposure, respectively) and strong CYP3A4 inducers ~~and moderate hepatic impairment~~. At doses of 0.6 and 1.2 mg, laquinimod is a weak inhibitor of CYP3A4 and a strong inducer of CYP1A2; therefore, laquinimod may affect the systemic exposure of other drugs metabolized by CYP3A4 and CYP1A2. For additional information on concomitant use of laquinimod with CYP1A2 and CYP3A4 substrates, please refer to the IB. Studies in subjects with mild and moderate hepatic impairment resulted in an increase of laquinimod exposure by approximately 1.3- and 2.3-fold, respectively. In subjects with moderate renal impairment laquinimod exposure was increased by 1.4-fold. A physiologically based pharmacokinetic model was further used to predict the effect of hepatic impairment and renal impairment on the pharmacokinetics of laquinimod after a single and multiple doses of 0.6 to 1.5 mg in comparison to healthy subjects (Study DP-2015-017). The model predictions indicated that mild hepatic impairment and moderate renal impairment would result in further modest increases in exposure to laquinimod following multiple 0.6 mg dose administration based on unbound drug concentration (1.71-fold and 1.65-fold respectively). More significant increases in laquinimod exposure, in particular in terms of unbound drug fraction, are predicted in patients with moderate and severe hepatic impairment (3.41- and 6.51-fold respectively) and severe renal impairment (1.86-fold). The model predictions indicated similar increases in systemic laquinimod exposure with a given stage of organ impairment across the 0.6 to 1.5 mg dose range following single or multiple dose administration, demonstrating that the dose proportional pharmacokinetics of laquinimod is maintained in subjects with hepatic impairment (mild to severe) and renal impairment (moderate to severe) across this dose range.	and parent laquinimod is the main systemically circulating entity. Laquinimod pharmacokinetics are affected by moderate and strong CYP3A4 inhibitors (2.5- and 3.1-fold increase in laquinimod systemic exposure, respectively) and strong CYP3A4 inducers. At doses of 0.6 and 1.2 mg, laquinimod is a weak inhibitor of CYP3A4 and a strong inducer of CYP1A2; therefore, laquinimod may affect the systemic exposure of other drugs metabolized by CYP3A4 and CYP1A2. For additional information on concomitant use of laquinimod with CYP1A2 and CYP3A4 substrates, please refer to the IB. Studies in subjects with mild and moderate hepatic impairment resulted in an increase of laquinimod exposure by approximately 1.3- and 2.3-fold, respectively. In subjects with moderate renal impairment laquinimod exposure was increased by 1.4-fold. A physiologically based pharmacokinetic model was further used to predict the effect of hepatic impairment and renal impairment on the pharmacokinetics of laquinimod after a single and multiple doses of 0.6 to 1.5 mg in comparison to healthy subjects (Study DP-2015-017). The model predictions indicated that mild hepatic impairment and moderate renal impairment would result in further modest increases in exposure to laquinimod following multiple 0.6 mg dose administration based on unbound drug concentration (1.71-fold and 1.65-fold respectively). More significant increases in laquinimod exposure, in particular in terms of unbound drug fraction, are predicted in patients with moderate and severe hepatic impairment (3.41- and 6.51-fold respectively) and severe renal impairment (1.86-fold). The model predictions indicated similar increases in systemic laquinimod exposure with a given stage of organ impairment across the 0.6 to 1.5 mg dose range following single or multiple dose administration, demonstrating that the dose proportional pharmacokinetics of laquinimod is maintained in subjects with hepatic impairment (mild to severe) and renal impairment (moderate to severe) across this dose range.	background for new stopping rules
1.4.1. Known and Potential Risks and Benefits for Laquinimod		
Note: the table has been updated in line with the updated Reference Safety Information; myocardial infarction and cerebrovascular accident are now included.	Note: the table has been updated in line with the updated Reference Safety Information; myocardial infarction and cerebrovascular accident are now included.	Updated in line with changes to the IB

Original text with changes shown	New wording	Reason/Justification for change
Table 3: Tabulated List of Adverse Reactions ~~in the Pooled ALLEGRO and BRAVO Studies~~ *Cardiac disorders* Uncommon: Myocardial infarction *Nervous system disorders* Very Common: Headache Rare Cerebrovascular accident	Table 3: Tabulated List of Adverse Reactions *Cardiac disorders* Uncommon: Myocardial infarction *Nervous system disorders* Very Common: Headache Rare Cerebrovascular accident	
1.4.1.1.7. Cardiovascular Events (on Doses Above Laquinimod 0.6 mg)		
(new section)	On 30 December 2015, a DMC review of 8 unblinded cases from the ARPEGGIO and CONCERTO studies found an imbalance in serious cardiovascular events in the high dose treatment arms in the study: 6 cases of myocardial infarction in the CONCERTO 1.2 mg treatment arm, compared to no events in the 0.6 mg or placebo treatment arms, along with a cerebral infarction in a 31 year old man on the 1.2 mg treatment arm. In the ARPEGGIO study, 1 myocardial infarction event was identified in the laquinimod 1.5 mg treatment arm. The decisions were largely based on data from 15 November 2015 when total exposure in CONCERTO was 3070 patient-years in 2199 individuals and total exposure in ARPEGGIO was 35 patient-years in 191 individuals. Due to these events, the DMC recommended stopping all laquinimod treatment arms above 0.6 mg in the laquinimod MS trials. The DMC did not identify any overt cardiovascular risk in the 0.6 mg treatment arm, but felt that long term monitoring for emergence of any signal was necessary. The DMC also recommend that study subjects continuing on laquinimod 0.6 mg be reconsented with information about the cardiovascular risk seen in higher doses. Currently the mechanism of the cardiovascular events remains unknown. Although no specific time-to-event patterns have been identified, cardiovascular risk factors and demographics may play a role. Different pre-existing risk factors were noted, including hypertension, high cholesterol, and/or smoking history. While all	Text added to reflect cardiovascular findings at doses higher than 0.6 mg laquinimod

Original text with changes shown	New wording	Reason/Justification for change
	cases exhibited signs of myocardial tissue injury, the cardiac work-up in these cases revealed heterogeneous etiologies. Of note, the cases all had some established cardiovascular risk factors, including patients with probable myocarditis or with probable familial hypercholesterolemia. Further investigation into potential predictors and the potential causality are ongoing.	
1.4.1.2.2. Cancer		
These findings are likely related to ~~the administration procedure or to~~ species-specific mechanisms, regardless, a relevance of these cancers to humans cannot be definitively excluded.	These findings are likely related to species-specific mechanisms, regardless, a relevance of these cancers to humans cannot be definitively excluded.	Administration procedure no longer considered a factor
1.4.1.2.3. Cardiotoxicity and Systemic Inflammation		
In clinical studies performed with laquinimod's predecessor molecule, roquinimex, pericarditis/pleuritis and ischemic heart disorders were identified as important safety concerns. ~~Roquinimex demonstrated clinical efficacy in MS in Phase 2 studies.~~ ~~However,~~ serious toxicities ~~(including myocardial infarction, pericarditis and pleuritis)~~ that occurred during Phase 3 trials led to discontinuation of these trials. Roquinimex demonstrated serious toxicities including increased rates of myocardial infarction, pericarditis and pleuritis that were observed in three Phase 3, placebo-controlled studies in MS patients. The mechanism by which roquinimex caused these events was not identified, but they were considered to be possible manifestations of a systemic inflammatory response, an assessment which was also supported by roquinimex nonclinical findings. A thorough analysis was done on the laquinimod safety data (which is mostly reflective of the 0.6 mg/day dose) to evaluate ~~these~~ similar potential safety issues. Based on 2347 patients exposed to laquinimod 0.6 mg for over 10,000 patient-years. as well as the patients exposed to 0.6 mg in the CONCERTO and ARPEGGIO study, analyses~~This analysis~~ showed that ~~none of~~ these safety issues do not constitute a clear signal ~~of concern~~ for laquinimod in doses up to 0.6 mg/day. However, at doses of 1.2 and 1.5 mg, laquinimod manifested clinical evidence of myocardial infarction.	In clinical studies performed with laquinimod's predecessor molecule, roquinimex, pericarditis/pleuritis and ischemic heart disorders were identified as important safety concerns. Serious toxicities that occurred during Phase 3 trials led to discontinuation of these trials. Roquinimex demonstrated serious toxicities including increased rates of myocardial infarction, pericarditis and pleuritis that were observed in three Phase 3, placebo-controlled studies in MS patients. The mechanism by which roquinimex caused these events was not identified, but they were considered to be possible manifestations of a systemic inflammatory response, an assessment which was also supported by roquinimex nonclinical findings. A thorough analysis was done on the laquinimod safety data (which is mostly reflective of the 0.6 mg/day dose) to evaluate similar potential safety issues. Based on 2347 patients exposed to laquinimod 0.6 mg for over 10,000 patient-years. as well as the patients exposed to 0.6 mg in the CONCERTO and ARPEGGIO study, analyses showed that these safety issues do not constitute a clear signal for laquinimod in doses up to 0.6 mg/day. However, at doses of 1.2 and 1.5 mg, laquinimod manifested clinical evidence of myocardial infarction.	
1.4.2. Overall Risk Benefit Statement		
(new text)	Due to cardiovascular events and a DMC recommendation to stop	Text added to reflect

Original text with changes shown	New wording	Reason/Justification for change
	all laquinimod treatment arms above 0.6 mg in the MS trials, the 1.5 mg treatment arm was discontinued as of 01 January 2016. The risk/benefit balance of this dose was considered negative at that point. The DMC did not identify any overt cardiovascular risk in the 0.6 mg treatment arm, but felt that long term monitoring for emergence of any signal was necessary. As of 29 September 2015, 2347 patients had been exposed to laquinimod 0.6 mg for 10,417 patient-years. It is estimated that the rate for myocardial infarction and cardiovascular death for patients treated with laquinimod 0.6 mg is about 0.16 per 100 person years which is within range of the expected cardiovascular event incidence in the underlying population. Therefore, while no increased risk was seen with laquinimod 0.6 mg, because of the findings with higher doses, there is a potential risk that some individuals may be at increased risk of cardiovascular events while taking laquinimod 0.6 mg. Appropriate risk mitigation procedures have been implemented via a protocol amendment to restrict excess drug exposure due to disallowed medications or organ impairment, as well as to assure evaluation and management of cardiovascular risk factors.	cardiovascular findings at doses higher than 0.6 mg laquinimod
3.1. General Design and Study Schema (Other sections affected by change: 3.4.1. Investigational Product and Dosage, 5.1. Study Drugs Administered)		
Prior to 01 January 2016, eligible patients ~~will be~~were randomized in a 1:1:1 ratio into 1 of the following treatment arms (a total of 286 patients were randomized 1:1:1 prior to 01 January 2016): • Laquinimod 0.6 mg daily • Laquinimod 1.5 mg daily • Daily placebo As of 01 January 2016, following a decision to discontinue the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1 ratio into one of the following treatment arms: • Laquinimod 0.6 mg daily • Daily placebo	Prior to 01 January 2016, eligible patients were randomized in a 1:1:1 ratio into 1 of the following treatment arms (a total of 286 patients were randomized 1:1:1 prior to 01 January 2016): • Laquinimod 0.6 mg daily • Laquinimod 1.5 mg daily • Daily placebo As of 01 January 2016, following a decision to discontinue the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1 ratio into one of the following treatment arms: • Laquinimod 0.6 mg daily • Daily placebo	1.5 mg arm has been discontinued. Additional study schema added to reflect the revised design.
3.1. General Design and Study Schema (Other sections affected by change: 3.5. Duration of Patient Participation, 3.11.5. Completion Visit)		
After up to approximately 24 weeks of Part B, or once data analysis	After up to approximately 24 weeks of Part B, or once data	Clarification

