Amended Protocol following Global Amendments 01 to 10
(including Statistical Analysis Plan)

An Active Extension of LAQ/5062 Study. a Multinational, Multi-Center, Randomized, Double-Blind, Parallel-Group Study, to Evaluate the Safety, Tolerability and Efficacy of Two Doses (0.3 mg and 0.6 mg) of Laquinimod, Orally Administered in Relapsing Remitting (R-R) Multiple Sclerosis (MS) Subjects (Study LAQ/5063 Active Double-Blind Phase) Followed by an Open Label Phase of Laquinimod 0.6 mg Daily (LAQ/5063 OL)

LAQ/5063 OL

NCT00745615

Amended Protocol following Global Amendments 01 to 10 Approval Date: 25 February 2016

TEVA PHARMACEUTICAL INDUSTRIES LTD., ISRAEL

CLINICAL STUDY PROTOCOL

Study Title:	An Active Extension of LAQ/5062 Study. a Multinational, Multi-Center, Randomized, Double-Blind, Parallel-Group Study, to Evaluate the Safety, Tolerability and Efficacy of Two Doses (0.3 mg and 0.6 mg) of Laquinimod, Orally Administered in Relapsing Remitting (R-R) Multiple Sclerosis (MS) Subjects Study LAQ/5063 Active Double-Blind Phase) Followed by an Open Label Phase of Laquinimod 0.6 mg Daily (LAQ/5063 OL).
Protocol No.:	LAQ/5063
EUDRACT number:	2005-004334-41
Clinical Phase:	Phase IIb
Protocol Version and Date:	Final - September 11, 2005
Global Amendment # 1:	November 24, 2005
Global Amendment # 2:	October 23, 2006
Global Amendment # 3:	June 19, 2007
Global Amendment # 4:	November 22, 2007
Global Amendment # 5:	July, 30, 2008
Global Amendment # 6:	August, 28, 2008
Global Amendment # 7:	November 9, 2009
Global Amendment # 8:	September 15, 2011
Global Amendment # 9:	17 July 2014
Global Amendment # 10:	25 February 2016
Principal Investigator:	[redacted] Italy
MRI Principal Investigator and MRI Analysis Center:	[redacted] Italy
Sponsor:	Teva Pharmaceutical Industries, Ltd 5 Basel St, Petach-Tikva 49131, Israel
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Sponsor's Medical Expert	**Sponsor's Safety Officer**
[redacted]	[redacted]
Teva Pharmaceutical Industries, Ltd	Teva Pharmaceutical Industries, Ltd
[redacted]	[redacted]

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 Harmonisation) Guidelines and Directive 2001/20/EC of the European Parliament and the Council of the European Union.
The information in this document is considered privileged and confidential, and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board/Ethics Committee opinions, patient informed consent and the approval of local regulatory authorities as required by local law.

PROTOCOL APPROVAL PAGE

EUDRACT No.: 2005-004334-41
PROTOCOL No. LAQ/5063
Protocol Version and Date: Final, November 22, 2007
Including Global Amendments No. 1 to 10

Sponsor's Authorized Representative	**Signature:** [redacted]	**Date:** 25 FEB 2016
[redacted] Teva Pharmaceutical Industries, Ltd	[redacted]	

Study Principal Investigator	**Signature:** [redacted]	**Date:** 25 FEB 2016
[redacted] Italy		

