Clinical Study Protocol with Amendment 03
(including Statistical Analysis Plan)

A Multinational, Multicenter, Open-Label, Single-Assignment Extension of the MS-LAQ-301 (ALLEGRO) Study, to Evaluate the Long-Term Safety, Tolerability and Effect on Disease Course of Daily Oral Laquinimod 0.6 mg in Subjects with Relapsing Multiple Sclerosis

Study Number MS-LAQ-301E

NCT00988052

Protocol with Amendment 03 Approval Date: 25 February 2016

TEVA PHARMACEUTICAL INDUSTRIES LTD., ISRAEL

CLINICAL STUDY PROTOCOL

Study Title:	A Multinational, Multicenter, Open-Label, Single-Assignment Extension of the MS-LAQ-301 (ALLEGRO) Study, to Evaluate the Long-Term Safety, Tolerability and Effect on Disease Course of Daily Oral Laquinimod 0.6 mg in Subjects with Relapsing Multiple Sclerosis
Protocol No:	MS-LAQ-301E
EudraCT/IND No:	2009-012989-30 / 071287
Clinical Phase:	III Open-Label Extension Study
Protocol Version Date:	June 04, 2009
Global Amendment # 1	November 1, 2009
Global Amendment # 2	17 July 2014
Global Amendment # 3	25 February 2016
Principal Investigator(s):	[redacted] Italy
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Sponsor's Safety Officer

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Teva Pharmaceutical Industries, Ltd

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This clinical study will be conducted in accordance with the Sponsor's Standard Operating Procedures (SOPs), current Good Clinical Practice (GCP), the provisions of ICH (International Conference on Harmonization) Guidelines and EU Directives

PROTOCOL REVIEW & APPROVAL

PROTOCOL No. MS-LAQ-301E
ALLEGRO OPEN-LABEL EXTENSION STUDY
Protocol Version: June 04, 2009
Including Global Amendments No. 1, No. 2, and No. 3

Sponsor's Authorized Representative	Signature: [redacted]	Date: 25 FEB 2016
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Study Principal Investigator	Signature: [redacted]	Date: 25 FEB 2016
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1. SYNOPSIS

Protocol Number:	MS-LAQ-301E
Eudract/IND Numbers:	2009-012989-30 / 071287
Study Title:	A Multinational, Multicenter, Open-Label, Single-Assignment Extension of the MS-LAQ-301 (ALLEGRO) Study, to Evaluate the Long-Term Safety, Tolerability and Effect on Disease Course of Daily Oral Laquinimod 0.6 mg in Subjects with Relapsing Multiple Sclerosis
Number of Centers:	All centers that randomized subjects in the MS-LAQ-301 study
Clinical Phase:	III, open-label extension study
Study Duration:	Treatment phase: starting from completion of the MS-LAQ-301 study (Termination visit), as long as the Sponsor continues the development of laquinimod 0.6 mg for Relapsing Remitting Multiple Sclerosis (RMMS).
Study Population:	Subjects, who completed the Termination visit of the MS-LAQ-301 double-blind treatment phase according to the MS-LAQ-301 protocol, signed an informed consent form for the open-label extension study and met all eligibility criteria for this study.
Study Objective(s):	To make laquinimod 0.6 mg available to all subjects who completed the placebo-controlled MS-LAQ-301 study according to the protocol and to evaluate the long-term safety, tolerability and effect on disease course of daily oral laquinimod 0.6 mg in subjects with relapsing multiple sclerosis.
Study Design:	This is a multinational, multicenter, open-label, single-assignment extension of the MS-LAQ-301 study, to evaluate the long-term safety, tolerability and effect on disease course of daily oral laquinimod 0.6 mg in subjects with relapsing multiple sclerosis. Eligible subjects will be treated with laquinimod 0.6 mg capsules once daily. Subjects completing the full-duration of the double-blind MS-LAQ-301 study (completion of Termination visit) according to the MS-LAQ-301 protocol will be offered the opportunity to enter the MS-LAQ-301E study. In this open-label study, the subjects will be treated with laquinimod 0.6 mg (regardless of their initial treatment assignment during the MS-LAQ-301 study) as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS. Scheduled in-clinic visits will be conducted at Baseline (Month 0E) (the Termination visit of MS-LAQ-301 will serve as the baseline visit of MS-LAQ-301E) and at months 1E, 2E, 3E, 6E and every 6 months thereafter, until Termination/Early discontinuation. The following assessments will be performed at the specified time points: • Vital signs will be measured at each study visit. At month 0E [Baseline (Termination visit of the MS-LAQ-301 study)] vital signs will be measured also 30 and 60 minutes after the administration of the first dose of laquinimod 0.6 mg.

	• Weight will be measured at all visits until Termination/early discontinuation. • A physical examination will be performed at months 0E [Baseline (Termination visit of the MS-LAQ-301 study)], 6E, 12E and then every 12 months (every other scheduled visit) thereafter, until Termination/Early discontinuation visit. The following safety clinical laboratory tests will be performed: • Complete blood count (CBC) with differential – at all scheduled visits. • Serum chemistry (including electrolytes, liver enzymes, direct and total bilirubin, pancreatic amylase, creatine phosphokinase [CPK], and estimated glomerular filtration rate) – at all scheduled visits. • Hematology. • A urine dipstick beta human Chorionic Gonadotropin (β-hCG) test will be performed in women of child-bearing potential (at site) - at all scheduled visits. • Serum β-hCG in women of child-bearing potential - at all scheduled study visits. • Starting after visit Month 3E a urine dipstick β-hCG test will be performed at home in women of child-bearing potential every 28 (±2) days. The subject will be contacted by telephone within 72 hours after the test is scheduled to be performed and will be asked specific questions regarding the test. In any case of suspected pregnancy (positive urine β-hCG test result, delay of menstruation or any other reason suggesting pregnancy), the caller will make sure that the study drug has been discontinued and the subject will be instructed to arrive to the site as soon as possible with all study drugs. • Serum conventional high-sensitivity C-reactive protein (hs-CRP) and fibrinogen - at all scheduled visits. • In case of abnormal CPK result: troponin and CPK-MB will be tested. In case of CPK >2000 U/L urine myoglobin will be tested and the following tests will be repeated: CPK, CPK-MB, blood urea nitrogen, creatinine, electrolytes including potassium, calcium, phosphate, hs-CRP and fibrinogen • Lipase will be tested in case of abnormal pancreatic amylase results • The use of effective contraception will be ascertained at every visit. Starting from Visit Month 6E, all subjects will be regularly contacted by telephone every 3 months between the scheduled visits and asked a general question regarding their well-being (for women of child-bearing potential, there is no need to perform a separate call, as this question will be a part of the monthly pregnancy urine test call). Electrocardiogram (ECG), neurological evaluations, including Expanded Disability Status Scale (EDSS), 25 foot walk test/Ambulation Index (AI), Functional systems (FS), Multiple Sclerosis Functional Composite (MSFC),

	subject-reported fatigue as assessed by the Modified Fatigue Impact Scale (MFIS) and Binocular low-contrast visual acuity using the 100%, 2.5% and 1.25% contrast level charts [Sloan letter or Tumbling-E] will be performed at months 0E [Baseline (Termination visit of the MS-LAQ-301 study)], 6E and then at every scheduled study visit thereafter, until Termination/Early discontinuation visit. Adverse events (AEs) will be monitored throughout the study. Concomitant medications will be monitored throughout the study. Relapses will be confirmed/monitored throughout the study. The allowed treatment for a relapse will be intravenous methylprednisolone 1 g/day or oral steroids for up to 5 consecutive days. Magnetic Resonance Imaging (MRI) scan at Termination/Early discontinuation visit will be performed on subjects who participated in the MRI ancillary study only. Subjects who discontinue treatment for any reason will continue follow-up according to scheduled visits. <u>Ancillary studies:</u> MRI: Subjects who participated in the Frequent MRI ancillary study during the MS-LAQ-301 study will be offered to continue to undergo MRI scans during the open-label extension study. During the MS-LAQ-301E study, these scans will be performed at Months 0E [Baseline (This is the Termination scan of the MS-LAQ-301 study)] and then every 12 months thereafter, until Termination/Early discontinuation. Magnetization Transfer (MT): Subjects who participated in the MT ancillary study during the MS-LAQ-301 study will be offered to continue to undergo MT scans during the open-label extension study. During the MS-LAQ-301E study, these scans will be performed at Months 0E [Baseline (Termination visit of the MS-LAQ-301 study)] (this scan is a part of the MT ancillary study under the MS-LAQ-301 protocol) and then every 12 months thereafter until Termination/Early discontinuation. Magnetization Resonance Spectroscopy (MRS): Subjects who participated in the MRS ancillary study during the MS-LAQ-301 study will be offered to continue to undergo MRS scans during the open-label extension study. During the MS-LAQ-301E study, these scans will be performed at Months 0E [Baseline (Termination visit of the MS-LAQ-301 study)] (this scan is a part of the MRS ancillary study under the MS-LAQ-301 protocol) and then every 24 months thereafter, until Termination/Early discontinuation. For purposes of neurological/medical assessments, the study will be divided into 2 periods: **Period 1**: in which all subjects will continue to be evaluated by 2 distinct physicians - a Treating and an Examining Neurologists/ Physician (as in the MS-LAQ-301 study). **Period 2**: in which all subjects will be assessed by a single Study Physician/ Neurologist.

	All neurological/medical assessments may be performed by a single Study Physician/Neurologist since all the sites are now in Period 2 of the study. Female subjects of childbearing potential who might want to get pregnant in the future, and are interested in re-starting laquinimod treatment following delivery and cessation of breastfeeding may be able to re-enroll in the study after meeting inclusion/exclusion criteria. Re-enrollment will be permitted on a case-by-case basis. Notwithstanding, Teva is under no obligation to re-enroll such subjects and reserves the right to re-enroll or reject enrolment of such returning subjects for no reason and on its sole discretion. A new informed consent form should be signed before re-enrollment.
Number of Subjects:	A total of 1106 subjects were randomized to the MS-LAQ-301 study. A total of 839 subjects who completed the Termination visit of the MS-LAQ-301 study according to the MS-LAQ-301 protocol, signed an informed consent form for the open-label extension study, and met all eligibility criteria for this study enrolled to the MS-LAQ-301E study.
Inclusion/Exclusion Criteria:	<u>Inclusion Criteria:</u> 1. Subjects must have completed the Termination visit of MS-LAQ-301 (completion of all Termination visit activities) according to the MS-LAQ-301 protocol. 2. Women of child-bearing potential (for example women who are not postmenopausal or surgically sterilized) must practice two 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 in this open label extension phase include: intrauterine devices, barrier methods (condom or diaphragm with spermicide), and hormonal methods of birth control (e.g. oral contraceptive, contraceptive patch, and long-acting injectable contraceptive)]. 3. Subjects must be willing and able to comply with the protocol requirements for the duration of the study. 4. Subjects must be able to comprehend, sign and date a written informed consent prior to entering the MS-LAQ-301E study. <u>Exclusion Criteria:</u> 1. Premature discontinuation from the MS-LAQ-301 study, for any reason. 2. Pregnancy [according to urine dipstick β-hCG test performed at Baseline (Month 0E) visit] or breastfeeding. 3. Subjects with clinically significant or unstable medical or surgical condition detected or worsened during the MS-LAQ-301 study, which preclude safe participation and completion of the MS-LAQ-301E study. Acute exacerbation of MS will not exclude participation in the MS-LAQ-301E study. 4. Use of inhibitors of cytochrome P450 (CYP) 3A4 within 2 weeks prior to baseline visit (V0E, Month 0E).
Route and Dosage Form:	One capsule containing 0.6 mg laquinimod to be administered orally once daily.

Outcome Measures:	To assess the long-term safety and tolerability of daily oral laquinimod 0.6 mg in subjects with relapsing multiple sclerosis. Safety and Tolerability Outcome Measures: **Safety:** • AE • Vital signs • ECG findings • Clinical laboratory parameters **Tolerability:** • Proportion of subjects (%) who prematurely discontinued from the study, reason of discontinuation and the time to withdrawal. • Proportion of subjects (%) who prematurely discontinued from the study due to AEs and the time to withdrawal **Efficacy** To assess the long-term effect of laquinimod 0.6 mg on disease course, as assessed by several parameters: • Number of confirmed relapses • Progression of disability as measured by the EDSS score (including FS and AI) • Progression of disability as measured by the MSFC score • Binocular low-contrast visual acuity using the 100%, 2.5% and 1.25% contrast level charts [Sloan letter or Tumbling-E] • Subject-reported fatigue as assessed by the MFIS
Statistical Considerations:	An estimate of sample size is not applicable, since it is an active extension study. Summary statistics will be prepared for demographic, safety and efficacy variables.

2. LIST OF ABBREVIATIONS

9-HPT	9-Hole Peg Test
ACTH	Adrenocorticotrophic Hormone
ADME	Absorption/Distribution/Metabolism/Elimination
AE	Adverse Event
AI	Ambulation Index
AhR	Aryl Hydrocarbon Receptor
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (SGPT)
AST	Aspartate Aminotransferase (SGOT)
ARR	Annualized Relapse Rate
ASMA	Anti-Smooth Muscle Antibodies
AUC	Area Under the Concentration by Time Curve
BP	Blood Pressure
ß-hCG	Beta-human Chorionic Gonadotropin
CA	Competent Authority
CAB	Clinical Advisory Board
CBC	Complete Blood Count
CCSVI	Chronic Cerebrospinal Venous Insufficiency
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSF	Cerebrospinal Fluid
CSU	Clinical Supplies Unit
CT	Computed Tomography
CYP	Cytochome P450
DLC	Dioxin-like Compound
DLT	Digital Linear Tape
DM	Data Management
DMC	Data Monitoring Committee
EAE	Experimental Autoimmune Encephalomyelitis

EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
EU	European Union
FDA	Food and Drug Administration
FS	Functional Systems
FOV	Field of View
g	gram
GCP	Good Clinical Practice
Gd	Gadolinium
Gd-DTPA	Gadolinium-Gadopentetic Acid
GdE	Gadolinium Enhancing
GFR	Glomerular filtration rate
GGT	Gamma-Glutamyl Transpeptidase
GMP	Good Manufacturing Practice
HDL	High Density Lipoprotein
hs-CRP	High-sensitivity C-reactive Protein
I3C	Indole-3-Carbinol
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IFN-β	Interferon-beta
Ig	Immunoglobulin
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-To-Treat
IV	Intravenous
IVIG	Intravenous Immunoglobulin
IVRS/ IWRS	Interactive Voice Response System
kg	kilogram
L	Liter
LCM	Local Clinical Management
LDL	Low Density Lipoprotein
LKM	Liver Kidney Microsomal
LSO	Local Safety Officer

MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MFIS	Modified fatigue Impact Scale
mg	Milligram
ml	Milliliter
mm	Millimeter
MOA	Mechanism Of Action
MRI	Magnetic Resonance Imaging
MRI-AC	Magnetic Resonance Imaging Analysis Center
MRS	Magnetization Resonance Spectroscopy
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MT	Magnetization Transfer
MTR	Magnetization Transfer Ratio
NAA	N-Acetyl Aspartate
PASAT	Paced Auditory Serial Addition Task
PO	Per Os
QA	Quality Assurance
RDC	Remote Data Capture
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCDD	Tetrachloro-p-dibenzodioxin
T_{max}	Time to Maximal Plasma Drug Concentration
ULN	Upper Limit of the Normal Range
VOI	Volume of Interest
WBC	White Blood Cell (Count)

3. INTRODUCTION

3.1. Background

3.1.1. General

Multiple Sclerosis (MS) is a chronic, relapsing or progressive, inflammatory demyelinating disease of the central nervous system (CNS), which leads to disability of various degrees and has different progression rates in different patients. Its prevalence rate varies between races and geographical latitude. MS is a common disease, affecting approximately 2,500,000 subjects world-wide, the majority being in the temperate areas in Europe and North America. Women are affected 1.5-2 times more frequently than men (EMEA Guideline for MS 2006). There is, as yet, no cure. Treatment has been aimed at controlling symptoms and slowing progression of disease (Neuhaus et al 2003). Authorized disease-modifying drugs for Relapsing Remitting Multiple Sclerosis (RRMS) given by injection include interferon-beta (IFN-β) 1a (Avonex®[a], Rebif®[b]) or 1b (Betaseron®[c], Extavia®[d]), glatiramer acetate (Copaxone®[e]), mitoxantrone (Novantrone®[f]), natalizumab (Tysabri®[g]; for patients non-responsive to other medications), and alemtuzumab (Lemtrada®). Oral disease modifying treatments for RRMS include fingolimod (Gilenya®[h]), teriflunomide (Aubagio®[i]), and dimethyl fumarate (Tecfidera®[j]). Oral symptomatic treatment with dalfampridine (Ampyra®[k]) is approved for the improvement of walking in adult patients with MS with walking disability (Expanded Disability Status Scale [EDSS] 4.0-7.0).

3.1.2. Study Drug

The investigational medicinal product (IMP), laquinimod, also known by the laboratory code TV-5600 or ABR-215062 sodium salt, is a quinoline-3-carboxamide derivative. It is an oral formulation indicated for the treatment of RRMS.

Laquinimod has demonstrated efficacy in various types of experimental autoimmune encephalomyelitis (EAE) models, as well as in cuprizone induced demyelination, all accepted models of MS.

Laquinimod relates to a predecessor compound, roquinimex. It is the result of a structure activity-relationship screening program whose aim was to identify a new, pharmacologically modified substance active in MS animal models which, when compared to roquinimex, would

[a] Avonex is a registered trademark of Biogen Idec
[b] Rebif is a registered trademark of EMD Serono, Inc
[c] Betaseron is a registered trademark of Bayer
[d] Extavia is a registered trademark of Novartis Pharmaceuticals
[e] Copaxone® is a registered trademark of Teva Pharmaceutical Industries Ltd.
[f] Novantrone is a registered tradfemark of Serono Inc.
[g] Tysabri is a registered trademark of Biogen Idec.
[h] Gilenya is a registered trademark of Novartis Pharmaceuticals
[i] Aubagio is a registered trademark of Genzyme corporation
[j] Tecfidera is a registered trademark of Biogen Idec
[k] Ampyra is a registered trademark of Acorda therapeutics

have a superior safety profile. Roquinimex demonstrated clinical efficacy in MS in Phase 2 studies. However, serious cardiopulmonary toxicities (including myocardial infarction, pericarditis and pleuritis) occurring during Phase 3 studies led to early termination of these studies.

The precise mechanism of action (MOA) of laquinimod in MS is still under investigation. Available data support that laquinimod is an immunomodulator that acts in the periphery and within the CNS. The suggested mode of action of laquinimod includes modulation of peripheral inflammation and direct modulation of the CNS resident parenchymal cells, including down-regulation of the astrocytic pro-inflammatory response (a process known as astrogliosis). By these suggested protective mechanisms, laquinimod restricts peripheral inflammation as well as tissue damage and neurodegeneration in MS.

Laquinimod demonstrates a predictable and linear pharmacokinetics (PK) profile (see Section 3.3.1) 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).

3.2. Nonclinical Experience

3.2.1. Pharmacology

In models of MS (EAE and cuprizone), the 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 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.

3.2.2. 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 marked 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 Absorption/Distribution/Metabolism/Elimination (ADME)-PK program of laquinimod, please refer to the laquinimod Investigator's Brochure (IB).

3.2.3. 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 100- to 810-fold above the intended clinical dose of 0.6 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 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 (>99) above the intended clinical dose of 0.6 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 2006) 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 2014). 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 rat offspring exposed in utero to laquinimod at doses slightly higher than the clinical dose of 0.6 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 questionable. 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 28-fold the expected plasma exposure at intended clinical dose of 0.6 mg/day.

Based on the above, humans should not be exposed to laquinimod during pregnancy.

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 subjects, frequent and proactive monitoring of subjects and appropriate stopping rules. Furthermore, an independent data monitoring committee (DMC) is assigned to assess the data (see Section 20.2).

3.3. Clinical Experience

Detailed information concerning all clinical studies with laquinimod is presented in the IB.

3.3.1. 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 maximal 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. For additional information, 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 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.

3.3.2. 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 end-points (EDSS, cumulative gadolinium enhancing [GdE]) T_1 lesions and cumulative new T_2 lesions) were met (Table 1).

Table 1: ALLEGRO: Summary of Efficacy Results

End-Points	% 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 T_1 lesions	37% (0.0003)
Cumulative number of new T_2 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 magnetic resonance imaging (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

End-Points	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 T_1 lesions[c]	21.5% (0.07)	21.7% (0.062)	61.5% (<0.0001)	60% (<0.0001)
Cumulative number of new T_2 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[l]]. In addition, treatment with laquinimod demonstrated reduction in brain atrophy: ALLEGRO: 32.8% [p<0.0001], BRAVO[l]: 27.4% [p<0.0001]).

On 30 December 2015 the DMC for the LAQ-MS-305 (CONCERTO) and TV5600-CNS-20006 (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). Due to these events and the DMC recommendation to stop all laquinimod treatment arms above 0.6 mg in the MS trials, the 1.2 mg treatment arm in the CONCERTO 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 arms in the CONCERTO and ARPEGGIO studies will be continued while the sponsor closely monitors cardiovascular events in all laquinimod studies, such as this one. This is discussed further in Section 3.4.1.1.7.

3.4. Known and Potential Risks and Benefits to Human Subjects

3.4.1. 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 (WBC) count increased, platelets decreased) and elevation of blood C-reactive protein (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)

[l] 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

- 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.

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	
Common:	Anemia[a],
Very common:	Decreased platelets, Increased white blood cells
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, 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.

3.4.1.1. Details of Important Adverse Drug Reactions:

3.4.1.1.1. 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 two 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

The percentages listed in the table below refer to all patients with normal values at baseline. 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%)

ULN = Upper limit of normal range; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = Gamma-Glutamyl Transpeptidase ; IU/L = international units/L

3.4.1.1.2. 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.

3.4.1.1.3. Elevated Blood C-Reactive Protein Level

An increase in blood CRP level has not been found in clinical studies in subjects 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 both CRP and fibrinogen was slightly higher in the laquinimod group compared to placebo. An increase of CRP and fibrinogen was seen in the dose-escalating studies with higher doses than 0.6 mg.

3.4.1.1.4. Back and Neck Pain

Treatment with laquinimod has been associated with an increased incidence of back and neck pain. Back and neck pain 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.

3.4.1.1.5. 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.

3.4.1.1.6. 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 WBCs: Treatment with laquinimod has been associated with a generally mild increase of the total WBC count that was consistent across WBC subtypes, without clinical manifestations.

3.4.1.1.7. Cardiovascular Events (Laquinimod 1.2 and 1.5 mg)

On 30 December 2015, a DMC review of 8 unblinded cases from the LAQ-MS-305 (CONCERTO) and TV5600-CNS-20006 (ARPEGGIO) studies found an imbalance in serious

cardiovascular events in the high dose treatment arms in the study: 6 cases 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 infarct in a 31-year old man on the 1.2 mg treatment arm. In the ARPEGGIO study, 1 heart attack 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 the above, the 0.6 mg treatment arm will be continued in the CONCERTO and ARPEGGIO studies while the sponsor closely monitors cardiovascular events in all laquinimod studies, including the present study. Additional measures implemented in this protocol amendment include an additional emphasis on disallowed medications, medications and stopping rules for organ impairment (ie, factors which may increase laquinimod exposure), as well as regular evaluation and treatment management of major modifiable cardiovascular risk factors, and collection of unscheduled blood samples, eg, for clinical laboratory tests.

The DMC also recommend that study subjects continuing on laquinimod 0.6 mg be re-consented 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.

3.4.1.2. Potential Safety Issues with Laquinimod

3.4.1.2.1. 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 higher than the clinical dose of 0.6 mg/day in humans (Section 3.2.3). The relevance to humans of these findings is not known, but cannot be excluded.

Exposure to laquinimod during pregnancy must be avoided.

To prevent such exposure, women who are of childbearing potential (for example women who are not postmenopausal or surgically sterilized) must practice an acceptable method of birth control (Section Section 8.3.2.2) for 30 days before taking the study drug and two acceptable methods of birth control during all study duration and until 30 days after the last dose of study medication. Acceptable methods of birth control include: intrauterine devices, barrier method (condom or diaphragm with spermicide) and hormonal methods of birth control (eg, oral

contraceptive, contraceptive patch and 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. If pregnancy is suspected despite all recommended precautions (e.g., positive urine beta-human chorionic gonadotropin [β-hCG] test result, delay of menstruation or any other reason suggesting pregnancy), treatment should be discontinued immediately. The subject should be reminded of the potential risk to the fetus, and all options, including termination of pregnancy, should be discussed.

All subjects 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.

3.4.1.2.2. Cancer

The 2-year carcinogenicity studies in rats demonstrated an increase in uterine and oral cancers (see Section 3.2.3). It is the sponsor's position that 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 laquinimod 0.6 mg/day with an increased risk of cancer.

3.4.1.2.3. 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 10000 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.

4. STUDY OBJECTIVES

To make treatment with oral laquinimod 0.6 mg available to all subjects who participated in the double-blind, placebo-controlled MS-LAQ-301 study and who completed the Termination visit of this study according to the MS-LAQ-301 protocol as long as the Sponsor continues the development of laquinimod 0.6 mg for RMMS.

To assess the long-term safety and tolerability of laquinimod 0.6 mg once daily in subjects with relapsing MS.

To assess the long-term effects of laquinimod 0.6 mg on the disease course, as measured by clinical efficacy outcomes, which were evaluated in the double-blind treatment phase in this subject population.

4.1. Ancillary Studies

The following ancillary studies will be performed in a subset of subjects:

MRI: Subjects who participated in the Frequent MRI ancillary study during the MS-LAQ-301 study will be offered to continue to undergo MRI scans during the open-label extension study. During the MS-LAQ-301E study, these scans will be performed at Months 0E [Baseline (This is the Termination scan of the MS-LAQ-301 study)] and then every 12 months thereafter, until Termination/Early discontinuation.

Magnetization Transfer (MT): Subjects who participated in the MT ancillary study during the MS-LAQ-301 study will be offered to continue to undergo MT scans during the open-label extension study. During the MS-LAQ-301E study, these scans will be performed at Months 0E [Baseline (Termination visit of the MS-LAQ-301 study)] (this scan is a part of the MT ancillary study under the MS-LAQ-301 protocol) and then every 12 months thereafter until Termination/Early discontinuation.

Magnetic Resonance Spectroscopy (MRS): Subjects who participated in the MRS ancillary study during the MS-LAQ-301 study will be offered to continue to undergo MRS scans during the open-label extension study. During the MS-LAQ-301E study, these scans will be performed at Months 0E [Baseline (Termination visit of the MS-LAQ-301 study)] (this scan is a part of the MRS ancillary study under the MS-LAQ-301 protocol) and then every 24 months thereafter, until Termination/Early discontinuation.

5. STUDY DESIGN

5.1. Overview And Plan

This is a multinational, multicenter, open-label, single-assignment extension of the MS-LAQ-301 study, to evaluate the long-term safety, tolerability and effect on disease course of daily oral laquinimod 0.6 mg in subjects with relapsing MS.

Eligible subjects will be treated with laquinimod 0.6 mg capsules once daily.

Subjects completing the full duration of the double-blind MS-LAQ-301 study (completion of the Termination visit) according to the MS-LAQ-301 protocol will be offered the opportunity to enter into the open label extension MS-LAQ-301E study. In this open-label study they will be treated with laquinimod 0.6 mg once daily, regardless of their initial treatment assignment during the MS-LAQ-301 study.

Scheduled in-clinic visits will be conducted at Baseline (month 0E; the Termination visit of MS-LAQ-301 will serve as the baseline visit of MS-LAQ-301E) and at months 1E, 2E, 3E, 6E and every 6 months thereafter, as long as the Sponsor continues the development of laquinimod 0.6 mg for RMMS. At this time point, subjects will be invited to attend a Termination visit.

Subjects who discontinue treatment for any reason will continue follow-up according to scheduled visits.

5.1.1. Study Periods

As of the implementation of Protocol Amendment #2, the medical/neurological assessments of the subjects at each clinical site will no longer be performed differently since all the sites are now in study period 2.

Period 1:

In this period, either two separate Neurologists or two Physicians will continue to assess the subjects in the MS-LAQ-301E study (as in the MS-LAQ-301 study). An Examining Neurologist/Physician will assess the subject’s neurological status, unaware of subject’s well-being and a Treating Neurologist/Physician will decide whether a subject experienced a relapse and will treat the subject as needed.

In order to maintain reliable evaluation and reduce the potential for bias the following actions will be undertaken:

The Examining Neurologist/Physician will be the only one to evaluate the subject neurologically.

The Examining Neurologist/ Physician will have no access to the subject's file, including previous neurostatus forms, remote data capture (RDC) system and adverse events (AEs).

A decision as per treatment of a relapse will be under the sole responsibility of the Treating Neurologist/ Physician.

Period 2:

In this period, there will be no need for 2 separate physicians to assess the subjects in the MS-LAQ-301E study. Subjects participating in the MS-LAQ-301E study will be assessed by a single physician/Neurologist ("Study Physician/ Neurologist").

5.1.1.1. Revealing the MS-LAQ-301 Study Treatment Assignment during the Open-Label Study

The investigator may request the Sponsor to provide the original treatment allocation of the subject in the MS-LAQ-301 study. This will be possible only after transition to Period 2.

5.2. Rationale for Study Design, Dose and Population

The open-label extension MS-LAQ-301E study is designed to:

Provide laquinimod 0.6 mg once daily to all subjects who successfully complete the double-blind, placebo-controlled MS-LAQ-301 study as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS.

Provide information on laquinimod's long-term safety, tolerability and effect on disease course in this subject population.

The 0.6 mg daily dose was selected, since this was the dose used in the double-blind, placebo-controlled MS-LAQ-301 study.

6. STUDY POPULATION

One thousand, one hundred and six (1106) subjects were randomized to the MS-LAQ-301 study. All subjects who complete the Termination visit of the MS-LAQ-301 study (according to the MS-LAQ-301 protocol), meet the eligibility criteria and sign an informed consent form will be enrolled to the MS-LAQ-301E study.

6.1. Inclusion Criteria

Subjects must meet all inclusion criteria in order to be eligible for the study:

1. Subjects must have completed the Termination visit of MS-LAQ-301 (completion of all Termination visit activities) according to the MS-LAQ-301 protocol.

2. Women of child-bearing potential (for example women who are not postmenopausal or surgically sterilized) must practice two 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 in this open label extension phase include: intrauterine devices, barrier methods (condom or diaphragm with spermicide), and hormonal methods of birth control (e.g. oral contraceptive, contraceptive patch, and long-acting injectable contraceptive)].

3. Subjects must be willing and able to comply with the protocol requirements for the duration of the study.

4. Subjects must be able to comprehend, sign and date a written informed consent prior to entering the MS-LAQ-301E study.

6.2. Exclusion Criteria

Any of the following conditions will exclude the subject from entering the study:

1. Premature discontinuation from the MS-LAQ-301 study, for any reason.

2. Pregnancy [according to urine dipstick β-hCG test performed at Baseline (Month 0E) visit] or breastfeeding.

3. Subjects with clinically significant or unstable medical or surgical condition detected or worsened during the MS-LAQ-301 study, which preclude safe participation and completion of the MS-LAQ-301E study. Acute exacerbation of MS will not exclude participation in the MS-LAQ-301E study.

4. Use of inhibitors of CYP3A4 within 2 weeks prior to baseline visit (V0E, Month 0E).

Female subjects of childbearing potential who may want to get pregnant in the future, and are interested in re-starting laquinimod treatment following delivery and cessation of breastfeeding

may be able to re-enroll in the study after meeting inclusion/exclusion criteria in Appendix G. Re-enrollment will be permitted on a case-by-case basis. Notwithstanding, Teva is under no obligation to re-enroll such subjects and reserves the right to re-enroll or reject enrolment of such returning subjects for no reason and on its sole discretion. A new informed consent form should be signed before re-enrollment (Appendix G).

7. MEDICATIONS/THERAPIES – ALLOWED AND DISALLOWED

7.1. Allowed Concomitant Medications/Therapies

Symptomatic MS agents, such as anti-cholinergic and spasmolytic drugs, are permitted at clinically appropriate doses.

Short-term treatment with corticosteroids will be allowed during relapses. Allowed treatment for relapses is a fixed dose of intravenous (IV) methylprednisolone 1 g/day or oral steroids for a maximum of 5 consecutive days. No tapering off is allowed.

Other medications, excluding those mentioned in Section 7.2 may be given concomitantly as needed for the subject's welfare.

Topical and inhaled steroids are allowed at the discretion of the Study Physician/Neurologist for indications other than MS.

Administration of all medications, including indication, dose, frequency, and route of administration will be recorded in the source documentation file and in the electronic Case Report Form (eCRF).

Clinical studies have shown laquinimod 0.6 mg to be a strong inducer of CYP1A2. Subjects taking drugs that are metabolized by CYP1A2 (examples listed in Appendix F) 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 mg and 1.2 mg. These studies show that laquinimod at both doses is a weak inhibitor of CYP3A4. Subjects taking drugs that are metabolized by CYP3A4 (specifically those with a Narrow Therapeutic Index listed in Appendix F) should be advised that plasma levels of these drugs could increase when combined with laquinimod.