Original text with changes shown	New wording	Reason/Justification for change
has been completed and the design of a potential extension study ~~design~~ has been finalized (including blinded or open-label treatment allocation), patients will be invited to the clinic for the completion visit and will be offered the opportunity to continue into an extension study, if applicable.	analysis has been completed and the design of a potential extension study design has been finalized (including blinded or open-label treatment allocation), patients will be invited to the clinic for the completion visit and will be offered the opportunity to continue into an extension study, if applicable.	
3.2.7. Pharmacokinetic Measures and Endpoints (Other sections affected by change: 9.9. Pharmacokinetic Analysis)		
Pharmacokinetics of laquinimod will be evaluated in this study using a population pharmacokinetics (PPK) approach. The PPK model may also include any unscheduled pharmacokinetic samples collected to assist with further investigations of cardiovascular events or other clinical event of interest (see Section 8.1).	Pharmacokinetics of laquinimod will be evaluated in this study using a population pharmacokinetics (PPK) approach. The PPK model may also include any unscheduled pharmacokinetic samples collected to assist with further investigations of cardiovascular events or other clinical event of interest (see Section 8.1).	PPK analysis can include the newly added unscheduled PK samples.
3.3. Randomization and Blinding (Other sections affected by change: 3.8. Maintenance of Randomization and Blinding)		
This is a randomized, double-blind, placebo-controlled study. Patients will be randomly assigned to receive treatment with laquinimod at a dosage of 0.6 or 1.5 mg/day, or placebo in a 1:1:1 ratio (prior to 01 January 2016) or randomly assigned to receive treatment with laquinimod at a dosage of 0.6 mg/day, or placebo in a 1:1 ratio (from 01 January 2016). Patients, investigators, and study site personnel will remain blinded to treatment assignment during the study. Laquinimod and placebo will be packaged and administered in a blinded manner. All patients that discontinued the 1.5 mg dose have been unblinded.	This is a randomized, double blind, placebo controlled study. Patients will be randomly assigned to receive treatment with laquinimod at a dosage of 0.6 or 1.5 mg/day, or placebo in a 1:1:1 ratio (prior to 01 January 2016) or randomly assigned to receive treatment with laquinimod at a dosage of 0.6 mg/day, or placebo in a 1:1 ratio (from 01 January 2016). Patients, investigators, and study site personnel will remain blinded to treatment assignment during the study. Laquinimod and placebo will be packaged and administered in a blinded manner. All patients that discontinued the 1.5 mg dose have been unblinded.	1.5 mg arm has been discontinued and patients on that arm unblinded
3.6.3. Cancer (Other sections affected by change: APPENDIX B. GUIDANCE ON SAFETY MONITORING)		
Patients who are diagnosed with ~~invasive cancer~~ a malignant solid or liquid tumor while participating in the study should stop study medication.	Patients who are diagnosed with a malignant solid or liquid tumor while participating in the study should stop study medication.	Correction of terminology
3.6.4. Liver Impairment (Other sections affected by change: APPENDIX B. GUIDANCE ON SAFETY MONITORING)		
(new section)	To avoid exposures to higher levels of laquinimod (see Section 1.3.2.1), a stopping role related to liver impairment has been introduced. Patients who develop any chronic liver disease associated with hepatic function impairment while participating in the study should stop study medication.	New stopping rule implemented to avoid increased exposure to laquinimod in cases of organ impairment
3.6.5. Renal Impairment (Other sections affected by change: APPENDIX B. GUIDANCE ON SAFETY MONITORING)		

Original text with changes shown	New wording	Reason/Justification for change
(new section)	To avoid exposures to higher levels of laquinimod (see Section 1.3.2.1), a stopping role related to renal impairment has been introduced. Patients who develop renal disease associated with moderate or severe functional impairment, defined as glomerular filtration rate (GFR) ≤60 mL/min/1.73 m^2, while participating in the study should stop study medication temporarily and the GFR assessment should be repeated. If the renal impairment is confirmed (GFR ≤60 mL/min/1.73 m^2), the patient should stop study medication permanently.	New stopping rule implemented to avoid increased exposure to laquinimod in cases of organ impairment
3.6.7. Early Termination (ET)		
(new text)	Early termination refers to the study drug termination and not termination of the patient from the study. Patients will be encouraged to continue all scheduled visits and procedures after study drug discontinuation (with the exception of drug dispensing and accountability, pregnancy testing, and pharmacokinetic sampling).	Clarification due to discontinuation of 1.5 mg arm
3.11.3. Scheduled Treatment Visits (Visits 1 to 6, Weeks 4 to 48, and Every 12 weeks Thereafter)		
(new text)	* Patients who are discontinued from study treatment will be encouraged to continue all scheduled visits and procedures after study drug discontinuation (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, GFR testing, and pharmacokinetic sampling).	Clarification due to discontinuation of 1.5 mg arm
3.11.5. Completion Visit		
(new text)	Patients who discontinue study drug but continue to attend scheduled study visits for follow up are not considered to have completed the study.	Clarification due to discontinuation of 1.5 mg arm
3.11.5. Completion Visit		
However patient compliance/drug accountability, review of concomitant medications, vital signs, ECG, and recording of adverse events must be performed in any case.	However patient compliance/drug accountability, review of concomitant medications, vital signs, ECG, and recording of adverse events must be performed in any case.	Added ECG to list of activities that must be performed at completion visit.
3.11.6. Unscheduled Visit		
(new text)	According to the judgment of the investigator or medical monitor, the following unscheduled procedures may be performed:	Additional assessments for monitoring of cardiac risk

Original text with changes shown	New wording	Reason/Justification for change
	• urgent safety laboratory test panel (see Section 7.3.4) • collection of unscheduled pharmacokinetic blood sample • collection of sample for potential biomarker analysis	
4.3.1. Patient Withdrawal Criteria		
(new text)	For patients in the 1.5 mg arm who were withdrawn from study treatment, the reason will be recorded as 'sponsor requested patient to be withdrawn'.	Clarification due to discontinuation of 1.5 mg arm
5.2.2.1. Allowed Medications/Therapies During Study		
• Short-term treatment (up to 5 days) with intravenous corticosteroids will be allowed during ~~acute~~ relapses, although these are rare in PPMS. The suggested treatment for a relapse will be intravenous methylprednisolone 500 to 1000 mg/day for 3 to 5 consecutive days.	• Short-term treatment (up to 5 days) with intravenous corticosteroids will be allowed during relapses, although these are rare in PPMS. The suggested treatment for a relapse will be intravenous methylprednisolone 500 to 1000 mg/day for 3 to 5 consecutive days.	Treatment can be given for any relapses (not just acute relapses) and short-term defined.
5.2.2.2. Disallowed Concomitant Medications/Therapies During Study		
(new text)	Laquinimod is extensively metabolized predominantly by CYP3A4, and ketoconazole and fluconazole, strong and moderate inhibitors of CYP3A4, were found to inhibit the metabolism, leading to 2.5 and 3.1 fold increases in laquinimod exposure, respectively.	Rationale for disallowed medication added
5.4. Total Blood Volume		
The total amount of blood to be drawn during the study for serum chemistry, CBC, pharmacokinetic, biomarker and PGx measurements is approximately ~~500~~ 550 mL/patient.	The total amount of blood to be drawn during the study for serum chemistry, CBC, pharmacokinetic, biomarker and PGx measurements is approximately 550 mL/patient.	Adjustment to allow for unscheduled tests
6.4.5. Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) Score		
• Brief Visuospatial Memory Test – Revised (BVMT-R) (first 3 recall trials): this requires the patient to inspect a 2 × 3 stimulus array of abstract geometric figures (Form 1 from the Recall Stimulus Booklet). There are 3 learning trials of 10 seconds. The array is removed and the patient is required to draw the array from memory, with the correct shapes	• Brief Visuospatial Memory Test – Revised (BVMT-R) (first 3 recall trials): this requires the patient to inspect a 2 × 3 stimulus array of abstract geometric figures (Form 1 from the Recall Stimulus Booklet). There are 3 learning trials of 10 seconds. The array is removed and the patient is required to draw the array from memory, with the correct shapes	Details of scoring added

Original text with changes shown	New wording	Reason/Justification for change
in the correct position. Scoring of the BVMT-R drawings will be performed by a central expert vendor.	in the correct position. Scoring of the BVMT-R drawings will be performed by a central expert vendor.	
7.1.6. Protocol Defined Adverse Events for Expedited Reporting		
~~No protocol-defined adverse events for expedited reporting were identified for this study.~~ Ischemic cardiac events (such as myocardial infarction, unstable angina, acute coronary syndrome etc), and cerebrovascular events (such as cerebral arterial occlusion, cerebral ischemia, etc) should be reported to the sponsor within 48 hours, including completion of the corresponding dedicated CRF.	Ischemic cardiac events (such as myocardial infarction, unstable angina, acute coronary syndrome etc), and cerebrovascular events (such as cerebral arterial occlusion, cerebral ischemia, etc) should be reported to the sponsor within 48 hours, including completion of the corresponding dedicated CRF.	Due to cardiovascular findings at higher dose levels, adverse events for expedited reporting have been identified.
7.3.1. Serum Chemistry		
– in case of CPK results >ULN, creatine kinase MB isoenzyme (CK-MB) and troponin will be tested by the central laboratory.	– in case of CPK results >ULN, creatine kinase MB isoenzyme (CK-MB) and troponin will be tested by the central laboratory.	Troponin added (in case of CPK >ULN) to give additional cardiovascular assessment.
7.3.4. Urgent Safety Laboratory Panel (Other sections affected by change: 3.11. Study Procedures)		
(new section)	Unscheduled urgent safety laboratory samples may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event. The following tests will be performed on these samples: • serum chemistry panel (see Section 7.3.1) • CBC panel (see Section 7.3.2) • CK-MB • troponin	Unscheduled laboratory test samples may be collected to allow further investigation of events of interest.
7.4. Vital Signs and Weight (Other sections affected by change: 3.11. Study Procedures)		
(new text)	Weight will be measured at all visits.	Weight will be used in association with GFR estimation, so needs to be measured at each visit.
7.7. Glomerular Filtration Rate Estimation (Other sections affected by change: 7.3.1. Serum Chemistry, 3.11. Study Procedures)		
Significant changes in laquinimod exposure, in particular in terms	Significant changes in laquinimod exposure, in particular in terms	Extra GFR monitoring

Original text with changes shown	New wording	Reason/Justification for change
of unbound drug fraction, are predicted in patients with severe renal impairment (see Section 1.3.2.1). Consequently, GFR will be estimated at all visits to monitor renal function in the study in order to identify patients with potentially impaired laquinimod clearance. Patients with a confirmed GFR ≤60 mL/min/1.73 m^2 should stop study medication temporarily and the GFR assessment should be repeated. If the renal impairment is confirmed (GFR ≤60 mL/min/1.73 m^2), the patient should stop study medication permanently (see Section 3.6.5). ~~GFR is a test used to check renal function.~~ Following recent findings connecting Gd based contrast agents and nephrogenic systemic sclerosis, the GFR result should be available prior to the baseline MRI scan. GFR ~~calculation~~ estimation will be done in accordance with the central laboratory creatinine value measurement performed at the screening visit. The central laboratory will report ~~calculated~~ estimated GFR; however, if the result is not available prior to the baseline MRI scan, the CKD-EPI Creatinine Equation (2009) from the following online GFR calculator should be used by the investigator:	of unbound drug fraction, are predicted in patients with severe renal impairment (see Section 1.3.2.1). Consequently, GFR will be estimated at all visits to monitor renal function in the study in order to identify patients with potentially impaired laquinimod clearance. Patients with a confirmed GFR ≤60 mL/min/1.73 m^2 should stop study medication temporarily and the GFR assessment should be repeated. If the renal impairment is confirmed (GFR ≤60 mL/min/1.73 m^2), the patient should stop study medication permanently (see Section 3.6.5). Following recent findings connecting Gd based contrast agents and nephrogenic systemic sclerosis, the GFR result should be available prior to the baseline MRI scan. GFR estimation will be done in accordance with the central laboratory creatinine value measurement performed at the screening visit. The central laboratory will report estimated GFR; however, if the result is not available prior to the baseline MRI scan, the CKD-EPI Creatinine Equation (2009) from the following online GFR calculator should be used by the investigator:	added in case of decrease in renal function. Changed terminology to be more accurate: estimation instead of calculation.
7.8. Cardiovascular Risk Assessment and Management (Other sections affected by change: 3.11. Study Procedures)		
(new section)	Evaluation and management of major modifiable cardiac risk factors (eg, diabetes, high blood pressure, hyperlipidemia, tobacco smoking) will be performed at the time points indicated in Table 5 and Table 6. In addition, an evaluation should take place as soon as possible for patients already in the study, following approval of Global Amendment 2. Cardiovascular risk management should be conducted according to evidence-based, local standard-of-care procedures. Patients will undergo referral to a suitable clinic if needed.	Additional assessments for monitoring of cardiac risk
8.1. Pharmacokinetic Variables (Other sections affected by change: 9.9. Pharmacokinetic Analysis)		
(new text)	Unscheduled pharmacokinetic blood samples may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.	Unscheduled samples may be collected to allow further investigation of events of interest.
8.2. Potential Biomarker Measures		