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Protocol Number	LAQ/5063
EudraCT Number	2005-004334-41
Protocol Title	An Active Extension of LAQ/5062 Study. a Multinational, Multicenter, Randomized, Double-Blind, Parallel-Group Study, to Evaluate the Safety, Tolerability and Efficacy of Two Doses (0.3 mg and 0.6 mg) of Laquinimod, Orally Administered in Relapsing Remitting (R-R) Multiple Sclerosis (MS) Subjects (Study LAQ/5063 Active Double-Blind Phase) Followed by an Open Label Phase of Laquinimod 0.6 mg Daily (LAQ/5063 OL).
Participating Countries	Europe (Italy, Germany, Spain, Czech Republic, Russia, Poland, U.K., Hungary) and Israel
Clinical Phase	IIb
Investigational Medicinal Product (IMP) & Dosage	For the initial extension phase (double-blind active extension phase): • 0.3 mg arm: one white to off-white round biconvex tablet of 0.3 mg of laquinimod and one matching placebo tablet to be administered orally once daily. • 0.6 mg arm: two white to off-white round biconvex tablets each of 0.3 mg of laquinimod to be administered orally once daily. Following approval of the Global Amendment # 4 to Protocol LAQ/5063 all subjects were switched to receive one white opaque cap and body, hard gelatin capsule containing laquinimod sodium equivalent to 0.6 mg laquinimod, to be administered orally once daily.
Study Duration	LAQ/5063 active double-blind phase (either completion of the full 36 weeks or as requested by the Sponsor) and an additional 24 months for the open label (OL) phase followed by further extension for a period of 36 months. Upon completion of this extension phase, subjects may continue to participate in the study as long as the Sponsor continues the development of laquinimod 0.6 mg for relapsing-remitting multiple sclerosis (RRMS).
Study Population	Subjects completing 36 weeks of the LAQ/5062 study in compliance with the protocol and meeting all inclusion/exclusion criteria will be eligible to be included in the extension study (LAQ/5063 active double-blind phase). Following the termination of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), subjects will be eligible to be enrolled in the open label phase (LAQ/5063 OL) if all inclusion/exclusion criteria are met.

Study Objectives	To make treatment with laquinimod available to all subjects who previously participated in both the LAQ/5062 study and the LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor). To assess the long-term safety, and tolerability in the group that received active treatment in LAQ/5062 protocol and additional short term safety and tolerability in the group who received placebo treatment. The LAQ/5063 OL phase will assess long-term safety and tolerability of 0.6 mg laquinimod administered once daily. Further efficacy data will be obtained by comparing baseline to termination in the group who received placebo treatment in LAQ/5062 (core study) protocol.
Study Design	This is a continuation of the LAQ/5062 study as a multinational, multicenter, randomized, double-blind, parallel group study, assessing the safety, tolerability and efficacy of two doses of laquinimod in subjects with RRMS followed by an open label phase of laquinimod 0.6 mg daily (LAQ/5063 OL). Subjects will enter this randomized, two active arms study immediately after completion of the LAQ/5062 core study. The blinding in both, core study (LAQ/5062) and its active double-blind extension phase (LAQ/5063), will be maintained. Subjects will enter the open-label phase (LAQ/5063 OL) upon the termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor). Subjects previously treated with placebo in the LAQ/5062 study will be equally randomized to one of the active treatment groups: • 0.6 mg of laquinimod per os (p.o.) once daily • 0.3 mg of laquinimod p.o. once daily Subjects previously treated with laquinimod 0.6 mg or laquinimod 0.3 mg will continue on their original treatment assignment. Upon the termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor) and after meeting the eligibility criteria of the open-label phase, all subjects will be treated with laquinimod 0.6 mg once daily.
Study Design	During the active double-blind phase subjects will be evaluated at study sites for 7 scheduled visits or until Sponsor's request: Baseline (Week 0 / Termination (Week 36) of Core Study LAQ/5062), Week 4, Week 8, Week 12, Week 16, Week 24 and Week 36 (completion of the full 36 weeks of LAQ/5063 active double-blind phase or as requested by the Sponsor). During the open label phase, the visits will be performed at monthly intervals for the