7.2. Disallowed Concomitant Medications During Study

- Natalizumab (Tysabri®)
- Fingolimod (Gilenya)
- IFN-β 1a or 1b
- Dimethyl fumarate (Tecfidera)
- Glatiramer Acetate (Copaxone®)

- Teriflunomide (Aubagio)
- Alemtuzumab (Lemtrada)
- Cladribine
- Rituximab
- Ocrelizumab
- Atacicept
- Belimumab
- Ofatumumab
- Inducers of CYP3A4 such as rifampin or carbamazepine (more examples are provided in Appendix E). Use of CYP3A4 inducers may results in reduced laquinimod plasma concentrations and reduced effectiveness
- Moderate/strong inhibitors of CYP3A4, for example, ketoconazole and erythromycin (as listed in Appendix E) are disallowed for 2 weeks prior to the baseline visit through to 30 days after the final dose of laquinimod. 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 (Novantrone®)
- Oral and parenteral steroids (except if given as defined by protocol for treatment of a relapse as specified in Section 7.1)
- Adrenocorticotrophic hormone (ACTH)
- Chemotherapeutic agents
- Cytotoxic agents
- Cyclophosphamide
- IV Immunoglobulin (Ig)
- Plasmapheresis
- Any other experimental agents
- Other Immunosuppressive or immunomodulating agents

8. STUDY CONDUCT

8.1. Study Period

The study assessments will be performed according to the summary of the Study Task Flow Sheet (see Table 5 – Study Task Flow Chart.)

A month in the treatment period is defined as 30 days ± 4 days.

The study, in which all eligible subjects will be treated with daily laquinimod 0.6 mg, will last as long as the Sponsor continues the development of laquinimod 0.6 mg for RMMS. Subjects who discontinue treatment for any reason will continue follow-up according to scheduled visits.

Table 5. Study Task Flow Chart for Extension Phase

Visit	V0E[a]	V1E	V2E	V3E	V4E	Every 6 months	Every 12 months	Every 24 months	Termination/ Early Discontinuation	Unscheduled Visit[b,c]
Month	**0E**	**1E**	**2E**	**3E**	**6E**					
Informed Consent	X									
Eligibility Criteria	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Cardiovascular risk factor assessment and management[d]							X	X		
First Dose at Site	X									
Physical Examination	X				X		X	X	X	X
Vital Signs	X[e]	X	X	X	X	X[f]	X[f]	X[f]	X[f]	X
ECG	X				X	X	X	X	X	X
Safety Laboratory Evaluation (CBC, Chemistry, GFR estimation, markers of inflammation)	X	X	X	X	X	X	X	X	X	X
Serum β-hCG[g]	X	X	X	X	X	X	X	X	X	X
Urine β-hCG[g] (on site)	X	X	X	X	X	X	X	X		X
Ascertaining use of effective contraception	X	X	X	X	X	X	X	X	X	X
Urine β-hCG[g] (self check, at home)					**EVERY 1 MONTH BETWEEN SCHEDULED VISITS**					
AE	X	X	X	X	X	X	X	X	X	X
Neurological examination (EDSS/FS/AI/ 25 foot walk)	X				X	X	X	X	X	X
Evaluation of Relapse[h]	X	X	X	X	X	X	X	X	X	X
MSFC[i]	X				X	X	X	X	X	
Binocular Low-Contrast Visual Acuity	X				X	X	X	X	X	
MFIS	X				X	X	X	X	X	
MRI (T_1, T_2) (Ancillary study, sub-group)	X						X	X	X[j]	
MT MRI (ancillary study, sub-group)	X						X	X	X[k]	
MRS (ancillary study, sub-group)	X							X	X[k]	
Mandatory phone calls (pregnancy tests)[l]					**EVERY 1 MONTH BETWEEN SCHEDULED VISITS**					

Visit	V0E[a]	V1E	V2E	V3E	V4E	Every 6 months	Every 12 months	Every 24 months	Termination/ Early Discontinuation	Unscheduled Visit[b,c]
Month	**0E**	**1E**	**2E**	**3E**	**6E**					
Mandatory phone calls (general well-being, all subjects)[m]						**EVERY 3 MONTHS BETWEEN SCHEDULED VISITS**				
Drug Compliance & Dispensing	X	X	X	X	X	X	X	X	X[n]	X
Termination Documentation and Notification of Early Termination									X	
Unscheduled Samples										X[o]

AE = adverse event, AI = ambulation index, β-hCG = beta-human chorionic gonadotropin, CBC = complete blood count, ECG = electrocardiogram, EDSS = Kurtzke's expanded disability status scale, FS = functional systems, GFR = glomerular filtration rate, MFIS = modified fatigue impact scale, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, MSFC = multiple sclerosis functional composite, MT = magnetization transfer

[a] The Termination visit of the MS-LAQ-301 study will serve as the Baseline visit of the MS-LAQ-301E study. Therefore, all activities, excluding Urine β-hCG (on site), informed consent, eligibility criteria and first dose at site are a part of the Termination visit of the MS-LAQ-301 study and therefore should not be repeated.

[b] Vital signs and AEs are mandatory activities in an unscheduled visit. All other activities are optional and may be performed as deemed necessary by the investigator. Chest X-ray may also be performed in this visit.

[c] Post treatment follow up visit in cases of early discontinuation (In which vital signs, review of AEs and concomitant medications, as well as pregnancy test are mandatory. All other marked activities are optional).

[d] In addition, an evaluation should take place as soon as possible for subjects already in the study, following approval of Amendment #3

[e] Post-dose vital signs will be measured at Baseline and after 30 and 60 minutes, whereas the pre-dose vital signs will be taken from the last measurement in the MS-LAQ-301 study.

[f] Weight will be measured at every visit until Termination/Early discontinuation.

[g] For women of childbearing potential

[h] Relapse evaluation will be performed in scheduled as well as unscheduled visits as deemed necessary by the Investigator/Coordinator

[i] The PASAT and 9-HPT will be performed at Months 0E [Baseline (Termination visit of the MS-LAQ-301 study)], 6E and every 6 months (every scheduled visit) thereafter, until Termination/early discontinuation visit. The Timed 25 Foot walk test will be performed each time neurological evaluation is performed.

[j] In case Termination visit of the study is scheduled to less than 14 days after the performance of a scheduled scan – the scan should not be repeated.

[k] In case Termination visit of the study is scheduled to less than 30 days after the performance of a scheduled scan – the scan should not be repeated.

[l] For women of child-bearing potential; to be performed within 72 hours of the scheduled home pregnancy test

[m] The call will be documented in the source documents. For women of child-bearing potential, there is no need to perform a separate call, as this question will be a part of the monthly pregnancy urine test call.

[n] Only drug retrieval

[o] 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.

Subjects who are discontinued from study treatment will be encouraged to continue all scheduled visits and procedures until completion of the study (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, and GFR estimation [including body weight measurement]).

8.2. Detailed Study Plan

8.2.1. Baseline Visit (Month 0E) (Visit 0E) (Termination Visit of the MS-LAQ-301 Study) Procedures:

After completion of all procedures of the Termination visit of the MS-LAQ-301 study according to the MS-LAQ-301 protocol, and placing a call to the interactive voice response system (IVRS) to notify the subject's completion of the MS-LAQ-301 study, the subject will be offered to participate in the MS-LAQ-301E study. The subject will be informed about all aspects of the study, including scheduled study visits and activities, and must sign and date the informed consent form. A copy of the informed consent form must be given to the subject. Eligibility for participation in the MS-LAQ-301E study will be established by the investigator.

The Baseline visit of the MS-LAQ-301E open-label extension study will occur at the Termination visit of the MS-LAQ-301 study. Therefore, many of the activities/assessments of the Termination visit of the MS-LAQ-301 study will serve as the Baseline visit (Month 0E) procedures of the MS-LAQ-301E study.

The following list includes all Baseline (Month 0E) activities. These activities were performed under the scope of the Termination visit of the MS-LAQ-301 study and therefore should not be repeated, unless otherwise specified.

- Vital signs (temperature, pulse, blood pressure [BP] and weight)
- Physical examination
- Complete neurological examination including functional system (FS), ambulation index (AI), 25 foot walk, EDSS
- MSFC
- Evaluation of a relapse
- Electrocardiogram (ECG)
- Review of concomitant medications.
- MRI: This activity is performed as a part of the Termination visit activities in the MS-LAQ-301 study in all subjects. This scan will serve as the Baseline (Month 0E) assessment in those subjects who participated in the frequent-MRI ancillary study in the MS-LAQ-301 study and signed a special informed consent form for this sub-study in the MS-LAQ-301E study and will include:
  - T_1-weighted, after administration of Gd-gadopentetic acid (Gd-DPTA)
  - T_2-weighted

  - 3D T_1-weighted

- MT: This activity is performed as a part of the Termination visit activities in the MS-LAQ-301 study subjects who took part in the MT ancillary study. This scan will serve as the Baseline (Month 0E) assessment in those subjects who participated in the MT ancillary study in the MS-LAQ-301 study and signed a special informed consent form for this sub-study in the MS-LAQ-301E study.

- MRS: This activity is performed as a part of the Termination visit activities in the MS-LAQ-301 study subjects who took part in the MRS ancillary study. This scan will serve as the Baseline (Month 0E) assessment in those subjects who participated in the MRS ancillary study in the MS-LAQ-301 study and signed a special informed consent form for this sub-study in the MS-LAQ-301E study

- AE recording

- Safety laboratory tests including:

  - Serum pregnancy test (β-hCG) for women of child-bearing potential. In case of positive result, the subject will not be eligible to participate in the extension and will be considered a screening failure for the extension phase.

  - Urinalysis

  - Hematology (Complete blood count [CBC], including differential)

  - Serum chemistry (including electrolytes, liver enzymes, direct and total bilirubin, pancreatic amylase and creatine phosphokinase [CPK]).

  - Markers of inflammation (serum conventional CRP and fibrinogen)

  - Subject-reported fatigue will be assessed by the Modified Fatigue Impact Scale (MFIS) (see Appendix H)

  - Binocular low-contrast visual acuity assessment, using 100%, 2.5% and 1.25% contrast charts [Sloan letter or Tumbling E (see Appendix J and Appendix K)].

New activities to be performed at Baseline visit (Month 0E, Visit 0E) (not part of the Termination visit) are:

- Subjects will be given all the necessary supplies and detailed instructions for administration of IMP, which will be reviewed with the subject during the visit. In addition, subjects will be instructed to contact the study center if any questions or problems arise.

- Urine pregnancy test (β-hCG) for all women of child-bearing potential. In case of positive result, the subject will not be eligible to participate in the study.

- For all subjects who are female of child-bearing potential:
  - The use of effective contraception will be ascertained at each study visit (should be recorded in the source documents).
  - Subjects will be instructed during each visit about the teratogenicity and potential delayed risks for a child exposed in uterus to laquinimod.
  - Subjects will be reminded about (should be recorded in the source documents) importance of stopping the study drug and informing the site in any case of suspected pregnancy (positive home urine test result, delay of menstruation or any other reason suggesting pregnancy).
- A call to the IVRS will be made to allocate a pack number for the open-label extension phase.
- First dose administration of the IMP.
- Post-dose vital signs (30 & 60 minutes, pulse and BP only) (pre-dose vital signs will be taken from the Termination visit vital signs measurement).
- AE recording will be performed upon any subjects' complaint following study drug administration (if relevant) or staff observation.
- Subjects will be instructed to contact the study site in the event of any change in their medical condition, the appearance of any AEs or any symptom suggestive of a relapse.

8.2.2. Scheduled Treatment Visits [Months 1E (Visits 1E) and Onwards]

Subjects will visit the study center at months 1E, 2E, 3E, 6E (visits 1E, 2E, 3E, 4E, respectively) and then every 6 months thereafter. Subjects who discontinue treatment for any reason will continue follow-up according to scheduled visits.

Following approval of Global Amendment #3, subjects continuing on laquinimod 0.6 mg will be re-consented with information about the cardiovascular risk seen in higher doses (see Section 3.4.1.1.7).

The following procedures and evaluations will be performed at each scheduled visit:

- Vital signs (temperature, pulse, BP).
- Review concomitant medications (ensuring no disallowed medication is being used)
- Record of AEs
- Evaluation of relapse

- Subject compliance (IMP accountability)
- Review instructions on IMP administration and dispensing
- Ascertaining use of effective contraception (should be recorded in the source documents).
- For all subjects who are female of child-bearing potential:
  - The use of effective contraception will be ascertained at each study visit (should be recorded in the source documents).
  - Subjects will be instructed during each visit about the teratogenicity and potential delayed risks for a child exposed in uterus to laquinimod.
  - Subjects will be reminded about (should be recorded in the source documents) importance of stopping the study drug and informing the site in any case of suspected pregnancy (positive home urine test result, delay of menstruation or any other reason suggesting pregnancy) and importance of performing the home pregnancy urine tests every one month (starting after visit Month 3E).
- 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 is available and pregnancy is either confirmed or excluded (see Appendix G). In case of suspected pregnancy, the rest of the visit activities should be performed as well.
  - Hematology (CBC with differential).
  - Serum chemistry (including electrolytes, liver enzymes, direct and total bilirubin, pancreatic amylase, CPK, and estimated GFR).
  - Markers of inflammation (serum conventional high-sensitivity C-reactive protein [hs-CRP] and fibrinogen).
- IVRS call to obtain pack number.

The following procedures and evaluations will be performed at Month 6E (visit 4E) and at all scheduled visits thereafter:

- Complete neurological examination including FS, EDSS, AI and Timed 25 Foot walk.

- MSFC.
- Binocular low-contrast visual acuity assessment, using 100%, 2.5% and 1.25% contrast charts [Sloan letter or Tumbling E (see Appendix J and Appendix K)].
- Subject-reported fatigue will be assessed by the MFIS.

In addition, the following procedures/assessment will be performed:

- Physical examination will be performed at months 6E (visit 4E), 12E (visit 5E) and then every 12 months thereafter (every other scheduled visit).
- ECG will be performed at month 6E (visit 4E) and at every scheduled visit thereafter.
- MRI Ancillary Study: The scan will be performed at Month 12E (Visit 5E) and every 12 months thereafter and will include:
  - T_1-weighted, after administration of Gd-DPTA.
  - T_2-weighted.
  - 3D T_1-weighted.
- MT Ancillary Study: The scan will be performed at Month 12E (Visit 5E) and every 12 months thereafter.
- MRS Ancillary Study: The scan will be performed at Month 24E (Visit 7E) and every 24 months thereafter.
- Weight will be measured at all visits.
- Evaluation and management of major modifiable cardiac risk factors (eg, diabetes, high blood pressure, hyperlipidemia, tobacco smoking) will be performed every 12 months, with referral to treatment and follow-up in a suitable clinic if needed. In addition, an evaluation should take place as soon as possible for subjects already in the study, following approval of Amendment #3.

Starting from Month 3E (Visit 3E), the following actions will be taken for female subjects of child-bearing potential:

- The subject will be provided with home pregnancy urine β-hCG test kits and will be guided how to perform the test. The site staff will schedule the home test to be performed every 28 ± 2 days.
- In order to verify whether the test has been performed and to record the result of the test (see Appendix G), a mandatory phone call will be performed by the Study Neurologist/ Physician 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 make sure that the study drug has been stopped and the subject will be instructed to arrive to the study site as soon as possible to return all study drugs.

Starting from Visit Month 6E, all subjects will be regularly contacted by telephone every 3 months between the scheduled visits and asked a general question regarding their well-being (for women of child-bearing potential, there is no need to perform a separate call, as this question will be a part of the monthly pregnancy urine test call). Performance of this call will be documented in the source documents.

The sequence of assessments performed during the visits should be as follows:

1. MFIS (when applicable)

2. The 9-Hole Peg (9-HPT) and paced auditory serial additional task (PASAT) components of the MSFC (Timed 25 Foot walk may be performed later) (when applicable)

3. The rest of the visit activities, as described above

8.2.3. Termination/ Early Discontinuation

The Termination visit date may be different in each country. Upon a decision of the Sponsor to stop the development of laquinimod 0.6 mg for RRMS patients, the local clinical trial management will notify the site teams when to invite the subjects to the site, in order to perform the Termination visit.

Subjects who have performed all Termination visit activities (in case the Sponsor decides to stop the development of laquinimod 0.6 mg for RMMS patients) will be regarded as completers.

Early discontinuation is defined as any withdrawal from the study prior to the completion of the treatment period. The treatment period is defined between Month 0E visit (Visit 0E, Baseline) (Termination visit of the MS-LAQ-301 study) (after administration of the first dose) and Termination visit, included. Subjects who are discontinued from study treatment will be encouraged to continue all scheduled visits and procedures until completion of the study (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, and GFR estimation [including body weight measurement]).

All reasons for discontinuation of therapy will be documented in the source documents as well as the eCRF comment form. Only one reason (the most severe) for early discontinuation should be recorded in the eCRF Termination form.

In the event that the study IMP was discontinued early, the following forms should be completed as close to the last dosing date as possible:

- Termination/ Early discontinuation visit form.

- Last visit that the subject attended.

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

- Vital signs (temperature, pulse, BP, weight).
- Physical examination.
- Safety laboratory tests:
  - Serum pregnancy test (β-hCG) for women of child-bearing potential
  - Hematology (CBC with differential)
  - Serum chemistry (including electrolytes, liver enzymes, direct and total bilirubin, pancreatic amylase, CPK, and estimated GFR)
  - Markers of inflammation (serum conventional hs-CRP and fibrinogen).
- ECG.
- Review concomitant medications. Note: 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.
- Record of AEs.
- If an AE is still ongoing, or a new AE is present at the termination visit, it will be followed until resolution or until it is considered stable or chronic and will be recorded in the subject's source documents and in the eCRF.
- Complete neurological examination including FS, AI, EDSS and Timed 25 Foot walk.
- MSFC.
- For all subjects who are female of child-bearing potential:
  - The use of effective contraception will be ascertained (should be recorded in the source documents) and they will be reminded to use two acceptable methods of contraception up to 30 days from the date of the last dose of the IMP.
  - Subjects will be instructed about the teratogenicity and potential delayed risks for a child exposed in uterus to laquinimod.
  - Female subjects of child-bearing potential will be reminded about (should be recorded in the source documents) importance of stopping the study drug and

informing the site in any case of suspected pregnancy (positive home urine test result, delay of menstruation or any other reason suggesting pregnancy)

- Binocular low-contrast visual acuity assessment, using 100%, 2.5%, and 1.25% contrast charts [Sloan letter or Tumbling E (see Appendix J and Appendix K)].
- Evaluation of relapse.
- MRI Ancillary Study: The scan will include:
  - T_1-weighted, after administration of Gd-DPTA
  - T_2-weighted
  - 3D T_1-weighted.

  If Termination visit is scheduled/performed less than 14 days after the performance of a scheduled MRI scan – the scan should not be repeated.
- MT Ancillary Study: An MT scan will be performed. If Termination/Early discontinuation visit is scheduled/performed less than 1 month after the performance of a scheduled MT scan – the scan should not be repeated.
- MRS Ancillary Study: An MRS scan will be performed. If Termination/Early discontinuation visit is scheduled/performed less than 1 month after the performance of a scheduled MRS scan – the scan should not be repeated.
- Subject-reported fatigue will be assessed by the MFIS (see Appendix H).
- Subject compliance (IMP accountability).
- IVRS call to report subject's termination/early discontinuation.

The sequence of assessments performed during the visit should be as follows:

1. MFIS
2. The 9-Hole Peg and PASAT components of the MSFC (Timed 25 Foot walk may be performed later)
3. The rest of the visit activities, as described above

8.3. Early Treatment Discontinuation

Subjects who are discontinued from study treatment will be encouraged to continue all scheduled visits and procedures until completion of the study (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, and GFR estimation [including body weight measurement]).

An early termination visit should be completed for all subjects who prematurely discontinue from the study and do not agree to or cannot continue all scheduled visits and procedures. It includes subjects who took at least one dose in the MS-LAQ-301E study.

Every attempt should be made to follow the early discontinued subjects. The subjects who prematurely discontinue the study should be treated by the investigator in a customary manner. In case of early discontinuation due to ongoing AE, manifestation of a severe degree of intolerance to IMP and/or ongoing MS relapse, the subject should remain under medical observation and followed until the medical condition returns to baseline or is considered stable or chronic.

8.3.1. Criteria for Early Treatment Discontinuation

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

1. Subject withdrew consent
2. Sponsor requested subject to be withdrawn (this does not include declaration of study termination by the Sponsor)
3. Request of primary care physician or investigator
4. Protocol violation/ Non-compliance
5. Lost to follow-up/failure to return
6. AE (specify primary AE in the AE log)
7. Pregnancy
8. Planned pregnancy
9. Lack of efficacy (according to the Investigator's decision)
10. Death

Any attempt should be made to clarify and to document the exact reason for discontinuation.

8.3.1.1. Post Early Discontinuation Follow-Up Visit

Note: This section specifically pertains to subjects that discontinue treatment early but do not agree to continue follow up.

In case of early discontinuation due to AE, the subject should be invited to attend an unscheduled visit, which will serve as a post-treatment follow-up visit. The post treatment follow-up visit should occur at 30 +/- 4 days from the last dose taken in the study.

Women of child-bearing potential should continue using contraception methods up to 30 days after the last study drug dose was taken.

Moderate and strong CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered.

The following procedures will be performed during this visit:

Mandatory procedures:

- Vital signs
- Review of concomitant medications
- Evaluation of AEs
- Pregnancy test (serum β-hCG test only; for women of child-bearing potential)

Optional procedures:

- Evaluation of a suspected relapse/follow-up
- ECG
- Physical examination
- Neurological examination
- Safety laboratory tests
- Chest X-ray

8.3.2. Safety Stopping Rules

8.3.2.1. Liver Enzymes

In any increase of ALT or AST to ≥ 2 times ULN the "Guidance on Safety Monitoring" (see Appendix G) should be thoroughly followed.

In the following circumstances, study drug will be discontinued **immediately** and liver enzymes will be monitored until normalization or stabilization of the abnormality, according to the Guidance in Appendix G:

- Any increase in ALT or AST to ≥3 times ULN, combined with International Normalized Ratio (INR) >1.5 or total bilirubin >2xULN.
- Any increase in ALT or AST to ≥3 times ULN, which is accompanied by nausea, vomiting, fever, rash, or eosinophilia.

- Any increase in ALT or AST to levels ≥5 but <8 times ULN, which is persistent for ≥2 weeks of repeated measurements.

- Any increase in ALT or AST to levels ≥8 times ULN.

- In any case where monitoring of liver enzymes cannot be performed according to the protocol guidance (see Appendix G).

8.3.2.2. Pregnancy

To further emphasize the importance of use of effective contraception and avoidance of pregnancy under laquinimod exposure (see Section 3.4), and to reduce as much as possible the exposure to laquinimod if a pregnancy occurs despite all recommended measures, all subjects 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 subjects will also be counseled about the importance of using effective contraception 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 (positive home urine test result, delay of menstruation or any other reason suggesting pregnancy).

To strengthen the preventative measures, the measures for pregnancy prevention now include a requirement for two contraception methods (as recommended by the DMC), and a requirement for using a contraception method 30 days prior to enrollment. Furthermore, a serum β-hCG test prior to enrollment and additional follow up measures and clarifications are added. These subjects will also be counseled about the importance of stopping treatment immediately if pregnancy is suspected (positive home urine test result, delay of menstruation or any other reason suggesting pregnancy).

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).

The subjects' 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, monthly pregnancy tests (urine dipstick and/or serum pregnancy β-hCG test, as applicable per the relevant time point) will be performed (except for where subjects have discontinued study drug but are continuing to attend study visits for follow-up).

All pregnancies of women participating in study and 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 Local Safety Officer (LSO)/CRO with the pregnancy form.

The process for reporting a pregnancy is the same as that for reporting a serious adverse event (SAE see Section 11).

Any woman who becomes pregnant during the study will discontinue treatment. Subjects 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 AE or SAE, as appropriate.

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

- For a spontaneous abortion, report as a SAE.
- For an elective abortion due to developmental anomalies, report as a SAE.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form.

8.3.2.3. Cancer

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

8.3.2.4. Liver Impairment

To avoid exposures to higher levels of laquinimod (see Section 3.3.1), a stopping rule related to liver impairment has been introduced. Subjects who develop any chronic liver disease associated with hepatic function impairment while participating in the study should stop study medication.

8.3.2.5. Renal Impairment

To avoid exposures to higher levels of laquinimod (see Section 3.3.1), a stopping rule related to renal impairment has been introduced. Subjects who develop renal disease associated with moderate or severe functional impairment, defined as glomerular filtration rate (GFR) $\leq$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 $\leq$60 mL/min/1.73 m^2), the subject should stop study medication permanently.

8.3.3. Replacement of Withdrawn Subjects

Not applicable.

8.3.4. Temporary Discontinuation of Study Drug Treatment

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

The reasons for temporary IMP/study drug discontinuation should be recorded in the appropriate section of the IMP/study drug dispensing and return form in the eCRF and the local clinical management (LCM) should be notified.

The subject will report any temporary discontinuation to the investigator and will be instructed by the investigator regarding continuation of treatment.

8.3.5. Unscheduled Visit

An unscheduled visit may be performed at any time during the study at the subject'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:

- Appearance of a new AE or an AE follow-up
- Change in concomitant medications
- Possible relapse
- Relapse follow-up
- Laboratory follow-up
- Post early-discontinuation follow-up visit (see Section 8.3.1)
- IMP dispensing, accountability and/or replacement
- Subject compliance
- Other (should be specified)

Should the visit be related to a relapse, this will be clearly indicated on the eCRF and the Study Neurologist/Physician will carry out a complete neurological evaluation (FS/AI/EDSS/ Timed 25 Foot walk).

Additional analyses may be performed by the investigator and stated in the source documentation.

Mandatory Unscheduled Visit Procedures

- Vital signs
- Evaluation of AEs

Optional Unscheduled Visit Procedures

- Evaluation of a suspected relapse/follow-up
- ECG
- Physical examination
- Neurological examination
- Safety laboratory tests (including estimation of GFR)
- In case of drug dispensing/replacement call IVRS to obtain a pack number
- IMP accountability
- Subject compliance
- Review of concomitant medications
- For all subjects who are female of child-bearing potential:
  - Serum or urine β-hCG test may be performed
  - The use of effective contraception will be ascertained (should be recorded in the source documents) and they will be reminded to use two acceptable methods of contraception up to 30 days from the date of the last dose of the IMP.
  - Subjects will be instructed about the teratogenicity and potential delayed risks for a child exposed in uterus to laquinimod.
  - Female subjects of child-bearing potential will be reminded about (should be recorded in the source documents) importance of stopping the study drug and informing the site in any case of suspected pregnancy (positive home urine test result, delay of menstruation or any other reason suggesting pregnancy) and importance of performing the home pregnancy urine tests every one month (starting after visit Month 3E).

8.3.5.1. Unscheduled Samples

According to the judgment of the investigator or medical monitor, the following unscheduled samples may be collected to assist with further investigations of cardiovascular events or other clinical event of interest:

- urgent safety laboratory test panel (see Section 10.2.3.1)
- pharmacokinetic blood sample

- sample for potential biomarker analysis

8.3.5.1.1. Unscheduled Pharmacokinetic Samples

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.

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

8.3.5.1.2. Unscheduled Biomarker Samples

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.

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) RNA analysis; 3) proteomic profile; and/or 4) other relevant biomarkers.

Details of sample collection and processing are provided in the Laboratory Manual. Since new biomarker techniques continue to be developed, the method and laboratory that will be recommended cannot be anticipated.

8.3.6. Visits during Relapses (Scheduled and Unscheduled)

Subjects will be instructed to contact their study site within 48 hours should any symptoms suggestive of a relapse occur (see Appendix B).

The Study Physician/ Neurologist, will evaluate the subject within 7 days of symptoms onset, conditional upon a symptomatic period of ≥ 48 hours.

The relapse assessment will be documented in the source documents and in the eCRF accordingly. A complete neurological assessment, including FS, AI, EDSS and Timed 25 Foot walk, will be performed by the Study Neurologist/Physician.

The decision as to whether the neurological change is considered a relapse will be made by the Study Neurologist/Physician, based on the criteria listed in Appendix B].

Corticosteroids therapy (as described in Section 7.1) may be given for a confirmed relapse at the discretion of the Study Neurologist/Physician and must be recorded in the source documents and eCRF.

8.3.6.1. Relapse Follow-up:

Upon a confirmed relapse, subject's neurological condition must be followed up closely within scheduled or unscheduled visits. The stabilization of a relapse date/ approximate date should be indicated in the source document and the eCRF.

Every attempt should be made to document the resolution of relapses.

At all the follow up visits for a confirmed relapse a full neurological examination (EDSS including FS and AI and 25 foot walk) must be performed. This should be done at a visit that is close to stabilization or no later than 2 weeks after stabilization date.

9. INVESTIGATIONAL MEDICINAL PRODUCTS/STUDY DRUGS

9.1. Treatment Administered

All subjects will be administered one capsule of laquinimod 0.6 mg to be taken orally at the same hour every day.

Capsules should be swallowed with a glass of water.

Subjects are allowed to omit study drug up to 3 consecutive days.

9.2. Method of Assigning Subjects Numbers

The same randomization number which was used to identify a certain subject in the MS-LAQ-301 study will serve this purpose in the MS-LAQ-301E study as well. At baseline (month 0E, visit 0E) (Termination visit of the MS-LAQ-301 study), the investigator will enter the subject's number (the same as was used in the MS-LAQ-301 study) to the IVRS in order to dispense the study drug.

The IVRS will keep track of subjects' visits and status.

9.3. Description of Investigational Medicinal Product/Study Drug

Laquinimod 0.6 mg capsules are manufactured in compliance with current Good Manufacturing Practice (GMP) standards and guidelines applicable to IMPs by Teva Pharmaceutical Industries Ltd. Israel. Laquinimod 0.6 mg capsules are white opaque cap and body; hard gelatin capsules filled with white to off-white granulate.

9.4. Packaging and Labeling

The study drug is packaged in round 50 cc white high density polyethylene bottles containing 35 capsules. The bottles are capped with child-resistant polypropylene caps, each equipped with a silica desiccant insert.

The primary packaging is performed under the responsibility of the Clinical Manufacturing Unit of Teva Pharmaceutical Industries Ltd. The secondary packaging and labeling for subjects is performed under the responsibility of the Clinical Supplies Unit (CSU) of Teva Pharmaceutical Industries Ltd, according to European Union (EU) regulations and International Conference on Harmonisation (ICH) guidelines as adopted by the Food and Drug Administration (FDA) – Good Clinical Practice (GCP) (E6).

Each bottle will be identified by a unique bottle number.

The label on the bottles will include a fixed information section (to include the product name, storage conditions, instructions etc.) and variable information section. The variable information

section will include 3 parts: One detachable part, which will be attached to the subject's file upon bottle dispensing, one part to remain on the bottle and the third may be used according to local needs (pharmacy, prescription, etc). The variable information section will include the following variable data: batch number, bottle number, and expiration date (all to be pre-printed) and blank fields for the dispensing investigator's name, visit number and subject number. These blank fields will be manually filled-in by the Investigator upon provision of bottle to the subject.

9.5. Distribution and Shipment

Distribution and shipment of IMPs will be performed by a Contract Research Organization (CRO), according to the distribution guidelines.

The IMP bottles will be packed and shipped at room temperature (15-25^{o}C/59-77^{o}F) in appropriate storage boxes. If the IMP supplies appear to be damaged/missing upon arrival at the investigational site, the Sponsor should be contacted immediately.

Each shipment of IMPs supplies for the study will contain a shipment form describing the content of shipment. This form will assist in maintaining current and accurate inventory records. When a shipment is received, the site investigator/ site coordinator/pharmacist will acknowledge receipt of the IMP supply by making "Confirm Shipment" call (via the IVRS/IWRS).

When a shipment is received in a depot, acknowledgement of receipt of the IMP supply will be received by the CSU.

Importing of the IMP by an EU member will be carried out according to the provisions of Directive 2001/20/EC, Article 13.

9.6. Storage, Dispensing and Return

IMP supplies will be kept in a secure, limited-access, temperature-controlled storage area.

Only authorized personnel will have access to the IMP. The study site personnel at each site will be responsible for correct storage and handling of the IMP.

All IMP bottles must be stored at room temperature (15-25^{o}C/59-77^{o}F).

Apart of Termination visit, the IMP bottles will be dispensed to the subject at the study site at each study visit starting at baseline visit (Month 0E; Termination visit of the MS-LAQ-301 study). The bottles will be assigned to subjects by using an IVRS/IWRS. After assigning a bottle number to the subject, the site personnel should fill in the subject's number, the visit number and the dispensing investigator's name on the label of the dispensed bottle as well as on the detachable parts that would be attached to the subject's file.

At each visit from baseline (Month 0E; Termination visit of the MS-LAQ-301 study) to Month 3E visit the subject will receive 1 bottle of IMP (baseline, Month 1E and Month 2E). At visit month 3 the subject will receive 3 bottles of IMP. From visit month 6 onward the subject will

receive 6 IMP bottles according to visit duration, an amount that will suffice until the following scheduled dispensing visit.

Subjects will be instructed to return all used empty bottles and unused IMP at each visit. The Site Investigator/site coordinator is responsible for performing IMP accountability at the site. The Monitor is responsible for the accountability of the returned IMPs.