Original text with changes shown	New wording	Reason/Justification for change
(new text)	Unscheduled samples for potential biomarker assessments may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.	Unscheduled samples may be collected to allow further investigation of events of interest.
9.2. Sample Size and Power Considerations		
~~Under the above assumptions 113 patients enrolled per arm (339 total) will provide 80% power to detect statistically significant result for each laquinimod arm comparison to placebo separately. To adjust for the anticipated 10% dropouts, the sample size was increased to 375 patients in total (125 per arm).~~ Under the above assumptions 252 patients enrolled for 0.6 mg and placebo (126 per arm) will provide 84% power to detect a statistically significant result for 0.6 mg laquinimod arm comparison to placebo. To adjust for the anticipated 10% dropouts, the sample size was increased to 280 patients. Adding 95 patients on 1.5 mg yields a total of 375 patients.	Under the above assumptions 252 patients enrolled for 0.6 mg and placebo (126 per arm) will provide 84% power to detect a statistically significant result for 0.6 mg laquinimod arm comparison to placebo. To adjust for the anticipated 10% dropouts, the sample size was increased to 280 patients. Adding 95 patients on 1.5 mg yields a total of 375 patients.	Adjusted due to discontinuation of 1.5 mg arm.
9.6. Efficacy Analysis		
(new text)	Due to the decision from 01 January 2016 to discontinue the laquinimod 1.5 mg dose arm, and a low study exposure at this time, the laquinimod 1.5 mg dose arm will be presented descriptively only, and will not be included in any inferential analyses. In addition, all efficacy analyses will be performed based on the measurements recorded during the study treatment period, ie, data captured following an early termination visit as described in Section 3.6.7 will be excluded from the analyses. The data captured after an early termination visit will be used for the sensitivity analyses of the primary and secondary endpoints.	Revisions to statistical analyses following discontinuation of the 1.5 mg arm
9.6.4.1. Primary Efficacy Analysis (Other sections affected by change: 9.6.4.3. Secondary Efficacy Analysis)		
The primary efficacy variable for this study is BA as measured by the PBVC from baseline to week 48. This endpoint will be analyzed using the mITT1 population with at least 1 post baseline PBVC value and will include assessments taken up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis). BA will be	The primary efficacy variable for this study is BA as measured by the PBVC from baseline to week 48. This endpoint will be analyzed using the mITT1 population with at least 1 post baseline PBVC value and will include assessments taken up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis). BA	Revisions to statistical analyses following discontinuation of the 1.5 mg arm

Original text with changes shown	New wording	Reason/Justification for change
analyzed using baseline-adjusted repeated measures analysis of covariance (ANCOVA- SAS® PROC MIXED) in which 1~~2~~ contrast~~s~~ will be constructed in order to compare between ~~each dose of~~ laquinimod ~~(~~0.6~~ and 1.5~~ mg~~)~~ and placebo. The model will be comprised from the treatment group as a class variable (~~3~~ 2 levels).	will be analyzed using baseline-adjusted repeated measures analysis of covariance (ANCOVA- SAS® PROC MIXED) in which 1 contrast will be constructed in order to compare between laquinimod 0.6 mg and placebo. The model will be comprised from the treatment group as a class variable (2 levels).	
9.6.4.2. Sensitivity Analyses		
(new text)	• Repeat the primary analysis while including observations that were recorded following an early termination visit.	New analysis added
9.6.4.3. Secondary Efficacy Analysis		
a. Time to CDP as measured by EDSS confirmed after at least 12 weeks will be analyzed using the ITT population and data from all the study assessments up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis). This analysis will be performed using a baseline adjusted Cox's proportional hazards regression model (SAS® PROC PHREG) in which ~~2~~ 1 contrast~~s~~ for comparing ~~each of~~ laquinimod ~~doses~~ 0.6 mg to placebo will be constructed. In addition to treatment group, categorical EDSS at baseline (≤4.5 or >4.5), age at baseline, natural logarithm of T2 lesion volume at baseline, and CGR will be used as covariates. The adequacy of the proportional hazards assumption will be confirmed by including 1~~2~~ time-dependent covariate~~s~~ of dose (as dummy variable~~s~~) by log (time) interactions in the analysis model and testing each of them at the 5% level. In case the proportional hazards assumption will be rejected ~~for a certain dose~~, the log rank test (SAS® PROC LIFTEST) will be used for statistical inference ~~in this dose~~.	a. Time to CDP as measured by EDSS confirmed after at least 12 weeks will be analyzed using the ITT population and data from all the study assessments up to/including early termination/study completion visit (data recorded following an early termination visit will be excluded from this analysis). This analysis will be performed using a baseline adjusted Cox's proportional hazards regression model (SAS® PROC PHREG) in which 1 contrast for comparing laquinimod 0.6 mg to placebo will be constructed. In addition to treatment group, categorical EDSS at baseline (≤4.5 or >4.5), age at baseline, natural logarithm of T2 lesion volume at baseline, and CGR will be used as covariates. The adequacy of the proportional hazards assumption will be confirmed by including 1 time-dependent covariate of dose (as dummy variable) by log (time) interactions in the analysis model and testing each of them at the 5% level. In case the proportional hazards assumption will be rejected, the log rank test (SAS® PROC LIFTEST) will be used for statistical inference.	Revisions to statistical analyses following discontinuation of the 1.5 mg arm. Similar changes made to bullets b through d in this section.
9.6.4.3. Secondary Efficacy Analysis		
(new text)	All the secondary analyses mentioned in this section will be repeated while including observations that were recorded	Additional analyses

Original text with changes shown	New wording	Reason/Justification for change
	following an early termination visit.	
9.6.4.4. Dose Response (section deleted)		
~~A separate model using the above primary analysis methodology with treatment group as a continuous variable will be constructed in order to test a linear dose response relationship. Placebo patients will be assigned with zero value and laquinimod patients will be assigned with a numeric value of either 0.6 or 1.5 reflective of their treatment assignments. One contrast for linear slope will be constructed.~~	(section deleted)	Analysis removed as only 0.6 mg dose following discontinuation of 1.5 mg laquinimod.
APPENDIX C. MODERATE/STRONG CYP3A4 INHIBITORS AND CYP3A4 INDUCERS		
(new text)	Moderate and strong CYP3A4 inhibitors are prohibited because concomitant administration is predicted to increase laquinimod exposure and may increase the likelihood of adverse events.	Clarification

17.2. Amendment 01 Dated 01 July 2015

The primary reasons for this global amendment were to introduce an additional secondary efficacy endpoint (change from baseline to week 48 in the T25FW score) and an additional exploratory efficacy measure (mRS). The T25FW endpoint was added due to its established role in quantifying clinically meaningful benefit in MS, and due to the beneficial effects seen on this measure in previous RRMS trials of laquinimod.

Other important changes include:

- Omission of the interim analysis (this was intended to provide actionable information with respect to an ongoing planned Phase 3 trial; however, the rationale no longer applies, since that trial will not be initiated in parallel with ARPEGGIO).
- Omission of baseline CSF sampling (omitted in order to maximize participation in the week 48 sampling, which is more important scientifically; the decision was taken based feedback from an expert who noted that previous trials were not successful in consistently collecting 2 CSF samples, whereas the yield was better with a single CSF collection).
- Creation of 2 separate mITT populations: mITT1 and mITT2 (mITT1 introduced specifically for the primary endpoint; mITT2 is what was previously defined as the mITT population).

Table 5 and Table 6 (Study Procedures and Assessments) have been revised to reflect changes described below.

The revisions listed below have been made to the protocol (and protocol synopsis, as appropriate). A determination of which changes are considered to be substantial will be dependent on the region, and will be indicated in the covering letter or application form that accompanies the amendment in that region.

Where appropriate, the informed consent form will be amended to reflect the changes introduced into the protocol.

Table 8: Changes to the Protocol (Global Amendment 01)

Original text with changes shown	New wording	Reason/Justification for change
1.3.1.2. Metabolism and Pharmacokinetics ((Other sections affected by change: 5.2.2.1. Allowed Medications/Therapies during Study)		
Laquinimod was shown to cause a ~~marked~~ decrease of CYP3A4 activity and is a ~~potent~~ strong inducer of CYP1A enzymes	Laquinimod was shown to cause a decrease of CYP3A4 activity and is a strong inducer of CYP1A enzymes	Language updated to make consistent with other laquinimod protocols and Investigator's Brochure
1.3.1.3. Toxicology		
(new text added)	Based on calculations from a study to determine laquinimod levels in monkey semen, in which the semen:plasma ratio of laquinimod was 0.32, the estimated exposure to a female partner of laquinimod-treated male patient via semen is approximately 600 fold lower than the exposure after oral administration of laquinimod at a dose of 1.5 mg, indicating that the risk of male-mediated embryo-fetal toxicity through laquinimod treatment is negligible.	Rationale added for male patients not needing to specifically use contraception due to study drug
1.3.2.1. Clinical Pharmacology Studies (Other sections affected by change: 3.6.5. Early Termination (ET); 3.11.4. Early Termination (ET) Visit; 3.11.5. Completion Visit)		
At doses of 0.6 and 1.2 mg, laquinimod is a weak inhibitor of CYP3A4 and a strong inducer of CYP1A2; therefore, laquinimod may affect the systemic exposure of other drugs metabolized by CYP3A4 and CYP1A2. For additional information on concomitant use of laquinimod with CYP1A2 and CYP3A4 substrates, please refer to the IB.	At doses of 0.6 and 1.2 mg, laquinimod is a weak inhibitor of CYP3A4 and a strong inducer of CYP1A2; therefore, laquinimod may affect the systemic exposure of other drugs metabolized by CYP3A4 and CYP1A2. For additional information on concomitant use of laquinimod with CYP1A2 and CYP3A4 substrates, please refer to the IB.	Clarification and reference to Investigator's Brochure (which discusses these issues more comprehensively) added
3.2.2. Secondary Efficacy Measures and Endpoints (Other sections affected by change: 6.2. Secondary Efficacy Variables; 9.6.2. Secondary Variables; 9.6.4.3. Secondary Efficacy Analysis)		
Change from baseline to week 48 in the T25FW score.	(new text)	Secondary endpoint added
~~Change from baseline to week 48 in the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) score.~~	(text moved from section)	Changed from secondary to exploratory endpoint
3.2.3. Exploratory Efficacy Measures and Endpoints (Other sections affected by change: 3.11.3. Scheduled Treatment Visits (Visits 1 to 6, Weeks 4 to 48, and Every 12 weeks Thereafter); 6.3. Exploratory/Other Efficacy Variables; 9.6.3. Exploratory/Other Variables)		
Change from baseline to week 48 in the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) score (California Verbal Learning Test–II [CVLT-II], Brief Visuospatial	(text moved to this section and details of specific assessment added)	Changed from secondary to exploratory endpoint