	first 3 months and at three-month intervals for the period of 24 months. Upon completion of the 24-month treatment period, visits will be performed at 6 months intervals thereafter, where, for the purpose of this study, a month is 30 days and a visit is defined as X months ± 7 days. During the open label phase subjects will be evaluated at study sites for the following scheduled visits: Baseline (Month 0 / Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor)), Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 30, Month 36, Month 42, Month 48, Month 54, Month 60 and every 6 months thereafter, until termination (may continue to participate in the study as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS) or early discontinuation. Subjects who discontinue treatment for any reason will continue follow-up according to scheduled visits. *Magnetic resonance imaging (MRI) scans*: this section is relevant only for the LAQ/5063 double-blind phase and the first 24 months of the LAQ/5063 Open-Label phase. During the active double-blind phase MRI will be performed at Baseline (Week 0 / Termination (Week 36) of Core Study LAQ/5062), and Week 36 (completion of the full 36 weeks of LAQ/5063 active double-blind phase or as requested by the Sponsor). For the open label phase MRI will be performed at baseline (Month 0 / Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), Month 12 and Month 24. Subjects who performed the MRI scan within a window of ≤ 14 days, as part of the termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), will not need to undergo another MRI scan for baseline visit of the open-label phase. *Neurological evaluations*: during the active double-blind phase will be performed at Baseline (Week 0 / Termination (Week 36) of Core Study LAQ/5062), Week 12, Week 24 and Week 36 (completion of the full 36 weeks of LAQ/5063 active double-blind phase or as requested by the Sponsor). For the open label phase Neurological evaluations will be performed at Baseline (Month 0 / Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), Month 3, Month 6, Month 12, Month 18 and Month 24. Following Month 24 visit, neurological evaluations will be performed every 6 months thereafter. Subjects who performed the Neurological evaluations within a window of ≤ 30 days, as part of the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor) will not need to undergo a Neurological evaluation for the baseline visit of the open-label phase. *Multiple Sclerosis Functional Composite (MSFC)* will be assessed at Baseline (Week 0 / Termination (Week 36) of Core Study LAQ/5062), and Week 36

	(completion of the full 36 weeks of LAQ/5063 active double-blind phase or as requested by the Sponsor). For the open label phase MSFC will not be performed. *Adverse Events* (AEs) will be monitored throughout the study. *Vital signs* will be measured at each study visit throughout the study. *Physical examination* will be performed at each study visit throughout the study. Subjects who performed the physical examination within a window of ≤ 30 days, as part of the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), will not need to undergo another physical examination. *Clinical laboratory testing* (including hematology, serum chemistry including liver enzymes and serum β-human chorionic gonadotropin (β-hCG) in women of child-bearing potential) will be performed at all visits during the active double-blind phase and the open-label phase. Subjects who performed the clinical laboratory testing within a window of ≤ 14 days, as part of the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), will not need to undergo another clinical laboratory testing at baseline visit of the open-label phase. *A rapid urine β-hCG* test will be performed in women of child-bearing potential at each scheduled study visit (at site). A rapid urine β-hCG test will be performed 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 asked specific questions regarding the test (see Appendix 10). In 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. (see Appendix 10) *Electrocardiogram (ECG)* will be performed at all visits during the active double-blind phase. For the open label phase ECG will be performed at Baseline (Month 0) / Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), Month 1, Month 2, Month 3, Month 6, Month 12, Month 18 and Month 24. After Month 24 visit, ECG will be performed every 6 months. Subjects who performed the ECG within a window of ≤ 30 days, as part of the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), will not need to undergo another ECG at baseline visit of the open-label phase. Testing for *Factor V Leiden Mutation* will be performed within scheduled or unscheduled visits during the open label phase, but will not be measured throughout the extension open label phase period. Carriers of the mutation will be discontinued from the study.

	Relapses will be monitored throughout the study**.** *Ancillary Studies* (For LAQ/5063 active double-blind phase only): • Pharmacokinetic Study (PK): blood samples for PK analysis will be collected from a sub-group of subjects (the same subjects who participated in the LAQ/5062 PK study) at Baseline (Week 0 / Termination (Week 36) of Core Study LAQ/5062) and at Week 36 and post treatment period. • Population Pharmacokinetic Study (PPK): blood samples for PPK analysis will be collected from all subjects at Week 36 (termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor). For subjects participating in the PK sub-study of LAQ/5063 active double-blind phase, will enter the open-label phase following a gap of at least 14 days from the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), in order to complete PK sample collection.
Number of Subjects	Subjects who successfully completed the LAQ/5062 study and wished to continue to the extension study (approximately 264 subjects) Following the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), subjects will be enrolled in the open-label phase (LAQ/5063 OL) phase if all inclusion/exclusion criteria are met.
Inclusion/Exclusion Criteria	Inclusion Criteria for LAQ/5063 active double-blind phase 1. Subjects must have completed 36 weeks of treatment in the LAQ/5062 study and all its activities in accordance with the 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 give signed, written informed consent prior to entering this extension study. Inclusion Criteria for the LAQ/5063 OL open-label phase