9.7. Verification of Compliance With Treatment Regimen

At each study visit the investigator /site coordinator will assess the subject's compliance with the prescribed regimen for the study medication. This will include checks of protocol compliance and use of study drug in order to assess the reliability of subject-generated data. Subjects who fail to comply with the study requirements may be withdrawn from the study, following consultation with the Sponsor.

Compliance with the dosing regimen will be determined by performing IMP accountability of returned bottles of the used and unused IMP. The number of used and unused capsules will be recorded on the eCRF by site personnel. Percent compliance will be calculated as the number of used capsules divided by the number of total capsules expected to be used, multiplied by 100. Subjects with less than 75% overall compliance during the entire study will be considered non-compliant.

9.8. Accountability and Compliance

IMP accountability records must be maintained at the site at all times.

Upon Teva's (or Teva's designee) monitor visit at the site, accountability of the returned IMPs should be performed and recorded by the monitor. The subject number, the date, batch code, bottle number and quantity of IMP returned by the subject will be checked for correctness and recorded via the IVRS or on the appropriate accountability forms, to be provided by the CSU.

During the study, all IMPs (used and unused bottles) and the corresponding accountability forms (if applicable) must be returned by the monitor to the Sponsor or Sponsor's designee (CRO) on an on-going basis for reconciliation and destruction. A photocopy of these records must be kept at the study sites.

10. ASSESSMENT METHODS

10.1. Efficacy Assessment Methods

10.1.1. On-Study Relapse Evaluation & Determination

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

The Study Physician/Neurologist will evaluate the subject once any symptom suggestive of a relapse occurs.

In case of a suggestive relapse during a scheduled or unscheduled visit:

- The evaluation of symptoms as well as the neurological evaluations/EDSS will be made by the Study Physician/Neurologist.
- Based on the assessment of symptoms and the EDSS/FS evaluation, the Study Physician/Neurologist will decide whether a subject experienced a relapse and will treat the subject as needed.

In any case, the neurological evaluation of the subject by the Study Physician/Neurologist will be performed within 7 days of symptoms onset, conditional upon a symptomatic period of ≥ 48 hours.

In the case of an ongoing or just-started relapse at the study termination/early discontinuation visit, subjects will be followed up until relapse stabilization (see Section 8.3.6.1).

10.1.2. Neurological Evaluations

A complete neurological assessment will be performed at Months 0E [Baseline (Termination visit of the MS-LAQ-301 study)], 6E and every 6 months thereafter until termination/early discontinuation of the study. At each of the study Periods, every effort should be made to ensure that the same Neurologist/Physician performs the neurological assessment at all visits for a particular subject.

FS and EDSS will be assessed based on a slightly modified neurological examination (Neurostatus: L. Kappos, Dept. of Neurology, University Hospital, CH-4031/Basel. Version 12/05). The results will be recorded on standardized and validated examination forms (see Appendix C) as well as in the eCRF.

Mental Functional System Score 1b (due to mild fatigue) will contribute to the EDSS score while mental Functional System Score 1a will not contribute to the EDSS score**.**

10.1.3. MSFC

The MS Functional Composite consists of 3 clinical examinations, the results of which are combined using z-scores. The three clinical examinations include the PASAT, Timed 25 Foot walk and 9-HPT.

The PASAT and 9-HPT will be performed at Months 0E [Baseline (Termination visit of the MS-LAQ-301 study)], 6E and every 6 months (every scheduled visit) thereafter, until Termination/early discontinuation visit.

The Timed 25 Foot walk test will be performed each time neurological evaluation is performed.

Appendix I presents the instructions for administering the MSFC.

10.1.4. Modified Fatigue Impact Scale (MFIS)

Subject-reported fatigue will be assessed by the MFIS at months 0E [Baseline (Termination visit of the MS-LAQ-301 study)], 6E and every 6 months (every scheduled visit) thereafter, until Termination/early discontinuation visit.

The MFIS is a validated specific subject-reported outcome measure that was developed to evaluate the impact of fatigue on the lives of people with MS. The instrument will be self-administrated during the visit and consists of total score and 3 subscales to assess the impact of fatigue on:

1. Cognitive function (10 items)
2. Physical function (10 items)
3. Psychosocial function (20 items)

The subject is asked to circle the appropriate response on a Likert scale: 0 – no problem; 1 – small problem; 2 - moderate problem; 3 – big problem; 4 – extreme problem. The MFIS takes approximately 10 minutes to complete and has good internal consistency as measured by Cronbach's alpha (0.98 for full sample analysis of the entire questionnaire and >0.87 for all subscale items by group) and has been shown to be able to discriminate between different subject populations as well as between groups with different severity levels in MS (see Appendix G).

10.1.5. Binocular Low- Contrast Visual Acuity

It has been demonstrated that low-contrast visual acuity, as measured using the Sloan Charts has a substantial capacity to capture visual dysfunction in subjects with MS.

The low-contrast visual acuity will be assessed binocularly at Months 0E [Baseline (Termination visit of the MS-LAQ-301 study)], 6E and every 6 months (every scheduled visit) thereafter, until Termination/early discontinuation visit, along with the MSFC assessments. 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 subject's usual distance correction. In case the subject is not familiar with the English/Roman alphabet, the Tumbling E charts will be used.

Appendix J and Appendix K present the instructions for administering the binocular low-contrast visual acuity test.

10.1.6. Ancillary Studies

10.1.6.1. MRI Ancillary Study:

The scan will be performed only for those subjects who participated in the frequent MRI ancillary study (in the MS-LAQ-301 study) and signed a separate informed consent form at Baseline visit (Termination visit of the MS-LAQ-301 study) of the MS-LAQ-301E study. The scan will be performed at Month 0E [Baseline; **this is the same scan as the Termination scan of the MS-LAQ-301 study** (there is no need to repeat it) and should be performed prior to the first dose administration in the MS-LAQ-301E study] and every 12 months thereafter and will include:

- T_1-weighted, after administration of Gd-DPTA
- T_2-weighted
- 3D T_1-weighted

MRI scans can be performed within ±4 days of the scheduled visits except for Termination/early discontinuation visit where the MRI should be performed within 4 days prior to the visit day.

Steroid treatment for relapse (see Section 7.1) will not affect the schedule of this optional MRI scan. Where possible, the scan should be performed prior to steroid treatment.

All MRI data will be interpreted by the MRI analysis center (MRI-AC).

For the MRI Protocol, see Appendix D.

10.1.6.2. MT Ancillary Study:

MT Ancillary Study: In contrast to conventional MRI techniques, which acquire their signal from the free water protons, MT contrast is based on the saturation of the macromolecular protons and the subsequent exchange of magnetization into the free proton pool. This study provides values that strongly correlate with axonal integrity in MS lesions (for protocol see Appendix D). The scan will be performed only for those subjects who participated in the MT ancillary study in the MS-LAQ-301 study and signed a separate informed consent form at Baseline visit of the MS-LAQ-301E study (Termination visit of the MS-LAQ-301 study).

The scan will be performed again at Months 12E and every 12 months thereafter. MT scans can be performed within ±4 days of the scheduled visits except for Month 0E (which is the Termination of the MS-LAQ-301 study) and Termination/early discontinuation visit where the scan should be performed within 4 days prior to the visit day.

10.1.6.3. MRS Ancillary Study:

Magnetic resonance spectroscopy (MRS) provides an *in vivo* method for characterization of tissue metabolites, including N-acetyl aspartate (NAA), choline-containing compounds, creatinine plus phosphocreatine, lactate and inositol in localized areas of the brain. NAA is present in high concentration in neurons and oligodendrocyte-type 2 astrocyte (O-2A) progenitors but absent in other cells (NAA is undetectable in mature oligodendrocytes). Decreased levels of NAA may therefore be used as marker for axonal loss (for protocol see Appendix D). The scan will be performed only for those subjects who participated in the MRS ancillary study in the MS-LAQ-301 study and signed a separate informed consent form at Baseline visit of the MS-LAQ-301E study (Termination visit of the MS-LAQ-301 study).

The scan will be performed again at Months 24E and every 24 months thereafter. MRS scans can be performed within ±4 days of the scheduled visits except for Month 0E (which is the Termination of the MS-LAQ-301 study) and Termination/early discontinuation visit where the scan should be performed within 4 days prior to the visit day.

10.2. Safety Parameters

10.2.1. Adverse Events

AEs will be recorded from when a subject has signed the Informed Consent Form and throughout the study, including the follow-up period. They should be reviewed and updated at each subsequent visit and during any phone contact with the subject.

10.2.1.1. 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.

10.2.2. Abdominal Computed Tomography Scan

In case of pancreatitis or suspected pancreatitis, an abdominal computed tomography (CT) scan should be performed as soon as possible in order to clarify the diagnosis and enable assessment of severity of this condition. An MRI may be performed as an alternative to the CT scan.

10.2.3. Safety Laboratory Evaluations

Unless specified otherwise all laboratory testing will be performed by a central laboratory facility.

In cases in which close follow-up is required, as described in Section 8.3.2 and Safety Monitoring Guidance, Appendix G, certain tests may be performed in a local laboratory.

Laboratory tests (including pregnancy test for women of child-bearing potential) will be performed at each scheduled study visit (in unscheduled visit upon need).

The following tests will be performed:

* Those tests may also be performed in a local lab according to the Safety Monitoring Guideline.

Serum Chemistry

- Glucose
- Creatinine (including estimation of GFR)
- Bilirubin (direct and total)*
- Urea
- AST (SGOT)*
- ALT (SGPT)*
- GGT*
- Total Protein*
- Albumin*
- hs-CRP
- CPK
  - In case of abnormal CPK result: troponin and CPK-MB will be tested
  - In case of CPK > 2000 U/L urine myoglobin will be tested and the following tests will be repeated: CPK, CPK-MB, blood urea nitrogen, creatinine, electrolytes including potassium, calcium, phosphate, hs-CRP and fibrinogen
- Alkaline Phosphatase (ALP)*
- Pancreatic Amylase
- Lipase will be tested in case of abnormal pancreatic amylase results (see Appendix G for guidance on monitoring subjects with elevated pancreatic amylase levels)

Electrolytes

- Sodium
- Potassium
- Calcium
- Phosphorous

Coagulation

- Fibrinogen
- INR (to be performed in local laboratory, only if required according to Safety Monitoring Guidance, Appendix G)

Pregnancy tests

- Serum β-hCG pregnancy tests (to be performed in women of child-bearing potential, at all scheduled study visits)
- Urine β-hCG pregnancy test (to be performed in women of child-bearing potential), at all scheduled study visits (excluding Termination) and every 28 ± 2 days, at home, starting from visit Month 3E.

Pregnancy tests do not need to be performed for women who have discontinued study treatment but are continuing to attend scheduled study visits for follow-up.

Hematology

- Hemoglobin.
- Mean Corpuscular Hemoglobin (MCH)
- Mean Corpuscular Volume (MCV)
- Mean Corpuscular Hemoglobin Concentration (MCHC)
- Hematocrit
- Red Blood Cells count (RBC)
- WBC count + differential*
- Platelet count

Serology (to be performed only for a confirmed abnormality of liver enzymes, according to Appendix G):

- Anti-Hepatitis A IgM antibodies
- Hepatitis B Surface antigen
- Anti-Hepatitis B Core IgM antibodies
- Anti- Hepatitis C IgG antibodies
- Anti-nuclear antibodies

- Anti-Smooth Muscle antibodies (ASMA)
- Anti-Liver-Kidney Microsomal (LKM)-1 antibodies

10.2.3.1. 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 (and others, if required) will be performed on these samples:

- serum chemistry panel, including fibrinogen and hs-CRP
- hematology panel
- CPK-MB
- troponin I

10.2.4. Vital Signs and Weight

Vital signs (temperature, pulse and BP) will be completed at all scheduled and unscheduled visits.

BP and pulse will be recorded in a sitting position after resting for 5 minutes.

All measurements and time of measurements will be recorded in the source documents.

Body weight will be measured at all visits until Termination/early discontinuation, and as long as the subject continues study drug treatment.

10.2.5. ECG

ECG will be performed at months 0E [Baseline (Termination visit of the MS-LAQ-301 study)] and every 6 months thereafter, until Termination/Early discontinuation visit.

The subject should rest for at least 10 minutes before measurement is taken. Twelve-lead ECG should be performed following the subject being in a supine position for 5 minutes.

The interpretation of the ECG will be made only locally, by the investigator, and the clinical evaluation remains under the investigator's/ local cardiologist responsibility. Therefore, the investigator/local cardiologist will be responsible to determine whether ECG findings are of clinical significance.

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.

The investigator's interpretation of the ECG will be recorded in the eCRF.

10.2.6. Physical Examination

Physical examination will be performed at months 0E [Baseline (Termination visit of the MS-LAQ-301 study)], 6E, 12E and then every 12 months thereafter, until Termination/early discontinuation visit.

Any finding on physical examination (whether a new condition or worsening of a pre-existing condition) should be recorded as an AE.

10.2.7. 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 3.3.1). Consequently, GFR will be estimated at all visits to monitor renal function in the study in order to identify subjects with potentially impaired laquinimod clearance. Subjects 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 subject should stop study medication permanently (see Section 8.3.2.5).

Following recent findings connecting Gd-based contrast agents and nephrogenic systemic sclerosis, GFR value should be evaluated prior to performing an MRI scan, where administration of Gd-based contrast agent is planned. The central laboratory will provide the GFR value prior to the scheduled MRI tests. In case GFR estimation is not provided by the central laboratory, calculation should be done at the site, prior to any MRI scan via the following web calculator:

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

In case GFR is ≤60 mL/min, the MRI scan should be performed without contrast (Gd) and further evaluation of renal impairment is required (refer to Section 8.3.2.5)

10.2.8. 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. In addition, an evaluation should take place as soon as possible for subjects already in the study, following approval of Amendment #3.

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

11. SAFETY AND PHARMACOVIGILANCE

Adverse Event

An AE is defined as any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with the treatment.

In the study, any event occurring after the clinical trial subject has signed the study Informed Consent should be recorded and reported as an AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

A new condition or the worsening of a pre-existing condition will be considered an AE. Stable chronic conditions such as arthritis that is present prior to study entry and do not worsen during the study will not be considered AEs.

Worsening of the disease under study will be measured by MS relapse or by EDSS parameters, and should only be recorded as an AE if the outcome is more serious than would normally be expected from the normal course of the disease in a particular subject.

An abnormal result of diagnostic procedures including abnormal laboratory findings will be considered an AE if it:

- Results in subject's withdrawal by the investigator
- Is associated with a SAE
- Is associated with clinical signs or symptoms
- Is considered by the physician to be of clinical significance

The intensity or severity of the AE will be characterized as:

- Mild: AE which is easily tolerated
- Moderate: AE sufficiently discomforting to interfere with daily activity.
- Severe: AE which prevents normal daily activities.

Unlabeled/ Unexpected AE - A reaction which is not included in the Adverse Reaction section of the relevant Reference Safety Information by its **specificity, severity, outcome or frequency. The safety reference of this study is the IB.**

The relationship of an AE to the study drug is characterized as:

TERM	DEFINITION	CLARIFICATION
No Reasonable Possibility	This category applies to those adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those adverse events, which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	An adverse event may be considered as "No Reasonable Possibility" if it is clearly due to extraneous causes or when (must have two): It does not follow a reasonable temporal sequence from the administration of the test drug. It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. 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	This category applies to those 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 or felt with a high degree of certainty to be related to the test drug.	An adverse event may be considered as "Reasonable Possibility" if or when (at least two of the following): It follows a reasonable temporal sequence from administration of the drug. It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject. 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.

The date of onset, a description of the AE, severity, seriousness, action taken, relationship to the study drug, outcome of the event and date of resolution will be recorded.

Serious Adverse Event

An SAE is defined as an AE that results in any of the following:

- death
- life-threatening
- requires hospitalization or prolongs existing inpatients' hospitalization
- results in persistent or significant disability or incapacity
- results in a congenital abnormality or birth defect
- an important medical event which requires medical intervention to prevent any of the above outcomes.

Important medical events are those which may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. 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; resulting in an AE will normally be considered serious by this criterion.

Inpatient **hospitalization** or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event. It does not refer to pre-planned elective hospital admission for treatment of a pre-existing condition that has not significantly worsened, or to diagnostic procedure. It does not refer either to hospitalization for iv steroid treatment of a relapse, unless it is a worsening of condition beyond expected disease progression (as described below).

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

Any new SAE that occurs after the study period and is considered to be related (reasonable possibility) to the IMP or study participation should be recorded and reported immediately. The study period for the purpose of SAE reporting is defined as the period from the subject's signature on the informed consent form until the end of the follow-up period (30 days following the last dose).

SAE Reporting

In order to satisfy regulatory requirements, any SAE, whether deemed IMP-related or not, must be reported to the CRO as soon as possible after the investigator or coordinator has become aware of its occurrence. The SAE form completion and reporting must not be delayed even if all of the information is not available at the time of the initial contact.

The SAE should be submitted within 24 hours of becoming aware of the event to the CRO. The CRO will forward the report to the appropriate Pharmacovigilance unit at Teva or the LSO who will forward the SAE report to the appropriate Pharmacovigilance unit at Teva:

SAE originated in Europe and rest of the world should be sent to:

Global Drug Safety and Pharmacovigilance Unit (Israel)

[redacted]

SAE originated in USA will be sent to:

Teva USA clinical safety mailbox

[redacted]

SAE originated in Canada will be sent to:

Teva Canada clinical safety mailbox

[redacted]

SAE originated in Germany will be sent to:

Teva Germany safety mailbox

[redacted]

Only in the event of difficulty transmitting the form via email send the form to fax, or contact the sponsor's study personnel identified above for further instruction.

Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the site within 24 hours of the information becoming available to the CRO.

For both initial and follow-up SAE reports the CRO forwards this information to the appropriate Pharmacovigilance unit at Teva or the LSO who forwards it to the appropriate Pharmacovigilance unit at Teva within 48 hours. The Pharmacovigilance units at Teva will submit a summary of the clinical course of the SAEs back to the CRO/LSO for local submission to the regulatory authorities (competent authorities [CA]) and Ethics Committee (EC)/Institutional Review Boards (IRBs) and investigators according to regulations.

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

1. Investigator Name and Center Number
2. Subject Number
3. Clinical Event
    a. description
    b. date of onset
    c. severity
    d. treatment
    e. relationship to study drug (causality)
    f. action taken regarding study drug
4. If the AE results in Death

a. cause of death (whether or not the death was related to study drug)

a. autopsy findings (if available)

5. Medical History case report form (CRF) (copy)
6. Concomitant Medication CRF (copy)
7. Any relevant reports (laboratory, discharge, X-ray, etc)

This information should be sent to the LCM/LSO who will forward the information to the appropriate Pharmacovigilance Centre at Teva.

In the EU the procedures for notification of suspected unexpected serious adverse reactions (SUSARs) shall be carried out in accordance with EU Directives. SAEs should be reported by the Sponsor to EC/IRB according to local requirements.

In non-EU countries, SAEs should be reported by the site to their local EC/IRB as dictated by their board's policies and procedures.

Subjects who have had an SAE during the treatment period must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Any newly emergent SAEs after treatment is discontinued or the subject has completed the study and is considered to be related to the IMP or study participation should be recorded and reported immediately. The post-study period for the purpose of SAE reporting is routinely for up to 30 days following last visit of the study or until SAE is resolved or stabilized. In certain cases, such as where the drug has a long half-life, a longer follow-up period may be required.

Pregnancy reports: Pregnancies should be reported throughout the study. This includes also normal pregnancies without AE. The pregnancy should be followed up 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. The pregnancies reporting procedure should be the same as the SAE reporting procedure.

Pregnancy follow-up should be recorded on a specific CRF provided by CRO.

12. STATISTICAL METHODOLOGY

A total of up to 1106 subjects, who were enrolled in study MS-LAQ-301 are expected to be recruited into this study.

The statistical analyses of this study will be exploratory in nature. Continuous variables will be presented by descriptive statistics (mean, standard deviation, minimum, median and maximum values), by treatment group. For categorical variables, treatment group counts and percentage from total subject population will be tabulated.

12.1. Sample Size Rationale

Subjects that completed the full double-blind treatment period of protocol MS-LAQ-301 will be eligible for inclusion in this trial. MS-LAQ-301 subjects have no obligation to enter this study, therefore the number of subjects in this study is not determined, but is expected to be less than 1106 subjects.

12.2. Randomization Procedure

As this is an open label single arm study, no randomization procedure is applied.

12.3. Subjects Analysis Sets

A single analysis set is defined for this clinical trial. This analysis set is:

Intent-to-treat analysis set (ITT): Consists of all subjects who have been enrolled to the study and received at least one dose of IMP. In accordance with the ITT principle, all subjects randomized will be kept in their originally assigned treatment group.

12.4. Definition of baseline values

The last observed values from study MS-LAQ-301 will serve as the baseline values for this study.

12.5. Efficacy Assessment

The statistical analyses of this study will be exploratory in nature. Continuous variables will be presented by descriptive statistics (mean, standard deviation, minimum, median and maximum values), for the whole study population, as well as by original treatment group in study MS-LAQ-301. For categorical variables, counts and percentage from total subject population will be tabulated, as well as counts and percentages by original treatment group in study MS-LAQ-301.

12.6. Safety And Tolerability Assessments

12.6.1. Data presentation

All data summary tables will be presented for the whole study population, as well as by original treatment group in study MS-LAQ-301.

12.6.2. Adverse Events

The incidence and frequency of AEs will be presented by System Organ Class and preferred terminology according to Medical Dictionary for Regulatory Activities (MedDRA) dictionary. AEs will also be presented by System Organ Class, High Level Term and preferred terminology.

Data will be tabulated by gender, maximal severity, maximal outcome and maximal relationship to the tested drug.

SAEs and seriousness criteria will be listed, tabulated and discussed on a case by case basis as well.

12.6.3. Laboratory Data

Laboratory quantitative parameters will be summarized and presented by using descriptive statistics.

All laboratory values recorded during the study will be individually listed and flagged for values outside reference ranges and potential clinical significance.

12.6.4. ECG

Distribution of Subjects by Investigators ECG Interpretation will be presented.

The ECG interpretation of the investigators will be individually listed.

12.6.5. Vital Signs

Vital signs parameters will be summarized and presented by using descriptive statistics.

Incidence of measurements of potential clinical significance will be provided.

Vital signs parameters recorded during the study will be individually listed and flagged for potential clinical significance values.

12.6.6. Drug Tolerability & Drop-Out Assessment

The number and percentage of subjects who failed to complete the study will be provided.

The number and percentage of subjects who prematurely discontinued from the study due to AEs will be provided.

13. REGULATORY AND ETHICAL ISSUES

13.1. Compliance with Regulations Applicable to Clinical Trials

The study will be conducted according to the laws, regulations and administrative provisions relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use, as applicable by national legislation and EU Directives and US 21 CFR Part 11, 50, 54, 56, 312.

13.2. Informed Consent

The principles of Informed Consent, according to the Declaration of Helsinki and its updates, ICH guidelines on GCP, 21 CFR part 50 of the FDA regulations and/or EU Directives, will be followed. A subject should not enter a clinical study until he/she has been properly informed, has been given time to contemplate participation, and has freely given his/her consent by signing and dating the EC/IRB approved informed consent form. This must be done prior to performing any study related procedures.

The proposed consent form and any other documents relevant to the consent process must be submitted to the EC/IRB, together with the protocol, and must be approved prior to study start.

A copy of the fully signed and dated Informed Consent Form and any other documents relevant to the consent process will be given to the subject and the original will be maintained at the site.

Subjects continuing on laquinimod 0.6 mg will be re-consented with information about the cardiovascular risk seen in higher doses (see Section 3.4.1.1.7).

13.3. Subject Confidentiality

All subject data will be identified by a subject identification number.

After obtaining subject's consent, the investigator will permit the study monitor, independent auditor or regulatory agency personnel to review that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical history to verify eligibility, laboratory tests results, admission/discharge summaries for hospital admissions occurring while the subject is on study and autopsy reports for deaths occurring during the study (if applicable).

13.4. Ethics Committee (EC) / Institutional Review Board (IRB)

The study must have unconditional approval in writing, by an appropriate EC/IRB. A copy of the Letter of Approval from the EC/IRB, which contains the list of the documents approved, must be received by Teva/CRO prior to site initiation.

Any amendments to the protocol or subsequent changes to the informed consent form as a result of changes to the protocol and/or IB that is approved by Teva, must also be approved by the EC/IRB and documentation of this approval provided to Teva. Records of the EC/IRB review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to the Sponsor's audit and/or regulatory authority inspection, during or after completion of the study.

SAEs must also be reported to the EC/IRB by the investigator or the Sponsor.

Periodic status reports must be submitted to the EC/IRB as required, as well as notification of completion of the study and a final report where applicable. A copy of all reports submitted to the EC/IRB must be sent to the Sponsor.

13.5. Protocol Amendments

Changes to the protocol should only be made by an approved protocol amendment. Protocol amendments must be approved by the Regulatory/CAs (if applicable), Central EC/IRB (if applicable) and/or each respective site's EC/IRB (if applicable), prior to implementation.

For clinical trial sites located in EU Member States, the procedures outlined in Directive 2001/20/EC, Article 10(a), are applicable.

13.6. Declaration of the End of the Clinical Trial

For clinical trial sites located in EU, a declaration of the end of the clinical trial will be made according to the procedures outlined in Directive 2001/20/EC, Article 10(c).

For those countries outside EU local regulations will be followed.

13.7. Liability And Insurance

A Certificate of Clinical Trials Insurance will be provided to the study centers by Teva Pharmaceutical Industries, Ltd, where required.

14. DOCUMENTATION

14.1. Study File and Site Documents

Prior to the initiation of the study, the following items must be received by the Sponsor from the site:

1. Confidential Disclosure Agreement
2. Signed protocol, and amendment(s) page(s)
3. The Principal Investigator's curriculum vitae and where required current medical license.
4. Signed Clinical Study Agreement
5. Competent/Regulatory Authority written approval (if applicable)
6. EC/IRB written approval for the protocol, amendment(s), Informed Consent Form, Subject Information Sheet (if applicable), advertisements (if applicable)
7. EC/IRB Membership list or an official statement from the EC/IRB stating the EC/IRB is in compliance with 21 CFR part 56 and/or EU Directive on GCP.
8. Hospital Management written opinion (if applicable)
9. Financial Disclosure Form (FDA Form 1572 in US)
10. Data protection form
11. Local laboratory certification and normal ranges (if applicable).

14.2. Study Documents Supplied by the Sponsor

The Sponsor will supply the investigator with the following items:

- Current version of the IB.
- CRF or a hard copy of the eCRF in PDF format (Master CRF)
- Subjects study binder, including 'source pages' to be used during the study if hospital clinic records are not to be used (if applicable)
- User manual for RDC®
- Regulatory Binder

- Country Model Informed Consent Form
- Central Laboratory Certification and Normal Ranges
- Insurance Certificate
- Operations Manual

14.3. Maintenance and Retention of Records

It is the responsibility of the investigator to maintain a comprehensive and centralized filing system of all relevant documentation.

Investigators will be instructed to retain all study records required by Teva and regulatory authorities in a secure and safe facility with limited access for one of the following time periods based on notification from Teva

A period of at least two years from last marketing authorization and notification from Sponsor

Or a period of at least two years after discontinuation of clinical development of the investigational product as confirmed by Teva

Or longer if required by local regulations.

The investigator will be instructed to consult with Teva before disposal of any study records and to provide written notification to Teva of any change in the location, disposition, or custody of the study files.

14.4. Data Handling

14.4.1. Data Collection via Remote Data Capture (RDC)

14.4.1.1. Data Collection

The site teams should be trained to use the RDC® system. In any case of change in study teams, appropriate training will be given.

Teva will provide each study site with one hard copy of the reference template for data collection tools (Master CRF).

Data will be entered at the site by the Site Investigator, Study Coordinator, the Site Coordinator or other appropriately designated and trained study personnel, using the validated Oracle Clinical RDC® application, which provides a framework for entering clinical data on a CRF. The Oracle Clinical RDC® application is integrated with the Teva clinical data management (DM) validated system, conforms to 21 CFR part 11 requirements.

The eCRFs are used to record study data and are an integral part of the study and subsequent reports. Therefore, the CRFs must be completed for each enrolled subject, according to the subject's source data on a per-visit basis.

Subjects should not be identified by name. Appropriately coded identification must be used. The Site Investigator must keep a separate log of subject names, non-identifiable initials (if applicable) and addresses (i.e., Subject Identification Log).

Each entered CRF must be approved by the Site Investigator on a per-visit basis and verified against the subject's source documents by the Clinical Research Associate (CRA)/monitor. Each entry will be monitored by the CRAs and the DM personnel. Once all the CRFs for a subject have been approved, verified, reviewed and cleaned, the subject's CRFs will be locked. Site Investigators, Site Coordinators, CRAs, DM personnel, Medical Monitors and quality assurance (QA) personnel will be trained by authorized Teva staff on the use of the RDC® application before receiving authorization to use the application. The assignment of user privileges will be according to the following user roles:

- Site Coordinator: data entry
- Study Coordinator: data entry and updating, discrepancy handling
- Site Investigator: data entry and updating, discrepancy handling and CRF approval
- CRA: discrepancy handling and CRF verification
- Medical Monitor: discrepancy handling.
- DM: data updating, discrepancy handling, data locking
- QA: read only for data audit
- Read Only: browsing of data only

14.4.1.2. Discrepancy Handling

The internal consistency and data integrity of the study database are defined by a validated set of rules. A deviation from this set of pre-defined computerized rules creates a database discrepancy which can be handled using the RDC® application data management facility. Any modification in these rules requires re-validation according to departmental Standard Operating Procedures (SOPs).

There are 2 main types of discrepancies:

Automatic discrepancies are generated automatically during data entry or following execution of logical checks.

Manual discrepancies can be generated by a system user any time.

Note that the RDC® application discrepancy management facility is fully supported by an accepted regulatory audit trail of procedures and logs.

14.4.1.3. Data Correction

Data correction can also be performed using the validated RDC® application update facility. For each instance of data modification, the system requires the reason and justification for change. The system keeps a full audit trail of the data values, date and time of modification, and the electronic signature of the user who performed the change.

14.4.1.4. Data Extract

The Oracle Clinical® system stores the data in generic tables. The data is extracted from Oracle Clinical® to SAS® on a per data collection module basis. Each extracted file contains all the visits of the corresponding form. The data is extracted on a scheduled basis for data management and data analysis purposes.

14.4.1.5. Source Documents

Prescription forms, label logs, laboratory test results and ECG strips/interpretations, as well as all other source documents should be maintained and kept at the study site in the subject study binder.

14.4.1.6. Electronic CRF

At the end of the study, the Sponsor will supply the site investigator a copy of the site's subject electronic CRF in PDF format.

14.5. Additional Documents and Records

1. Subject Screening and Assignment Log – A listing of all subjects who signed the informed consent and entered the MS-LAQ-301E study.

2. Subject Identification Log – A listing of all randomized subjects. This allows linking of the enrolled subject to the study. Information should include, but is not limited to: subjects' name, date of birth and contact information and subject non-identifiable initials (if applicable). This confidential list will be maintained by the investigational site and should not be forwarded to the Sponsor.

3. Drug Accountability Log - This form documents the total amount of study drug dispensed to and returned by each subject (if applicable).

15. QUALITY ASSURANCE AUDITS

15.1. Good Clinical Practice

The study described in this protocol will be carried out according to the local regulatory requirements and ICH accepted standards of GCP. All procedures described in this protocol will be performed according to approved written SOPs unless otherwise stated.

15.2. Quality Laboratory Standards

Laboratory tests/evaluations described in this protocol will be conducted in accordance with quality laboratory standards. See Central Laboratory Manual unless otherwise stated.

15.3. Quality Assurance Program

This clinical trial may be audited according to the Teva QA program.

The purpose of these audits is to determine whether the study is being conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and local regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a subsequent inspection by any regulatory authority. Such audits, if necessary, will be pre-arranged with the site and conducted within a reasonable time frame.

15.4. Regulatory Inspections

The study may be inspected by regulatory agencies. These inspections may take place at any time during or after the study and are based on the national regulations, as well as ICH guidelines.

16. STUDY MONITORING

16.1. Monitors/CRAs and Monitoring Visits

The Study Monitor/CRA will be responsible for ensuring adherence to FDA, EU Directives, ICH guidelines and the Sponsor's SOPs. Study Monitors for this trial will be provided by the Sponsor. The monitors will follow the current "Guideline for the Monitoring of Clinical Investigators" supplied by the FDA or will operate according to the EU Directives and in compliance with ICH guidelines.

Experienced independent monitors or monitors from CROs will also be trained in Teva's SOPs, study protocol and the study monitoring conventions.

Regular monitoring of study data at each site will be performed as defined by the study specific monitoring plan. Individual sites will be monitored to verify that enrollment rate, data recording, and protocol adherence are satisfactory. The frequency of monitoring individual sites may fluctuate depending upon enrollment rate, quantity of data collected and the complexity of the study, and will be described in the monitoring plan.