Original text with changes shown	New wording	Reason/Justification for change
Memory Test – Revised [BVMT-R], and symbol digit modalities test [SDMT])		
Modified Rankin scale (mRS) (at week 72, visit 8)	(new text)	Exploratory endpoint added
~~SDMT~~	(deleted)	SDMT no longer considered as an exploratory endpoint in isolation
3.3.1. Emergency Code Breaking		
In case of a serious adverse event, pregnancy, or in cases when knowledge of the study drug assignment is needed to make treatment decisions, the investigator may unblind the patient's drug assignment ~~through the IRT system~~, as deemed necessary, mainly in emergency situations. Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) at the study center via the IRT, via the internet. If possible, the sponsor should be notified of the event prior to breaking of the code, ~~if possible~~. If this is not possible, the sponsor should be notified immediately afterwards, and the patient's drug code assignment should not be revealed. Breaking of the treatment code can always be performed by the site without prior approval by the sponsor. … For adverse events that are defined as: Suspected, Unexpected, Serious, Adverse Reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance may independently request that the treatment code be revealed (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct, analysis, and reporting of the data.~~break patient's code to comply with regulatory requirements.~~	In case of a serious adverse event, pregnancy, or in cases when knowledge of the study drug assignment is needed to make treatment decisions, the investigator may unblind the patient's drug assignment as deemed necessary, mainly in emergency situations. Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) at the study center via the IRT, via the internet. If possible, the sponsor should be notified of the event prior to breaking of the code. If this is not possible, the sponsor should be notified immediately afterwards, and the patient's drug code assignment should not be revealed. Breaking of the treatment code can always be performed by the site without prior approval by the sponsor. … For adverse events that are defined as: Suspected, Unexpected, Serious, Adverse Reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance may independently request that the treatment code be revealed (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct, analysis, and reporting of the data.	Text has been updated in line with current Teva standards
3.11.2.2. Up to 42 days Prior to Baseline (Other sections affected by change: 8.4.1. Cerebrospinal Fluid (CSF) Assessment)		
~~CSF collection (in selected sites) will be performed in all patients who signed an appropriate, EC approved informed consent form (see Section 8.4.1 for further details of the assessments).~~	(text deleted)	Procedure no longer performed at baseline

Original text with changes shown	New wording	Reason/Justification for change
3.11.4. Early Termination (ET) Visit		
BICAMS and OCT: ET visit will only include BICAMS and OCT for patients who prematurely terminate treatment subsequent to the week 24 visit and prior to week 48. Patients who stop treatment before week 24 or after week 48 will not have BICAMS and OCT at ET visit.	(new text)	Additional assessments for certain patients at ET visit
4.2. Patient Exclusion Criteria		
26. GFR ≤60 mL/min/1.73 m^2 at screening visit.	26. GFR ≤60 mL/min/ 1.73 m^2 at screening visit.	Clarification of units
5.2.2.1. Allowed Medications/Therapies during Study		
Symptomatic MS agents, such as anti-cholinergic and spasmolytic drugs, are permitted at clinically appropriate doses. Dose changes and initiation of symptomatic treatments during the study should be avoided if possible.	Symptomatic MS agents, such as anti-cholinergic and spasmolytic drugs, are permitted at clinically appropriate doses. Dose changes and initiation of symptomatic treatments during the study should be avoided if possible.	Clarification
Clinical studies have shown laquinimod to be a ~~potent~~ strong inducer of CYP1A2. Patients taking drugs that are metabolized by CYP1A2 (examples listed in Appendix E) should be advised that plasma levels of these drugs could decrease when combined with laquinimod. In general, as a precautionary measure, it is recommended to avoid the use of CYP1A2 substrates in clinical trials of laquinimod. Therapeutic alternatives may be considered in the appropriate clinical context. Additional information on concomitant use of laquinimod and CYP1A2 substrates is presented in the laquinimod IB.	Clinical studies have shown laquinimod to be a strong inducer of CYP1A2. Patients taking drugs that are metabolized by CYP1A2 (examples listed in Appendix E) should be advised that plasma levels of these drugs could decrease when combined with laquinimod. In general, as a precautionary measure, it is recommended to avoid the use of CYP1A2 substrates in clinical trials of laquinimod. Therapeutic alternatives may be considered in the appropriate clinical context. Additional information on concomitant use of laquinimod and CYP1A2 substrates is presented in the laquinimod IB.	Clarification
Drug drug interaction studies have ~~shown~~ been performed with laquinimod doses of 0.6 and 1.2 mg. These studies showed that laquinimod, at both doses, is a weak inhibitor of CYP3A4	Drug-drug interaction studies have been performed with laquinimod doses of 0.6 and 1.2 mg. These studies showed that laquinimod, at both doses, is a weak inhibitor of CYP3A4	Clarification
5.4. Total Blood Volume		
The total amount of blood to be drawn during the study for serum chemistry, CBC, pharmacokinetic, biomarker and PGx measurements is approximately 500 mL/patient.	The total amount of blood to be drawn during the study for serum chemistry, CBC, pharmacokinetic, biomarker and PGx measurements is approximately 500 mL/patient.	Clarification
6.4.5. Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) Score		
Brief Visuospatial Memory Test – Revised (BVMT-R) (first	Brief Visuospatial Memory Test – Revised (BVMT-R)	Additional details added

Original text with changes shown	New wording	Reason/Justification for change
3 recall trials): this requires the patient to inspect a 2 × 3 stimulus array of abstract geometric figures (Form 1 from the Recall Stimulus Booklet).	(first 3 recall trials): this requires the patient to inspect a 2 × 3 stimulus array of abstract geometric figures (Form 1 from the Recall Stimulus Booklet).	
6.4.6. Symbol Digit Modalities Test (SDMT) (Other sections affected by change: 3.11.2.4. Pre-randomization; 3.11.3. Scheduled Treatment Visits (Visits 1 to 6, Weeks 4 to 48, and Every 12 weeks Thereafter))		
~~Two forms of the SDMT (Form A and Form B) will be used in this study. Alternating SDMT forms will be administered as follows: Form A (at baseline, week 24, week 48, and every 24 weeks until completion/ET); Form B (at week 12, week 36, and every 24 weeks until completion/ET).~~	(text deleted)	Alternating forms will no longer be used
6.4.7. Modified Rankin Scale		
The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability (Rankin 1957; Farrell et al 1991). The scale runs from 0 (no symptoms) to 5 (severe disability), with a score of 6 used in the event of a death (Appendix J).	(new section)	New efficacy measure added
7.1.5.3.1 Invesigator Responsibility		
The following information should be provided to record the event accurately and completely: … • ~~patient initials~~ • onset date and detailed description of adverse event ... Additional information may include the following: … • explanation of assessment of relatedness … ~~On the basis of this assessment, a decision will be made concerning the need for further medical intervention.~~ … For all countries, the sponsor's Global Patient Safety and Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO/CRO for local submission to the regulatory authorities and IEC/IRBs and investigators, according to	The following information should be provided to record the event accurately and completely: … • onset date and detailed description of adverse event ... Additional information may include the following: … • explanation of assessment of relatedness … For all countries, the sponsor's Global Patient Safety and Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO/CRO for local submission to the regulatory authorities and IEC/IRBs and investigators, according to regulations. The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with local regulations.	Text has been updated in line with current Teva standards

Original text with changes shown	New wording	Reason/Justification for change
regulations. The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with local regulations. ~~There are countries where the investigator must ensure that the IEC/IRB is also informed of the event, in accordance with local regulations.~~		
8.4.2. Optical Coherence Tomography (OCT) Evaluation (Other sections affected by change: 3.11.3. Scheduled Treatment Visits (Visits 1 to 6, Weeks 4 to 48, and Every 12 weeks Thereafter); APPENDIX L. OCT ANCILLARY STUDY DESIGN AND METHODOLOGY)		
OCT (to be performed in selected sites) will be performed in all patients who signed an appropriate, EC approved informed consent form, at week 0 (can be performed up to 42 days prior to baseline),~~and~~ week 48 (or ET visit if performed after the week 24 visit and prior to week 48), and week 96 to assess retinal thickness.	OCT (to be performed in selected sites) will be performed in all patients who signed an appropriate, EC approved informed consent form, at week 0 (can be performed up to 42 days prior to baseline), week 48 (or ET visit if performed after the week 24 visit and prior to week 48), and week 96 to assess retinal thickness.	Additional assessment added at week 96
9.3.2. Modified ITT 1 (mITT1) Population (Other sections affected by change: 9.3.5. Per Protocol (PP) Population; 9.5.1. Patient Disposition; 9.6.4. Planned Method of Analysis; 9.6.4.1. Primary Efficacy Analysis)		
The modified ITT 1 (mITT1) population is a subset of the ITT set. It will include all patients in the ITT population with at least 1 post baseline ~~efficacy~~ PBVC assessment.	The modified ITT 1 (mITT1) population is a subset of the ITT set. It will include all patients in the ITT population with at least 1 post baseline PBVC assessment.	Refinement of statistical analysis set definition
9.3.3. Modified ITT 2 (mITT2) Population (Other sections affected by change: 9.5.1. Patient Disposition; 9.6.4. Planned Method of Analysis)		
The modified ITT 2 (mITT2) population is a subset of the ITT set. It will include all patients in the ITT population with at least 1 post baseline efficacy assessment.	(new text)	Additional statistical analysis set included
9.6.2. Secondary Variables		
Let E_t be an EDSS measurement of the patient under consideration observed at time (measured by ~~months~~ weeks from the patient's baseline date). ... Let $s = t$ +~~3~~ 12. ... 5. 3. For any $t < q_1 < s$, if the patient's EDSS was evaluated at	Let E_t be an EDSS measurement of the patient under consideration observed at time (measured by weeks from the patient's baseline date). ... Let $s = t$ +12. ... 9. 3. For any $t < q_1 < s$, if the patient's EDSS was	Modification to time of CDP algorithm

Original text with changes shown	New wording	Reason/Justification for change
time q_1, then $E_{q1} \geq E_0 + \Delta$ 6. *4.* $E_{q2} \geq E_0 + \Delta$ for some $q_2 \geq s$, and at time q_2, the patient was not experiencing a relapse. 7. ~~3. $E_q \geq E_0 + \Delta$ for some $q > s$, and at time q, the patient was not experiencing a relapse.~~ 8. ~~4. For any $t < q < s$, if the patient's EDSS was evaluated at time q, then $E_q \geq E_0 + \Delta$.~~ ... In case time t exists without fulfilling conditions 3 and 4 because time *q2* is after the patient completed Part A of the study (or performed ET), and therefore cannot be seen, then the right censored will be on time t and not in the last EDSS evaluation.	evaluated at time q_1, then $E_{q1} \geq E_0 + \Delta$ 10. *4.* $E_{q2} \geq E_0 + \Delta$ for some $q_2 \geq s$, and at time q_2, the patient was not experiencing a relapse. ... 11. In case time t exists without fulfilling conditions 3 and 4 because time *q2* is after the patient completed Part A of the study (or performed ET), and therefore cannot be seen, then the right censored will be on time t and not in the last EDSS evaluation.	
9.6.4.2. Sensitivity Analyses		
Repeat of the primary analysis without introduction of covariates except for the treatment group, week, and treatment by week interaction.	Repeat of the primary analysis without introduction of covariates except for the treatment group, week, and treatment by week interaction.	Modification made to the sensitivity testing
9.6.4.3. Secondary Efficacy Analysis		
a. Time to CDP as measured by EDSS confirmed after at least 12 weeks...In addition to treatment group, categorical EDSS at baseline (≤4.5 or >4.5), ~~categorical~~ age at baseline ~~(≤51 or >51 years)~~, natural logarithm of T2 lesion volume at baseline, and CGR will be used as covariates. ... b. Time to CDP, confirmed after at least 12 weeks as measured by EDSS or T25FW...In addition to treatment group, categorical EDSS at baseline (≤4.5 or >4.5), ~~categorical~~ age at baseline baseline ~~(≤51 or >51 years)~~, T25FW at baseline, natural logarithm of T2 lesion volume at baseline, and CGR will be used as covariates. ... c. Change from baseline in the T25FW score at week 48 will be	a. Time to CDP as measured by EDSS confirmed after at least 12 weeks...In addition to treatment group, categorical EDSS at baseline (≤4.5 or >4.5), age at baseline, natural logarithm of T2 lesion volume at baseline, and CGR will be used as covariates. ... b. Time to CDP, confirmed after at least 12 weeks as measured by EDSS or T25FW...In addition to treatment group, categorical EDSS at baseline (≤4.5 or >4.5), age at baseline, T25FW at baseline, natural logarithm of T2 lesion volume at baseline, and CGR will be used as covariates. ... c. Change from baseline in the T25FW score at week 48	Continuous age (not categorical) will be used as covariate for time to CDP. Clarification that it will be mITT1 population for new T2 brain lesion analysis and addition of age at baseline as a covariate. Change from baseline in the T25FW score added as a secondary analysis.