	1. Subjects must have completed the 36 weeks of treatment (completion of the full 36 weeks or as requested by the Sponsor), of the active double-blind phase 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 open-label phase (LAQ/5063 OL). 4. Subjects must give signed, written informed consent prior to entering the open-label phase (LAQ/5063 OL). <u>Inclusion Criteria for the LAQ/5063 OL open-label phase - further extension (after visit Month 24):</u> 1. Subjects must have completed the 24 months of treatment of the first period of the open label phase. 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)].
Inclusion/Exclusion Criteria	<u>Exclusion Criteria for LAQ/5063 active double-blind phase</u> 1. Premature discontinuation from core study LAQ/5062 for any reason. 1. Pregnancy or breastfeeding. 2. Subjects with clinically significant or unstable medical or surgical condition detected or worsened during the core study, which would preclude safe and complete study participation. <u>Exclusion Criteria for the LAQ/5063 OL open-label phase</u> 1. Premature discontinuation from LAQ/5063 active double-blind phase for any

	reason other than sponsor's request. 2. Pregnancy or breastfeeding. 3. Subjects with clinically significant or unstable medical or surgical condition, detected or worsened during the active double-blind phase of LAQ/5063, which would preclude safe and complete study participation 4. Use of experimental drugs, immunosuppressive drugs, and/or participation in clinical studies within the period from termination of LAQ/5063 active double-blind phase to the open-label phase (LAQ/5063 OL). 5. Previous treatment with immunomodulators with the exception of laquinimod (including [IFN] 1a and 1b, Glatiramer Acetate and intravenous [IV] immunoglobulin) within 2 months prior to entering the open-label phase for those subjects who have a time gap between termination of LAQ/5063 active double-blind phase to the open-label phase (LAQ/5063 OL). 6. Use of corticosteroids within 30 days prior to entering the open-label phase, except for IV methylprednisolone 1 g/day for a maximum of 3 days, in the period from termination of LAQ/5063 active double-blind phase to the open-label phase (LAQ/5063 OL). 7. Use of potent inhibitors of CYP3A4 within 2 weeks prior to open label phase (LAQ/5063 OL) and/or use of fluoxetine one month prior entering the open label phase (LAQ/5063 OL), in the period from termination of LAQ/5063 active double-blind phase to the open-label phase (LAQ/5063 OL) (see list in Appendix 5). 8. Use of the following substrates of CYP1A2: theophylline and/or warfarin within 2 weeks prior to entering the open-label phase (LAQ/5063 OL), in the period from termination of LAQ/5063 active double-blind phase to the open-label phase (LAQ/5063 OL) 9. Use of amiodarone in the period from termination of LAQ/5063 active double-blind phase to the open-label phase (LAQ/5063 OL). 10. Following the switch to new formulation (capsules), hypersensitivity to: mannitol, meglumine or sodium stearyl fumarate <u>Exclusion Criteria for the LAQ/5063 OL open-label phase- further extension (after visit Month 24):</u> 1. Premature discontinuation from LAQ/5063 OL phase prior to completion of 24 months of treatment period. 2. Pregnancy or breastfeeding

	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. 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.
Relapse Treatment	Allowed treatment for relapse is a fixed dose of 1 g/day IV methylprednisolone or oral steroids for a maximum of 5 consecutive days.
Outcome Measures	<u>Safety</u> • AEs • Physical examinations • Vital signs and ECG • Clinical laboratory parameters <u>Tolerability</u> • Number and percentage of subjects who prematurely discontinued from the study • Number and percentage of subjects who prematurely discontinued from the study due to AEs <u>Efficacy</u> • Relapse Rate • The proportion of relapse free subjects • Number of enhancing lesions on T_1-weighted images • Number of new T_2 lesions • Volume of T_2 lesions • Number of new hypointense T_1 lesions • EDSS score

Outcome Measures	<u>Ancillary Studies</u> • Pharmacokinetic Study (PK): maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the concentration by time curve (AUC) and elimination rate constant (λ) will be calculated. • PPK: Fitness of a population model to different covariates will be evaluated. A separate PK and PPK protocol will be prepared for PK/PPK analysis.
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