These monitoring visits will be performed for the purposes of verifying adherence to the protocol and the completeness and accuracy of data entered on the CRF. The study monitor will verify CRF entries by comparing them with the primary source documents (hospital/clinic/office records), which will be made available for this purpose. The monitor will review the maintenance of regulatory documentation and drug accountability. The monitor will review the progress of the study with the investigator and other site personnel on a regular basis. At the end of the study, a close-out monitoring visit will be performed. Monitoring visits will be arranged in advance with site personnel at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the monitor to review CRFs and relevant source documents. The coordinator and/or investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits will be made available by the investigator.

16.2. Primary Source Documents

The investigator must maintain primary source documents to support CRF data entries. These documents, which are considered "source data", may include but are not limited to:

- Demographic information
- Evidence supporting the diagnosis/condition for which the subject is being studied
- General information supporting the subject's participation in the study
- Medical history and physical findings

- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any relevant findings/notes by the investigator(s), occurrence (or lack) of AEs, and changes in medication usage, including the date the study drug was commenced and stopped.
- Any additional visits during the study
- Any relevant telephone conversations with the subject regarding the study or possible AEs
- Original, signed informed consent forms for study participation

The investigator must also retain all subject specific printouts/reports of tests/ procedures performed as a requirement of the study. During monitoring visits the monitor will need to verify data in the eCRFs against these source data.

17. 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 or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center 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 subject's drug supply) should be sent back to the sponsor for investigative testing whenever possible.

17.1. 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
- subject identifier (subject study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies

- subject 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 product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

17.2. Handling of 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 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 subject.

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

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 11).

17.4. Documenting a Product Complaint

The investigator will record in the source documentation a description of the product complaint, and any actions taken to resolve the complaint and to preserve the safety of the subject. 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.

18. USE OF INFORMATION AND PUBLICATION

18.1. Confidential Information

All information supplied by Teva in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the IB, clinical protocol, CRFs and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of Teva, shall not be disclosed to others without the written consent of Teva, and shall not be used except in the performance of this study.

The information developed during the conduct of this clinical study is also considered confidential, and will be used by Teva in connection with the development of the drug. The information may be disclosed as deemed necessary by Teva. To allow the use of the information derived from this clinical study, the investigator is obliged to provide Teva with complete test results and all data developed in this study.

The Sponsor has full ownership of the original CRFs completed as part of the study.

By signing the clinical study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The information obtained during this study may be made available to other investigators who are conducting similar studies.

It is agreed that, consistent with scientific standards, publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol.

Should the investigator wish to publish the results of this study, the investigator agrees to provide Teva with a manuscript for review 60 days prior to submission for publication.

Teva retains the right to delete from the manuscript information that is confidential and proprietary and to object suggested publication and/or its timing (at the Company’s sole discretion).

In the event that Teva chooses to publish the data from this study a copy will be provided to the investigator at least 30 days prior to the expected date of submission to the intended publisher.

19. STUDY PERSONNEL

19.1. Investigative Site

19.1.1. The Principal Investigator

At each investigational center, a physician will be appointed to serve as a principal investigator and will have overall responsibility to lead the site study team (Neurologist, radiologists, technician and clinical coordinator as appropriate) and aspects of the study at the respective site. The Principal Investigator will oversee the accrual of appropriate subjects, the conduct of the study according to the trial protocol and the collection of required data.

19.1.2. The Study Physician/ Neurologist

The Study Physician/Neurologist will be responsible for the general medical evaluations as well as the neurological assessments. The Study Physician/Neurologist will make the decision as to whether the neurological change is considered a relapse, based on EDSS/FS scores obtained by him/her.

19.1.3. The MRI Radiologist and Technician

The radiologist will be responsible for determining the subject's capability to undergo MRI scans; the performance of the MRI scan according to the protocol guidelines for the entire duration of the study; and the preparation of adequate electronic material. He/she will also be responsible for the quality of such material as well as for providing adequate storage and back-ups of the primary data at the site. The MRI scans will be transferred in electronic format only to the MRI-AC.

The radiologist is responsible for reviewing all MRI scans for non-MS related pathology.

The MRI technician is responsible for performing the MRI scans according to the protocol; preparing the electronic copies; and performing the required back-ups and documentation of such procedures.

19.1.4. Study Coordinator or Designee

A study coordinator or other staff member designated by the Principal Investigator will be responsible for subject scheduling and completion of all subjects' eCRFs and recording of AEs. He/she will instruct the subject on proper study drug administration. He/she will collect and forward blood samples and requests to the appropriate laboratories, will obtain and forward laboratory results and perform other duties delegated by the Principal Investigator as instructed.

19.2. The Sponsor

19.2.1. Global Clinical Leader

The Global Clinical Leader maintains overall responsibility for the study and is responsible for ensuring good conduct and adequate resources; for providing high-quality study management and data management and for the coordination of all study committees.

19.2.2. Global Operations Manager

The Global Operations Manager is responsible for day-to-day operations of the study, and also for coordinating and handling all subject study data from the investigational sites. This includes daily maintenance of all study aspects and study status on internal periodic reports.

19.2.3. Data Management & Biostatistics

Global Biostatistics and Data Management units are responsible for the adequate performance of the data management application (Oracle Clinical); the conduct of the routine data management procedures; and the performance of the statistical analysis as defined in this protocol. All procedures will be performed according to the common units' SOPs in line with ICH regulations.

At the discretion of the Sponsor Data Management may be performed by a CRO.

19.2.4. Local Clinical Management

The LCM is responsible for the local day-to-day activities of the study and to ensure that the Sponsor supplies adequate resources to provide high quality study management, monitoring and data management. The LCM is responsible for submitting safety reports to local regulatory authorities, EC/IRB and investigators, where required.

19.2.5. Clinical Research Associate/Monitor

The CRA/monitor is responsible for monitoring the conduct of the study at the study centers. Monitoring visits will be arranged in advance, at a mutually acceptable time, with site personnel. Refer to Section 16.1 in this protocol for detailed monitoring activities.

19.2.6. Global Drug Safety and Pharmacovigilance

Global Drug Safety & Pharmacovigilance is responsible for: reviewing safety issues that arise during the study, assessing and evaluating the causality of SAEs occurring during the study and submission of relevant SAEs to health authorities/CA as per regulations.

19.2.7. Medical Monitor

The Medical Monitor is responsible for reviewing all safety clinical data in an ongoing basis through the course of the study. The medical monitor is reviewing individual safety subject’s safety data as well as listings and tabulated safety data.

The medical monitor is responsible to evaluate any emerging data driven safety issues during the course of the study, and alert the clinical leader, responsible LCM/CRA, safety officer and notify the DMC.

The action plan of any safety emerged issues will be coordinated by the medical monitor and clinical leader. The narratives of any safety issues with medical importance will be prepared by the medical monitor.

The medical monitor is also responsible to follow up the safety emerged issues through the study, their capture within the eCRF, and SAE reports (if necessary), and the execution of the action plan/follow up of a subject as recommended by safety officer and DMC.

The medical monitor is responsible to prepare the safety information periodical reports for the DMC meetings and present the data during the open session of the DMC meetings.

20. STUDY COMMITTEES

20.1. Steering Committee

The Steering Committee may offer expert opinion as to clinical aspects of the protocol design and may be consulted during the course of the study. Periodical teleconferences will be held to assess and discuss clinical and operative progress of the study. Protocol amendments, safety issues and potential publications will be discussed with the committee and recommendations may be made to the Sponsor as appropriate. The Steering Committee will include designees from the participating countries/regions Principal Investigators.

20.2. Data Monitoring Committee (DMC)

The DMC will be composed of external independent physicians with expertise in MS, internal medicine, cardiology, as well as a specialist in hepatic diseases and a statistician. Ad-hoc consultations may be made with additional specialists as will be deemed necessary during the course of the study.

The DMC responsibilities are:

To review the progress of the trial and the accumulation of data, both periodically and on an ad-hoc basis, in order to ensure subjects' welfare.

- To oversee the emerging safety data of the study.
- To review efficacy data, as deemed necessary.
- To assess whether there is any basis upon which to recommend modification or premature termination of the study.

The DMC Chairperson is responsible for all DMC interactions with the Sponsor, through the Global Clinical Leader. The Global Clinical Leader is responsible for addressing safety issues identified by the DMC. He/she will report to the DMC about the risk management plan established by the Sponsor.

A DMC plan/charter will be prepared in the first meetings of the DMC, and signed by the DMC members and Sponsor's designees. The charter describes the function and manner of operation of the DMC.

DMC meetings will take place at a set schedule, according to study characteristics, needs, and progress.

Meetings may be in a teleconference or face to face, according to study needs.

In case of need for an urgent discussion of a safety issue, the DMC chair or the Sponsor may call an unscheduled meeting.

Participants of the meetings are: DMC chair, DMC members, clinical leader, study medical monitor, and Sponsors' DMC statistician.

DMC meeting minutes and conclusions are a part of the study's documents and risk management plan.

All DMC reports should be available upon request to regulatory and ethical authorities.

The Sponsor will work closely with the committee to provide the necessary data for review. The list of DMC members will be detailed in the DMC plan/charter.

20.3. Clinical Advisory Board (CAB)

The Clinical Advisory Board (CAB) will be responsible for the clinical development plan of the study including all clinical issues regarding study design and conduct. For a list of CAB members please refer to the Operation Manual.

The committee's responsibilities will include involvement in:

- design of the clinical development plan
- design of study protocols
- interpretation of results analysis upon study completion

20.4. Publication Committee

The publication committee will be responsible for developing the publication plan consistent with the study end points and out comes, and the needs of the medical community and the Sponsor.

This committee will be composed of the chair of the steering committee, designees from the CAB, which are taking a pivotal role in the study, and also the Sponsor's designee.

The publication plan will be prepared in the after completion of subject recruitment into the study.

This plan will determine the publication policy of the study outcomes and recommend on the main publishers. The plan will be consistent with Teva policy on use of confidential information (see Section 18.1).

TEVA Pharmaceutical Industries, Ltd.

Protocol No. MS-LAQ-301E

INVESTIGATOR'S AGREEMENT

I have carefully read the foregoing protocol including all appendices and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current GCP guidelines and will attempt to complete the study within the time designated.

I will provide copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by the Sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all subject information (CRFs, shipment and drug return forms and all other information collected during the study) in accordance with the current GCP and local regulations.

Principal Investigator's name	Teva Representative's name
Signature	Signature
Date	Date
Institution	

21. REFERENCES

EMEA Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis (CPMP/EWP/561/98 Rev. 1, Nov. 2006)

Neuhaus O, Archelos JJ, Hartung HP. Immunomodulation in multiple sclerosis: from immunosuppression to neuroprotection. Trends Pharmacol Sci 2003;24:131-8.

NTP TR-521: National Toxicology Program. NTP technical report on the toxicology and carcinogenesis studies of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (CAS No. 1746-01-6) in female Harlan Sprague-Dawley rats (Gavage Studies). Natl Toxicol Program Tech Rep Ser. 2006 Apr;(521):4-232.

NTP TR-584: National Toxicology Program. NTP technical report on the toxicology studies of indole-3-carbinol (CAS No. 700-06-1) in F344/N rats and B6C3F1/N mice and toxicology and carcinogenesis studies of indole-3-carbinol in Harlan Sprague Dawley rats and B6C3F1/N mice (Gavage Studies). Draft - Scheduled Peer Review Date: May 22, 2014.

Sormani MP, Bonzano L, Roccatagliata L, Mancardi GL, Uccelli A, Bruzzi P. Surrogate endpoints for EDSS worsening in multiple sclerosis. A meta-analytic approach. Neurology. 2010 Jul 27;75(4):302-9

22. RATIONALE FOR PROTOCOL AMENDMENT AND SUMMARY OF CHANGES

22.1. Global Amendment #3

At the time of issuance of this amendment there are 542 ongoing subjects in the study.

The primary purpose of this amendment is to introduce additional safety measures due to cardiovascular findings in other MS studies where higher doses of laquinimod (1.2 and 1.5 mg) were administered. These cardiovascular events resulted in the discontinuation of patients treated with 1.2 and 1.5 mg from the respective studies in line with the DMC recommendations (see Section 3.4.1.1.7). 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. The concerned investigators and ECs/IRBs were informed in advance of these recommendations and the planned amendment. Changes include:

- all ongoing subjects will be asked to re-consent to a revised form that includes information on the cardiovascular risk findings at higher doses of laquinimod (1.2 and 1.5 mg)
- stopping rules added for renal and hepatic impairment (to avoid administration of laquinimod in the event of organ impairment, which may lead to increased exposure)
- GFR monitoring (and measurement of weight) will be performed at all visits, to assess renal function
- extra emphasis placed on moderate/strong inhibitors of CYP3A4 being disallowed (again, these could lead to increased laquinimod exposure)
- 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
- addition of cardiovascular risk assessment and management procedure
- ischemic cardiac events and cerebrovascular events are now classed as protocol-defined adverse events for expedited reporting, and should be reported to the sponsor within 48 hours, including completion of the corresponding dedicated CRF
- Table 3 amended to show additional events in line with the updated Reference Safety Information

- Subjects who are discontinued from study treatment will be encouraged to continue all scheduled visits and procedures until completion of the study (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, and GFR estimation [including body weight measurement])

In addition to the major revisions this amended protocol includes:

- added recommendation to avoid the use of CYP1A2 substrates
- change to the listed address of the sponsor (for consistency with other clinical trial related documents, only the headquarters address is listed in the protocol)
- change to the Clinical Project Physician
- language related to oral cavity tumors update to make consistent with current IB
- product complaint section added
- addition of CT scan or MRI in case of pancreatic or suspected pancreatitis
- removal of urinalysis and anemia panel from the clinical laboratory evaluations
- in the study flow chart, urine HCG test at termination/early discontinuation has been removed to make consistent with the text

These changes did not alter the study population or endpoints.

Rationales for the major changes are given and all substantive changes are listed in the summary table below.

Deletions are indicated with a ~~strikethrough~~, additions with an <u>underline</u>.

Original text with changes shown	New wording	Reason/Justification for change
TITLE PAGE		
Teva Pharmaceutical Industries, Ltd 12 Hatrufa St., P.O. Box 8077 Sapir Industrial Zone Netanya, Israel 5 Basel St, Petach-Tikva 49131, Israel	Teva Pharmaceutical Industries, Ltd 5 Basel St, Petach-Tikva 49131, Israel	Change of address (for consistency with other clinical trial related documents, only the headquarters address is listed in the protocol)
[redacted] Teva Pharmaceutical Industries, Ltd [redacted]	[redacted] Teva Pharmaceutical Industries, Ltd [redacted]	Change of Sponsor's Safety Officer
Section 3.1.1. General		
Authorized disease-modifying drugs for Relapsing Remitting Multiple Sclerosis (RRMS) given by injection include interferon-beta (IFN β) 1a (Avonex® , Rebif®) or 1b (Betaseron® , Extavia®), glatiramer acetate (Copaxone®), mitoxantrone (Novantrone®), natalizumab (Tysabri® ; for patients non-responsive to other medications), and alemtuzumab (Lemtrada®). Oral disease modifying treatments for RRMS include fingolimod (Gilenya®), teriflunomide (Aubagio®), and dimethyl fumarate (Tecfidera®) ~~and alemtuzumab (Lemtrada®)~~.	Authorized disease-modifying drugs for Relapsing Remitting Multiple Sclerosis (RRMS) given by injection include interferon-beta (IFN β) 1a (Avonex® , Rebif®) or 1b (Betaseron® , Extavia®), glatiramer acetate (Copaxone®), mitoxantrone (Novantrone®), natalizumab (Tysabri® ; for patients non-responsive to other medications), and alemtuzumab (Lemtrada®). Oral disease modifying treatments for RRMS include fingolimod (Gilenya®), teriflunomide (Aubagio®), and dimethyl fumarate (Tecfidera®).	Correction; Lemtrada is not administered orally.
Section 3.1.2. Study Drug		
(new text)	Laquinimod relates to a predecessor compound, roquinimex. It is the result of a structure activity-relationship screening program whose aim was to identify a new, pharmacologically modified substance active in MS animal models which, when compared to roquinimex, would have a superior safety profile. Roquinimex demonstrated clinical efficacy in MS in Phase 2 studies. However, serious cardiopulmonary toxicities (including myocardial infarction, pericarditis and pleuritis) occurring during Phase 3 studies led to early termination of these studies.	Additional information added to give context.
Section 3.2.2. Metabolism and Pharmacokinetics		
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 marked decrease of CYP3A4 activity and is a strong inducer of CYP1A enzymes.	Change of terminology for consistency with the IB

Original text with changes shown	New wording	Reason/Justification for change
Section 3.2.3. Toxicology		
~~Finally, a small~~ In addition, an increase in the incidence of oral ~~cavity squamous cell carcinoma~~ 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 ~~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.~~ 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	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.	Updated for consistency with the IB

Original text with changes shown	New wording	Reason/Justification for change
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.		
Section 3.3.1. Clinical Pharmacology Studies		
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 ~~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. For additional information, 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 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	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. For additional information, 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 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	Updated for consistency with the IB

Original text with changes shown	New wording	Reason/Justification for change
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.	hepatic impairment (mild to severe) and renal impairment (moderate to severe) across this dose range.	
Section 3.3.2. Clinical Safety and Efficacy Studies		
(new text)	On 30 December 2015 the DMC for the LAQ-MS-305 (CONCERTO) and TV5600-CNS-20006 (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). Due to these events and the DMC recommendation to stop all laquinimod treatment arms above 0.6 mg in the MS trials, the 1.2 mg treatment arm in the CONCERTO 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 arms in the CONCERTO and ARPEGGIO studies will be continued while the sponsor closely monitors cardiovascular events in all laquinimod studies, such as this one. This is discussed further in Section 3.4.1.1.7.	Information regarding safety findings in the CONCERTO and ARPEGGIO studies
Section 3.4.1. 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. 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	Note: the table has been updated in line with the updated Reference Safety Information; myocardial infarction and cerebrovascular accident are now included. Table 3: Tabulated List of Adverse Reactions ... Cardiac disorders Uncommon: Myocardial infarction ... Nervous system disorders Very Common: Headache Rare: Cerebrovascular accident	Update to Reference Safety Information

Original text with changes shown	New wording	Reason/Justification for change
Section 3.4.1.1.7. Cardiovascular Events (Laquinimod 1.2 and 1.5 mg)		
(new section)	On 30 December 2015, a DMC review of 8 unblinded cases from the LAQ-MS-305 (CONCERTO) and TV5600-CNS-20006 (ARPEGGIO) studies found an imbalance in serious cardiovascular events in the high dose treatment arms in the study: 6 cases 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 infarct in a 31 year old man on the 1.2 mg treatment arm. In the ARPEGGIO study, 1 heart attack 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 the above, the 0.6 mg treatment arm will be continued in the CONCERTO and ARPEGGIO studies while the sponsor closely monitors cardiovascular events in all laquinimod studies, including the present study. Additional measures implemented in this protocol amendment include an additional emphasis on disallowed medications, medications and stopping rules for organ impairment (ie, factors which may increase laquinimod exposure), as well as regular evaluation and treatment management of major modifiable cardiovascular risk factors, and collection of unscheduled blood samples, eg, for clinical laboratory tests. The DMC also recommend that study subjects continuing on laquinimod 0.6 mg be re consented 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	Information regarding safety findings in the CONCERTO and ARPEGGIO studies

Original text with changes shown	New wording	Reason/Justification for change
	causality are ongoing.	
Section 3.4.1.2.2. Cancer		
It is the sponsor's position that these findings are likely related to ~~the administration procedure or to~~ species-specific mechanisms	It is the sponsor's position that these findings are likely related to species-specific mechanisms	Administration procedure no longer considered a factor
Section 3.4.1.2.3. Cardiotoxicity and Systemic Inflammation		
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 10000 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 infarctionThis analysis showed that none of these safety issues constitute a signal of concern for laquinimod.	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 10000 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.	Information added on safety of 0.6 mg dose
Section 5.1. Overview And Plan (Other sections affected by this change: Section 8.1. Study Period; Section 8.2.2. Scheduled Treatment Visits [Months 1E (Visits 1E) and Onwards]; Section 8.3.2.1. Liver Enzymes)		
(new text)	Subjects who discontinue treatment for any reason will continue follow-up according to scheduled visits.	Additional follow-up added for safety reasons
Section 7.1. Allowed Concomitant Medications/Therapies		
Short-term treatment with corticosteroids will be allowed during ~~acute~~ relapses.	Short-term treatment with corticosteroids will be allowed during relapses.	Treatment can be used for any relapses (not just acute relapses)
Clinical studies have shown laquinimod 0.6 mg to be a ~~potent~~ strong inducer of CYP1A2. Subjects taking drugs that are	Clinical studies have shown laquinimod 0.6 mg to be a strong inducer of CYP1A2. Subjects taking drugs that are metabolized	Wording made consistent with IB

Original text with changes shown	New wording	Reason/Justification for change
metabolized by CYP1A2 (examples listed in Appendix F) 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. ~~Physicians should consider increasing the dose of such medications upon initiation of laquinimod treatment; in this case, dose reduction of the CYP1A2 inhibitor should be considered if laquinimod is stopped.~~	by CYP1A2 (examples listed in Appendix F) 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.	
Section 7.2. Disallowed Concomitant Medications During Study (Other sections affected by this change: Section 8.2.3 Termination/ Early Discontinuation)		
~~Interferons~~ IFN-β 1a or 1b ... Moderate/strong inhibitors of CYP3A4, for example, ketoconazole and erythromycin (as listed in Appendix E) are disallowed for 2 weeks prior to the baseline visit through to 30 days after the final dose of laquinimod. 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.	IFN-β 1a or 1b ... Moderate/strong inhibitors of CYP3A4, for example, ketoconazole and erythromycin (as listed in Appendix E) are disallowed for 2 weeks prior to the baseline visit through to 30 days after the final dose of laquinimod. 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.	Clarification
Section 8.2.3. Termination/ Early Discontinuation (Other sections affected by this change: Section 8.3. Early Treatment Discontinuation)		
(new text)	Subjects who are discontinued from study treatment will be encouraged to continue all scheduled visits and procedures until completion of the study (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, and GFR estimation [including body weight measurement]).	Additional follow-up added for safety reasons
Female subjects of child-bearing potential will be reminded about (should be recorded in the source documents) importance of stopping the study drug and informing the site in any case of suspected pregnancy (positive home urine test result, delay of menstruation or any other reason suggesting pregnancy) ~~and importance of performing the home pregnancy urine tests every one month (starting after visit Month 3E).~~	Female subjects of child-bearing potential will be reminded about (should be recorded in the source documents) importance of stopping the study drug and informing the site in any case of suspected pregnancy (positive home urine test result, delay of menstruation or any other reason suggesting pregnancy)	Pregnancy tests not required in this context.

Original text with changes shown	New wording	Reason/Justification for change
Section 8.3. Early Treatment Discontinuation		
An early termination visit should be completed for all subjects who prematurely discontinue from the study and do not agree to or cannot continue all scheduled visits and procedures. It includes subjects who took at least one dose in the MS-LAQ-301E study.	An early termination visit should be completed for all subjects who prematurely discontinue from the study and do not agree to or cannot continue all scheduled visits and procedures. It includes subjects who took at least one dose in the MS-LAQ-301E study.	Clarification
Section 8.3.1.1. Post Early Discontinuation Follow-Up Visit		
(new text)	Note: This section specifically pertains to subjects that discontinue treatment early but do not agree to continue follow up.	Clarification
In case of early termination of the study due to an AE for which the relationship with the study drug is characterized as 'Reasonable Possibility',Moderate and strong CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered.	Moderate and strong CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered.	Text removed as this restriction is more general
Section 8.3.2.2. Pregnancy (Other sections affected by this change: 10.2.3. Safety Laboratory Evaluations; APPENDIX G. GUIDANCE ON SAFETY MONITORING)		
Teva considers the prevention of exposure to laquinimod during pregnancy to be of great importance, and following consultation with the CHMP and Data Safety Committee (DMC) has decided to introduce additional language and measures for pregnancy prevention in this amendment and in a revised informed consent form.	(text deleted)	Text removed as was specific to a previous amendment
Additionally, monthly pregnancy tests (urine dipstick and/or serum pregnancy β-hCG test, as applicable per the relevant time point) will be performed (except for where subjects have discontinued study drug but are continuing to attend study visits for follow-up).	Additionally, monthly pregnancy tests (urine dipstick and/or serum pregnancy β-hCG test, as applicable per the relevant time point) will be performed (except for where subjects have discontinued study drug but are continuing to attend study visits for follow-up).	Clarification
Section 8.3.2.3. ~~Invasive~~ Cancer (Other sections affected by this change: APPENDIX G. GUIDANCE ON SAFETY MONITORING)		
Subjects who are diagnosed with a malignant solid or liquid tumor ~~invasive cancer~~ while participating in the study should stop study drug.	Subjects who are diagnosed with a malignant solid or liquid tumor while participating in the study should stop study drug.	Correction of terminology
Section 8.3.2.4. Liver Impairment		
(new section)	To avoid exposures to higher levels of laquinimod (see Section 3.3.1), a stopping rule related to liver impairment has been introduced. Subjects who develop any chronic liver disease associated with hepatic function impairment while participating	New stopping rule to avoid higher exposures to laquinimod

Original text with changes shown	New wording	Reason/Justification for change
	in the study should stop study medication.	
Section 8.3.2.5. Renal Impairment		
(new section)	To avoid exposures to higher levels of laquinimod (see Section 3.3.1), a stopping rule related to renal impairment has been introduced. Subjects 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 subject should stop study medication permanently.	New stopping rule to avoid higher exposures to laquinimod
Section 8.3.5. Unscheduled Visit		
(new text)	Serum or urine β-hCG test may be performed	Added to make consistent with study flow chart
Section 8.3.5.1. Unscheduled Samples		
(new section)	According to the judgment of the investigator or medical monitor, the following unscheduled samples may be collected to assist with further investigations of cardiovascular events or other clinical event of interest: urgent safety laboratory test panel (see Section 10.2.3.1) pharmacokinetic blood sample sample for potential biomarker analysis	Additional samples can be collected
Section 8.3.5.1.1. Unscheduled Pharmacokinetic Samples		
(new section)	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. Details of sample collection and processing are provided in the Laboratory Manual.	Additional samples can be collected
Section 8.3.5.1.2. Unscheduled Biomarker Samples		
(new section)	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. Potential biomarker assessments to better understand laquinimod	Additional samples can be collected

Original text with changes shown	New wording	Reason/Justification for change
	MoA, as well as to explore response predictive markers for efficacy or safety, may include 1) cytokines and other soluble marker levels; 2) RNA analysis; 3) proteomic profile; and/or 4) other relevant biomarkers. Details of sample collection and processing are provided in the Laboratory Manual. Since new biomarker techniques continue to be developed, the method and laboratory that will be recommended cannot be anticipated.	
Section 10.2.1.1. Protocol Defined Adverse Events for Expedited Reporting		
(new section)	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.
Section 10.2.2. Abdominal Computed Tomography Scan		
(new section)	In case of pancreatitis or suspected pancreatitis, an abdominal computed tomography (CT) scan should be performed as soon as possible in order to clarify the diagnosis and enable assessment of severity of this condition. An MRI may be performed as an alternative to the CT scan.	Added for consistency with other laquinimod protocols
Section 10.2.3. Safety Laboratory Evaluations (Other sections affected by this change: Section 8.2.2. Scheduled Treatment Visits [Months 1E (Visits 1E) and Onwards]; Section 8.2.3. Termination/ Early Discontinuation)		
hs-CRP	hs-CRP	It is specifically hs-CRP that should be measured
In case of abnormal CPK result: troponin ~~or~~ and CPK-MB will be tested	In case of abnormal CPK result: troponin and CPK-MB will be tested	Both troponin and (not or) CPK-MB will be measured
In case of hemoglobin decrease of > 1g/dL from the subject's hemoglobin level at Baseline, subjects will be re-tested to ascertain true decrease. If true decrease, a thorough anemia work-up will be done including: directed medical history and physical examination blood smear, serum iron, ferritin, total iron binding capacity, folic acid, B12, haptoglobin, IL-1, IL-6, IFN-γ, TNF-α, and hepcidin additional investigations and follow-up per Investigator's discretion or Sponsor's request	(text deleted)	Anemia panel will no longer be performed (this assessment was included to help understand the mode of action of laquinimod, with any changes expected to occur in the first few months of treatment, and was not pertinent to subject's direct safety)
Urinalysis pH	(text deleted)	Urinalysis will no longer be performed for consistency with

Original text with changes shown	New wording	Reason/Justification for change
Glucose Ketones Erythrocytes, Leukocytes Protein		other laquinimod studies and because the clinical information gained from such a test would be minimal in this study.
Section 10.2.3.1. Urgent Safety Laboratory Panel		
(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 (and others, if required) will be performed on these samples: serum chemistry panel, including fibrinogen and hs-CRP hematology panel CPK-MB troponin I	Unscheduled samples can be collected for further investigation of clinical events of interest
Section 10.2.4. Vital Signs and Weight (Other sections affected by this change: Section 8.2.2. Scheduled Treatment Visits [Months 1E (Visits 1E) and Onwards])		
Body weight will be measured at ~~Month 0E [Baseline (Termination visit of the MS-LAQ-301 study)] and every 12 months thereafter,~~all visits until Termination/early discontinuation, and as long as the subject continues study drug treatment.	Body weight will be measured at all visits until Termination/early discontinuation, and as long as the subject continues study drug treatment.	Weight will now be measured at all visits
Section 10.2.7. Glomerular Filtration Rate Estimation (Other sections affected by this change: Section 8.2.2. Scheduled Treatment Visits [Months 1E (Visits 1E) and Onwards]; Section 10.2.3. Safety Laboratory Evaluations)		
(new section)	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 3.3.1). Consequently, GFR will be estimated at all visits to monitor renal function in the study in order to identify subjects with potentially impaired laquinimod clearance. Subjects with a confirmed GFR $\leq$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 $\leq$60 mL/min/1.73 m^2), the subject should stop study medication permanently (see Section 8.3.2.5). Following recent findings connecting Gd based contrast agents and nephrogenic systemic sclerosis, GFR value should be evaluated prior to performing an MRI scan, where administration	GFR estimation added to monitor renal function

Original text with changes shown	New wording	Reason/Justification for change
	of Gd-based contrast agent is planned. The central laboratory will provide the GFR value prior to the scheduled MRI tests. In case GFR estimation is not provided by the central laboratory, calculation should be done at the site, prior to any MRI scan via the following web calculator: http://www kidney.org/professionals/kdoqi/gfr_calculator.cfm In case GFR is ≤60 mL/min, the MRI scan should be performed without contrast (Gd) and further evaluation of renal impairment is required (refer to Section 8.3.2.5)	
Section 10.2.8. Cardiovascular Risk Assessment and Management (Other sections affected by this change: Section 8.2.2. Scheduled Treatment Visits [Months 1E (Visits 1E) and Onwards])		
(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. In addition, an evaluation should take place as soon as possible for subjects already in the study, following approval of Amendment #3. Cardiovascular risk management should be conducted according to evidence-based, local standard-of-care procedures. Subjects will undergo referral to a suitable clinic if needed.	Additional safety precautions for cardiovascular risks
Section 11. SAFETY AND PHARMACOVIGILANCE (Other sections affected by this change: Section 13.3. Subject Confidentiality; Section 14.4.1.1. Data Collection; APPENDIX D. MRI PROTOCOLS (INCLUDING MT AND MRS))		
The following information should be provided to accurately and completely record the event: 1. Investigator Name and Center Number 2. Subject Number 3. Subject initials 4. Subject Demographics	The following information should be provided to accurately and completely record the event: 1. Investigator Name and Center Number 2. Subject Number	Subject initials and demographics should no longer be recorded
Section 13.2. Informed Consent (Other sections affected by this change: 8.2.2. Scheduled Treatment Visits [Months 1E (Visits 1E) and Onwards]		
(new text)	Subjects continuing on laquinimod 0.6 mg will be re-consented with information about the cardiovascular risk seen in higher doses (see Section 3.4.1.1.7).	Subjects continuing on the study with this amendment will be re-consented.
Section 17. CLINICAL PRODUCT COMPLAINTS		
(new section)	A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:	Section added for consistency with sponsor's current protocol template

Original text with changes shown	New wording	Reason/Justification for change
	suspected contamination questionable stability (eg, color change, flaking, crumbling, etc) defective components missing or extra units (eg, primary container is received at the investigational center 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 subject's drug supply) should be sent back to the sponsor for investigative testing whenever possible.	
Section 17.1. Product Complaint Information Needed from the Investigational Center		
(new section)	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 subject identifier (subject study number) and corresponding visit numbers, if applicable product name and strength for open-label studies subject 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	Section added for consistency with sponsor's current protocol template

Original text with changes shown	New wording	Reason/Justification for change
	Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.	
Section 17.2. Handling of Study Drug at the Investigational Center		
(new section)	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 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 subject.	Section added for consistency with sponsor's current protocol template
Section 17.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint		
(new section)	If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 11).	Section added for consistency with sponsor's current protocol template
Section 17.4. Documenting a Product Complaint		
(new section)	The investigator will record in the source documentation a description of the product complaint, and any actions taken to resolve the complaint and to preserve the safety of the subject. 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.	Section added for consistency with sponsor's current protocol template
APPENDIX D. MRI PROTOCOLS (INCLUDING MT AND MRS)		
Check that the subject can successfully undergo MRI examination, including GFR estimation. Following recent findings connecting Gd based contrast agents and nephrogenic systemic sclerosis, GFR value should be evaluated prior to performing an MRI scan, where	Check that the subject can successfully undergo MRI examination, including GFR estimation. Following recent findings connecting Gd based contrast agents and nephrogenic systemic sclerosis, GFR value should be evaluated prior to performing an MRI scan, where administration	Added requirement for GFR estimation

Original text with changes shown	New wording	Reason/Justification for change
administration of Gd-based contrast agent is planned. The central laboratory will provide the GFR value prior to the scheduled MRI tests. In case GFR estimation is not provided by the central laboratory, calculation should be done at the site, prior to any MRI scan via the following web calculator: http://www kidney.org/professionals/kdoqi/gfr_calculator.cfm In case GFR is ≤60 mL/min, the MRI scan should be performed without contrast (Gd) and further evaluation of renal impairment is required (refer to Section 8.3.2.5)	of Gd-based contrast agent is planned. The central laboratory will provide the GFR value prior to the scheduled MRI tests. In case GFR estimation is not provided by the central laboratory, calculation should be done at the site, prior to any MRI scan via the following web calculator: http://www kidney.org/professionals/kdoqi/gfr_calculator.cfm In case GFR is ≤60 mL/min, the MRI scan should be performed without contrast (Gd) and further evaluation of renal impairment is required (refer to Section 8.3.2.5)	
APPENDIX E. MODERATE/STRONG CYP3A4 INHIBITORS AND CYP3A4 INDUCERS:		
(section, including tables, updated to make consistent with current IB)	(see Appendix E for new wording)	Updated for consistency with current IB
APPENDIX F. LIST OF MEDICATIONS THAT SHOULD BE USED WITH CAUTION		
(section, including tables, updated to make consistent with current IB)	(see Appendix F for new wording)	Updated for consistency with current IB
APPENDIX G. GUIDANCE ON SAFETY MONITORING		
(new text)	4. Guidance on Monitoring Subjects 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 and on all follow up visits until normalization of pancreatic amylase levels. In case of suspected pancreatitis, the subject 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. An MRI may be performed as an alternative to the CT scan. 5. Liver Impairment Subjects who develop any chronic liver disease associated with liver functional impairment while participating in the study should stop study medication. 6. Renal Impairment Subjects 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 subject should stop study medication permanently.	Guidance updated for consistency with body of the protocol

22.2. Global Amendment #2

At the time of issuance of this amendment there were 639 ongoing subjects in the study.