Original text with changes shown	New wording	Reason/Justification for change
analyzed on the mITT2 population. Since this variable might not follow normal distribution, the ranked values of this measurement will be defined and analyzed using baseline adjusted repeated measures ANCOVA (SAS® PROC MIXED) in which 2 contrasts will be constructed in order to compare between each dose of laquinimod (0.6 and 1.5 mg) and placebo. In addition to treatment group, T25FW score at baseline and CGR will be used as covariates. Due to the fact that the ANCOVA model will use ranked values and not the actual changes in the T25FW, Hodges Lehmann estimates will be used in order to present the magnitude of the treatment effect and the corresponding two-sided 95% confidence. ~~c.~~ d. The number of new brain T2 lesions at week 48 will be analyzed using the mITT1 population with at least 1 post baseline T2 scan available if it was performed at least 36 weeks under treatment. This analysis will be performed using baseline adjusted negative binomial regression model (SAS® PROC GENMOD) in which 2 contrasts for comparing each of laquinimod doses to placebo will be constructed. In addition to the treatment group, the natural logarithm of T2 lesion volume at baseline, age at baseline, and CGR will be used as covariates. ... ~~d. Change from baseline to week 48 in the BICAMS score will be analyzed using the mITT population with at least 1 post baseline BICAMS score, if it was performed at least 36 weeks under treatment. This analysis will be performed using baseline adjusted analysis of covariance (ANCOVA - SAS® PROC GLM) in which 2 contrasts for comparing each of laquinimod doses to placebo will be constructed. In addition to treatment group, BICAMS score at baseline and CGR will be used as covariates.~~	will be analyzed on the mITT2 population. Since this variable might not follow normal distribution, the ranked values of this measurement will be defined and analyzed using baseline adjusted repeated measures ANCOVA (SAS® PROC MIXED) in which 2 contrasts will be constructed in order to compare between each dose of laquinimod (0.6 and 1.5 mg) and placebo. In addition to treatment group, T25FW score at baseline and CGR will be used as covariates. Due to the fact that the ANCOVA model will use ranked values and not the actual changes in the T25FW, Hodges Lehmann estimates will be used in order to present the magnitude of the treatment effect and the corresponding two-sided 95% confidence. d. The number of new brain T2 lesions at week 48 will be analyzed using the mITT1 population with at least 1 post baseline T2 scan available if it was performed at least 36 weeks under treatment. This analysis will be performed using baseline adjusted negative binomial regression model (SAS® PROC GENMOD) in which 2 contrasts for comparing each of laquinimod doses to placebo will be constructed. In addition to the treatment group, the natural logarithm of T2 lesion volume at baseline, age at baseline, and CGR will be used as covariates.	
9.10. Planned Interim Analysis		
No interim analysis is planned for this study ~~An interim analysis for futility is planned once 50% of patients have completed the week 48 MRI scan. Based on recruitment estimates this is expected to occur 72 weeks after study initiation. Interim analysis will be based on the PBVC outcome on week 48. If the results of the analysis suggest the possibility of futility, a sequence of additional analyses will be conducted prior to study termination, including PBVC at week 24~~	No interim analysis is planned for this study.	Interim analysis removed from study

Original text with changes shown	New wording	Reason/Justification for change
~~for which the majority of data are expected to be available at this time. Details of the analytical approach will be specified in the Statistical Analysis Plan for Interim Analysis.~~		
11.4. Clinical Product Complaints		
A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies and/or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to the following: • suspected contamination • questionable stability (eg, color change, flaking, crumbling, etc.) • defective components • missing or extra units (eg, primary container is received at the site with more or less than the designated number of units inside) • incorrect packaging or incorrect or missing labeling/labels • unexpected or unanticipated taste or odor or both • device not working correctly or appears defective in some manner Each investigational center will be responsible for reporting a possible clinical product complaint by completing the Product Complaint Form provided by Teva and emailing it to [redacted] within 48 hours of becoming aware of the issue. For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving a drug product, all relevant samples (eg, the remainder of the patient's drug supply) should be sent back to the sponsor for investigative testing whenever possible. **11.4.1 Product Complaint Information Needed from the Investigational Center** In the event that the Product Complaint Form cannot be completed,	(new text)	Text has been added in line with current Teva standards

Original text with changes shown	New wording	Reason/Justification for change
the investigator will obtain the following information, as available: • investigational center number and principal investigator name • name, phone number, and address of the source of the complaint • clinical protocol number • patient identifier (patient study number) and corresponding visit numbers, if applicable • product name and strength for open-label studies • patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies • product available for return Yes/No • product was taken or used according to protocol Yes/No • description or nature of complaint • associated serious adverse event Yes/No • clinical supplies unblinded (for blinded studies) Yes/No • date and name of person receiving the complaint Note: Reporting a complaint must not be delayed because not all the required information can be immediately obtained. Known information must be immediately reported. The sponsor will collaborate with the investigator to obtain any outstanding information. **11.4.2 Handling the Study Drug at the Investigational Center** The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the study drug. If it is determined that the investigational center must return all of the study drug, the sponsor will provide the information needed to handle the return. The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious		

Original text with changes shown	New wording	Reason/Justification for change
adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient. **114.3 Adverse Events or Serious Adverse Events Associated with a Product Complaint** If there is an adverse event or serious adverse event, the protocol should be followed. **11.4.4 Documenting a Product Complaint** The investigator will record a description of the product complaint in the source documentation as well as any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.		
12.1. Informed Consent		
Overall, this study includes: (I) an informed consent for the clinical study (main study) ~~and~~ (II) informed consent forms for the ancillary studies (CSF and OCT), and (III) informed consent forms for dummy run scans (MRI and OCT) required prior to initiation of the study and ancillary study respectively.	Overall, this study includes: (I) an informed consent for the clinical study (main study),(II) informed consent forms for the ancillary studies (CSF and OCT), and (III) informed consent forms for dummy run scans (MRI and OCT) required prior to initiation of the study and ancillary study respectively.	For completeness, dummy run informed consent added to this section
APPENDIX B. GUIDANCE ON SAFETY MONITORING		
a. b. If the blood test is negative, the ~~subject~~ patient will be contacted and informed about the test result and the study drugs will be ~~sent to her by courier~~dispensed as soon as possible.	b. b. If the blood test is negative, the patient will be contacted and informed about the test result and the study drugs will be dispensed as soon as possible.	It has been clarified that it is not acceptable to courier study drug to the patient in this manner
12. **5. Guidance on monitoring patients with elevated pancreatic amylase levels** Pancreatic amylase will be measured at each study visit. Lipase will be tested in case of abnormal pancreatic amylase results. In case of suspected pancreatitis, the patient should undergo a thorough clinical evaluation including an abdominal CT scan as soon as possible in order to clarify the diagnosis and enable assessment of severity of this condition.	(new text)	Subsection added for consistency with other laquinimod protocols and on the advice of the Data Monitoring Committee
APPENDIX C. MODERATE/STRONG CYP3A4 INHIBITORS AND CYP3A4 INDUCERS		
(additional CYP3A4 inhibitors added to the medication classes	(see Appendix C for revised section)	Section updated in accordance

Original text with changes shown	New wording	Reason/Justification for change
antivirals [danoprevir, ledipasvir, elvitegravir] and antiemetics [casopitant, netupitant], and medication class antiarrhythmics [dronedarone] added. List of CYP3A4 inducers replaced with table)		with Investigator's Brochure
APPENDIX E. CYP3A4 and CYP1A2 substrates		
(original protocol text replaced by table)	(see Appendix E for revised section)	Section updated in accordance with Investigator's Brochure
APPENDIX J. MODIFIED RANKIN SCALE		
(new appendix)	(see Appendix J)	Appendix added to document the efficacy measure that has been added to the study
APPENDIX L. OCT ANCILLARY STUDY DESIGN AND METHODOLOGY		
The following criteria lead to exclusion of affected eyes only. However, the patient can participate in the OCT ancillary study with a single eye, if it is unaffected.	(new text)	Clarification that only affected eyes are excluded from the OCT assessments, such that patients with an unaffected eye can participate for that eye only
(in Table 10, the following changes have been made: • title amended to add 'of affected eyes' • more than 4 diopters (instead of more than 6 diopters) of myopia or hyperopia will exclude an eye • correction of error, should be 'systemic lupus erythematosus', not 'systemic lupus erythematodes' • footnote added for selected categories, 'Indicates conditions which are likely to affect both eyes and therefore lead to exclusion of the patient, even if 1 eye is considered unaffected')	(see Appendix L for revised table)	Corrections and clarifications

APPENDIX A. RELAPSE DEFINITION

Relapse (attack)

A relapse will be defined as the appearance of 1 or more new neurological abnormalities or reappearance or worsening of 1 or more previously observed neurological abnormalities. This change in clinical state must last at least 48 hours and be immediately preceded by an improving neurological state of at least thirty (30) days from onset of previous relapse.

This criterion is different from the clinical definition of relapse: “at least 24 hours duration of symptoms.” Since "in study" relapse definition must be supported by an objective neurological evaluation (see next paragraph), a neurological deficit must be sustained long enough to eliminate pseudo-relapses.

An event is counted as a relapse only when the patient’s symptoms are accompanied by observed objective neurological changes. A change in bowel/bladder function or in cognitive function must not be entirely responsible for the changes.

The patient must not be undergoing any acute metabolic changes such as fever or other medical abnormality.

Relapse Evaluation Procedures

Patients will be instructed to telephone their study site within 48 hours should any symptoms suggestive of a relapse appear.

The Treating Neurologist will evaluate the patient once any symptom suggestive of a relapse occurs.

In case of a suggestive relapse during a scheduled or unscheduled visit, the Treating Neurologist will refer the patient to the Examining Neurologist.

The Examining Neurologist will evaluate the patient within 7 days of symptoms onset, conditional upon a symptomatic period of ≥48 hours.

Patient Evaluation by the Examining Neurologist

EDSS and FSS will be administered.

Clinical Relapse Determination by the Treating Neurologist

The determination whether objective neurological changes are present consistent with a relapse will be made by the Treating Neurologist, without reference to the EDSS and FSS administered by the Examining Neurologist.

Follow-up visits to monitor the course of the relapse will be made at the Treating Neurologist’s discretion.

Protocol-Defined Relapse

In addition to the criteria used by the Treating Neurologist to determine that a clinical relapse has occurred, a per-protocol relapse definition will make use of EDSS data to confirm that the objective neurological changes include at least 1 of the following:

- an increase of at least 0.5 in the EDSS score as compared to previous evaluation

- an increase of 1 grade in the score of 2 or more of the 7 functions from the FSS as compared to previous evaluation
- an increase of 2 grades in the score of 1 function from the FSS as compared to the previous evaluation

APPENDIX B. GUIDANCE ON SAFETY MONITORING

1. Guidance on Monitoring Patients with Elevated Liver Function Tests

Liver enzymes (ALT, AST, GGT, ALP), as well as direct and total bilirubin will be measured at each study visit.