ABR-215062	laquinimod
ACTH	Adrenocorticotrophic Hormone
AE	Adverse Event
AhR	Aryl Hydrocarbon Receptor
AI	Ambulation Index
ALT	Alanine Aminotransferase (SGPT)
AST	Aspartate Aminotransferase (SGOT)
AUC	area under the concentration by time curve
CA	Competent Authority
CAB	Clinical Advisory Board
CDOC	Clinical Data Quality Control
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CRP	C-reactive Protein
CSC	Clinical Steering Committee
CSU	Clinical Supplies Unit
CT	Computed Tomography
CYP	Cytochrome P
DLC	Dioxin-like Compound
DLT	Digital Linear Tape
DM	Data Management
DMC	Data Monitoring Committee
EAE	Experimental Autoimmune Encephalomyelitis
EC	Ethics Committee
ECG	Electrocardiogram
EDSS	Kurtzke's Expanded Disability Status Scale
EU	European Union
FS	Functional Systems
g	Gram
GCP	Good Clinical Practice
Gd	Gadolinium

Gd-DTPA	Gadolinium-Gadopentetic Acid
GdE	Gadolinium Enhancing
GFR	Glomerular filtration rate
GTT	Gamma Glutamyl Transferase
HDL	High Density Lipoprotein
hs-CRP	High-sensitivity C-reactive Protein
I3C	Indole-3-Carbinol
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IFN	Interferons
IFN-ß	Interferon ß
IG	Immunoglobulin
IL	Interleukin
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
IVIG	Intravenous Immunoglobulin
IVRS	Interactive Voice Response System
kg	Kilogram
LCM	Local Clinical Management
LDL	Low Density Lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
ml	Milliliter
mm	Millimeter
MOA	Mode of Action
MRI	Magnetic Resonance Imaging
MRI-AC	Magnetic Resonance Imaging Analysis Center
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
PASAT	Paced Auditory Serial Addition Task
PCS	Potentially Clinically Significant
PK	Pharmacokinetics
PO	Per Os
PPK	Population Pharmacokinetics
PSI	Principal Site Investigator
QA	Quality Assurance

RDC	Remote Data Capture
R-R	Relapsing-Remitting
RRMS	Relapsing-Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SGOT	Serum Glutamate Oxaloacetic Transaminase
SGPT	Serum Glutamate Pyruvic Transaminase
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T_1	Relaxation Time T_1
T_2	Relaxation Time T_2
TCDD	2,3,7,8-tetrachloro-p-dibenzodioxin
t_{max}	Time to Maximum Plasma Concentration
λ	elimination rate constant
ß-hCG	ß–human Chorionic Gonadotropin

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 people 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 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 (IFN)-β 1a (Avonex®[a], Rebif®[b]), IFN-β 1b (Betaseron®[c], Extavia®[d]), glatiramer acetate (Copaxone®[e]), mitoxantrone (Novantrone®[f]), and natalizumab (Tysabri®[g]; for patients non-responsive to other medications). 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 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.

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[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

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).

The precise mechanism of action 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 (MOA) 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). Laquinimod is extensively metabolized predominantly by cytochrome P450 (CYP) 3A4.

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 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 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 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.

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 PK, 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 PK is 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% (0.0423b)	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 lesionsc	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[1]]. In addition, treatment with laquinimod demonstrated reduction in brain atrophy: ALLEGRO: 32.8% [p<0.0001], BRAVO[1] : 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 3.4.1.7.

3.4. Known and Potential Risks and Benefits to Human Subjects

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

[1] 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

- Uncommon (≥ 1/1000 to < 1/100)
- Rare (≥ 1/10000 to < 1/1000)
- Very rare (< 1/10000)
- Not known (cannot be estimated from the available data)

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

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. Details of Important Adverse Drug Reactions

3.4.1.1. 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

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 906
	>1 and <3x ULN	90 (9.7%)	147 (16.2%)
	> 3 and <5x ULN	11 (1.2%)	22 (2.4%)
	> 5 and <8x ULN	1 (0.1%)	6 (0.7%)

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

3.4.1.2. 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.

3.4.1.3. 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.