This amendment included: updates to the introduction and safety sections based on accumulating data with laquinimod; and more stringent pregnancy prevention measures.

In addition to the major revisions this amended protocol included updates, modifications and clarifications in sections related to stopping rules, disallowed medication, and study duration.

These changes did not alter the study population, study design, or endpoints.

Rationales for the major changes are given and all substantive changes are listed in the summary table below.

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 8.2: Detailed Study Plan		
None.	• For all subjects who are female of child-bearing potential: – The use of effective contraception will be ascertained at each study visit (should be recorded in the source documents). – Subjects will be instructed during each visit about the teratogenicity and potential delayed risks for a child exposed in uterus to laquinimod – Subjects will be reminded about (should be recorded in the source documents) the importance of stopping the study drug and informing the site in any case of suspected pregnancy (positive home urine test result, delay of menstruation or any other reason suggesting pregnancy)	Teva considers the prevention of exposure to laquinimod during pregnancy to be of great importance, and following consultation with the CHMP and Data Safety Committee (DMC) has decided to introduce additional language and measures for pregnancy prevention in this amendment and in a revised informed consent form. To strengthen the preventative measures, the amended protocol now includes: a requirement for two contraception methods (as recommended by the DMC), and a requirement for using a contraception method 30 days prior to enrollment, furthermore a serum beta HCG test prior to randomization
Section 8.2.1: Baseline Visit (Month 0E) (Visit 0E) (Termination visit of the MS-LAQ-301 study) Procedures		
Serum pregnancy test (β-hCG) for women of child-bearing potential	Serum pregnancy test (β-hCG) for women of child-bearing potential. <u>In case of positive result, the subject will not be eligible to participate in the extension and will be considered a screening failure for the extension phase.</u>	
Section 8.2.3: Termination/ Early discontinuation Visit		
Female subjects of child-bearing potential will be reminded to continue using an acceptable method of contraception up to 30 days from the date of the last dose of the IMP	<u>The use of effective contraception will be ascertained (should be recorded in the source documents) and they will be reminded to use two acceptable methods of contraception</u> up to 30 days from the date of the last dose of the IMP	

Previous approved wording	Amended or new wording	Reason/Justification for change
Clinical study protocol synopsis (study design), Section 8.2.1: Baseline Visit Month 0E) (Visit 0E) (Termination visit of the MS-LAQ-301 study) Procedures, Section 8.2.2: Scheduled treatment visits [Months 1E (Visit 1E) and onwards]		
in any case of suspected pregnancy […]	in any case of suspected pregnancy (positive urine β-hCG test results, delay of menstruation or any other reasons suggesting pregnancy) […]	
Section 8.3.2.2: Pregnancy (NEW SECTION)		
None.	See Section 8.3.2.2	
Appendix G – Guidance on safety monitoring		The section has been greatly revised to bring in line with current experience. Please see section for full details.
-	See Appendix G.	
Clinical study protocol synopsis AND Section 6.2: Exclusion criteria (note regarding returning subjects)		
None.	Female subjects of childbearing potential who may want to get pregnant in the future, and are interested in re-starting laquinimod treatment following delivery and cessation of breastfeeding may be able to re-enroll in the study after meeting inclusion/exclusion criteria in Appendix G. Re-enrollment will be permitted on a case-by-case basis. Notwithstanding, Teva is under no obligation to re-enroll such subjects and reserves the right to re-enroll or reject enrolment of such returning subjects for no reason and on its sole discretion. A new informed consent form should be signed before re-enrollment […]	The Sponsor realized that there might be female subjects of childbearing potential who are participating in this long-term study that might want to get pregnant in the future, and might be interested in continuing taking Laquinimod after giving birth. The Sponsor would like to assure that these women do not conceive during treatment with laquinimod and are given the opportunity to return to the study, if they wish, following childbirth and lactation. Therefore, the protocol has been amended to say that these subjects may be re-enrolled after meeting inclusion/exclusion criteria.

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 7.1: Allowed concomitant medications/therapies		
~~The use of CYP1A2 substrates (e.g. theophylline, warfarin) during the treatment period is permitted. However, due to the fact that laquinimod is an inducer of CYP1A2 in vitro, subjects who are treated with these medications should be monitored for a possible reduction in their effect or blood level and their (CYP1A2 substrates) dose should be adjusted accordingly.~~	Clinical studies have shown laquinimod 0.6 mg to be a potent inducer of CYP1A2. Subjects taking drugs that are metabolized by CYP1A2 (examples listed in Appendix F) should be advised that plasma levels of these drugs could decrease when combined with laquinimod. Physicians should consider increasing the dose of such medications upon initiation of laquinimod treatment; in this case, dose reduction of the CYP1A2 inhibitor should be considered if laquinimod is stopped. Drug-Drug interaction studies have been performed with laquinimod doses of 0.6 mg and 1.2 mg. These studies show that laquinimod at both doses is a weak inhibitor of CYP3A4. Subjects taking drugs that are metabolized by CYP3A4 (specifically those with a Narrow Therapeutic Index listed in Appendix F) should be advised that plasma levels of these drugs could increase when combined with laquinimod.	Laquinimod is a potent inducer of CYP1A2. A recently completed drug-drug interaction study confirmed that laquinimod at the dose of 1.2 mg is also a weak CYP3A4 inhibitor. Therefore, these paragraphs were included to emphasize the risk related to the concomitant use of laquinimod and drugs that are metabolized by CYP1A2 or CYP3A4. In addition, a new appendix (Appendix F) has been added to present partial lists of CYP3A4 substrates with a narrow therapeutic index and of drugs known to be metabolized by CYP1A2.
Appendix F – List of allowed medication during the study that should be used with caution (NEW APPENDIX)		
None.	Appendix F	
Clinical study protocol synopsis		
The allowed treatment for a relapse will be intravenous methylprednisolone 1 g/day for up to 5 consecutive days.	The allowed treatment for a relapse will be intravenous methylprednisolone 1 g/day <u>or oral steroids</u> for up to 5 consecutive days.	In order to align the protocol with more recent clinical study protocols with laquinimod, allowed treatment for relapses includes a short course of glucocorticosteroids (e.g., IV methylprednisolone 1g/day for up to 5 consecutive days or oral steroids). Extended courses of steroids beyond 5 days constitute a protocol violation. No tapering off is allowed.
Section 7.1: Allowed concomitant medications/therapies		
Short-term treatment with corticosteroids will be allowed during acute relapses; Allowed treatment for relapses is a fixed dose of IV methylprednisolone 1 g/day for a maximum of five consecutive days. No tapering off is allowed.	Short-term treatment with corticosteroids will be allowed during acute relapses; Allowed treatment for relapses is a fixed dose of IV methylprednisolone 1 g/day <u>or oral steroids</u> for a maximum of five consecutive days. No tapering off is allowed.	
Section 7.2: Disallowed concomitant medications during study		
• -Oral steroids • -Parenteral steroids (except if given as defined by protocol for treatment of an acute relapse as specified in	• Oral steroids and parenteral steroids (except if given as defined by protocol for treatment of an acute relapse as specified in Section 7.1)	

<table>
<tr><th>Previous approved wording</th><th>Amended or new wording</th><th>Reason/Justification for change</th></tr>
<tr><td>Section 7.1)</td><td></td><td></td></tr>
<tr><td colspan="3">Section 7.2: Disallowed concomitant medications during study</td></tr>
<tr><td>● Inhibitors of CYP3A; for example ketocanozole and erythromycin (as listed in Appendix E)</td><td>● <u>Moderate/strong</u> inhibitor of CYP3A; for example ketocanozole and erythromycin (as listed in Appendix E)
● <u>Inducers of CYP3A4 such as rifampin or carbamazepine (more examples are provided in Appendix E). Use of CYP3A4 inducers may results in reduced laquinimod plasma concentrations and reduced effectiveness</u></td><td rowspan="5">Laquinimod is mainly metabolized by the CYP3A4 isoenzyme. Following in vivo study in healthy volunteers (LAQ DDI-125 study), rifampin, a strong inducer of CYP3A4 was found to significantly enhance the metabolism of laquinimod and lead to an approximately 80% reduction in the plasma levels of laquinimod, as measured by the area under the plasma concentration-time curve (AUC). Use of CYP3A4 inducers (Carbamazepine, Phenytoin, Phenobarbital, St. John's Wort) may result in reduction of laquinimod plasma concentrations and may reduce its effectiveness. Therefore, CYP3A4 inducers have been added as disallowed medications in all clinical studies with Laquinimod. The Laquinimod Investigator's Brochure Edition 7 has been updated with the above information in Section 6.7.1.
In addition, the list of moderate/strong CYP3A4 inhibitor not allowed in the study was updated.</td></tr>
<tr><td colspan="2">Section 8.3.1.1: Post early discontinuation follow-up visit</td></tr>
<tr><td>In case of early termination of the study due to an AE for which the relationship with the study drug is characterized as ‘Reasonable Possibility’, CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered.</td><td>In case of early termination of the study due to an AE for which the relationship with the study drug is characterized as ‘Reasonable Possibility’, <u>moderate and strong</u> CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered.</td></tr>
<tr><td colspan="2">Appendix E – List* of systematically-administered** CYP3A4 inhibitors which are disallowed prior and during the study and CYP3A4 inducers</td></tr>
<tr><td><s>Cardiac drugs/antiarrhythmic agents</s>
<s>amiodarone</s>
<s>diltiazem</s>
<s>nifedipine</s>
<s>verapamil</s>
<s>mibefradil</s>
<s>Antimicrobial agents</s>
<s>Erythromycin</s>
<s>Clarithromycin</s>
<s>Troleandomycin</s>
<s>Telithromycin</s>
<s>Antifungals/Imidazoles</s>
<s>Fluconazole</s>
<s>Itraconazole</s>
<s>Ketoconazole</s>
<s>Miconazole</s>
<s>Voriconazole</s></td><td>A partial list of moderate/strong CYP3A4 inhibitors:
<table>
<tr><th>Medication class</th><th>Drug name</th></tr>
<tr><td>Protease inhibitors</td><td>indinavir, saquinavir, lopinavir, nelfinavir, amprenavir,atazanavir, darunavir, ritonavir</td></tr>
<tr><td>Antivirals</td><td>boceprevir, telaprevir</td></tr>
<tr><td>Antifungals</td><td>Ketoconazole, Itraconazole, voriconazole, posaconazole, fluconazole</td></tr>
<tr><td>Antibiotics</td><td>troleandomycin, clarithromycin, telithromycin, ciprofloxacin, erythromycin</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Previous approved wording</th><th>Amended or new wording</th><th>Reason/Justification for change</th></tr>
<tr><td>~~HIV drugs:~~
~~Protease Inhibitors, such as indinavir, ritonavir and others~~
~~Delavirdine~~
~~Antidepressants~~
~~fluoxetine~~
~~fluvoxamine~~
~~nefazodone~~
~~Others/antituberculosis and antimalarial~~
~~isoniazid~~
~~quinine~~
~~cimetidine~~
~~zileuton~~
~~aprepitant~~

[…]
***In case of early termination of the study due to AE which is considered as 'Reasonable Possibility' related to the study drug, CYP3A4 inhibitors are disallowed during 30 days after the last dose of the study drug was taken.</td><td><table><tr><td>Antidepressant</td><td>nefazodone</td></tr><tr><td>Calcium channel blocker</td><td>Diltazem, verapamil, mibefradil</td></tr><tr><td>Antiemetics</td><td>Aprepitant</td></tr><tr><td>Diuretics</td><td>Conivaptan</td></tr><tr><td>Antineoplastic agents</td><td>Imatinib</td></tr></table>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, we do not predict that such interactions are expected with laquinimod.
• Moderate/strong CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered.
A partial list of CYP3A4 inducers:
• carbamazepine
• phenobarbital
• phenytoin
• rifabutin
• rifampin
• St. John’s Wort
[…]</td><td></td></tr>
<tr><td colspan="3">Section 7.2: Disallowed concomitant medications during study</td></tr>
<tr><td>• Interferons
• Glatiramer Acetate (Copaxone®)
• Natalizumab (Tysabri®)
• Inhibitors of CYP3A4; for example, ketoconazole and erythromyicin (as listed in Appendix 5)
• Mitoxantrone (Novantrone®)</td><td>• Natalizumab (Tysabri®)
• Fingolimod (Gilenya)
• Interferons
• Dimethyl fumarate (Tecfidera)
• Glatiramer Acetate (Copaxone®)</td><td>The protocol has been updated to include several new drugs recently approved for use in RRMS.
In addition, the medication 4-amino pyridine (Ampyra,</td></tr>
</table>

Previous approved wording	Amended or new wording	Reason/Justification for change
• Oral steroids • Parenteral steroids (except if given as defined by protocol for treatment of an acute relapse as specified in Section 7.1). • Chemotherapeutic agents • 4-amino pyridine or 3,4 diaminopyridine • IV Immunoglobulin (Ig) and any other experimental agents • Other Immunosuppressive or immunomodulating agents	• Teriflunomide (Aubagio) • Alemtuzumab (Lemtrada) • Cladribine • Rituximab • Ocrelizumab • Atacicept • Belimumab • Ofatumumab • Inducers of CYP3A4 such as rifampin or carbamazepine (more examples are provided in Appendix E). Use of CYP3A4 inducers may results in reduced laquinimod plasma concentrations and reduced effectiveness • Moderate/strong inhibitors of CYP3A4, for example, ketoconazole and erythromycin (as listed in Appendix E) • Mitoxantrone (Novantrone®) • Oral steroids • Parenteral steroids (except if given as defined by protocol for treatment of an acute relapse as specified in Section7.1) • Adrenocorticotrophic hormone (ACTH) • Chemotherapeutic agents • Cytotoxic agents • Cyclophosphamide • IV Immunoglobulin (Ig) • Plasmapheresis • Any other experimental agents • Other Immunosuppressive or immunomodulating agents	Fampyra) has been removed from the list of disallowed concomitant medications. Indeed, this drug is now allowed during the study as it is no longer an experimental drug (it has received FDA approval and indicated to improve walking in adult subjects with multiple sclerosis MS who have walking disability).
Clinical study protocol synopsis AND Section 10.2.2: Safety laboratory evaluations		
CPK	– In case of abnormal CPK result: troponin or CPK-	The Sponsor has decided to

Previous approved wording	Amended or new wording	Reason/Justification for change
– Alkaline Phosphatase – Pancreatic Amylase […] – Hemoglobin.	MB will be tested – . In case of CPK > 2000 U/L urine myoglobin will be tested and the following tests will be repeated: CPK, CPK-MB, blood urea nitrogen, creatinine, electrolytes including potassium, calcium, phosphate, CRP and fibrinogen – Lipase will be tested in case of abnormal pancreatic amylase results [……] • Hemoglobin. In case of hemoglobin decrease of > 1 g/dL from the subject's hemoglobin level at Baseline, subject will be re-tested to ascertain true decrease. If true decrease, a thorough anemia work-up will be done including: – directed medical history and physical examination – blood smear, serum iron, ferritin, total iron binding capacity, folic acid, B12, haptoglobin, IL-1, IL-6, IFN-γ, TNF-α, and hepcidin – additional investigations and follow-up per the Investigator's discretion or Sponsor's request.	remove the stopping rules of monitoring of inflammatory conditions, monitoring the potential of developing thrombosis and monitoring of serum pancreatic amylase based on updated safety analyses and to align the protocol with more recent clinical study protocol with laquinimod. Complete blood count, amylase, CRP and fibrinogen are routinely monitored during scheduled visits. The subjects with these laboratory abnormalities should be managed and treated according to the best medical practice. In case of abnormal CPK results, testing of troponin or CPK MB (which was formally only specified as reflex testing in the laboratory manual) are currently specified in the protocol. A requirement for testing urine myoglobin in case of CPK >2000 U/L, was added. In addition, in case of abnormal pancreatic amylase results, lipase will be tested. In case of low hemoglobin levels, a thorough anemia work-up will be done. Following discussion with the
Section 8.3.2: Safety stopping rules		
~~Inflammatory Events:~~ ~~The subject's participation in the study will be discontinued immediately upon meeting either one of the following criteria:~~ ~~A combination of elevated CRP (≥3xULN) or WBC (≥2xULN) or fibrinogen (≥ 3x ULN) with significant signs/symptoms suggestive of inflammation of non-infectious origin (e.g. arthralgia, chest pain, chest discomfort or edema).~~ ~~An established diagnosis of either of the following: pericarditis,~~	New subsections added; see Section 8.3.2.2 and Section 8.3.2.3 for full text.	

Previous approved wording	Amended or new wording	Reason/Justification for change
~~pleuritis, pleural effusion, newly-diagnosed non-infectious arthritis or primary peritonitis.~~ ~~Thromboembolic events:~~ ~~In any suspicion for thrombotic events, all measures should be taken in order to establish or to exclude the diagnosis. The decision as per the continuation of the study drug will be made on a case by case basis.~~ ~~Pancreatitis:~~ ~~Any subject with an established diagnosis (radiographically/sonographically-based) of acute pancreatitis will be immediately withdrawn from the study.~~		European Medicines Agency, two new conditions were included among the stopping rules (women who become pregnant during the study and subjects diagnosed with invasive cancer).
Clinical study protocol synopsis – Study duration		
Study duration: Treatment phase: starting from completion of the MS-LAQ-301 study (Termination visit), ~~until laquinimod 0.6 mg is commercially available for the treatment of multiple sclerosis (MS) patients or until~~ the development of laquinimod 0.6 mg for ~~MS is stopped by the Sponsor~~. **Study design:** In this open-label study, the subjects will be treated with laquinimod 0.6 mg (regardless of their initial treatment assignment during the MS-LAQ-301 study) ~~until laquinimod 0.6 mg is commercially available for the treatment of MS patients or until its development for MS is stopped~~.	**Study duration:** Treatment phase: starting from completion of the MS-LAQ-301 study (Termination visit), <u>as long as the Sponsor continues the development of laquinimod 0.6 mg for Relapsing Remitting Multiple Sclerosis (RMMS)</u>. **Study design:** In this open-label study, the subjects will be treated with laquinimod 0.6 mg (regardless of their initial treatment assignment during the MS-LAQ-301 study) <u>as long as the Sponsor continues the development of laquinimod 0.6 mg for RMMS</u>.	The Sponsor reasoned that the long term follow-up for safety and efficacy is of utmost importance and would like to maintain the subjects under this clinical protocol. The Sponsor would like to prolong the study as long as the Sponsor continues the development of laquinimod 0.6 mg for RMMS patients. Therefore, the duration of the study will no longer be dependent on commercial availability of laquinimod 0.6mg.
Section 4: Study objectives		
To make treatment with oral laquinimod 0.6 mg available to all subjects who participated in the double-blind, placebo-controlled MS-LAQ-301 study and who completed the Termination visit of this study according to the MS-LAQ-301 protocol ~~until laquinimod 0.6 mg is commercially available for the treatment of MS patients or until its development for MS is stopped~~.	To make treatment with oral laquinimod 0.6 mg available to all subjects who participated in the double-blind, placebo-controlled MS-LAQ-301 study and who completed the Termination visit of this study according to the MS-LAQ-301 protocol <u>as long as the Sponsor continues the development of laquinimod 0.6 mg for RMMS</u>.	

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 5.1: Overview and plan		
Scheduled in-clinic visits will be conducted at Baseline (month 0E; the Termination visit of MS-LAQ-301 will serve as the baseline visit of MS-LAQ-301E) and at months 1E, 2E, 3E, 6E and every 6 months thereafter, ~~until laquinimod 0.6 mg is commercially available for the treatment of MS patients or its development for MS is stopped~~.	Scheduled in-clinic visits will be conducted at Baseline (month 0E; the Termination visit of MS-LAQ-301 will serve as the baseline visit of MS-LAQ-301E) and at months 1E, 2E, 3E, 6E and every 6 months thereafter, as long as the Sponsor continues the development of laquinimod 0.6 mg for RMMS.	
Section 5.2: Rational for study design, dose and population		
Provide laquinimod 0.6 mg once daily to all subjects who successfully complete the double-blind, placebo-controlled MS-LAQ-301 study until ~~it is commercially available (in each of the relevant countries)~~.	Provide laquinimod 0.6 mg once daily to all subjects who successfully complete the double-blind, placebo-controlled MS-LAQ-301 study as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS.	
Section 8.1: Study period		
The study, in which all eligible subjects will be treated with daily laquinimod 0.6 mg, will last ~~until laquinimod 0.6 mg is commercially available for the treatment of MS patients or~~ until ~~its development for MS is stopped.~~	The study, in which all eligible subjects will be treated with daily laquinimod 0.6 mg, will last as long as the Sponsor continues the development of laquinimod 0.6 mg for RMMS.	
Section 8.2.3: Termination early discontinuation		
Upon ~~commercial availability of laquinimod 0.6 mg for the treatment of MS patients (or~~ a decision of the Sponsor to stop the development of laquinimod 0.6 mg for MS patients~~)~~, the local clinical trial management will notify the site teams when to invite the subjects to the site, in order to perform the Termination visit. Subjects who have performed all Termination visit activities (~~either in case of commercial availability of laquinimod 0.6 mg for MS patients or~~ in case the Sponsor decides to stop the development of laquinimod 0.6 mg for MS patients) will be regarded as completers.	Upon a decision of the Sponsor to stop the development of laquinimod 0.6 mg for RMMS patients, the local clinical trial management will notify the site teams when to invite the subjects to the site, in order to perform the Termination visit. Subjects who have performed all Termination visit activities (in case the Sponsor decides to stop the development of laquinimod 0.6 mg for RMMS patients) will be regarded as completers.	

Previous approved wording	Amended or new wording	Reason/Justification for change
Clinical study protocol synopsis – MRI scan at Termination/early discontinuation visit		
~~Following the results of the MS-LAQ-301 study, the Sponsor may decide to perform a Magnetic Resonance imaging (MRI) scan at Termination/early discontinuation visit for all subjects (not only those who participate in the MRI ancillary study).~~	Magnetic Resonance Imaging (MRI) scan at Termination/early discontinuation visit will be performed on subjects who participated in the MRI ancillary study only.	The Sponsor has decided not to perform Termination/Early discontinuation visit MRI assessments for all subjects in the study. No changes apply to the MRI assessments for the MRI ancillary study.
Section 8.1: Study period (Task flow chart)		
In the table: ~~MRI (T1, T2) all subjects (Termination/early discontinuation)~~ *In the footnote of the table:* i ~~Optional. Following the results of the MS-LAQ-301 study, the Sponsor may decide to perform an MRI scan at Termination/early discontinuation visit for all subjects (not applicable for those who participate in the MRI ancillary study). In case of completion according to the protocol, this scan may be performed within 14 days prior to the Termination or as late as 14 days after Termination visit, (provided the subject was not treated with another immunomodulating/ immunosuppressive treatment for MS). In case of early termination, this scan may be performed as late as 14 days after early termination visit, (provided the subject was not treated with another immunomodulating/ immunosuppressive treatment for MS).~~	None.	
Section 8.2.3: Termination/Early discontinuation		
~~Following the results of the MS-LAQ-301 study, the Sponsor may decide to perform an MRI scan at Termination/early discontinuation visit for all subjects (not aaplicable for those who participate in the MRI ancillary study). In case of completion according to the protocol this scan may be performed within 14 days prior to the Termination or as late as 14 days after Termination visit, (provided the subject was not treated with another immunomodulating/ immunosuppressive treatment for MS). In case of early termination, this scan may be performed as late as 14 days after early termination visit, (provided the subject was not treated with another~~	None.	

Previous approved wording	Amended or new wording	Reason/Justification for change
~~immunomodulating/ immunosuppressive treatment for MS). This scan will include:~~ ~~□ T1-weighted, after administration of Gd-gadopentetic acid (Gd-DPTA)~~ ~~□ T2-weighted~~ ~~□ 3D T1-weighted~~		
Section 10.1.7: Optional assessment – Termination MRI scan		
~~Following the results of the MS-LAQ-301 study, the Sponsor may decide to perform an MRI scan at Termination/early discontinuation visit for all subjects (not applicable for those who participate in the MRI ancillary study). In case of completion according to the protocol, this scan may be performed within 14 days prior to the Termination or as late as 14 days after Termination visit, (provided the subject was not treated with another immunomodulating/ immunosuppressive treatment for MS). In case of early termination, this scan may be performed as late as 14 days after early termination visit, (provided the subject was not treated with another immunomodulating/ immunosuppressive treatment for MS). This scan will include:~~ ~~□ T1-weighted, after administration of Gd-gadopentetic acid (Gd-DPTA)~~ ~~□ T2-weighted~~ ~~□ 3D T1-weighted~~ ~~The following parameters will be assessed in this optional scan:~~ ~~Number of T1 Gd-enhancing lesions~~ ~~Number of new T2 lesions~~ ~~Volume of T2 lesions~~ ~~Number of new hypointense T1 lesions on enhanced T1 scans ("black holes")~~ ~~Volume of new hypointense T1 lesions on enhanced T1 scans~~ ~~Brain volume~~ ~~Steroid treatment for relapse (see Section 7.1) will not affect the schedule of this optional MRI scan. Where possible, the scan should be performed prior to steroid treatment.~~	None (the section has been removed).	

Previous approved wording	Amended or new wording	Reason/Justification for change
~~All MRI data will be interpreted by the MRI AC.~~		
Appendix D – MRI Protocols (including MT and MRS)		
~~OPTIONAL MRI SCAN~~ ~~Following the results of the MS-LAQ-301 study, the Sponsor may decide to perform an MRI scan at Termination/early discontinuation visit for all subjects (not applicable for those who participate in the MRI ancillary study). In case of completion according to the protocol, this scan may be performed within 14 days prior to the Termination or as late as 14 days after Termination visit, (provided the subject was not treated with another immunomodulating/ immunosuppressive treatment for MS). In case of early termination, this scan may be performed as late as 14 days after early termination visit, (provided the subject was not treated with another immunomodulating/ immunosuppressive treatment for MS). This scan will include:~~ ~~ T1-weighted, after administration of Gd-gadopentetic acid (Gd-DPTA)~~ ~~ T2-weighted~~ ~~ 3D T1-weighted~~ ~~The following parameters will be assessed in this optional scan:~~ ~~Number of T1 Gd-enhancing lesions~~ ~~Number of new T2 lesions~~ ~~Volume of T2 lesions~~ ~~Number of new hypointense T1 lesions on enhanced T1 scans ("black holes")~~ ~~Volume of hypointense T1 lesions on enhanced T1 scans ("black holes")~~ ~~Brain volume: Percentage of brain volume change from Termination scan of MS-LAQ-301 core study.~~	None.	

Previous approved wording	Amended or new wording	Reason/Justification for change
Clinical study protocol synopsis		
~~The Sponsor will inform the sites when to change from Period 1 to Period 2.~~	All neurological/medical assessments may be performed by a single Study Physician/Neurologist since all the sites are now in Period 2 of the study.	There is no longer need to distinguish between study period 1 and 2 since all the subjects are now in the study period 2. Similarly, there is no need for distinction between the Treating and the Examining Physicians/ Neurologists.

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 5.1.1: Study periods		
The medical/neurological assessments of the subjects at each clinical site will be performed differently ~~in each of the~~ following study periods. Period 1 : In this period, either two separate Neurologists or two Physicians will continue to assess the subjects in the MS-LAQ-301E study (as in the MS-LAQ-301 study). An Examining Neurologist/Physician will assess the subject's neurological status, unaware of subject's well-being and a Treating Neurologist/Physician will decide whether a subject experienced a relapse and will treat the subject as needed. In order to maintain reliable evaluation and reduce the potential for bias the following actions will be undertaken: The Examining Neurologist/Physician will be the only one to evaluate the subject neurologically. The Examining Neurologist/ Physician will have no access to the subject's file, including previous neurostatus forms, RDC system and adverse events. A decision as per treatment of a relapse will be under the sole responsibility of the Treating Neurologist/ Physician. Period 2: In this period, there will be no need for 2 separate physicians to assess the subjects in the MS-LAQ-301E study. ~~From that moment, s~~subjects participating in the MS-LAQ-301E study will be assessed by a single physician/Neurologist ("Study Physician/ Neurologist"). ~~The study will begin with medical/neurological assessments which will be performed as described in Period 1 (identical to the assessment methods in the MS-LAQ-301 study)~~ ~~The sponsor will inform the sites when to change the method of medical/neurological assessments from Period 1 to Period 2.~~	The medical/neurological assessments of the subjects at each clinical site will <u>no longer</u> be performed differently <u>since all the sites are now in study period 2.</u> Period 1 : In this period, either two separate Neurologists or two Physicians will continue to assess the subjects in the MS-LAQ-301E study (as in the MS-LAQ-301 study). An Examining Neurologist/Physician will assess the subject's neurological status, unaware of subject's well-being and a Treating Neurologist/Physician will decide whether a subject experienced a relapse and will treat the subject as needed. In order to maintain reliable evaluation and reduce the potential for bias the following actions will be undertaken: The Examining Neurologist/Physician will be the only one to evaluate the subject neurologically. The Examining Neurologist/ Physician will have no access to the subject's file, including previous neurostatus forms, remote data capture (RDC) system and adverse events (AEs). A decision as per treatment of a relapse will be under the sole responsibility of the Treating Neurologist/ Physician. Period 2: In this period, there will be no need for 2 separate physicians to assess the subjects in the MS-LAQ-301E study. Subjects participating in the MS-LAQ-301E study will be assessed by a single physician/Neurologist ("Study Physician/ Neurologist").	

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 7.1: Allowed concomitant medications/therapies		
Topical and inhaled steroids are allowed at the discretion of the ~~Treating Physician (or the~~ Study Physician~~, were applicable, see Section 5.1.1)~~ for indications other than MS.	Topical and inhaled steroids are allowed at the discretion of the Study Physician/Neurologist for indications other than MS.	
Section 8.2.2: Scheduled treatment visit [Months 1E (Visit 1E) and onwards]		
□ In order to verify whether the test has been performed and to record the result of the test (see ~~Appendix F~~), a mandatory phone call will be performed by the~~Treating~~ Neurologist/ Physician ~~(or Study Physician, where applicable)~~ or by the site's nurse/ study coordinator within 72 hours after the test was scheduled to be performed.	• In order to verify whether the test has been performed and to record the result of the test (see Appendix G), a mandatory phone call will be performed by the Study Neurologist/ Physician or by the site's nurse/ study coordinator within 72 hours after the test was scheduled to be performed.	
Section 8.3.5: Unscheduled visit		
Should the visit be related to a relapse, this will be clearly indicated on the eCRF and the ~~Examining~~ Neurologist/Physician ~~(or Study Physician, where applicable)~~ will carry out a complete neurological evaluation (FS/AI/EDSS/Timed 25 Foot walk).	Should the visit be related to a relapse, this will be clearly indicated on the eCRF and the Study Neurologist/Physician will carry out a complete neurological evaluation (FS/AI/EDSS/Timed 25 Foot walk).	
Section 8.3.6: Visits during relapses (scheduled and unscheduled)		
The ~~Examining Neurologist/Physician (or~~ Study Physician/ Neurologist~~, where applicable, see Section 5.1.1)~~ will evaluate the subject within 7 days of symptoms onset, conditional upon a symptomatic period of ≥ 48 hours. The relapse assessment will be documented in the source documents and in the eCRF accordingly. A complete neurological assessment, including FS, AI EDSS and Timed 25 Foot walk, will be performed by the ~~Examining~~ Neurologist/Physician ~~(or Study Physician, where applicable, see Section 5.1.1)~~. The decision as to whether the neurological change is considered a relapse will be made by the ~~Treating~~ Neurologist/Physician ~~[or by the Study Physician, where applicable (see Section 5.1.1)~~, based on the criteria listed in Appendix B]. Corticosteroids therapy (as described in Section 7.1) may be given for a confirmed relapse at the discretion of the ~~Treating~~ Neurologist/Physician ~~(or by the Study Physician, where~~	The Study Physician/ Neurologist, will evaluate the subject within 7 days of symptoms onset, conditional upon a symptomatic period of ≥ 48 hours. The relapse assessment will be documented in the source documents and in the eCRF accordingly. A complete neurological assessment, including FS, AI EDSS and Timed 25 Foot walk, will be performed by the Study Neurologist/Physician. The decision as to whether the neurological change is considered a relapse will be made by the Study Neurologist/Physician, based on the criteria listed in Appendix B]. Corticosteroids therapy (as described in Section 1.7) may be given for a confirmed relapse at the discretion of the Study Neurologist/Physician and must be recorded in the source documents and eCRF.	