In any case of elevated ALT or AST to a level exceeding of ≥2×ULN (including patients whose baseline ALT or AST levels are ≥2× and ≤3× the ULN, who may be enrolled in the study), a thorough medical history and physical examination with a focus on liver disease should be undertaken[a]. In addition, the patient should be instructed to refrain from alcoholic beverages.

In case of symptoms compatible with drug-induced liver injury, the patient should be invited for an unscheduled visit to measure liver enzymes as soon as possible.

Solitary elevations of total bilirubin, not accompanied by elevations of ALT or AST should be managed according to the discretion of the Treating Neurologist.

1.1. Elevation of Either ALT or AST to ≥3 x ULN:

Confirmation of the abnormality (in case the abnormality is of ALT or AST ≥8×ULN, no confirmation is required prior to study drug discontinuation, but the assessments below should be performed):

- The day in which the abnormal value is received from the laboratory will be considered as Day 0.
- The Investigator should repeat the test before Day 2, for confirmation purposes (this may be performed in a local laboratory along with CBC and differential to assess for eosinophilia. In general, in case a blood sample is sent to a local laboratory, the following assessments [and reference ranges] are mandatory: ALT [serum glutamic pyruvic transaminase; SGPT], AST [serum glutamic oxaloacetic transaminase; SGOT], ALP, total bilirubin, CBC [with differential for eosinophil count, separate tube], and INR [separate tube; not to be sent in a confirmatory test]). The investigator should also question the patient regarding symptoms.

The abnormality will be regarded as confirmed in each of the following scenarios:

1. In case baseline value was within normal range and ALT or AST is still ≥3×ULN
2. In case baseline value was above ULN and ALT or AST is ≥2× the baseline value.

Upon confirmation of the abnormality as noted above, the following additional evaluations should be performed and results should be recorded in the CRF.

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[a] Thorough medical history with a focus on liver disease: Personal or family history of liver disease; personal history of a systemic disease with potential liver involvement; exposure to alcohol, medications (prescription or OTC), herbal preparations, dietary supplements, recreational drugs, special diets or environmental chemical agents; potential exposure to infectious agents (eg, travel to developing countries, history of potential exposure to blood or blood products, high-risk sexual relations) and any additional information deemed relevant by the investigator. Physical examination – including signs of chronic liver disease

Additional Tests/Evaluations

- Serology for Hepatitis A (antibody, immunoglobulin M and G), B (core antibody total, core immunoglobulin M, and surface antigen), and C viruses (central laboratory).
- Serology for autoimmune hepatitis: anti-nuclear antibodies (titer), Anti Smooth Muscle Antibodies (ASMA), anti-Liver Kidney Microsomal (LKM) antibodies (central laboratory). Further testing may be required in case of a positive result for Hepatitis B or C.
- An ultrasound examination of the liver and biliary tract.
- Other diagnostic tests/consultations, as deemed necessary by the investigator, eg, serology for hepatitis E virus in case of travel to endemic geography

Observation and Follow-Up (to be performed after the abnormality was confirmed as above)

1.1.1. ALT or AST ≥3× and ≤5×ULN (if baseline value is ≥2.5×ULN, ALT or AST ≥3.5×ULN and ≤5×ULN)

In addition to the above procedures required for any elevation to levels >3×ULN:

- ALT, AST, GGT, ALP, total and direct bilirubin, CBC and differential (to assess for eosinophilia) and INR should be monitored on days 5 (±2), 8 (±2), 14 (±2), and 28 (±2). On at least 1 of these days, the test should be performed centrally. (INR should be sent to a local laboratory only.)
- In cases where a local laboratory is used, the results should be recorded in the CRF, accompanied by the reference range of the relevant measurements.
- Should the abnormality (ALT or AST ≥3× and ≤5×ULN [if baseline value is ≥2.5×ULN, ALT or AST ≥3.5×ULN and ≤5×ULN]) persist further, the patient will be followed according to the investigator's discretion, but at least once a month a blood sample for ALT, AST, GGT, ALP, and total and direct bilirubin should be sent to the central laboratory.

1.1.2. ALT or AST ≥5× but less than 8×ULN

In addition to the above procedures required for any elevation to levels >3×ULN:

- ALT, AST, GGT, ALP, total and direct bilirubin, CBC and differential count (to assess for eosinophilia), and INR should be monitored twice a week.
- At least for every other measurement, the tests should be sent to the central laboratory. The rest of the tests may be sent to a local laboratory. INR should always be sent to a local laboratory.

1.1.3. ALT or AST ≥8×ULN

In addition to the above procedures required for any elevation to levels >3xULN:

- The study drug should be discontinued immediately and the ET visit should be performed.

- For follow-up guidance, please see below section "*Follow-up of Liver Enzymes after Stopping-Rules are met*".

1.2.Stopping Rules:

In the following circumstances, the study drug will be discontinued immediately:

- Any increase in ALT or AST to ≥3×ULN, combined with INR >1.5 or total bilirubin >2×ULN
- Any increase in ALT or AST to ≥3×ULN, which is accompanied by nausea, vomiting, fever, rash, or eosinophilia
- Any increase in ALT or AST to levels ≥5× but <8×ULN, which is persistent for ≥2 weeks of repeated measurements
- Any increase in ALT or AST to levels ≥8×ULN
- In any case where monitoring of liver enzymes cannot be performed according to the protocol guidance

1.2.1. Follow-Up of Liver Enzymes After Stopping-Rules Are Met:

- A patient who meets the above criteria for discontinuation of the study drug should be invited to the site to return the study drug. ET visit activities should be performed as soon as possible.
- Liver enzymes should be monitored until normalization or stabilization of the abnormality, according to the discretion of the investigator.
- In any case, following ET, the minimal follow-up period will be 30 days and will include measurement of liver enzymes at least QW (may be performed in a local laboratory, with at least 1 test being sent to the central laboratory).
- Every effort should be made to complete the additional tests/ evaluations, as described above.

2. Use of Moderate/Strong CYP3A4 Inhibitors

Laquinimod pharmacokinetics are affected by moderate and strong CYP3A4 inhibitors; therefore, moderate/strong CYP3A4 inhibitors are disallowed during study and 30 days after the last dose has been administered. A partial list of commonly used CYP3A4 inhibitors is presented in Appendix C.

3. Management of Patients who are Diagnosed with Cancer

Patients who are diagnosed with a malignant solid or liquid tumor while participating in the study should stop study medication.

4. Management of Pregnancy and Pregnancy Testing During the Study

Exposure to laquinimod during pregnancy should be avoided.

To further emphasize the importance of use of acceptable contraception and avoidance of pregnancy under laquinimod exposure (see Section 1.4), and to reduce as much as possible the exposure to laquinimod if a pregnancy occurs despite all recommended measures, all patients

who are women of child bearing potential will be instructed about the teratogenicity and potential delayed risks for a child exposed in uterus to laquinimod. These patients will also be counseled about the importance of using 2 acceptable methods of birth control throughout the entire treatment duration and until 30 days after the last dose of treatment was administered and about the need to stop treatment immediately if pregnancy is suspected.

Women of child-bearing potential (for example women who are not postmenopausal or surgically sterilized) must practice an acceptable method of birth control for 30 days before taking the study drug and 2 acceptable methods of birth control for the duration of the study and until 30 days after the last dose of study medication. Acceptable methods of birth control include: intrauterine devices, barrier methods (condom or diaphragm with spermicide) and hormonal methods of birth control (e.g. oral contraceptive, contraceptive patch, long-acting injectable contraceptive).

The patients' understanding of the importance of preventive pregnancy measures and their ability to follow the required instructions will be ascertained by the investigator and recorded in source documents at every visit. Any female patient who becomes pregnant during the study will discontinue her participation in the study and will not perform the activities described for scheduled follow-up visits.

At each scheduled visit, female patients of childbearing potential will undergo a urine β-hCG test. In addition, a serum pregnancy β-hCG test will be performed at each visit to the site. At baseline, serum β-hCG will be done within 7 days prior to the initiation of treatment, such that the result is available prior to the first dose.

1. In case the urine test is negative, study drugs will be dispensed according to planned visit tasks (see Table 5).
    a. If the blood test is positive, the patient will be contacted immediately and instructed to stop taking the study drug. The patient should be invited to attend an early termination visit.
    b. If the blood test is negative – study procedures will be undertaken as planned.
2. In case the urine test is positive – the study drug will not be dispensed (if this occurs at Baseline visit, the patient will not be eligible to participate in the study and will be considered as a screening failure)
    a. If the blood test is positive, the patient will be invited to the site for an early termination visit
    b. If the blood test is negative, the patient will be contacted and informed about the test result and the study drugs will be dispensed as soon as possible.
3. Starting from visit 3 (week 12), the following actions will be taken:
    a. The patient will be provided with home pregnancy urine β-hCG test kits and will be guided how to perform the test.
    b. The patient will be instructed to perform the test in monthly intervals (every 28 (±2) days) from the visit date. These dates should be recorded by the study coordinator and a telephone call, will be scheduled to be performed within 72 hours of the urine test date.

c. A mandatory phone call will be performed by the Treating Neurologist or by the site's nurse/ study coordinator every month in order to verify whether the test has been performed and to record the result of the test in the patient's file. In case of a suspected pregnancy, the patient will be instructed to stop taking the study drug and arrive to the site as soon as possible for an unscheduled visit, with the remaining study medications. In the site, a quantitative urine β-hCG pregnancy test should be performed and the rest of the activities will be as in 2.

In case of an established diagnosis of pregnancy, the Treating Neurologist should discuss with the patient the potential teratogenicity and delayed risks for a child exposed in utero to laquinimod. The possibility of termination of the pregnancy should be discussed. In case the patient decides to continue the pregnancy, she will be followed to determine outcome, including spontaneous or elective termination, details of birth, and presence or absence of any birth defect, congenital abnormalities or maternal and newborn complications.

5. Guidance on monitoring patients with elevated pancreatic amylase levels

Pancreatic amylase will be measured at each study visit. Lipase will be tested in case of abnormal pancreatic amylase results. In case of suspected pancreatitis, the patient should undergo a thorough clinical evaluation including an abdominal CT scan as soon as possible in order to clarify the diagnosis and enable assessment of severity of this condition.

6. Liver Impairment

Patients who develop liver disease associated with liver functional impairment while participating in the study should stop study medication.

7. Renal Impairment

Patients who develop renal disease associated with moderate or severe functional impairment, defined as glomerular filtration rate (GFR) ≤60 mL/min/1.73 m^2, while participating in the study should stop study medication temporarily and the GFR assessment should be repeated. If the renal impairment is confirmed (GFR ≤60 mL/min/1.73 m^2), the patient should stop study medication permanently.

APPENDIX C. MODERATE/STRONG CYP3A4 INHIBITORS AND CYP3A4 INDUCERS

Laquinimod pharmacokinetics are affected by moderate and strong CYP3A4 inhibitors; moderate/strong CYP3A4 inhibitors are disallowed within 2 weeks of baseline until 30 days after the last dose has been administered.

Moderate and strong CYP3A4 inhibitors are prohibited because concomitant administration is predicted to increase laquinimod exposure and may increase the likelihood of adverse events.

A partial list of moderate/strong CYP3A4 inhibitors follows:

Medication class	**Drug name**
Protease inhibitors	indinavir, saquinavir, lopinavir, nelfinavir, amprenavir, atazanavir, darunavir, ritonavir
Antivirals	boceprevir, telaprevir, danoprevir, ledipasvir, elvitegravir
Antifungals	ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole
Antibiotics	troleandomycin, clarithromycin, telithromycin, ciprofloxacin, erythromycin
Antidepressant	nefazodone
Calcium channel blocker	diltazem, verapamil, mibefradil
Antiemetics	aprepitant, casopitant, netupitant
Diuretics	conivaptan
Antineoplastic agents	imatinib
Antiarrhythmics	dronedarone

Note:

- Interactions between drugs and grapefruit juice are documented for drugs with low bioavailability due to pre-systemic gut-wall metabolism. Based on the suggested high oral bioavailability of laquinimod in humans, such interactions are not expected with laquinimod.