3.4.1.4. Back and Neck Pain

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

3.4.1.5. 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.

3.4.1.6. Hematological Changes

3.4.1.6.1. 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.

3.4.1.6.2. Decreased Platelets

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

3.4.1.6.3. Increased White Blood Cells

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

3.4.1.7. Cardiovascular Events (Laquinimod 1.2 and 1.5 mg)

On 30 December 2015, a DMC review of 8 unblinded cases from the CONCERTO and 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.

3.4.2. Potential Safety Issues with Laquinimod

3.4.2.1. 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.

To prevent such exposure, women of childbearing potential (for example women who are not postmenopausal or surgically sterilized) must practice an acceptable method of birth control (Section 5.3) for 30 days before taking the study treatment, and two acceptable methods of birth control throughout treatment 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 will 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.

3.4.2.2. 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.

3.4.2.3. 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.

3.5. Rationale For Study Design And Dosages

3.5.1. Study Design Rationale

This double-blind active extension study makes laquinimod available to subjects who successfully completed the double-blind placebo-controlled LAQ/5062, and enables the exploration of the long term safety, tolerability and clinical effect parameters during the disease.

LAQ/5062 study results analysis demonstrated that the 0.6 mg dose of laquinimod reached its primary endpoint, namely, reduction in the cumulative number of enhancing lesions. Accordingly, the open-label phase makes laquinimod 0.6 mg available to subjects who have completed the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), and enables the exploration of the long-term safety, tolerability and clinical effect parameters during the disease.

3.5.2. Study Drug Dose Rationale

The doses of 0.3 mg and 0.6 mg laquinimod per day that were chosen for the placebo-controlled protocol LAQ/5062 will be used in the active extension study.

Laquinimod has shown to have biological activity in animal models, PK studies, four phase I studies and two phase II clinical studies. The results of the phase II study demonstrated that administration of laquinimod (0.3 mg/day) to subjects with RRMS results in decreased numbers of active lesions in the brain.

Considering that the beneficial effects of laquinimod, as demonstrated in animal models and in the phase II study, are dose-dependent, this led to the assumption that a higher dose than that used in the phase II study may lead to increased efficacy, and strongly supports investigation of a higher but safe and tolerable dose. The core study, LAQ/5062 was designed to investigate 0.3 mg, as well as, 0.6 mg. The open-label safety clinical trial of laquinimod (0.9 mg/day) in RRMS patients has shown a reasonable safety profile. Therefore, it was decided to continue exploration of laquinimod doses of 0.3 mg and 0.6 mg in this extension study.

The data from the core LAQ/5062 study showed that oral formulation of laquinimod administered in a daily dose of 0.6 mg significantly reduced the mean cumulative number of Gd-enhancing lesions as compared to placebo. The 0.6 mg dose was well tolerated, and had a safety profile that was comparable to that of the 0.3 mg dose. Based on these positive results, all subjects participating in the open-label phase will receive *laquinimod tablets* (switched to capsules upon approval of Amendment # 4) in a daily dose of 0.6 mg.

4. STUDY OBJECTIVES

- To make treatment with laquinimod available to all subjects who previously participated in LAQ/5062 study and those who completed the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor).

- To assess the long-term safety, and tolerability in the group that received active treatment in LAQ/5062 protocol and additional short term safety and tolerability in the group who received placebo treatment. LAQ/5063 OL phase will assess long-term safety and tolerability of 0.6 mg laquinimod once daily.

Further efficacy data will be obtained by comparing baseline to termination in the group who received placebo treatment in LAQ/5062 core study protocol.

4.1. Safety And Tolerability

4.1.1. Safety

- Adverse Events (AEs)

- Physical examinations

- Vital signs and electrocardiogram (ECG)

- Clinical laboratory parameters

4.1.2. Tolerability

- Number and percentage of subjects who prematurely discontinued from the study

- Number and percentage of subjects who prematurely discontinued from the study due to AEs

4.1.3. Efficacy

- Relapse Rate

- The proportion of relapse free subjects

- Number of enhancing lesions on T_1-weighted images

- Number of new T_2 lesions

- Volume of T_2 lesions

- Number of new hypointense T_1 lesion
- EDSS Score

4.1.4. Ancillary Studies

PK assessments and population pharmacokinetics (PPK) evaluation.