Previous approved wording	Amended or new wording	Reason/Justification for change
~~applicable, see Section 5.1.1)~~ and must be recorded in the source documents and eCRF.		
Section 10.1.1: On study relapse evaluation & determination		
Subjects will be instructed to telephone their study site within 48 hours should any symptoms suggestive of a relapse appear. The ~~Treating Neurologist/Physician (or the~~ Study Physician/Neurologist~~, where applicable) (see Section 5.1.1 and Section 18.1.2)~~ will evaluate the subject once any symptom suggestive of a relapse occurs. ~~In case of a suggestive relapse during a scheduled or unscheduled visit in~~ ~~Period 1 (see Section 5.1.1):~~ ~~ The Treating Neurologist/Physician will refer the subject to the Examining Neurologist/Physician for performance of neurological evaluations and obtain EDSS score (see Section 18.1.3).~~ ~~ An Examining Neurologist/Physician will assess the subject's neurological status, unaware of subject's well being and a Treating Neurologist/ Physician will decide whether a subject experienced a relapse and will treat the subject as needed.~~ In case of a suggestive relapse during a scheduled or unscheduled visit ~~in Period 2 (see Section 5.1.1)~~: The evaluation of symptoms as well as the neurological evaluations/ EDSS will be made by the Study Physician ~~(see Section 18.1.4)~~. Based on the assessment of symptoms and the EDSS/FS evaluation, the Study Physician will decide whether a subject experienced a relapse and will treat the subject as needed. In any case, the neurological evaluation of the subject ~~(by The Examining Neurologist in Period 1 or~~ by the Study Physician/Neurologist ~~in Period 2)~~ will be performed within 7 days of symptoms onset, conditional upon a symptomatic period of ≥ 48 hours.	Subjects will be instructed to telephone their study site within 48 hours should any symptoms suggestive of a relapse appear. The Study Physician/Neurologist will evaluate the subject once any symptom suggestive of a relapse occurs. In case of a suggestive relapse during a scheduled or unscheduled visit: • The evaluation of symptoms as well as the neurological evaluations/ EDSS will be made by the Study Physician/Neurologist. • Based on the assessment of symptoms and the EDSS/FS evaluation, the Study Physician/Neurologist will decide whether a subject experienced a relapse and will treat the subject as needed. In any case, the neurological evaluation of the subject by the Study Physician/Neurologist will be performed within 7 days of symptoms onset, conditional upon a symptomatic period of ≥ 48 hours.	

Previous approved wording	Amended or new wording	Reason/Justification for change
Sections 18.1.2: The treating Neurologist/Physician (applicable in Period 1)		
~~The Treating Neurologist/Physician will be responsible for subject eligibility evaluation, the supervision of the study drug administration, the recording and treating of adverse events, the monitoring of safety assessments, including routine laboratory parameters, and coordinating MRI performance. He/she will determine if a subject experiences a relapse and whether to treat the relapse or not and he/she will decide whether to treat the subject as needed.~~	None.	
Section 18.1.3: The examining Neurologist/Physician (applicable in Period 1)		
~~The Examining Neurologist[1] will be responsible for all neurological examinations. Throughout the study, the Examining Neurologist/Physician will remain unaware of the safety profile. For each subject, the same Examining Physician should be used for all neurological exams performed throughout the study.~~ ~~It is particularly important that:~~ ~~The Treating Neurologist/Physician and the Examining Neurologist/Physician do not discuss safety issues with each other. The Examining Neurologist/Physician will not ask the subject any questions regarding his well being.~~ ~~The Treating Neurologist/Physician will inform the subject of the importance of not discussing safety issues with the Examining Neurologist/Physician.~~ *Footnote:* ~~[1]The Examining Neurologist can be a physician neurologist or other appropriately qualified and documented healthcare professional as deemed by the Principal Investigator and agreed upon by the Sponsor.~~	None.	

Previous approved wording	Amended or new wording	Reason/Justification for change
Old Section 18.1.4/New Section 18.1.2: The Study Physician/Neurologist		
The Study Physician/Neurologist ~~(applicable in Period 2)~~ ~~In case where there is no need for distinction between the Treating and the Examining Physicians/ Neurologists (Period 2) (to be communicated to the clinical sites by the Sponsor, or Sponsor's designee),~~ the Study Physician/-Neurologist will be responsible for the general medical evaluations as well as the neurological assessments. The Study Physician will make the decision as to whether the neurological change is considered a relapse, based on EDSS/FS scores obtained by him/her.	The Study Physician/Neurologist The Study Physician/Neurologist will be responsible for the general medical evaluations as well as the neurological assessments. The Study Physician/Neurologist will make the decision as to whether the neurological change is considered a relapse, based on EDSS/FS scores obtained by him/her.	
Section 19.2: Data monitoring committee (DMC)		
~~During Period 1, the DMC Chairperson will interact with the Sponsor's statistician. Within this work frame, the study un-blinded statistician, will produce and distribute reports to the DMC members. The statistician of the DMC will address any statistical question raised by the DMC during data review, and will perform data analyses according to the DMC's request. During Period 2, this interaction may be done via the Global Clinical Leader.~~	None.	
Appendix B - Definitions		
~~In Period 1 (see Section 5.1.1), the subjects' general medical evaluations will be assessed separately from their neurological assessment evaluations by two different Neurologists/ Physicians. An Examining Neurologist/Physician will assess the subject's neurological examination, unaware of subject's well being and a Treating Neurologist/ Physician will decide whether a subject experienced a relapse and will prescribe steroids or other concomitant medications as needed.~~ ~~The Treating Neurologist/Physician will make the decision as to whether the neurological change is considered a relapse, based on EDSS/FS scores as assessed by the Examining Neurologist/ Physician (see Relapse Definition, above).~~ ~~Follow-up visits to monitor the course of the relapse until stabilization will be made at the Treating Neurologist/Physician discretion, in addition to the assessment at the next scheduled visit.~~	In Period 2 (see Section 5.1.1), there will be no distinction between the Treating Neurologist/ Physician and the Examining Neurologist/ Physician. In such cases, a single Study Physician/Neurologist will be responsible for the general medical evaluations as well as the neurological assessments. The Study Physician/Neurologist will make the decision as to whether the neurological change is considered a relapse, based on EDSS/FS scores obtained by him/her. The Study Neurologist/ Physician will follow-up on the subject during the course of a relapse, until stabilization. Relapse Evaluation Procedures Subjects will be instructed to telephone their study site within 48 hours should any symptoms suggestive of a relapse appear. The Study Neurologist/ Physician will evaluate the subject	

Previous approved wording	Amended or new wording	Reason/Justification for change
In Period 2 (see Section 5.1.1), there will be no distinction between the Treating Neurologist/ Physician and the Examining Neurologist/ Physician. In such cases, a single Study Physician will be responsible for the general medical evaluations as well as the neurological assessments. The Study Physician will make the decision as to whether the neurological change is considered a relapse, based on EDSS/FS scores obtained by him/her. The Study Neurologist/ Physician will follow-up on the subject during the course of a relapse, until stabilization. Relapse Evaluation Procedures Subjects will be instructed to telephone their study site within 48 hours should any symptoms suggestive of a relapse appear. ~~In Period 1, the Examining~~ Neurologist/ Physician will evaluate the subject within 7 days of symptoms onset, conditional upon a symptomatic period of ≥ 48 hours: The ~~Treating~~ Neurologist/Physician will evaluate the subject once any symptom suggestive of a relapse occurs. ~~In case of a suggestive relapse during a scheduled or unscheduled visit, the Treating Neurologist/Physician will refer the subject to the Examining Neurologist/Physician.~~ ~~In Period 2, all of the above mentioned relapse evaluation activities will be performed by the Study Neurologist/ Physician.~~	within 7 days of symptoms onset, conditional upon a symptomatic period of ≥ 48 hours: The Study Neurologist/Physician will evaluate and treat the subject once any symptom suggestive of a relapse occurs.	

Previous approved wording	Amended or new wording	Reason/Justification for change
Appendix I: MSFC administration instruction		
For subjects with significant gait impairment, the ~~Treating~~ Neurologist/Physician should have the subject use a rolling walker even if this is not the subject's customary device.	For subjects with significant gait impairment, the Study Neurologist/Physician should have the subject use a rolling walker even if this is not the subject's customary device.	
Section 11: Safety and pharmacovigilance		
SAE reporting In order to satisfy regulatory requirements, any Serious Adverse Event, whether deemed IMP-related or not, must be reported to the ~~Local Clinical Management~~ as soon as possible after the investigator or coordinator has become aware of its occurrence. The SAE form completion and reporting must not be delayed even if all of the information is not available at the time of the initial contact. The SAE should be submitted within 24 hours of becoming aware of the event to the ~~Local Clinical Management~~. The ~~local Clinical Management~~ will forward the report to the Local Safety Officer who will forward the SAE report to the ~~Global~~ Pharmacovigilance Unit: SAE originated in Europe and rest of the world should be sent to: Global Drug Safety and Pharmacovigilance Unit (Israel) [redacted] SAE originated in USA will be sent to: [redacted] SAE originated in Canada will be sent to: [redacted]	SAE reporting In order to satisfy regulatory requirements, any SAE, whether deemed IMP-related or not, must be reported to the CRO as soon as possible after the investigator or coordinator has become aware of its occurrence. The SAE form completion and reporting must not be delayed even if all of the information is not available at the time of the initial contact. The SAE should be submitted within 24 hours of becoming aware of the event to the CRO. The CRO will forward the report to the appropriate Pharmacovigilance unit at Teva or the LSO who will forward the SAE report to the appropriate Pharmacovigilance unit at Teva: SAE originated in Europe and rest of the world should be sent to: Global Drug Safety and Pharmacovigilance Unit (Israel) [redacted] SAE originated in USA will be sent to: Teva USA clinical safety mailbox [redacted] SAE originated in Canada will be sent to: Teva Canada clinical safety mailbox [redacted]	

Previous approved wording	Amended or new wording	Reason/Justification for change
[redacted] Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the site within 24 hours of the information becoming available to the ~~Local Clinical Management~~. For both initial and follow-up SAE reports the ~~Local Clinical Management~~ forwards this information to the Local Safety Officer who forwards it to the appropriate Pharmacovigilance unit at Teva within 48 hours. The Pharmacovigilance units at Teva will submit a summary of the clinical course of the SAEs back to the ~~Local Clinical Management~~/ Local Safety Officer for local submission to the regulatory authorities (CA) and EC/IRBs and investigators according to regulations. ~~In Period 1, blinding will be maintained for the people who are involved directly in the study, therefore in case of a SUSAR case only the Local Safety Officer will receive the un-blinded report for regulatory submission, while the others will receive a blinded report (Teva S.O.P 50.11.16). This precaution is not relevant for Period 2.~~ […] ~~Pregnancy reports: Pregnancy reports should be forwarded to the Pharmacovigilance for data entry to the global safety database. This includes also normal pregnancies without AE. The pregnancies reporting procedure should be the same as the SAE reporting procedure.~~ ~~The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defect, congenital abnormalities or maternal and newborn complications. Pregnancy follow-up should be recorded on a specific eCRF provided by Local Clinical Trial Management.~~	SAE originated in Germany will be sent to: Teva Germany safety mailbox [redacted] Only in the event of difficulty transmitting the form via email send the form to fax, or contact the sponsor's study personnel identified above for further instruction. Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the site within 24 hours of the information becoming available to the contract research organization. For both initial and follow-up SAE reports the contract research organization forwards this information to the appropriate Pharmacovigilance unit at Teva or the LSO who forwards it to the appropriate Pharmacovigilance unit at Teva within 48 hours. The Pharmacovigilance units at Teva will submit a summary of the clinical course of the SAEs back to the CRO/ LSO for local submission to the regulatory authorities (competent authorities [CA]) and EC/Institutional Review Boards (IRBs) and investigators according to regulations. […] Pregnancy reports: Pregnancies should be reported throughout the study. This includes also normal pregnancies without AE. The pregnancy should be followed up 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. The pregnancies reporting procedure should be the same as the SAE reporting procedure. Pregnancy follow up should be recorded on a specific CRF provided by CRO.	

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 8.3.1: Criteria for early treatment discontinuation		
None.	[…] 8) Planned pregnancy 9) Lack of efficacy (according to the Investigator's decision) […]	Two additional criteria for early treatment discontinuation have been included: pregnancy (due to fact that laquinimod is contraindicated in pregnancy) and lack of efficacy.
Section 3: Introduction		
-	See section	The section has been greatly revised to bring in line with current experience. Please see section for full details.
SYNOPSIS AND Section 6.1 Inclusion Criteria		
2. Women of child-bearing potential must practice ~~an~~ acceptable method of birth control [acceptable methods of birth control in this open label extension phase include: ~~surgical sterilization,~~ intrauterine devices, ~~oral contraceptive, contraceptive patch (or hormone releasing vaginal ring), long-acting injectable contraceptive, partner's vasectomy or double-barrier method (condom or diaphragm with spermicide)] during the study and up to 30 days after the last dose of the study drug.~~.	2. Women of child-bearing potential **(for example women who are not postmenopausal or surgically sterilized**) must practice **two** acceptable method**s** 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 in this open label extension phase include: intrauterine devices, **barrier methods (condom or diaphragm with spermicide), and hormonal methods of birth control (e.g. oral contraceptive, contraceptive patch, and long-acting injectable contraceptive)].**	Teva considers the prevention of exposure to laquinimod during pregnancy to be of great importance, and following consultation with the CHMP and Data Monitoring Committee (DMC) has decided to introduce additional language and measures for pregnancy prevention in this amendment.
Section 18.2.6 Global Clinical Safety Director		
~~The Global Clinical Safety Director will be responsible for all safety aspects of the study. He/she will ensure that the safety of the subjects is appropriately assessed and maintained according to the study protocol, objectives and goals. He/she will assist in the approval and preparation of safety data as required and will act as liaison with the external DMC (see details below).~~	Section deleted	Text deleted to bring up to date with current process.
Section 18.2.7. Global Drug Safety and Pharmacovigilance		
Global Drug Safety & Pharmacovigilance is responsible for: reviewing any safety issues that arise during the study, assessing and evaluating the SAEs occurring during the study and submission of relevant SAEs to health authorities/CA as per regulations. ~~The Global Clinical Safety Officer is~~	Global Drug Safety & Pharmacovigilance is responsible for: reviewing safety issues that arise during the study, assessing and evaluating the causality of SAEs occurring during the study and submission of relevant SAEs to health authorities/CA as per regulations.	Text amended to bring up to date with current process.

Previous approved wording	Amended or new wording	Reason/Justification for change
~~responsible for all safety aspects of the study. He/she will ensure that the safety of the subjects is appropriately assessed and maintained according to the study protocol, objectives and goals. He/she will assist in the approval and preparation of safety data as required.~~		
Entire document		
-	Numbering of Appendices has been changed throughout the text.	Updated cross-references to appendices (due to addition of a new Appendix F). In addition, literature references have been changed to reflect the changes in the protocol

23. CHANGES TO PATIENT ENTRY CRITERIA

Not applicable.

APPENDIX A. DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS: 2005 REVISIONS TO THE "MCDONALD CRITERIA"

Every attempt will be made to obtain documentation of relapses that occurred within one and two years prior to study entry. If written documentation is not available, the Investigator will contact the subject's physician by phone in order to obtain all information of the subject's relapses. This should be documented as a phone-call report.

MS Diagnosis

Confirmation of RRMS diagnosis according to the revised McDonald criteria will be performed during screening.

In April 2001, an international panel in association with the NMSS of America recommended diagnostic criteria for multiple sclerosis. These criteria have become known as the McDonald criteria after their lead author. They make use of advances in MRI techniques and are intended to replace the Poser Criteria and the older Schumacher Criteria. In March 2005 in Amsterdam, nearly 5 years after the publication of the McDonald criteria [(a)], the International Panel reached consensus on the 2005 Revisions to the "McDonald Criteria Diagnostic Criteria for Multiple Sclerosis"[(a)].

[a] McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121–127

Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the "McDonald Criteria"

Clinical Presentation	Additional Data Needed
Two or more attacks[a]; objective clinical evidence of two or more lesions	None[b]
Two or more attacks[a]; objective clinical evidence of one lesion	Dissemination in space, demonstrated by: MRI[c] *or* Two or more MRI-detected lesions consistent with MS plus positive CSF[d] *or* Await further clinical attack[a] implicating a different site
One attack[a]; objective clinical evidence of two or more lesions	Dissemination in time, demonstrated by: MRI[e] or Second clinical attack[a]
One attack[a]; objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space, demonstrated by: MRI[c] or Two or more MRI-detected lesions consistent with MS plus positive CSF[d] *and* Dissemination in time, demonstrated by: MRI[e] or Second clinical attack[a]

[a] An attack is defined as an episode of neurological disturbance for which causative lesions are likely to be inflammatory and demyelinating in nature. There should be subjective report (backed up by objective findings) or objective observation that the event lasts for at least 24 hours

[b] No additional tests are required; however, if tests (MRI, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS. Alternative diagnoses must be considered. There must be no better explanation for the clinical picture and some objective evidence to support a diagnosis of MS.

[c] Space dissemination demonstrated by MRI should have three of the following conditions: At least one gadolinium-enhancing lesion or nine T_2 hyperintense lesions if there is no gadolinium enhancing lesion; At least one infratentorial lesion; At least one juxtacortical lesion; At least three periventricular lesions. A spinal cord lesion can be considered equivalent to a brain infratentorial lesion: an enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion, and individual spinal cord lesions can contribute together with individual brain lesions to reach the required number of T_2 lesions.

[d] Positive CSF determined by oligoclonal bands detected by established methods (isoelectric focusing) different from any such bands in serum, or by an increased IgG index .

[e] Time dissemination demonstrated by MRI should have one of the following conditions: Detection of gadolinium enhancement at least 3 months after the onset of the initial clinical event, if not at the site corresponding to the initial event; Detection of a new T2 lesion if it appears at any time compared with a reference scan done at least 30 days after the onset of the initial clinical event

CSF = cerebrospinal fluid, MRI = magnetic resonance imaging, MS = multiple sclerosis

APPENDIX B. DEFINITIONS

Relapse (attack)

A relapse will be defined as the appearance of one or more new neurological abnormalities or the reappearance of one 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[a]". Since "in study" relapse definition must be supported by an objective neurological evaluation (see next paragraph), a neurological deficit must sustain long enough to eliminate pseudo-relapses.

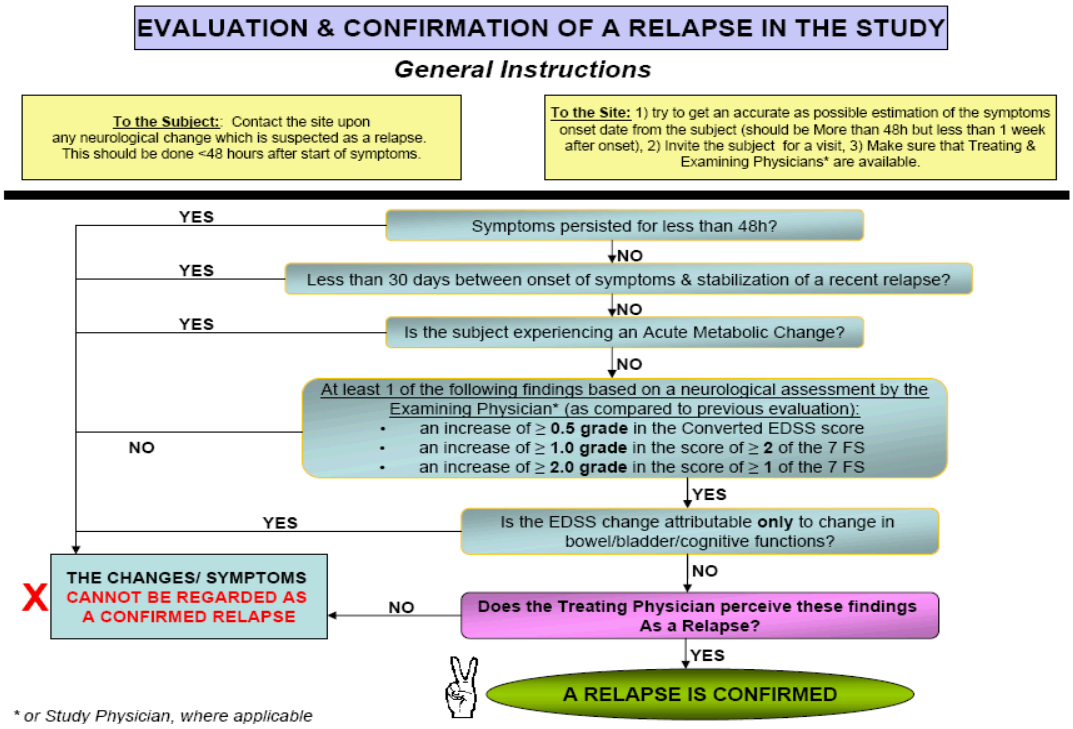
An event will be counted as a relapse only when the subject's symptoms are accompanied by observed objective neurological changes, consistent with at least one of the following:

- an increase of at least 0.5 in the EDSS score as compared to previous evaluation.
- an increase of one grade in the score of 2 or more of the 7 FS as compared to previous evaluation.
- an increase of 2 grades in the score of one FS as compared to the previous evaluation.

The EDSS/FS/AI (in the first visit indicative for a relapse, as well as in follow up visits) will be a part of a complete neurological assessment performed by the Examining Neurologist/ Physician (or the Study's Neurologist/ Physician, in case all subjects in the MS-LAQ-301 double-blind placebo-controlled study have completed (or early terminated) their treatment period).

The subject must not be undergoing any acute metabolic changes such as fever or other medical abnormality. A change in bowel/bladder function or in cognitive function must not be entirely responsible for the changes in EDSS or FS scores.

[a] Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis (McDonald, Ann. Neurol. 2001;50:121-127)


EVALUATION & CONFIRMATION OF A RELAPSE IN THE STUDY
General Instructions
To the Subject: Contact the site upon any neurological change which is suspected as a relapse. This should be done <48 hours after start of symptoms.
To the Site: 1) try to get an accurate as possible estimation of the symptoms onset date from the subject (should be More than 48h but less than 1 week after onset), 2) Invite the subject for a visit, 3) Make sure that Treating & Examining Physicians* are available.
Symptoms persisted for less than 48h?
YES
NO
Less than 30 days between onset of symptoms & stabilization of a recent relapse?
YES
NO
Is the subject experiencing an Acute Metabolic Change?
YES
NO
At least 1 of the following findings based on a neurological assessment by the Examining Physician* (as compared to previous evaluation):
• an increase of ≥ 0.5 grade in the Converted EDSS score
• an increase of ≥ 1.0 grade in the score of ≥ 2 of the 7 FS
• an increase of ≥ 2.0 grade in the score of ≥ 1 of the 7 FS
NO
YES
Is the EDSS change attributable only to change in bowel/bladder/cognitive functions?
YES
NO
Does the Treating Physician perceive these findings As a Relapse?
NO
X
THE CHANGES/ SYMPTOMS CANNOT BE REGARDED AS A CONFIRMED RELAPSE
YES
A RELAPSE IS CONFIRMED
* or Study Physician, where applicable

In Period 2 (see Section 5.1.1), there will be no distinction between the Treating Neurologist/ Physician and the Examining Neurologist/ Physician. In such cases, a single Study Physician/Neurologist will be responsible for the general medical evaluations as well as the neurological assessments. The Study Physician/Neurologist will make the decision as to whether the neurological change is considered a relapse, based on EDSS/FS scores obtained by him/her. The Study Neurologist/ Physician will follow-up on the subject during the course of a relapse, until stabilization.

Relapse Evaluation Procedures

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

The Study Neurologist/ Physician will evaluate the subject within 7 days of symptoms onset, conditional upon a symptomatic period of ≥ 48 hours.

The Study Neurologist/Physician will evaluate and treat the subject once any symptom suggestive of a relapse occurs.

Relapsing-Remitting (R-R) Multiple Sclerosis (MS)

RRMS is characterized by clearly defined acute attacks with full recovery or with sequelae and residual deficit upon recovery, periods between disease relapses characterized by a lack of disease progression (Lublin 1996)[a].

[a] Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis. Neurol 1996;46:907-911.

APPENDIX C. NEUROSTATUS

Standardized Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status (EDSS).

neurostatus

DEFINITIONS

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

By Stacy S. Wu, MD and Prof. Ludwig Kappos, MD

Slightly modified from J.F. Kurtzke, Neurology 1983:33,1444-52

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.

NEUROSTATUS (NS)

In the Neurostatus, "signs only" is noted when the examination reveals signs of which the patient is unaware.

FUNCTIONAL SYSTEMS (FS)

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. Signs or symptoms that are not due to multiple sclerosis will not be taken into consideration for assessments, but should be noted.

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 (use best available correction). Alternatively, best corrected near vision can be assessed, but this should be noted and consistently performed during 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 is 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

*optional

FUNCTIONAL SYSTEM SCORE

0 normal
1 disc pallor and/or mild 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 large scotoma and/or maximal visual acuity (corrected) of 20/30 to 20/59 (0.67–0.34)
3 worse eye with large scotoma or moderate decrease in fields and/or maximal visual acuity (corrected) of 20/60 to 20/99 (0.33–0.2)
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 (0.3) 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 (0.3) or less
6 grade 5 plus maximal visual acuity of better eye of 20/60 (0.3) or less

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
2 mild
3 moderate: cannot hear finger rub and/or 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 BULBAR 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
2a moderate nystagmus
2b other mild disability
3a severe nystagmus
3b marked extraocular weakness
3c moderate disability of other cranial nerves
4a marked dysarthria
4b 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 functional tests, such as hopping on one foot and walking on heels/toes, are 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 position 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

*optional

FUNCTIONAL SYSTEM SCORE

0 normal
1 abnormal signs without disability
2 minimal disability: patient complains of fatigability or reduced performance in strenuous motor tasks and/or BMRC grade 4 in one or two muscle groups
3a mild to moderate paraparesis or hemiparesis: usually BMRC grade 4 in more than two muscle groups or BMRC grade 3 in one or two muscle groups; movements against gravity are possible
3b severe monoparesis: BMRC grade 2 or less in one muscle group
4a marked paraparesis or hemiparesis: usually BMRC grade 2 in two limbs
4b moderate tetraparesis: BMRC grade 3 in three or more limbs
4c monoplegia: BMRC grade 0 or 1 in one limb
5a paraplegia: BMRC grade 0 or 1 in all muscle groups of the lower limbs
5b hemiplegia
5c marked tetraparesis: BMRC grade 2 or less in three or more limbs
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: abnormal balance only with tandem walking
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 ataxia alone (without severe truncal ataxia and severe ataxia in three or four limbs) results in a Cerebellar FS score of 3.
If weakness interferes with the testing of ataxia, score the patient's actual performance, but also indicate the possible role of weakness by marking an "X" after the Cerebellar FS score.

UE = upper extremities
LE = lower extremities

FUNCTIONAL SYSTEM SCORE

0 normal
1 abnormal signs without disability
2 mild ataxia
3a moderate truncal ataxia
3b moderate limb ataxia
3c moderate or severe gait ataxia
4 severe 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) interferes 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

0 = negative
1 = positive
(does not contribute to the Sensory FS score)

*PARAESTHESIAE (TINGLING)

0 = none
1 = present
(does not contribute to the Sensory FS score)

UE = upper extremities
LE = lower extremities
*optional

FUNCTIONAL SYSTEM SCORE

0 normal
1 mild vibration or figure-writing or temperature decrease only in one or two limbs
2a mild decrease in touch or pain or position sense and/or moderate decrease in vibration in one or two limbs
2b mild vibration or figure-writing or temperature decrease alone in three or four limbs
3a moderate decrease in touch or pain or position sense and/or essentially lost vibration in one or two limbs
3b mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs
4a marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs
4b moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs
5a loss (essentially) of sensation in one or two limbs
5b moderate decrease in touch or pain and/or loss 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

0 none
1 mild
2 moderate
3 severe
4 loss of function

NOTE

When determining the EDSS step, the Bowel and Bladder FS score is 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

*optional

FUNCTIONAL SYSTEM SCORE

0 normal
1 mild urinary hesitancy, urgency and/or constipation
2 moderate urinary hesitancy and/or urgency and/or rare urinary incontinence and/or severe constipation
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.

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.

NOTE

The presence of depression and/or euphoria alone results in a Cerebral FS score of 1a, but does not affect the EDSS step. However, a Cerebral FS score of 1b due to mild fatigue and/or signs only decrease in mentation contributes to the determination of the EDSS step.

FUNCTIONAL SYSTEM SCORE

0 normal
1a mood alteration (depression and/or euphoria) alone (does not affect EDSS step)
1b mild fatigue; signs only decrease in mentation
2 mild decrease in mentation; moderate or severe fatigue
3 moderate decrease in mentation
4 marked decrease in mentation
5 dementia

8 AMBULATION

DEFINITIONS

Observe the patient walking unassisted for a minimum distance of 500 meters, if possible. If the patient walks with assistance, observe the patient walking with the assistive device for a minimum distance of 130 meters, if possible.

If a patient walks without assistance and the walking range determines the EDSS step, please note that the definitions mark the lower limit for each step. For example, if a patient is able to walk 280 meters without aid or rest, the EDSS step is still 5.0. An EDSS step of 4.5 is defined by an unassisted walking distance of ≥ 300 meters (but < 500 meters).

The definitions of EDSS steps 6.0 and 6.5 include both a description of the type of assistance required when walking and the walking range. In general, the type of assistance required (unilateral vs. bilateral) overrules the walking range when determining the EDSS step.

HOWEVER, THE FOLLOWING EXCEPTIONS APPLY:

1. If a patient is able to walk considerably longer than 100 meters (> 120 meters) with two sticks, crutches or braces, the EDSS step is 6.0.
2. If a patient needs two sticks, crutches or braces to walk between 10 and 120 meters, the EDSS step is 6.5.
3. If a patient is able to walk more than 50 meters with one stick, crutch or brace, the EDSS step is 6.0.
4. If a patient cannot walk more than 50 meters with one stick, crutch or brace, the EDSS step is 6.5.

NOTE

1. Assistance by another person (as opposed to one stick, crutch or brace) is equivalent to bilateral assistance.
2. The use of an ankle foot orthotic device, without any other type of assistive device, is not considered unilateral assistance.

When determining the EDSS step, the Visual FS and Bowel and Bladder FS scores are 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
Bowel and Bladder FS Score	6	5	4	3	2	1
Converted Bowel and Bladder FS Score	5	4	3	3	2	1

Please enter both the actual and converted scores.

9 KURTZKE'S EXPANDED DISABILITY STATUS SCALE

DEFINITIONS

- EDSS steps below 4 refer to patients who are fully ambulatory (able to walk ≥ 500 meters). The precise step is defined by the Functional System (FS) scores.
- EDSS steps between 4.0 and 5.0 are defined by both the FS scores and the walking range. In general, the more severe parameter determines the EDSS step.
- 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.
- From steps 0 to 4.0, the EDSS should not change by 1.0 step, unless there is a similar change in a FS score by 1 grade.
- The EDSS step should not be lower than the score of any individual FS, with the exception of the Visual and Bowel/Bladder FS.

NOTE

A Cerebral FS score of 1a due to depression and/or euphoria alone does not affect the EDSS step. However, a Cerebral FS score of 1b due to mild fatigue and/or signs only decrease in mentation contributes to the determination of the EDSS step.

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 ≥ 100 meters
6.0	unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting
6.5	constant bilateral assistance (canes or crutches) required to walk at least 20 meters without resting
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
10.0	death due to MS

APPENDIX D. MRI PROTOCOLS (INCLUDING MT AND MRS)

INTRODUCTION

All of the MRI scans will be evaluated in accordance with local clinical practice. Any pathological finding(s) not related to MS will be reported by the responsible radiologist to the Treating Investigator consistent with existing local procedures.