CYP3A4 inducers are disallowed within 2 weeks of baseline and during the treatment period.

A partial list of CYP3A4 inducers follows:

Medication class	**Drug name**
Antibiotics	rifampin, rifabutin, nafcillin
Anticonvulsants	phenytoin, carbamazepine, phenobarbital, oxcarbazepine
Antineoplastic agents	mitotane
Anti-retroviral	efavirenz, talviraline, etravirine, lersivirine
Protease inhibitors	lopinavir, tipranavir, ritonavir
Antilipemics agents	avasimibe
Antiandrogens	enzalutamide
Endothelin Receptor Antagonists	bosentan
Antipsychotics	thioridazine
Psychostimulants	modafinil, armodafinil
Herbal Medications	St. John's wort

APPENDIX D. DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS: 2010 REVISIONS TO "MCDONALD CRITERIA"

MS Diagnosis

Confirmation of PPMS diagnosis according to the 2010 revised McDonald criteria (Polman et al, 2011) will be performed during screening and documented in the CRF.

2010 McDonald criteria for diagnosis of MS in disease with progression from onset

PPMS may be diagnosed in patients with:
1. One year of disease progression (retrospectively or prospectively determined)
2. Plus 2 of the 3 following criteria[a]:
A. Evidence for DIS in the brain based on ≥1 T2[b] lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)
B. Evidence for DIS in the spinal cord based on ≥2 T2[b] lesions in the cord.
C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated immunoglobulin G index).

[a] If a patient has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the criteria.
[b] Gadolinium enhancement of lesions is not required
MS = multiple sclerosis; PPMS = primary progressive MS; DIS = lesion dissemination in space; CSF = cerebrospinal fluid; IgG = immunoglobulin G

Note: In this study, if criterion C (positive CSF) is applied toward the diagnosis of PPMS, the CRF documentation must be accompanied by source documentation of the results issued by the clinical laboratory which performed the analysis.

APPENDIX E. CYP3A4 AND CYP1A2 SUBSTRATES

Table 9: A Partial List of Cytochrome P450 3A4 Substrates with a Narrow Therapeutic Index

alfentanil
cyclosporine
diergotamine
ergotamine
fentanyl
pimozide
quinidine
sirolimus
tacrolimus

Table 10: A Partial List of Drugs that are Mainly Metabolized by Cytochrome P450 1A2

Medication class	Drug name
Antidepressant	Agomelatine, Duloxetine, Mirtazapine, Nortriptyline, Fluvoxamine
Antipsychotics	Chlorpromazine, **Clozapine**, Olanzapine, Thiothixene, Trifluoperazine
Migraine Treatments	Frovatriptan, Zolmitriptan
Anesthetics	Lidocaine (systemic use)
Antineoplastic agents	Erlotinib
Muscle relaxants	Cyclobenzaprine, **Tizanidine**
Sleep disorders	Melatonin, Ramelteon
Respiratory Agents	**Aminophylline, Theophylline**
Benzodiazepines	Chlordiazepoxide
Alpha adrenergic agonist	Guanabenz
Beta blockers	Propranolol
Parkinson's treatment	Rasagiline, **Ropinirole**
Alzheimer's Treatments	Tacrine
Diuretics	Triamterene
Miscellaneous agents	Alosetron (irritable bowel syndrome treatment), Riluzole (amyotrophic lateral sclerosis treatment), **Methadone**

Drugs with a narrow therapeutic index appear in bolded text

For additional information on concomitant use of laquinimod with CYP1A2 and CYP3A4 substrates, please refer to the IB.

APPENDIX F. MRI PROCEDURES

The patients will undergo up to 3 MRI scans: baseline (at least 14 days but not more than 42 days prior to baseline), week 24, and week 48 (or ET visit if performed after the week 36 visit and prior to week 48). Weeks 24 and 48 (or ET) MRI must be performed within 14 days of study visit. Gd will be administered at baseline MRI only. In case of steroid treatment, study MRI should be performed before or be delayed to allow a minimum of 14 days, but not more than 28 days, from the completion of the steroid course.

MRI scans will be obtained according to a standard protocol that will be provided by the MRI Reading Center. At baseline only, MRI scans will be obtained before and after Gd administration. GFR calculation at the site should be done prior to the baseline MRI scan.

MRI facilities will undergo a qualification procedure, which will include the performance of a healthy volunteer dummy run to ensure that the implementation of the standard sequences on their system produces appropriate images for measuring the endpoints specified in the protocol. The healthy volunteer must sign an EC approved informed consent form. Qualification of sites will be formally indicated by a dummy run approval certification. Sites must be qualified prior to the first patient inclusion.

Detailed instructions are provided in the MRI Technologist Manual and Operations Manual.

Confidential patient information such as patient full name must be omitted from the scan header, the compact-disc labels, and any accompanying documentation. MRI scans will be transferred to the MRI Reading Center in electronic format. The procedure for sending electronic data and accompanying documentation is specified in the MRI Technologist Manual.

The MRI reading center will perform QC of all images received. If a scan or sequence fails QC, it will need to be repeated. If the baseline scan fails QC, rescanning of the patient should be performed as soon as possible prior to baseline. In cases of failed QC at all other visits, the window for rescanning will be no longer than 2 weeks. Imaging should be reviewed, by the site, at the time of acquisition so that any sequences affected by obvious artifacts can be repeated immediately.

MRI scans are evaluated locally for any incidental pathology (ie, pathology unrelated to, or inconsistent with, the patient's known MS) according to locally determined procedures. If such pathology is found, the Treating Neurologist should be notified. The MRI reading center will evaluate the scans for the purposes of performing quantitative measurements and confirming Inclusion Criteria #2 (Lesions consistent with PPMS in either or both brain MRI and cervical spinal cord MRI). In order not to compromise blinding of the study, the MRI Reading Center will not report MRI findings back to the clinical site.

APPENDIX G. NEUROSTATUS

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

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 scoring

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

STUDY NAME

PERSONAL INFORMATION

Patient	
Date of Birth (04-Jun-1980)	– –
Centre Nr/Country	
Name of EDSS rater	
Date of Examination	– – 2 0

SYNOPSIS

1. Visual		Ambulation Score	
2. Brainstem			
3. Pyramidal		EDSS Step	
4. Cerebellar			
5. Sensory			
6. Bowel/Bladder		Signature	
7. Cerebral			

1. VISUAL (OPTIC) FUNCTIONS

OPTIC FUNCTIONS	OD	OS			
Visual acuity ☐ CC ☐ SC			Scotoma		
Visual fields			* Disc pallor		
			FUNCTIONAL SYSTEM SCORE	→	[1]

2. BRAINSTEM FUNCTIONS

CRANIAL NERVE EXAMINATION			
Extraocular movements (EOM) impairment		Hearing loss	
Nystagmus		Dysarthria	
Trigeminal damage		Dysphagia	
Facial weakness		Other cranial nerve functions	
		FUNCTIONAL SYSTEM SCORE	

3. PYRAMIDAL FUNCTIONS

REFLEXES	R	><	L			
Biceps				Knee extensors		
Triceps				Plantar flexion (foot/toes)		
Brachioradialis				Dorsiflexion (foot/toes)		
Knee				* Position test UE, pronation		
Ankle				* Position test UE, downward drift		
Plantar response				* Position test LE, sinking		
Cutaneous reflexes				* Able to lift only one leg at a time (grade in °)	°	°
* Palmomental reflex				* Walking on heels		
LIMB STRENGTH	R		L	* Walking on toes		
Deltoid				* Hopping on one foot		
Biceps				SPASTICITY		
Triceps				Arms		
Wrist/finger flexors				Legs		
Wrist/finger extensors				Gait		
Hip flexors				OVERALL MOTOR PERFORMANCE		
Knee flexors				FUNCTIONAL SYSTEM SCORE		

CC = corrected
SC = without correction
* = optional part of the examination
[1] = converted FS Score

4. CEREBELLAR FUNCTIONS

CEREBELLAR EXAMINATION	R	L			
Head tremor			Rapid alternating movements UE impairment		
Truncal ataxia			Rapid alternating movements LE impairment		
			Tandem walking		
Tremor/dysmetria UE			Gait ataxia		
Tremor/dysmetria LE			Romberg test		
			Other, e. g. rebound		
			FUNCTIONAL SYSTEM SCORE		

5. SENSORY FUNCTIONS

SENSORY EXAMINATION	R	L			
Superficial sensation UE			Position sense UE		
Superficial sensation trunk			Position sense LE		
Superficial sensation LE			* Lhermitte's sign		
Vibration sense UE			* Paraesthesiae UE		
Vibration sense LE			* Paraesthesiae trunk		
			* Paraesthesiae LE		
			FUNCTIONAL SYSTEM SCORE		

6. BOWEL/ BLADDER FUNCTIONS

Urinary hesitancy/retention		Bowel dysfunction	
Urinary urgency/incontinence		* Sexual dysfunction	
Bladder catheterisation		FUNCTIONAL SYSTEM SCORE	→ [1]

7. CEREBRAL FUNCTIONS

MENTAL STATUS EXAMINATION			
° Depression		Decrease in mentation	
° Euphoria		* Fatigue	
		FUNCTIONAL SYSTEM SCORE	

AMBULATION

Distance reported by patient (in meters)		Assistance	
Time reported by patient (in minutes)		Distance measured (in meters)	
		AMBULATION SCORE	

* = optional part of the examination
[1] = converted FS Score
° Depression and Euphoria are not taken into consideration for FS and EDSS calculation.
* 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.

UE = upper extremities
LE = lower extremities

Standardised Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale
Slightly modified from J.F. Kurtzke, Neurology 1983;33,1444-52

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

www.neurostatus.net

APPENDIX H. INSTRUCTIONS FOR THE TIMED 25-FOOT WALK

Description

The Timed 25-Foot Walk is a quantitative measure of lower extremity function. The patient is directed to 1 end of a clearly marked 25-Foot course and is instructed to walk 25 feet as quickly as possible, but safely. The task is immediately administered again by having the patient walk back the same distance. Patients may use assistive devices when doing this task.

Materials Needed

Stopwatch, clipboard, Timed 25-Foot Walk Record Form, marked 25-Foot distance in an unobstructed hallway, assistive device (if needed)

Time Limit Per Trial

3 minutes (180 seconds) per trial.

Discontinue Rules

If the patient cannot complete Trial 2 of the Timed Walk after a 5-minute rest period.

If the patient cannot complete a trial in 3 minutes.

Administration

Trial 1

Make sure that the stopwatch is set to 0:00. For the Timed 25-Foot Walk, the patient should be directed to 1 end of a clearly marked 25-Foot course (clearly defined on the floor or on the wall) and instructed to stand just behind the starting line. Point out where the 25-Foot course ends, then instruct the patient as follows: "*I'd like you to walk 25 feet as quickly as possible, but safely. Do not slow down until after you've passed the finish line. Ready? Go.*"

Begin timing when the lead foot is lifted and crosses the starting line. The examiner should walk along with the patient as s/he completes the task. Stop timing when the lead foot crosses the finish line. The examiner should then record the patient's walk time to within 0.1 second, rounding as needed. Round up to the next tenth if hundredth's place is > (greater than or equal to) .05, round down if hundredth's place is <.05 (eg, 32.45" would round to 32.5" but 32.44" would round to 32.4"). Once the time is recorded, be sure to reset the stopwatch.

Trial 2

After completing the first timed walk, position the patient just behind the line where s/he is not standing, repeat the same instructions, and have the patient complete the walk again.

Assistive Devices

The goal is to have the patient use the same assistive device at each study visit. The Treating Neurologist will select an assistive device at the beginning of the study for each patient that needs 1, keeping in mind that the patient may deteriorate modestly during the trial.