5. STUDY DESIGN

5.1. Overview and Plan

This is a multinational, multicenter, randomized, double-blind, parallel-group active extension of LAQ/5062 study, assessing the tolerability, safety and efficacy of two doses (0.3 mg and 0.6 mg) of laquinimod, orally administered, in RRMS subjects, followed by an open-label phase of laquinimod 0.6 mg daily (LAQ/5063 OL).

For the double-blind phase seven planned study visits or until the Sponsor's request (see Study Task Flow Sheet, Table 5) will be conducted at Baseline (Week 0 / Termination (Week 36) of Core Study LAQ/5062), Week 4, Week 8, Week 12, Week 16, Week 24 and Week 36. For the open-label phase the following study visits (see Study Task Flow Sheet, Table 6 and Table 7) will be conducted at Baseline (Month 0) / Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21 and Month 24. Additional visits during the further extension of the study will be at Months 30, 36, 42, 48, 54, 60 and every 6 months thereafter, until termination (as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS) or early discontinuation.

Subjects previously treated with placebo in the LAQ/5062 study will be equally randomized to one of the two active treatment groups:

- 0.6 mg of laquinimod per os (p.o.) once daily
- 0.3 mg of laquinimod p.o. once daily

Subjects previously treated with laquinimod 0.6 mg or laquinimod 0.3 mg will continue on their original treatment assignment. Once Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor) is performed, all subjects will continue on 0.6 mg daily.

Subjects will undergo MRI scans at Baseline (Week 0 / Termination (Week 36) of Core Study LAQ/5062), and Week 36 (Termination visit of LAQ/5063 active double-blind phase [completion of the full 36 weeks or as requested by the Sponsor]). For the open-label phase MRI will be performed at baseline (Month 0 / Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), Month 12 and Month 24. Subjects who performed the MRI scan within the past 14 days as part of the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), will not need to undergo another MRI scan for baseline visit of LAQ/5063 OL.

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

Unscheduled visits may be conducted whenever required due to various reasons, for example, AEs, or possible exacerbation.

Figure 1: Treatment Groups in MS-LAQ/5062 (Core Study) and the Double-Blind and Open-Label Phases of LAQ/5063 (Extension Study)