The electronic data derived from each MRI scan will be sent to the MRI-AC for approval and processing.

All subjects who participated in the Frequent MRI ancillary study (in the MS-LAQ-301 Study) and continue to the MS-LAQ-301E study will be offered to participate in an MRI ancillary study in the open-label extension. A separate informed consent form will need to be signed for this purpose. The MRI scans will be performed at months 0E [Baseline; this is the Termination scan of the MS-LAQ-301 study)] and every 12 months thereafter, until termination/early discontinuation visit.

The Baseline scan (month 0E) of the MS-LAQ-301E study will be the same scan as the Termination scan of the MS-LAQ-301 study (According to the MS-LAQ-301 protocol, the Termination MRI scan of the MS-LAQ-301 study will be performed within 4 days prior to the Termination visit). This scan is a part of the MS-LAQ-301 protocol.

In case the Termination visit of the study is scheduled to less than 14 days after the performance of a scheduled MRI scan – the scan should not be repeated.

The following parameters will be assessed at each scheduled scan:

- Number of T_1 Gd-enhancing lesions
- Number of new T_2 lesions
- Volume of T_2 lesions
- Number of new hypointense T_1 lesions on enhanced T_1 scans ("black holes")
- Volume of hypointense T_1 lesions on enhanced T_1 scans ("black holes")
- Brain volume: Percentage of brain volume change from:
  - Baseline scan of the MS-LAQ-301E (month 0E) (Termination visit of the MS-LAQ-301 study) to all of the scans obtained in MS-LAQ-301E study (i.e. month 12E, month 24E, etc).

SCANNER DEVICE

Devices supplied by various manufacturers can be used. The following requirements apply:

Scanners should have at least 1.5 Tesla magnetic field strength.

The same scanner must be used for each subject for the entire duration of the study.

Software and hardware upgrades may be permissible but must be reported to MRI-AC and may require a re-approval process (including Dummy Run, see below) for the site.

Scanner must be able to create a back up copy of all subject scans performed.

The back up copy of baseline scan obtained for the MS-LAQ-301E open-label extension Study should be used for subject repositioning during all study duration.

Electronic backups of all scans must be archived at each site.

POSITIONING THE SUBJECT

Given the importance of careful repositioning for serial MRI lesion counting and load assessments, great care should be taken when positioning the subjects in the scanner and head holder. The following rules apply to all the sites:

Check that the subject can successfully undergo MRI examination, including GFR estimation.

Following recent findings connecting Gd-based contrast agents and nephrogenic systemic sclerosis, GFR value should be evaluated prior to performing an MRI scan, where administration of Gd-based contrast agent is planned. The central laboratory will provide the GFR value prior to the scheduled MRI tests. In case GFR estimation is not provided by the central laboratory, calculation should be done at the site, prior to any MRI scan via the following web calculator:

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

In case GFR is ≤60 mL/min, the MRI scan should be performed without contrast (Gd) and further evaluation of renal impairment is required (refer to Section 8.3.2.5)

Enter the subject data into the scanner console, using:

- study number (protocol number, site number, subject number)
- date of birth/sex
- weight
- Visit number

Explain the scanning procedure to the subject and position her/him in the scanner in the most comfortable position.

Insert an IV needle in the subject's arm and connect it with a long-line catheter to a drip-infusion of saline; for contrast injection the operator will be able to use the long-line without moving the subject table from the scanner.

Position the subject's head and align it in the machine using land-marking devices provided with most of the equipment.

Position the subject's eyebrows at the center of the coil and make sure that the horizontal light beam runs over the eyebrows and as close as possible to the line marking the coil center.

Position the nose along the Z axis of the scanner, i.e., make sure that the vertical light beam runs over the nose.

To avoid subject's head movement, fix it with foam cushions and strips.

Move the subject into the scanner.

MRI ACQUISITION PROTOCOL

The acquisition protocol is accomplished with seven series of scans. The first three scans are for localization, the fourth for a quick check of localization, the fifth to provide T2-weighted and proton-density-weighted images, the sixth to provide a 3D pre-contrast T1-weighted sequence and the seventh to provide post-contrast delineation of enhancing lesions. As noted, the first three imaging scans are for the purpose of localization and for them a tri-pilot localizer scan, if available, may be substituted. If this option is employed, following the tri-pilot localizer the protocol continues with scans referred to as Series 4,5,6 and 7. In this case, there will be five scans in each protocol acquisition. The primary objective for the localizing scans is to provide an optimal prescription for the scans that will be subjected to quantitative analysis. The MRI-AC will perform this analysis on Series 5, 6 and 7. The prescribed scan parameters must be followed absolutely in order to make possible quantitative analysis. The only permitted exceptions are those noted below.

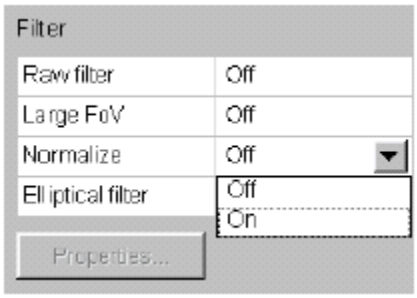
General Notes:

Do not use SMASH, SENSE, GRAPPA or related techniques. Parallel acquisition is not permitted by this protocol.

If using a multi-channel head coil, turn on intensity correction if available. This is done as follows:

On PHILIPS scanners: Acquire a coil sensitivity map. In the GEOMETRY tool select: CLEAR: YES. Body tuned: NO.

On SIEMENS scanners: in the Resolution task card, select NORMALIZE by activating this filter with the drop down option ON.



On GE scanners select SCIC (surface coil intensity correction).

Do not deviate from the specifications for the field of view (FOV). If the cranial size is large, the whole brain may not fall within the scanning range. In this case do not change slice number (44) and do leave slice group centered at the inferior borders of the genu and splenium of the corpus callosum. In this case the portion of the brain that is covered will be analyzed and the study will be valid.

Where a range of values are achievable for TE, use the smallest acceptable value.

The study allows a rectangular FOV for certain scans as noted below, but the protocol always requires **100% sampling in the frequency encode direction**. With some scanners care must be taken to avoid an automated reduction in this parameter that can result in scan rejection.

For Siemens, set "percentage sampling"=100% and "half fourier"=no

For Philips scanner, set "scan percentage"=100% and "half scan"=no

Leave the reconstruction matrix the same as the acquisition matrix and do not select the "interpolation" option, available on some scanners, by which reconstruction is done with a larger matrix than was acquired. All Siemens users must turn off "Interpolation" which is found under "Resolution" o the scanner console. Philips users should make sure that reconstruction matrix is 256.

The following order for sequences will be kept:

1) T_1-weighted axial scout

2) T_1-weighted coronal scout

3) T_1-weighted sagittal scout

These first three scans are for the purpose of localization and for them a tri-pilot localizer scan, if available, may be substituted. If this option is employed, following the tri-pilot localizer continue with #4.

4) Rapid T_1-weighted SE or T_2-weighted FSE/TSE axial (this is for repositioning check)

Sequences from 1 to 4 will be done to obtain reference images for subject's repositioning (For more details see MRI guideline). The MRI-AC center will not verify the acquisition parameters of these four sequences. In the MRI manual, acquisition parameters are suggested to help the set of these sequences.

The sequences of the main protocol, which will be checked in terms of acquisition parameters and quality of the images, are those numbered from 5 to 7.

5) T_2-weighted FSE/TSE

6) T_1 weighted MP-RAGE (for Siemens), 3D-fast SPGR (for GE), 3D-TFE (for Philips)

7) T_1-weighted SE post gadolinium

SEQUENCE PARAMETERS FOR 1.5 TESLA SCANNER

a) **Sequences for positioning and repositioning the subjects (no check by MRI-AC):**

Sequence 1: **T_1-weighted axial scout**

TR (ms)	TE (ms)	# of slices	Slice Thickness (mm)	Inter-Slice Gap	FOV (mm)	Matrix	# of average	Phase encoding
100	**10-20**	**3**	**5**	**5**	**210-230**	**256 x 128**	**1**	**L-R**

Using sequence 1 as a reference, make a coronal scout, parallel to the brain transverse diameter and depicting the midline of the brain best (i.e., at the level of the brainstem)

Sequence 2: **T_1-weighted coronal scout**

TR (ms)	TE (ms)	# of slices	Slice Thickness (mm)	Inter-Slice gap	FOV (mm)	Matrix	# of average	Phase encoding
100	**10-20**	**1**	**5**	**-**	**210-230**	**256 x 128**	**1**	**L-R**

From the coronal scout make a sagittal scout image, aligned with the falx cerebri and other midline structures, such as the third ventricle.

Sequence 3: **T_1-weighted sagittal scout**

TR (ms)	TE (ms)	# of slices	Slice Thickness (mm)	Inter-Slice gap	FOV (mm)	Matrix	# of average	Phase encoding
500-650	**10-20**	**1**	**5**	**-**	**210-230**	**256 x 128**	**1 to 3**	**A-P**

On the sagittal scout image previously obtained, position the axial image group, placing the center of the slice group at the inferior borders of the genu and splenium of the corpus callosum. **For a correct positioning of the subject at baseline and a subsequent repositioning during the follow up, the use of the inferior borders of the genu and splenium of the corpus callosum as reference is a main requirement of the protocol.**

Save the localizer image with the slices shown on it, to achieve the same slice positioning on subsequent scans; then make a rapid series of either T_1-weighted or T_2-weighted images (according to the site preference) in order to check the correct positioning of the slices.

Sequence 4a: **Rapid T_1-weighted Spin Echo**

TR (ms)	TE (ms)	# of slices	Slice Thickness (mm)	Inter-Slice Gap	FOV (mm)	Matrix	# of average	Phase encoding
600	10-20	22	3	3	250	140 x 128	1	L-R

OR

Sequence 4b: **T_2-weighted Turbo Spin Echo axial**

TR (ms)	TE (ms)	# of slices	Slice Thickness (mm)	Inter-Slice Gap	FOV (mm)	Matrix	# of average	Phase encoding
2200-3000	30-50/ 60-100	22	3	3	250	256 x 128	1	L-R

Please note that the back-up, (saved also on disc), of this first series of T_1 or T_2 axial images should be done only for the baseline scan and used as reference for repositioning the subsequent serial scans.

Write the slice positioning parameters (shift and rotation angle) of this series and use them for the subsequent series of the same scan (this is not necessary if the scanner has a repeat or history function).

b) **Sequences of the main protocol (check by MRI-AC):**

Sequence 5: T_2-weighted Fast/Turbo Spin Echo (axial)

a. a single series of 2 concatenated and interleaved packages of 22 slices each (44 images)

TR (ms)	TE (ms)	# of slices	Slice Thickness (mm)	Inter-Slice Gap	FOV (mm)	Matrix	# of average	Percentage of sampling	Phase encoding	ETL
2500-3500	14-50/ 90-120	22	3	0	250	256 x 256	1	100%	L-R	4-6

OR

b. two series of 22 images

TR (ms)	TE (ms)	# of slices	Slice Thickness (mm)	Inter-Slice Gap	FOV (mm)	Matrix	# of average	Percentage of sampling	Phase encoding	ETL
2500-3500	14-50/ 90-120	22	3	3	250	256 x 256	1	100%	L-R	4-6

Position an axial presaturation slab (50-80 mm) inferior to the slice group to suppress flow-related artifacts.

The 44 interleaved slices are acquired in a single series or, alternatively, in two series of 22 slices. **Scans with additional slices will not be accepted.**

Some scanners allow two separate acquisitions (each of 22 slices) to be performed sequentially and automatically from a single prescription. If the scanner used allows the acquisitions to be split automatically in this way, it is preferable to use this option. The number of acquisition is automatically calculated by the system according to the specified TR. Please, check that the number of acquisition is set to 2 (Siemens scanner refers to this parameter as "concatenation", GE scanners as "acquisitions", and Philips scanner as "Packages" on the "Info" page). If the number of acquisitions is greater than 2, adjust upward TR by small steps to obtain 2 acquisitions.

If two series of 22 slices may be acquired, the first series must have slice positions as fast series whereas the second one must have slice positions shifted 3 mm caudally compared with the first one, such that when both series are combined, the desired region is covered. The intent is to have contiguous coverage of the prescribed region with 44 interleaved slices (no slice gap).

Please, note that for the main protocol only 44 slices are required. Scans with additional slices will not be accepted.

Sequence 6:**T_1 weighted MP-RAGE (for Siemens), 3D-fast SPGR (for GE), 3D-TFE (for Philips)**

TR (ms)	TE (ms)	# of slices	Slice thickness (mm)	FOV (mm)	Matrix	# of average	Orientation	Flip Angle	TI (sec)	Phase encoding
8-15	3-5	160	1.2	256x256	256 x 256	1	Sagittal	10-15	1.1	A-P L-R

For Siemens scanners, set TR (which is intended as the time between inversion pulses) in the range of 2000-2300 ms.

For Philips scanners, set shot mode = multi shot and the TFE factor = 256; then set the shot interval in the range 2000-2300 ms.

Position the box in order to have the top just above the scalp. Rotate the box by the same amount that was used for sagittal scout.

Perform a bolus injection of Gd-DPTA using the IV long-line and without moving the subject from the scanner. Use contrast at a standard dose of 0.1 mmol/kg (i.e., 0.2 ml/kg). Before Gd administration the acquisition of additional sequences is allowed by negotiation with the MRI-AC ([redacted]). After a post-injection delay of 5 minutes, complete the scanning with post-Gd T_1-weighted SE images.

Sequence 7: **T_1-weighted conventional Spin Echo (axial)**

a. a single series of 2 concatenated packages of 22 slices each (44 images)

TR (ms)	TE (ms)	# of slices	Slice thickness (mm)	Inter-Slice gap	FOV (mm)	Matrix	# of average	Percentage of sampling	Phase encoding	Presaturation slab/flow compensation
600-650	10-20	22	3	0	250	256 x 256	2	100%	L-R	yes

OR

b. two series of 22 images

TR (ms)	TE (ms)	# of slices	Slice thickness (mm)	Inter-Slice gap	FOV (mm)	Matrix	# of average	Percentage of sampling	Phase encoding	Presaturation slab/flow compensation
600-650	10-20	22	3	3	250	256 x 256	2	100%	L-R	yes

Position an axial presaturation slab (50-80 mm) inferior to the slice group to suppress flow-related artifacts.

In case of two series acquisition, the second series will have a slice position shifted 3 mm caudally compared with the first one, so that when both series are combined, the whole brain is covered.

In case of post-contrast T_1-weighted images due either to subject movement artifacts, or to a change in slice position of 6 mm or more (i.e., > 2 slice thickness compared to baseline scan), post-contrast T_1-weighted sequence should be repeated within 20 minutes after Gadolinium-Gadopentetic Acid (Gd-DTPA) injection.

For dual-echo and post-contrast T1-weighted scans, if possible, to speed up the examination, use a rectangular 3/4 FOV (i.e., reduce the phase-encoding matrix by 25%). When using 3/4 FOV, the FOV is 187.5 in L > R direction and 250 mm in A > P direction; matrix is 256 (read) x 192 (phase).

MRI PARAMETERS FOR 3.0 TESLA SCANNER

Please, read the general rules listed in the MRI acquisition protocol section, before proceeding with sequences set up.

The scanning procedure is the same as of the 1.5 Tesla, using the following parameters for the main protocol:

T_2 weighted FSE/TSE

a. a single series of 2 concatenated packages of 22 slices each (44 images)

TR (ms)	TE1/ TE2 (ms)	ETL	# of slices	Slice thickness (mm)	Inter-Slice gap	FOV (mm)	Matrix	# of average	Percentage of sampling	Phase encoding
2200-3300	15-40/90-120	2-7	22	3	0	240	256 x 256	1	100%	L-R

OR

b. two series of 22 images

TR (ms)	TE1/ TE2 (ms)	ETL	# of slices	Slice thickness (mm)	Inter-Slice gap	FOV (mm)	Matrix	# of average	Percentage of sampling	Phase encoding
2200-3300	15-40/ 90-120	2-7	22	3	3	240	256 x 256	1	100%	L-R

Position an axial presaturation slab (50-80 mm) inferior to the slice group to suppress flow-related artifacts.

The 44 interleaved slices are acquired in a single series or, alternatively, in two series of 22 slices. **Scans with additional slices will not be accepted.**

Some scanners allow two separate acquisitions (each of 22 slices) to be performed sequentially and automatically from a single prescription. If the scanner used allows the acquisitions to be split automatically in this way, it is preferable to use this option. The number of acquisition is automatically calculated by the system according to the specified TR. Please, check that the number of acquisition is set to 2 (Siemens scanner refers to this parameter as “concatenation”, GE scanners as “acquisitions”, and Philips scanner as “Packages” on the “Info” page). If the number of acquisition is greater than 2, adjust upward TR by small steps to obtain 2 acquisitions.

If two series of 22 slices may be acquired, the first series must have slice positions as fast series whereas the second one must have slice positions shifted 3 mm caudally compared with the first

one, such that when both series are combined, the desired region is covered. The intent is to have contiguous coverage of the prescribed region with 44 interleaved slices (no slice gap).

Please, note that for the main protocol only 44 slices are required. Scans with additional slices will not be accepted.

Sequence 2: **T_1 weighted MP-RAGE (for Siemens), 3D-fast SPGR (for GE), 3D-TFE (for Philips)**

TR (ms)	TE (ms)	# of slices	Slice thickness	FOV (mm)	Matrix	# of average	Orientation	Flip Angle	TI (sec)	Phase encoding
8-15	**3-5**	**160**	**1.2**	**256x256**	**256 x 256**	**1**	**Sagittal**	**8-12**	**1.1**	**A-P L-R**

For Siemens scanners, set TR (which is intended as the time between inversion pulses) =3000 ms.

For Philips scanners, set shot mode = multi shot and the TFE factor = 256; then set the shot interval = 3000 ms.

Position the box in order to have the top just above the scalp. Rotate the box by the same amount that was used for sagittal scout.

Perform a bolus injection of Gd-DPTA using the IV long-line and without moving the subject from the scanner. Use contrast at a standard dose of 0.1 mmol/kg (i.e., 0.2 ml/kg). Before Gd administration the acquisition of additional sequences is allowed by negotiation with the MRI-AC ([redacted]). After a post-injection delay of 5 minutes, complete the scanning with post-Gd T_1-weighted 3D images.

Sequence 3. **T_1 weighted 3-D FLASH (for Siemens) SPGR (for GE) FFE (for Philips) post contrast images**

TR (ms)	TE (ms)	# of slices	Slice thickness (mm)	Slab thickness (mm)	Matrix	NEX
5-9	**2-5 In phase**	**44**	**3**	**132**	**256 x 192**	**1**

FOV (A-P) (mm)	FOV (L-R) (mm)	FOV (C-C) (mm)	Flip Angle	BW
240	**180**	**132**	**15°**	**62.5 kHz or 250Hz/pixel**

Data Transmission

Retain a digital copy of all imaging results (including scout images) at the participating site.

For each subject, forward a copy of all the images (axial-coronal and sagittal localizers, PD-T2-weighted FSE/TSE, pre- and post-contrast T1-weighted images) in digital form to the MRI-AC within 3 working days from the scan date (see MRI guideline). Do not send hard copies or films.

As a general guideline, the acceptable media, ordered by preference is listed below:

- Network transfer ftp
- CD-ROM
- Electronic tapes: 4mm DAT or 8mm tape digital linear tape (DLT)

Preferentially, the data will be exported in DICOM format. Compression of the data is allowed if it does not cause any loss of information.

Data sent by network transfer should respect the same time schedule and the transfer should be immediately notified to the MRI-AC with a detailed list of the data transferred. The e-mail addresses for network transfer will be provided separately to MRI sites.

In addition, the required MRI forms, completely filled in and signed, should be faxed to the MRI-AC in Italy to [redacted].

In case fax machine is not available, please scan the signed forms and send them by email.

MRI-AC will provide a password to sites that will choose network transfer option.

In any case, all electronic data of the scan, including scout images should be sent.

The site will keep electronic backups for all MRI data.

MRI SCAN QUALITY CONTROL

Each MRI scan received by the MRI-AC will be reviewed within 3 working days, starting from the time of the MRI approval and analysis forms have been produced (please, refer to the scan arrival date reported on the approval form).

The MRI-AC will notify the site radiologist, the LCM, and the Corporate Coordination Center via transmission of the Scan Acceptance Form. If a repeat of one or more scans is required, this should be accomplished as soon as possible and in all cases within two weeks of the rejected scan.

In case of unsatisfactory image quality, the scans will be rejected and it must be repeated within 2 weeks from the date of the first assessment.

MRI DUMMY RUN PROCEDURE

The dummy run procedure will be required in case of change/upgrade of the MRI scanner/machine or as requested by the MRI-AC.

The results of this procedure allow the MRI-AC to verify 1) that the data from a given site is of sufficient quality to support the quantitative analysis required by this study; 2) that the methods used by the site to acquire the data are consistent and adequate to obtain reproducible data; 3) that the acquisition parameters required by the protocol are stored in the image header.

The "dummy run" procedure should take in account the following points:

1. A scan must be performed on a clinically definite relapsing MS subject, to show that lesions can be visualized with adequate contrast for quantitative analysis.

2. The Dummy Run protocol consists of two executions of the standard MRI Acquisition protocol with the exceptions that IV access is not obtained and gadolinium contrast is not injected.

3. the subject should be properly positioned in the scanner

4. technician should use the same acquisition parameters defined by the protocol (see paragraphs "MRI parameters for 1.5 tesla scanner" and "MRI parameters for 3.0 tesla scanner")

5. the sequences to be acquired are:

    a. a dual echo scan

    a. 3D T_1-weighted scan

    b. post contrast T_1-weighted scan without administration to the subject of any contrast agent

Dummy run electronic data together with a complete MRI parameters form (see MRI guideline) must be sent to the MRI-AC within 3 working days.

The approval of the dummy run is crucial for the site eligibility. Only sites with approved dummy run scan will be allowed to perform MRI scans in subjects participating in the study.

The MRI AC will evaluate the consistency and adequacy of the study scanning procedures.

Any deviation from the MRI protocol requirement has to be motivated and discussed with the MRI-AC.

Only three attempts of dummy run scan are allowed.

(For the detailed procedure of MRI dummy run please refer to MRI guideline)

Magnetic Resonance Spectroscopy

Month 0E (Baseline) – this is the Termination visit scan of the MS-LAQ-301 study and therefore should not be repeated.

This scan will be performed again at Month 24E and every 24 months thereafter, until Termination visit. The Termination scan should be performed within 4 days prior to the Termination visit's date.

In case clinical Termination visit is scheduled to less than 1 month after the performance of a scheduled MRS scan – the scan should not be repeated.

Each site should use the same scanner for each subject for the entire duration of the study.

The electronic data should be sent to the MRI-AC in [redacted] Italy that will conduct the data analysis for the MRS sub-study.

MRS Protocol

Proton MRS data must be obtained from a volume of interest (VOI) located in the central white matter (50mm left-right x 70mm anterior-posterior x 15mm cranio-caudal) using a 90˚-180˚-180˚ (PRESS) volume selective sequence. The VOI must be centered on the body of the corpus callosum using a long echo time (TR 2000, TE 272). The MRS voxel should be positioned cranio-caudally on the FSE/TSE so that the superior portion of the lateral ventricles are visible only in the most inferior 1 or 2 MRI slices that intersect the MRS voxel. The VOI should be centred left-right so that the brain mid-line is located in the centre of the VOI and should be positioned anterior-posterior so that the anterior corners and posterior corners are equidistant from the skull.

The analysis of each examination will be based on within subject differences of the value for the NAA/creatinine ratio.

MR Images showing the MRS voxel placement superimposed on the intersecting MRI slices should be sent to the MRS-AC along with an image of the spectrum. These images may be provided as electronic picture files or as hardcopy. They will be used to verify correct positioning of the MRS voxel and to assess the quality of the spectrum (based on magnetic field homogeneity, signal to noise ratio, water suppression and freedom from other artifacts).

Dummy Run

In certain circumstances, this procedure may be requested by the MRI-AC in the MS-LAQ-301E study.

The same procedure as for the main protocol will be applied for centre certification.

Scanner change/upgrade

If the MR scanner is changed or upgraded in a way that will change the quantification of the MRS parameters over the course of the study, the MRI-AC and MRS-AC must be informed

Healthy Volunteers

To control for differences within and across sites, 3 healthy volunteers will be scanned at each site at each scheduled scan.

In case of scanner change/upgrade, the healthy volunteers must be rescanned before and after the scanner change/upgrade. This is to ensure that the upgrade did not result in a material change in the MRS sequences, or to allow correction for the change that occurred during the upgrade.

Electronic Data

The same procedures used for the main protocol should be used for the back-up and forwarding of MRS data. The raw, time-domain MRS data files should be exported in the appropriate scanner-specific data format and forwarded to the MRS-AC for central analysis

Analysis

The following analysis will be performed:

Change in NAA/creatinine resonance intensity ratio of the examined central brain region.

MAGNETIZATION TRANSFER (MT) PROTOCOL

Proton density weighted gradient-echo MR imaging will be performed with and without an MT saturation pulse at the following visits:

Month 0E (Baseline). This is the Termination scan of the MS-LAQ-301 study and will be a part of the MS-LAQ-301E MT ancillary study protocol

Month 12E: +/- 4 days of month 12 visit and then every 12 months thereafter, until Termination visit. Each scan will need to be performed +/- 4 days from the relevant visit schedule. Termination scan will need to be performed 4 days prior to the scheduled date of the Termination visit.

In case the clinical Termination visit is scheduled to less than 1 month after the performance of a scheduled MT scan – the scan should not be repeated.

Each center should use the same scanner for each subject for the entire duration of the study.

The electronic data should be sent to the MRI Analysis Center (MRI-AC) in [redacted] Italy that will conduct the data analysis for the MT sub-study.

For this study the following MT parameters will be assessed:

- Magnetization Transfer Ratio (MTR) of new MS lesions at study termination;
- MTR changes of selected NAWM areas;
- Average lesion MTR at entry, and at each scan thereafter
- MTR histogram analysis at entry, and at each scan thereafter.

SCANNING REQUIREMENTS

Scanning requirements are the same as for the MRI protocol. However, only centers using 1.5 Tesla scanners may participate in the MT protocol.

MT DUMMY RUN PROCEDURE

In certain circumstances, this procedure may be requested by the MRI-AC.

The same procedure of the MRI protocol will be applied for center certification, taking in account of the following:

1. The MT dummy run has to be performed on an healthy subject
2. The MT dummy run sequences to be acquired are two:
   a. Sequence 1: gradient-echo WITHOUT the MT pulse
   b. Sequence 2: gradient-echo WITH the MT pulse.

ACQUISITION PARAMETERS:

The MT scans will be performed after the T_2-weighted FSE/TSE scan, but before the 3D T1-weighted scan and the injection of gadolinium contrast agent.

The slice positioning parameters (shift and rotation angle) of the MT series shall be the same as for the previous T2-weighted FSE/TSE scan (see MRI main protocol). Use the "history" or "repeat" function if your scanner has this facility to reproduce the same slice positions.

The MT scans will comprise a total of two image series. The first series shall be performed without the MT pulse, and the second series with the MT pulse.

MT Sequence: **spoiled 2-dimensional gradient-echo**

a. Philps scanner

TR (ms)	TE (ms)	Excitation pulse flip angle	# of slices	Slice thickness (mm)	Orientation	FOV (mm)	Matrix	Inter-Slice gap	# average	Phase encoding
1850-2000	12-15	40 degrees	44, interleaved	3	axial	250 mm	256 x 256	0	1	L>R

Do not use any presaturation slabs.

Do Not use Rectangular Field of View.

b. Siemens, GE scanner

TR (ms)	TE (ms)	Excitation pulse flip angle	# of slices	Slice thickness (mm)	Orientation	FOV (mm)	Matrix	Inter-Slice gap	# average	Phase encoding
1400-1500	12-15	40 degrees	44, interleaved	3	axial	250 mm	256 x 256	0	1	L>R

Do not use any presaturation slabs.

Do Not use Rectangular Field of View.

For the second series, where an off-resonance MT pulse shall be applied, the MT pulse shall have the following characteristics:

MT pulse is applied once just before every excitation pulse. This is the standard way to apply MT for most scanners.

The characteristics of the MT saturation pulse shall be chosen according to the type of MRI scanner used

The characteristics of the MT saturation pulse shall be in concordance with the following guidelines (for any scanner type not listed below, please contact the MRI-AC for further guidance).

a. Siemens Scanners (including Magnetom Vision, Symphony and Sonata):

   Only one type of MT pulse is available. This is turned on and off using the check-box in the Protocol window. On the Symphony and Sonata, the check-box is in the "Contrast" tab.

c. Philips scanners:

   Choose the off-resonance MT saturation pulse option. This pulse has a Sinc-Gauss shape, an offset frequency of 1.1 kHz, a duration of 14.9 ms, and an effective flip angle of 620 degrees.

d. GE scanners:

   Use an MT pulse flip angle of 500 degrees (variable mtflip=500), and offset frequency of 1200 Hz (MT freq=1200), and an MT pulse shape of "8ms Fermi pulse" (opuser12=1). Please consult with your local GE application specialist for further information about how to set up the MT protocol if necessary.

e. Other scanner types:

   Please consult with your local scanner manufacturer's representative and the MRI-AC in order to implement the MT protocol. The protocol you should aim for is:

Duration of MT pulse	Flip angle	Frequency offset
Close to 7.68 milliseconds	500 degrees	1500 Hz

It must be ensured that the scanner makes no adjustments to the transmitter power and receiver gain settings between the non-MT and with MT series.

On **Siemens** Vision, Symphony and Avanto scanners, this requires no action on the part of the user.

On **Philips** machines, ensure that both series are performed as a "dynamic scan". On the "Contrast" page, choose the off-resonance MT saturation pulse option. On the "Dynamics" page, select 2 dynamics, and then select MT=on for the second dynamic only.

On **General Electric** machines (Signa and LX) perform an auto prescan for the first series as normal, then perform a manual prescan for subsequent series, accepting the settings without adjustment. Ask your local manufacturer representative for help with the procedure for MT scanning if these instructions are unclear.

In case machine constraints do not allow such image acquisition, the MRI-AC should be contacted and the image acquisition negotiated with it on a center-by-center basis.

HEALTHY VOLUNTEERS

To control for differences within and across sites, 3 healthy volunteers will be scanned at each site at each scheduled MT scan.

In healthy subjects, in addition to the MT sequences, a dual-echo sequence with the same parameters of the MRI protocol has to be acquired.

Any pathological findings will be reported by local radiologist to Treating Investigator according to local clinical practice.

ELECTRONIC DATA

The same procedures used for the MRI protocol should be used for the back-up and forwarding of MT data to the MRI-AC.

SCANNER CHANGE/UPGRADE

If the MR scanner is changed or upgraded in a way that will change the quantification of the MTR parameters over the course of the study, the MRI-AC must be informed and the healthy volunteers must be rescanned before and after the scanner change/upgrade, before subject scanning is resumed. This is to ensure that the upgrade did not result in a material change in the MT pulse sequence, or to allow correction for the change that occurred during the upgrade.

APPENDIX E. 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 (Table 6).

Table 6: A Partial List of Moderate/Strong CYP3A4 Inhibitors Disallowed 2 Weeks Prior to and During the Treatment Period and 30 Days After Last Dose

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:

- This is a partial list only
- Systemic drugs only. Topical preparations (vaginal preparations, creams, etc) are allowed.

Inducers of CYP3A4 are also disallowed during the study (Table 7).

Table 7: A Partial List of CYP3A4 Inducers

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 F. LIST OF MEDICATIONS THAT SHOULD BE USED WITH CAUTION

Laquinimod 0.6 mg/day increases the systemic exposure of midazolam (a sensitive CYP3A4 substrate) 1.5-fold. Therefore, plasma levels of drugs that are CYP3A4 substrates may increase when combined with laquinimod. Subjects taking drugs that are metabolized by CYP3A4 (specifically those with a Narrow Therapeutic Index) (Table 8) should be advised that plasma levels of these drugs could increase when combined with laquinimod.

Table 8: A Partial List of of CYP3A4 Substrates with a Narrow Therapeutic Index

alfentanil
cyclosporine
diergotamine
ergotamine
fentanyl
pimozide
quinidine
sirolimus
tacrolimus

Laquinimod 0.6 mg/day reduces the systemic exposure of caffeine (a sensitive CYP1A2 substrate) 5-fold. Laquinimod doses higher than 0.6 mg/day may further increase CYP1A2 induction and decrease exposure of CYP1A2 substrates. Plasma levels of drugs that are CYP1A2 substrates may decrease when combined with laquinimod. Also, during a period of 30 days following the last laquinimod dose these CYP1A2 substrates are potentially less effective due to decreased plasma levels. Table 9 presents a partial list of drugs that are mainly metabolized by CYP1A2, ie, CYP1A2 plays a major role in their biotransformation. The systemic exposure of these drugs is expected to be significantly reduced by laquinimod coadministration. Drugs that are mainly metabolized by CYP1A2 and have a narrow therapeutic index are of special concern and appear in bolded text.

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.

Table 9: 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

APPENDIX G. GUIDANCE ON SAFETY MONITORING

1. Guidance on Monitoring Subjects with Elevated Liver Function Tests

Liver enzymes (ALT, AST, GGT, ALP), as well as total bilirubin[1] will be measured at each study visit.