In general, patients should use their customary assistive device(s), NOT the least assistance possible to complete the test. For patients with significant gait impairment, the Treating Neurologist should have the patient use a rolling walker even if this is not the patient's customary

device. In general, non-wheeled walkers should not be used. If a patient does use an assistive device, this should be noted on the Record Form.

Completing the Record Form

Record any circumstances that you believe may have affected the patient's performance. These are factors that may have affected the trial but were not severe enough to necessitate repetition of the trial. Examples include, but are not limited to, the following:

- The patient had a cold or reports not feeling well.
- The patient tripped but did not fall.

If a situation arises that necessitates the repetition of a trial, indicate the reason a trial had to be repeated on the Record Form. Examples of reasons to repeat a trial include, but are not limited to, the following:

- The patient fell during the walk.
- Examiner forgot to start or stop stopwatch.
- Examiner forgot to reset stopwatch in between trials.
- The patient stopped to talk to someone while walking, or another person/thing somehow interfered with walk.

Record only the times for the 2 **successfully completed** trials of the Timed 25-Foot Walk. If the patient could not complete 1 or both of the trials of the Timed 25-Foot Walk, record this in the appropriate section of the Record Form. For example, if the patient's disease has progressed and/or physical limitations prohibit him or her from completing the trial, you should indicate "Unable to complete trial due to physical limitations" and record any specifics that you can observe (ie, patient in a wheelchair now and unable to walk, etc.). If the patient did not complete a trial for any other reason, specify this as well (eg, patient fell and was too fatigued to complete another trial, patient refused to complete trial).

APPENDIX I. INSTRUCTIONS FOR THE 9-HOLE PEG TEST

Description

The 9-HPT is a quantitative measure of upper extremity (arm and hand) function. The 9-HPT is the second component of the MSFC to be administered. Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand). It is important that the 9-HPT is administered on a solid table (not a rolling hospital bedside table) and that the 9-HPT apparatus be anchored.

Materials Needed

9-HPT Apparatus, Anchor, stopwatch, clipboard, 9-HPT Record Form

Time Limit per Trial

5 minutes (300 seconds) per trial

Discontinue Rules

1. If the subject cannot complete one trial of the 9-HPT in 5 minutes.
4. If the subject cannot complete a trial with his or her dominant hand within 5 minutes, move on to the trials with the non-dominant hand.
5. If the subject cannot complete a trial with his or her non-dominant hand, end the test.

Administration

Dominant Hand Trial 1

Make sure that the stopwatch is set to "0:00." Introduce this section by saying, "*Now, we're going to be measuring your arm and hand function.*" If this is the first visit, determine the dominant hand, ask, "*Are you right or left-handed*?" If the subject is not sure, then the dominant hand is determined by asking the subject which hand he/she did or does write with. Make a note of the dominant hand for subsequent instructions. Place the 9-HPT apparatus on the table, directly in front of the subject. Arrange the apparatus so that the side with the pegs is in front of the hand being tested and the side with the empty pegboard is in front of the hand not being tested. Secure with anchor.

Read the following instructions to the subject: "***On this test, I want you to pick up the pegs one at a time, using one hand only, and put them into the holes as quickly as you can in any order until all the holes are filled. Then, without pausing, remove the pegs one at a time and return them to the container as quickly as you can. We'll have you do this two (2) times with each hand. We'll start with your [DOMINANT] hand. You can hold the pegboard steady with your [NON-DOMINANT] hand. If a peg falls onto the table, please retrieve it and continue with the task. If a peg falls on the floor, keep working on the task and I will retrieve it for you. See how fast you can put all of the pegs in and take them out again. Are you ready? Begin.***"

Start timing as soon as the subject touches the first peg, and stop timing when the last peg hits the container. If a peg drops on the floor, the examiner may retrieve it and put it back in the peg box. However, if a peg drops onto the table, allow the subject to retrieve it.

Record the subject's time under "Dominant hand Trial 1." If the subject stops after having put all the pegs into the holes, prompt the subject to remove them as well by saying, "*And now remove them all*." If the subject begins to remove more than one peg at a time, correct him/her by saying, "*Pick up one peg at a time*."

Dominant Hand Trial 2

After the first trial with the dominant hand, say, "*Good. Now, I'd like you to do the same thing again, once again using your [DOMINANT] hand. See how fast you can put all of the pegs in and take them out again. Ready? Begin*." Again, start timing as soon as the subject touches the first peg, and stop timing when the last peg hits the container. Record the subject's time under "Dominant hand Trial 2."

Non-Dominant Hand Trials 1 and 2

After the second trial with the dominant hand, rotate the apparatus 180 degrees such that the side with the pegs is now in front of the non-dominant hand and the empty pegboard is in front of the dominant hand. Then say, "*OK. Now, I'd like you to switch and use your [NON-DOMINANT] hand. This time, you can use your [DOMINANT] hand to stabilize the pegboard. Ready? Begin*." Administer, time and record the two non-dominant hand trials following the procedures described above for dominant hand trials.

Completing the Record Form

Record any circumstances that you believe may have affected the subject's performance. These are factors that may have affected the trial but were not severe enough to necessitate repetition of the trial. Examples include, but are not limited to, the following:

- The subject dropped a peg.
- The subject has a cold.
- The subject forgot eyeglasses and had difficulty seeing pegs.
- The subject talked during the task.
- The subject knocked entire apparatus on the floor.

If a trial is repeated, indicate this and specify the reason it had to be repeated. Examples of reasons to repeat a trial include the following:

The subject knocked entire apparatus on the floor.

- The examiner forgot to start or stop stopwatch.
- The examiner forgot to reset the stopwatch in between trials.

Record only the times for the two **successfully completed trials** for each hand on the 9-HPT. If the subject could not complete one or both of the trials for either hand of the 9-HPT, record this in the appropriate section of the Record Form. If the subject's disease has progressed and/or physical limitations prohibit him or her from completing the trial, the examiner should mark, "Unable to complete trial due to physical limitations." and then record any specifics that can be observed (eg, subject unable to use right hand, subject could not complete within time limit, etc.). If the subject did not complete a trial for any other reason, describe the specific circumstances (eg, subject refused).

APPENDIX J. MODIFIED RANKIN SCALE

Table 11: Modified Rankin Scale Scores

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

APPENDIX K. 12-ITEM MULTIPLE SCLEROSIS WALKING SCALE (MSWS-12)

Version 1, 2000

MULTIPLE SCLEROSIS WALKING SCALE (MSWS-12)

- These questions ask about **limitations to your walking** due to MS **during the past two weeks**.
- For each statement, please circle the **one** number that best describes your degree of limitation.
- Please answer **all** questions even if some seem rather similar to others, or seem irrelevant to you.
- **If you cannot walk at all**, please tick this box. ☐

In the past two weeks, how much has your MS ...	Not at all	A little	Mod-erately	Quite a bit	Extreme-ly
1. Limited your ability to walk?	1	2	3	4	5
2. Limited your ability to run?	1	2	3	4	5
3. Limited your ability to climb up and down stairs?	1	2	3	4	5
4. Made standing when doing things more difficult?	1	2	3	4	5
5. Limited your balance when standing or walking?	1	2	3	4	5
6. Limited how far you are able to walk?	1	2	3	4	5
7. Increased the effort needed for you to walk?	1	2	3	4	5
8. Made it necessary for you to use support when walking indoors (e.g. holding on to furniture, using a stick, etc)?	1	2	3	4	5
9. Made it necessary for you to use support when walking outdoors (e.g. using a stick, a frame, etc)?	1	2	3	4	5
10. Slowed down your walking?	1	2	3	4	5
11. Affected how smoothly you walk?	1	2	3	4	5
12. Made you concentrate on your walking?	1	2	3	4	5

Please check that you have circled ONE number for EACH question

APPENDIX L. OCT ANCILLARY STUDY DESIGN AND METHODOLOGY

The patients participating in the OCT ancillary study will undergo scheduled OCT testing and ophthalmological examination at week 0 (up to 42 days prior to baseline), and follow-up OCT testing at weeks 48 and 96. Additional OCT and ophthalmological examinations may be performed in case of any AE concerning the patient's vision.

The assessments will be performed using the following methodology:

- Ophthalmological examinations at baseline will include slit lamp, impression tonometry, refractometry and funduscopy to identify retinal exclusion criteria to this ancillary study.
- Spectral domain OCT at week 0 (up to 42 days prior to baseline) and weeks 48 and 96 will be performed using a Spectralis® device (Heidelberg Engineering) assessing peripapillary RNFL, optic nerve head and macula.
- Confidentiality of study patients will be maintained and patients will be identified only by the study identification numbers.
- OCT results as well as ophthalmological parameters will be transferred directly to the OCT Reading Center via a designated web site. The OCT reading center will perform quality control (QC) of all results received. If a scan fails QC, it will need to be repeated.
- OCT facilities will undergo a qualification procedure, which will include the performance of a dummy run to ensure that the implementation of the specific OCT protocol technique in the facility's setting produces appropriate images for comparison with other centers and measurement of the endpoints specified in the protocol. For this purpose, after signing an EC approved informed consent form, 1 volunteer per site will undergo 2 consecutive OCT scans measurements on separate days prior to the first patient inclusion in the OCT ancillary study. OCT scans should be performed according to the manual using the software's follow-up function to ensure identical positioning on the follow up scan. Ophthalmologic examinations or visual testing are not necessary for these qualification scans. Qualification of sites will be formally indicated by a dummy run approval certification.
    - Detailed instructions are provided in the OCT operation manuals.

ANCILLARY STUDY ENDPOINTS

- Neuronal and axonal atrophy as defined by the change in thickness of the inner retinal layers (RNFL, ganglion cell layer, and inner plexiform layer) in macular volume scans and 12° peripapillary ring scans from baseline to weeks 48 and 96.
- Eyes with an acute optic neuritis during the study interval or with an ocular exclusion criterion will be excluded from analysis of the above endpoints.

ANCILLARY STUDY ADDITIONAL EXCLUSION CRITERIA

The following criteria lead to exclusion of affected eyes only. However, the patient can participate in the OCT ancillary study with a single eye, if it is unaffected.

1. Severe refraction anomaly defined as >4 diopters
2. Any history of eye surgery
3. Any history of confounding retinopathy (see Table 12)
4. Amblyopia

Table 12: Retinopathies and Other Ocular Diseases Leading to OCT Ancillary Study Exclusion of Affected Eyes

Summary	Diseases
Structural retinal pathology	Drusen, cysts, detachment, presence of myelinated axons, naevus, tumor, optic disc oedema, central serous chorioretinopathy, more than 4 diopters of myopia or hyperopia.
Vascular retinopathy	History of anterior ischemic optic neuropathy (AION) or posterior ischemic optic neuropathy (PION), cotton-wool spots, arteriovenous malformation of sinus cavernosus.
Immune retinopathy[a]	Neuromyelitis optica, systemic lupus erythematosus, uveitis, birdshot retinochoroiditis.
Infectious retinopathy[a]	Viral, bacterial, fungus, HIV, Lyme, secondary syphilis.
Hereditary retinopathy[a]	Leber's, dominant optic atrophy, albinism, cone dystrophy, retinitis pigmentosa.
Iatrogen retinal pathology	Retina surgery, photocoagulation, solar retinopathy, Purtscher's retinopathy, optic nerve sheet fenestration, brain surgery affecting the optic pathways.
Metabolic/toxic retinopathy[a]	Alcohol-, tobacco- and malnutrition-induced amblyopia, retinopathy induced by amiodarone, chloroquine, vigabatrin.
Other exclusion criteria[a]	Glaucoma, age dependent macular degeneration, acute posterior multifocal placoid pigment epitheliopathy, acute macular neuroretinopathy, history of optic neuritis in the last 6 months.

[a] Indicates conditions which are likely to affect both eyes and therefore lead to exclusion of the patient, even if 1 eye is considered unaffected

STATISTICAL METHODOLOGY

All statistical methodology will be specified in a separate SAP.