In any case of elevated ALT or AST to a level exceeding of ≥2xULN (including subjects whose Baseline ALT or AST levels are ≥2x and ≤3x 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[2]. In addition, the subject should be instructed to refrain from alcoholic beverages.

In case of symptoms compatible with drug-induced liver injury, the subject 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 Study Physician/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 times the 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 subject 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 ≥3xULN

[1] In case total bilirubin is >ULN, than direct bilirubin will be checked
[2] 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

2. In case Baseline value was above ULN and ALT or AST is ≥2 times 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 eCRF.

Additional Tests/Evaluations

- Serology for Hepatitis A, B, and C viruses (central laboratory).
- Serology for autoimmune hepatitis: anti-nuclear antibodies, ASMA, anti-LKM antibodies (central laboratory).
- An ultrasound examination of the liver and biliary tract.
- Other diagnostic tests/consultations, as deemed necessary by the investigator e.g. 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 >3xULN:

- 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 eCRF, accompanied by the reference range of the relevant measurements.
- Should the abnormality (≥3xULN in case Baseline within normal range or ≥2xULN in case the Baseline value was above ULN, but still <5xULN) persist further, the subject 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 ≥5x but less than 8xULN

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

- 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 ≥8xULN

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

- The study drug should be discontinued immediately and the early termination 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 ≥3xULN, combined with INR >1.5 or total bilirubin >2xULN
- Any increase in ALT or AST to ≥3xULN, which is accompanied by nausea, vomiting, fever, rash, or eosinophilia
- Any increase in ALT or AST to levels ≥5x but <8xULN, which is persistent for ≥2 weeks of repeated measurements
- Any increase in ALT or AST to levels ≥8xULN
- 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 subject who meets the above criteria for discontinuation of the study drug should be invited to the site to return the study drug. Early termination 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 early termination, the minimal follow-up period will be 30 days and will include measurement of liver enzymes at least weekly (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 PK is 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 E.

3. Cancers diagnosed during the study

Subjects that are diagnosed with a malignant solid or liquid tumor while participating in the study should stop study drug.

4. Guidance on Monitoring Subjects 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 and on all follow-up visits until normalization of pancreatic amylase levels. In case of suspected pancreatitis, the subject 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. An MRI may be performed as an alternative to the CT scan.

5. Liver Impairment

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

6. Renal Impairment

Subjects 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 subject should stop study medication permanently.

7. 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 effective contraception and avoidance of pregnancy under laquinimod exposure (see Section 3.4), and to reduce as much as possible the exposure to laquinimod if a pregnancy occurs despite all recommended measures, all subjects 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 subjects will also be counseled about the importance of using two 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 two 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 subjects' 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 subject 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 subjects 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. Subjects who have discontinued study drug but are continuing to attend study visits for follow-up do not need to perform pregnancy tests.

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 subject will be contacted immediately and instructed to stop taking the study drug. The subject 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 subject 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 subject will be invited to the site for an early termination visit

    b. If the blood test is negative, the subject will be contacted and informed about the test result and the study drugs will be sent to her by courier as soon as possible.

3. Starting from visit 3 (Month 3), the following actions will be taken:

    a. The subject will be provided with home pregnancy urine β-hCG test kits and will be guided how to perform the test.

    b. The subject 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 Study Neurologist/ Physician 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 subject's file. In case of a suspected pregnancy, the subject 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 Study Physician/Neurologist should discuss with the subject 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 subject 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.

Female subjects of child-bearing potential who might want to get pregnant in the future, and might be interested in continuing taking laquinimod after giving birth and have stopped breastfeeding may be able to re-enroll in the study after meeting inclusion/exclusion criteria below. Re-enrollment will be permitted on a case-by-case basis. Notwithstanding, Teva is under no obligation to re-enroll such subjects and reserves the right to re-enroll or reject enrolment of such returning subjects for no reason and on its sole discretion. A new informed consent form should be signed before re-enrollment.

Inclusion criteria for returning subjects

Subjects must meet all inclusion criteria in order to be eligible for the study:

1. Subjects must have completed the Termination visit of MS-LAQ-301E (completion of all Termination visit activities) according to the MS-LAQ-301E protocol.

2. Subjects must be ambulatory with Kurtzke's EDSS score of 0-5.5 in re-enrollment visits.

3. Subjects must be in a stable neurological condition, relapse-free and free of any corticosteroid treatment [IV, intramuscular (IM) and/or per os (PO)] or adrenocorticotrophic hormone (ACTH), 60 days prior to re-enrollment.

4. 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 two 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).

5. Subjects must be willing and able to comply with the protocol requirements for the duration of the study.

6. Subjects must be able to comprehend, sign and date a written informed consent prior to re-enrolling into the MS-LAQ-301E study.

Exclusion criteria for returning subjects

Any of the following conditions will exclude the subject from re-enrolling into the study:

1. Premature discontinuation from the MS-LAQ-301 study, for any other reason than planned pregnancy.

2. Subjects with progressive forms of MS or other non RRMS variant of neuroinflammatory or demyelinating diseases.

3. Use of experimental or investigational drugs and/or participation in drug clinical studies within 6 months prior to re-enrollment visit.

4. Use of immunosuppressive agents, or cytotoxic agents, including cyclophosphamide and azatioprine within 12 months prior to re-enrollment visit.

5. Use of either of the following within 2 years prior to re-enrollment: natalizumab (Tysabri®), rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab.

6. Previous treatment with glatiramer acetate (Copaxone®), Interferon-β (either 1a or 1b), fingolimod (Gilenya®), dimethyl fumarate (Tecfidera) or IV Ig (IVIG) within 2 months prior to re-enrollment visit.

7. Use of teriflunomde (Aubagio®) within- 2 years prior to re-enrollment, except if active washout (with either cholestyramine or activated charcoal) was done 2 months or more prior to randomization.

8. Use of mitoxantrone (Novantrone) within 5 years prior to re-enrollment in subjects with normal ejection fraction and who did not exceed the total lifetime maximal dose.

9. Previous use of cladribine and alemtuzumab (Lemtrada).

10. Previous total body irradiation or total lymphoid irradiation.

11. Previous stem cell treatment, autologous bone marrow transplantation, or allogenic bone marrow transplantation.

12. Acute infection within 2 weeks prior to re-enrollment visit.

13. Major trauma or surgery within 2 weeks prior to re-enrollment visit.

14. Use of moderate/strong inhibitors of CYP3A4 within 2 weeks prior to re-enrollment visit.

15. Use of inducers of CYP3A4 within 2 weeks prior to re-enrollment visit.

16. Pregnancy [according to serum β-hCG performed within 7 days prior to re-initiation of treatment] or breastfeeding.

17. Serum levels ≥3xULN of either ALT or AST at re-enrollment visit.

18. Serum direct bilirubin which is ≥2xULN at re-enrollment visit.

19. Subjects with clinically significant or unstable medical or surgical condition detected or worsened during the MS-LAQ-301 or MS-LAQ-301E study, which preclude safe participation and completion of the MS-LAQ-301E study.

20. Any malignancies, excluding basal cell carcinoma, in the 5 years prior to re-enrollment.

21. Subjects who underwent endovascular treatment for Chronic Cerebrospinal Venous Insufficiency (CCSVI) within 3 months prior to re-enrollment.

Table 10: Study Task Flow Chart for Returning Subjects after Planned Pregnancy

Visit	**V0E1**	**V1E1**	**V2E1**	**V3E1**	**V41**	**Every 6 months**	**Every 12 months**	**Every 24 months**	**Termination/ Early Discontinuation**	**Un-scheduled Visit**[a, b]
Month	**0E1**	**1E1**	**2E1**	**3E1**	**6E1**					
Informed Consent for returning females	X									
Eligibility Criteria for returning females	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Cardiovascular risk factor assessment and management [c]							X	X		
Physical Examination	X				X		X	X	X	X
Vital Signs	X[d]	X	X	X	X	X	X[e]	X[e]	X[e]	X
ECG	X				X	X	X	X	X	X
Safety Laboratory Evaluation (CBC, Chemistry, markers of inflammation, GFR estimation)	X	X	X	X	X	X	X	X	X	X
Serum β-hCG[f]	X	X	X	X	X	X	X	X	X	X
Urine β-hCG[f] (on site)	X	X	X	X	X	X	X	X	X	X
Ascertaining use of effective contraception	X	X	X	X	X	X	X	X	X	X
Discuss the importance of Contraception[f]	X	X	X	X	X	X	X	X	X	X
Urine β-hCG[f] (self check, at home)					**EVERY 1 MONTH BETWEEN SCHEDULED VISITS**					
AE	X	X	X	X	X	X	X	X	X	X
Neurological examination (EDSS/FS/AI/ 25 foot walk)	X				X	X	X	X	X	X
Evaluation of Relapse[g]	X	X	X	X	X	X	X	X	X	X
MSFC[h]	X				X	X	X	X	X	
Binocular Low-Contrast Visual Acuity	X				X	X	X	X	X	
MFIS	X				X	X	X	X	X	
Mandatory phone calls (pregnancy tests)[i]					**EVERY 1 MONTH BETWEEN SCHEDULED VISITS**					
Mandatory phone calls (general well-being, all subjects)[j]						**EVERY 3 MONTHS BETWEEN SCHEDULED VISITS**				
Drug Compliance & Dispensing	X	X	X	X	X	X	X	X	X[k]	X

Visit	**V0E1**	**V1E1**	**V2E1**	**V3E1**	**V41**	**Every 6 months**	**Every 12 months**	**Every 24 months**	**Termination/ Early Discontinuation**	**Un-scheduled Visit**[a, b]
Month	**0E1**	**1E1**	**2E1**	**3E1**	**6E1**					
Termination Documentation and Notification of Early Termination									X	
Unscheduled Samples										X[l]

[a] Vital signs and AEs are mandatory activities in an unscheduled visit. All other activities are optional and may be performed as deemed necessary by the investigator. Chest X-ray may also be performed in this visit.

AE = Adverse Event, AI = Ambulation Index, β-hCG = beta-human Chorionic Gonadotropin, CBC = Complete Blood Count, ECG = Electrocardiogram, EDSS = Kurtzkle's Expanded Disability Status Scale, FS = Functional System, GFR = glomerular filtration rate, MFIS = Modified Fatigue Impact Scale, MSFC = Multiple Sclerosis Functional Composite

[b] Post treatment follow up visit in cases of early discontinuation (In which vital signs, review of AEs and concomitant medications, as well as pregnancy test are mandatory. All other marked activities are optional).

[c] In addition, an evaluation should take place as soon as possible for subjects already in the study, following approval of Amendment #3

[d] Post-dose vital signs will be measured at Baseline and after 30 and 60 minutes, whereas the pre-dose vital signs will be taken from the last measurement in the MS-LAQ-301 study.

[e] Weight will be measured at every visit until Termination/Early discontinuation.

[f] For women of childbearing potential. Serum pregnancy test (β-hCG) for women of child-bearing potential within the 7 days prior to re-initiation of treatment

[g] Relapse evaluation will be performed in scheduled as well as unscheduled visits as deemed necessary by the Investigator/Coordinator

[h] The PASAT and 9-HPT will be performed at Months 0E [Baseline (Termination visit of the MS-LAQ-301 study)], 6E and every 6 months (every scheduled visit) thereafter, until Termination/early discontinuation visit. The Timed 25 Foot walk test will be performed each time neurological evaluation is performed.

[i] For women of child-bearing potential; to be performed within 72 hours of the scheduled home pregnancy test

[j] The call will be documented in the source documents. For women of child-bearing potential, there is no need to perform a separate call, as this question will be a part of the monthly pregnancy urine test call.

[k] Only drug retrieval

[l] 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.

Subjects who are discontinued from study treatment will be encouraged to continue all scheduled visits and procedures until completion of the study (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, and GFR estimation [including body weight measurement]).

Date: _____ Subject No.: _____

HOME PREGNANCY TEST QUESTIONNAIRE

Date of contacting the subject: ___/___/___
DD MM YY

Name of site staff person to contact the subject_____

Date in which home urine pregnancy test was performed: ___/___/___ ☐
DD MM YY ND

Home urine pregnancy test result: ☐ Positive/negative

IF HOME URINE PREGNANCY TEST WAS NOT PERFORMED:

Was a urine pregnancy test scheduled? ☐ Yes ☐ No

If yes – specify the date for which the next contact was scheduled ___/___/___
DD MM YY

APPENDIX H. MODIFIED FATIGUE IMPACT SCALE (MFIS)

INSTRUCTIONS

Following is a list of statements that describe how fatigue may affect a person. Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. In medical conditions like MS, feelings of fatigue can occur more often and have a greater impact than usual. Please read each statement carefully, and then circle the one number (0, 1, 2,…) that best indicates how often fatigue has affected you in this way during the past 4 weeks. Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you.

Because of my fatigue during the past 4 weeks…

		Never	Rarely	Sometimes	Often	Almost Always
1.	I have been less alert.	0	1	2	3	4
2.	I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3.	I have been unable to think clearly	0	1	2	3	4
4.	I have been clumsy and uncoordinated	0	1	2	3	4
5.	I have been forgetful	0	1	2	3	4
6.	I have had to pace myself in my physical activities	0	1	2	3	4

Because of my fatigue during the past 4 weeks…

		Never	Rarely	Sometimes	Often	Almost Always
7.	I have been less motivated to do anything that requires physical effort	0	1	2	3	4
8.	I have been less motivated to participate in social activities.	0	1	2	3	4

9. I have been limited in my ability to do things away from home.	0	1	2	3	4
10. I have had trouble maintaining physical effort for long periods.	0	1	2	3	4
11. I have had difficulty making decisions	0	1	2	3	4
12. I have been less motivated to do anything that requires physical effort	0	1	2	3	4
13. my muscles have felt weak	0	1	2	3	4
14. I have been physically uncomfortable	0	1	2	3	4
15. I have had trouble finishing tasks that require thinking	0	1	2	3	4

Because of my fatigue during the past 4 weeks…

	Never	Rarely	Sometimes	Often	Always
16. I have had difficulty organizing my thoughts when doing things at home or at work	0	1	2	3	4
17. I have been less able to complete tasks that require physical effort.	0	1	2	3	4
18. My thinking has been slowed down	0	1	2	3	4
19. I have had trouble concentrating	0	1	2	3	4
20. I have limited my physical activities.	0	1	2	3	4
21. I have needed to rest more often or for longer periods.	0	1	2	3	4

APPENDIX I. MSFC ADMINISTRATION INSTRUCTIONS

Multiple Sclerosis Functional Composite (MSFC)

The MS Functional Composite is an instrument assessing disability. It was developed by a special task force on clinical outcome assessments. It was the consensus of the task force that important clinical dimensions, not emphasized in existing rating scales, should be measured.

General Instructions

The MSFC should be administered as close to the beginning of a study visit as possible. The components of the MSFC should be administered in the following order:

1. Trial 1, Timed 25-Foot Walk
2. Trial 2, Timed 25-Foot Walk
3. Trial 1, Dominant Hand, 9-HPT
4. Trial 2, Dominant Hand, 9-HPT
5. Trial 1, Non-Dominant Hand, 9-HPT
6. Trial 2, Non-Dominant Hand, 9-HPT
7. PASAT-3"

Instructions for the Timed 25-Foot Walk

Description

The Timed 25-Foot Walk is a quantitative measure of lower extremity function. It is the first component of the MSFC administered at each visit. The subject 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 subject walk back the same distance. Subjects 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 subject cannot complete Trial 2 of the Timed Walk after a 5-minute rest period.

If the subject 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 subject should be directed to one 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 subject 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 subject as s/he completes the task. Stop timing when the lead foot crosses the finish line. The examiner should then record the subject'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 (e.g., 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 subject just behind the line where s/he is not standing, repeat the same instructions, and have the subject complete the walk again.

Assistive Devices

The goal is to have the subject 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 subject that needs one, keeping in mind that the subject may deteriorate modestly during the trial.

In general, subjects should use their customary assistive device(s), NOT the least assistance possible to complete the test. For subjects with significant gait impairment, the Study Neurologist/Physician should have the subject use a rolling walker even if this is not the subject's customary device. In general, non-wheeled walkers should not be used. If a subject 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 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 had a cold or reports not feeling well.

The subject 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 subject fell during the walk.
- Examiner forgot to start or stop stopwatch.
- Examiner forgot to reset stopwatch in between trials.
- The subject stopped to talk to someone while walking, or another person/thing somehow interfered with walk.

Record only the times for the two **successfully completed** trials of the Timed 25-Foot Walk. If the subject could not complete one 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 subject'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 (i.e., subject in a wheelchair now and unable to walk, etc.). If the subject did not complete a trial for any other reason, specify this as well (e.g., subject fell and was too fatigued to complete another trial, subject refused to complete trial).

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

If the subject cannot complete one trial of the 9-HPT in 5 minutes.

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.

If the subject cannot complete a trial with his or her non-dominant hand, move on to the PASAT.

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 (e.g., 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 (e.g., subject refused).

Instructions for the Paced Auditory Serial Addition Test (PASAT)

Description

The PASAT is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. The PASAT is the last measure administered at each visit. It is presented on CD player to control the rate of stimulus presentation. Single digits are presented every 3" and the subject must add each new digit to the one immediately prior to it. The test result is the number of correct sums given (out of 60 possible). To minimize familiarity with stimulus items, two alternate forms have been developed; the order of these should be counterbalanced across testing sessions.

Materials Needed

CD player, CD with PASAT stimuli, clipboard, PASAT Record Forms

Discontinue Rules

If the subject cannot get at least two answers correct (consecutive or not) on any one of the three 3" practice sequences.

If the subject cannot get at least one answer correct on PASAT-3" test, this subject is considered unable to perform the test.

Administration

Verify that you have the correct Record Form and CD player (Form A or B) *before* you start reading the instructions for the 3" Practice Trial to the subject.

PASAT-3 Practice Trial

For Part 1 (stimuli every 3") say, "*On this CD you are going to hear a series of single digit numbers that will be presented at the rate of one every 3 seconds. Listen for the first two numbers, add them up, and tell me your answer. When you hear the next number, add it to the one you heard on the tape right before it. Continue to add the next number to each preceding one. Remember, you are not being asked to give me a running total, but rather the sum of the last two numbers that were spoken on the tape.*"

Then give the following example: "*For example, if the first two numbers were '5' and '7,' you would say '12.' If the next number were '3,' you would say '10.' Then if the next number were '2,' you would say '5.'* If the subject is having difficulty understanding these instructions, write 5, 7, 3 and 2 on a sheet of paper and repeat the instructions demonstrating how the task is done.

Then say, "This is a challenging task. If you lose your place, just jump right back in---listen for two numbers in a row and add them up and keep going. There are some practice items at the beginning of the tape. Let's try those first." Play the sample items, stopping the CD after the last practice item. Repeat the practice items, if necessary, until the subject understands the instructions (up to three times). You should always administer at least one practice trial before administering the actual test. If the subject begins to give you a running total, stop the practice immediately and explain the task again, emphasizing that he/she is not to give you a running total. Then start the practice items again from the beginning. If the subject begins adding each number to the number two previous to it, again stop the practice immediately, explain the correct way to do the task, and start the practice items from the beginning. If the subject merely makes a math error, do not stop the tape; continue with the practice items. After two consecutive 'no responses,' prompt him/her to resume by saying, "Jump back in with the next two numbers you hear."

Administer the practice sequence a maximum of three times. Record answers in the space provided on the back of the PASAT Record Form.

PASAT-3

Once it is clear that the subject possesses sufficient understanding of the task, begin Part 1. Before starting Part 1, remind him/her: "*Remember if you get lost, just jump back in because I can't stop the test once it has begun.*" Discourage talking and oral calculations during the test, only the subject's answers should be spoken out loud. The subject may need prompting to continue the test if she/he gets lost. After five consecutive 'no responses,' redirect the subject quickly by saying, "*Jump back in*," but do not stop the tape.

Completing the PASAT Record Form

Circle all correct answers. Write in any incorrect responses in the space provided. Place a dash when no response was given. If the subject corrects him/herself after giving a response, count the amended answer as the response. The *amended* response is the one that will be used in determining total correct, regardless of whether it was the correct or incorrect response. *Slash through the old response and write in "SC" with a circle around it to indicate that the subject self-corrected*.

Each section of the PASAT has a maximum of 60 correct answers (i.e., 61 digits are presented for each part). Count the total number correct (number of circled answers) for PASAT-3 and record on both the PASAT Record Form and the Summary Score Sheet.

Finally 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:

Subtle noises outside of the testing room

Subject reports frustration or mild distress

Subject talked during test (other than to give answers)

If a trial must be repeated, indicate this and specify the reason why it had to be repeated. Examples of reasons to repeat a trial include, but are not limited to, the following:

Test interrupted (e.g. someone walked into the room or other major disturbance)

Examiner error, such as starting the tape in the wrong place or using the wrong form.

Record only totals for the **successfully completed** PASAT-3.

If the subject is unable to perform the PASAT (i.e., cannot get at least two correct on any 3" practice and at least one correct on the test portion), the examiner should indicate "Unable to complete due to cognitive limitations" and record any specific observations. If the subject did not complete a trial for any other reason, record the reasons for this as well (e.g., subject refused to complete test, etc.).

Scores from the MSFC component test results will be computed by the Data Management Center. Instructions will be included in the analytical plan.

APPENDIX J. LOW-CONTRAST SLOAN LETTER CHART TESTING FOR PATIENTS WITH MULTIPLE SCLEROSIS

Low-Contrast Sloan Letter Chart Testing
For Patients with Multiple Sclerosis:
Testing Protocol Manual
(BINOCULAR TESTING)

Laura J. Balcer, M.D., M.S.C.E.
University of Pennsylvania

The following are instructions for testing patients using the front illuminated Low-Contrast Sloan Letter Charts (LCSLC - Precision Vision, LaSalle, IL). The inter-rater reliability of this testing protocol has been shown to be extremely high in patients with multiple sclerosis and in visually-asymptomatic volunteers. A standardized script with instructions to be read to the patient by the examiner is included below. The examiner should read through the following instructions and practice testing prior to examining study patients.

Preparation and Set-Up:

1. Set room lighting level to 80-100 cd/m^2 (equivalent is about 80-100 foot-candles). This level illumination may be achieved in a bright exam room/hallway with fluorescent lighting. Having exact lighting is less important than using the same room/area for each patient/testing session.

2. Place the charts at 2 meters distance from the patient's eyes. An artist's easel or similar device may be used, as may a ledge, stand, or chair to prop the charts perpendicular to the floor. Use a pre-measured string or tape to measure the distance from the patient's eyes (bridge of nose) to the testing charts at the beginning of each testing session (each patient).

3. The 100%, 2.5%, and 1.25% charts will be used for testing.

4. Patients should wear their usual distance correction for testing (glasses or contact lenses that are used for driving, etc.). The same glasses or contact lenses (same prescription) should be used for each testing session throughout the study.

5. Patients should be asked to read the charts with both eyes open.

Vision Testing:

1. Instruct patient to read slowly, letters only, left to right, starting at the top of the chart.

2. Instruct the patient that they are not allowed to re-read any line.

3. The patient is allowed to correct a "mis-speak" of a single letter only if he/she does so before reading the next letter---instruct the patient of this.

4. During the chart reading, PUSH (encourage) the patient until he/she cannot read any letters after being told to guess.

5. The patient must guess at each letter, even if he/she cannot easily read it, until he/she cannot or does not correctly identify any of the 5 letters on a particular line.

6. Stopping Rule: Once the patient cannot or does not correctly identify any of the 5 letters on a line after attempting it, STOP. Go on to the next chart.

7. Test all 3 charts in the same order (100%, 2.5%, 1.25%) for each patient.

8. During testing, circle all letters read correctly on the data forms for each chart (with both eyes). Put an "X" through each incorrectly identified letter; leave unattempted letters unmarked.

9. Fill in the number of letters correct at the end of each line of 5 letters. Record the total number of letters correct for each chart at the bottom of the column. The Snellen visual acuity equivalent (i.e., 20/20 or 6/6) for the patient corresponds to the lowest line on the 100% chart (black on white) for which the patient identifies 3 or more letters correctly.

10. If a patient is unable to identify any of the letters correctly on the first line of any of the 3 charts, please indicate this at the top of the data collection form.

Script for Testing to be Read to Patient:

These instructions should be read to the patient once he/she is comfortably seated in front of the charts at 2 meters distance (see above for instructions on Preparation and Set-Up):

1. I am going to show you 3 different eye charts with letters on them. The letters will become increasingly lighter for each chart.

2. For each chart, please begin at the very top of the chart and read each letter slowly, from left to right on each line.

3. If you miss-speak on a letter or feel you have identified it incorrectly, you may correct your response only before you read the next letter.

4. You are not allowed to re-read an entire line.

5. Please try not to lean forward in the chair while reading the letters.

After the first chart (100% chart) has been uncovered, say:

1. You may begin reading the letters.
2. Please start at the top of the chart.

For each chart, allow the patient to continue reading letters until he/she either:

1. Does not identify any of the 5 letters on any given line correctly → say:

   You may stop. We will go on to the next chart now.

   OR

2. States that they are unable to read any more letters → point to the line which is next for the patient to attempt (use the yellow-tipped pointer only) and say:

   Can you read any of the letters on this line?

   a) If patient responds no → say: *Please guess if you can.*

   If patient responds that they cannot → say:

   You may stop. We will go on to the next chart now.

   b) If patient responds yes or begins reading, then continue to record responses until the patient cannot or does not correctly identify any of the 5 letters on a given line.

Stopping Rule: For each chart, once the patient cannot or does not identify any of the 5 letters correctly on a given line, say: *You may stop. We will go on to the next chart now.*

Please use the yellow-tipped pointer only to point to the charts (pens and fingers may leave marks). The examiner may point to the chart when requested by the patient to indicate the line that they are attempting/should attempt next.

Repeat the above procedure for each of the 3 charts (100%, 2.5%, and 1.25% in that order) with both eyes open.

APPENDIX K. LOW-CONTRAST TUMBLING-E CHART TESTING FOR PATIENTS WITH MULTIPLE SCLEROSIS

Low-Contrast Tumbling E Chart Testing For Patients with Multiple Sclerosis: Testing Protocol Manual (BINOCULAR TESTING)

Laura J. Balcer, M.D., M.S.C.E.
University of Pennsylvania

The following are instructions for testing patients using the front illuminated Low-Contrast Tumbling E Charts (Precision Vision, LaSalle, IL). The inter-rater reliability of this testing protocol has been shown to be extremely high in patients with multiple sclerosis and in visually-asymptomatic volunteers. A standardized script with instructions to be read to the patient by the examiner is included below. The examiner should read through the following instructions and practice testing prior to examining study patients.

Preparation and Set-Up:

1. Set room lighting level to 80-100 cd/m^2 (equivalent is about 80-100 foot-candles). This level illumination may be achieved in a bright exam room/hallway with fluorescent lighting. Having exact lighting is less important than using the same room/area for each patient/testing session.

2. Place the charts at 2 meters distance from the patient's eyes. An artist's easel or similar device may be used, as may a ledge, stand, or chair to prop the charts perpendicular to the floor. Use a pre-measured string or tape to measure the distance from the patient's eyes (bridge of nose) to the testing charts at the beginning of each testing session (each patient).

3. The 100%, 2.5%, and 1.25% charts will be used for testing.

4. Patients should wear their usual distance correction for testing (glasses or contact lenses that are used for driving, etc.). The same glasses or contact lenses (same prescription) should be used for each testing session throughout the study.

5. Patients should be asked to read the charts with both eyes together.

Vision Testing:

1. Instruct patient to read slowly, left to right, starting at the top of the chart. The patient should indicate the direction that the "E" character points, that is, which direction do the 3 lines of the "E" point (i.e. E, ∃, Ш, Ш) ? Patients can speak their native language equivalent of "right," "left," "up," or "down."

2. Instruct the patient that they are not allowed to re-"read" any line.

3. The patient is allowed to correct a "mis-speak" of the direction of a single letter "E" only if he/she does so before reading the next letter "E"---instruct the patient of this.

4. During the chart reading, **PUSH** (encourage) the patient until he/she cannot identify the direction any "E" letters after being told to guess.

5. The patient must guess at the direction of each letter "E," even if he/she cannot easily read it, until he/she cannot or does not correctly identify the directions of any of the 5 letters "E" on a particular line.

6. **Stopping Rule:** Once the patient cannot or does not correctly identify the direction of any of the 5 letters "E" on a line after attempting it, **STOP**. Go on to the next chart.

7. Test all 3 charts in the same order (100%, 2.5%, 1.25%) for each patient.

8. During testing, circle all letters "E" for which the direction is identified correctly on the data forms for each chart. Put an "X" through each incorrectly identified "E" direction; leave unattempted letters "E" unmarked.

9. Fill in the number of letters "E" for which the direction is identified correctly at the end of each line of 5 letters "E." Record the total number of letters correct for each chart at the bottom of the column. The **Snellen visual acuity equivalent** (i.e., 20/20 or 6/6) for the patient corresponds to the lowest line on the **100% chart** (black on white) for which the patient identifies the direction of 3 or more letters "E" correctly.

10. If a patient is unable to identify the direction of any of the letters "E" correctly on the first line of any of the 3 charts, please indicate this at the top of the data collection form.

Script for Testing to be Read to Patient:

These instructions should be read to the patient once he/she is comfortably seated in front of the charts at 2 meters distance (see above for instructions on **Preparation/Set-Up**):

1. ***I am going to show you 3 different eye charts with capital letters "E" on them. The letters will become increasingly lighter for each chart.***
2. ***For each chart, please begin at the very top of the chart and slowly identify which direction the three straight lines of the letter "E" is pointing. For example, if the letter looks like this (show patient an example written or printed E), you would say "to the right."***
3. ***Identify the direction of each letter "E" slowly, from left to right on each line.***
4. ***If you mis-speak on the direction of a letter "E" or feel you have identified it incorrectly, you may correct your response only before you read the next letter "E".***
5. ***You are not allowed to re-read an entire line.***
6. ***Please try not to lean forward in the chair while reading the letters.***

After the first chart (100% chart) has been uncovered, say:

1. ***You may begin reading the letters.***
2. ***Please start at the top of the chart.***

For each chart, allow the patient to continue reading letters until he/she either:

1) Does not identify the direction of any of the 5 letters "E" on any given line correctly → say: ***You may stop. We will go on to the next chart now.***

OR

2) States that they are unable to identify the direction of any more letters "E" → point to the line which is next for the patient to attempt (use yellow-tipped pointer only) and say: ***Can you identify which way any of the letters "E" on this line are pointing?***

a) If patient responds **no** → say: ***Please guess if you can.***
If patient responds that they cannot → say:
You may stop. We will go on to the next chart now.

b) If patient responds **yes** or begins reading, then continue to record responses until the patient cannot or does not correctly identify the direction of any of the 5 letters "E" on a given line.

Stopping Rule: For each chart, once the patient cannot or does not identify the direction of any of the 5 letters "E" correctly on a given line, say: ***You may stop. We will go on to the next chart now.***

Please use the yellow-tipped pointer only to point to the charts (pens and fingers may leave marks). The examiner may point to the chart when requested by the patient to indicate the line that they are attempting/should attempt next.

Low-Contrast Tumbling E Chart Testing – Binocular (both eyes open)

Name of Examiner: _____

Snellen Visual Acuity Equivalent			**100% Chart (2 meters)**		**2.5% Chart (2 meters)**		**1.25% Chart (2 meters)**	
Feet (20/x)	**Meters (6/x)**	Chart Line	Chart Symbols (circle correct)		Chart Symbols (circle correct)		Chart Symbols (circle correct)	
20/200	6/60	20M	Ǝ M Ǝ W E	____	M Ǝ E W E	____	Ǝ W Ǝ E M	____
20/160	6/48	16M	W E W Ǝ M	____	W M Ǝ E Ǝ	____	E Ǝ E M W	____
20/125	6/37.5	12M	E Ǝ M W Ǝ	____	E W M Ǝ M	____	M E M W Ǝ	____
20/100	6/30	10M	M E W Ǝ W	____	Ǝ E W M W	____	W M W Ǝ E	____
20/80	6/24	8M	W Ǝ M W E	____	E M Ǝ W Ǝ	____	E W E M Ǝ	____
20/64	6/19.2	6M	E M W E Ǝ	____	M E W Ǝ W	____	W E W Ǝ M	____
20/50	6/15	5M	Ǝ W E Ǝ M	____	Ǝ W M E M	____	M Ǝ M W E	____
20/40	6/12	4M	W E Ǝ M Ǝ	____	W Ǝ E M E	____	Ǝ M Ǝ E W	____
20/32	6/9.6	3M	Ǝ M E W E	____	Ǝ M W E M	____	M Ǝ W M E	____
20/25	6/7.5	2.5M	E W M Ǝ W	____	W E Ǝ M E	____	Ǝ M E Ǝ W	____
20/20	6/6	2M	W Ǝ E W M	____	M W E Ǝ W	____	W E Ǝ W M	____
20/16	6/4.8	1.6M	M W M Ǝ E	____	E Ǝ M W Ǝ	____	E W M E Ǝ	____
			Total correct	____	**Total correct**	____	**Total correct**	____

Snellen visual acuity equivalent _____
(Snellen equivalent (i.e., 6/6 in meters) for lowest line on **100% chart** for which subject identifies 3 or more correctly)