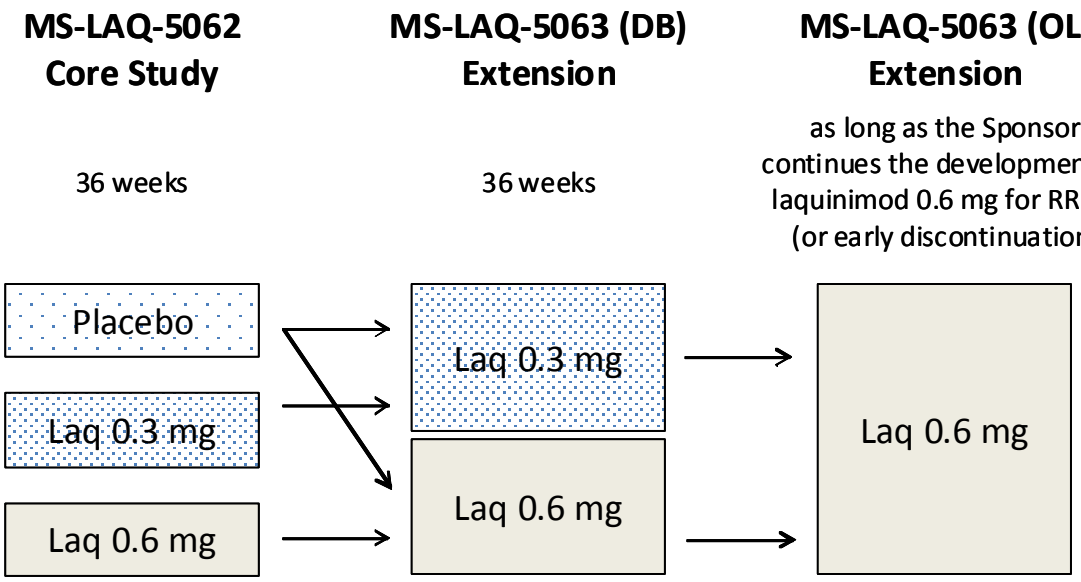


Figure 2: Study Flowchart for MS-LAQ/5062 Core Study

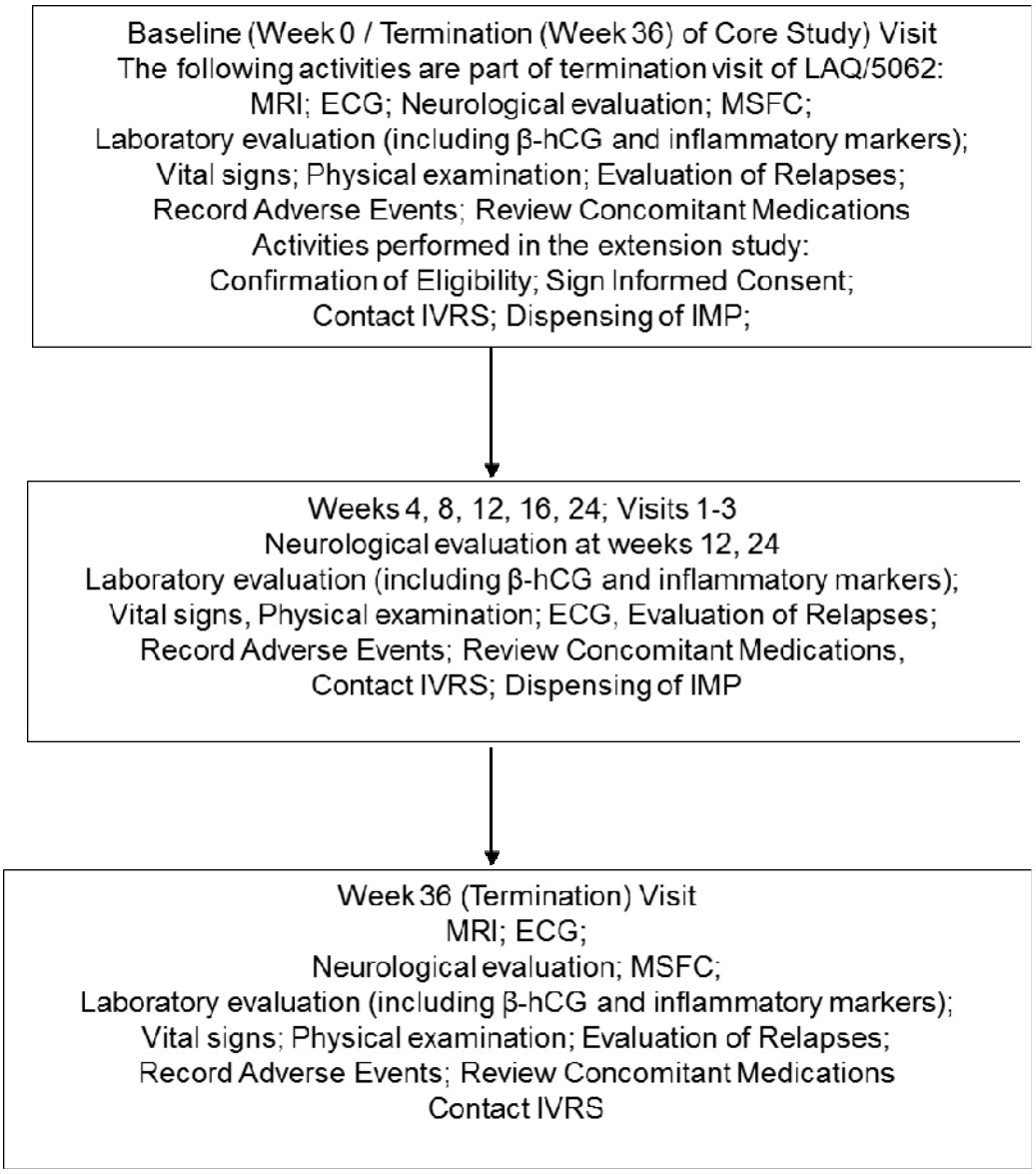
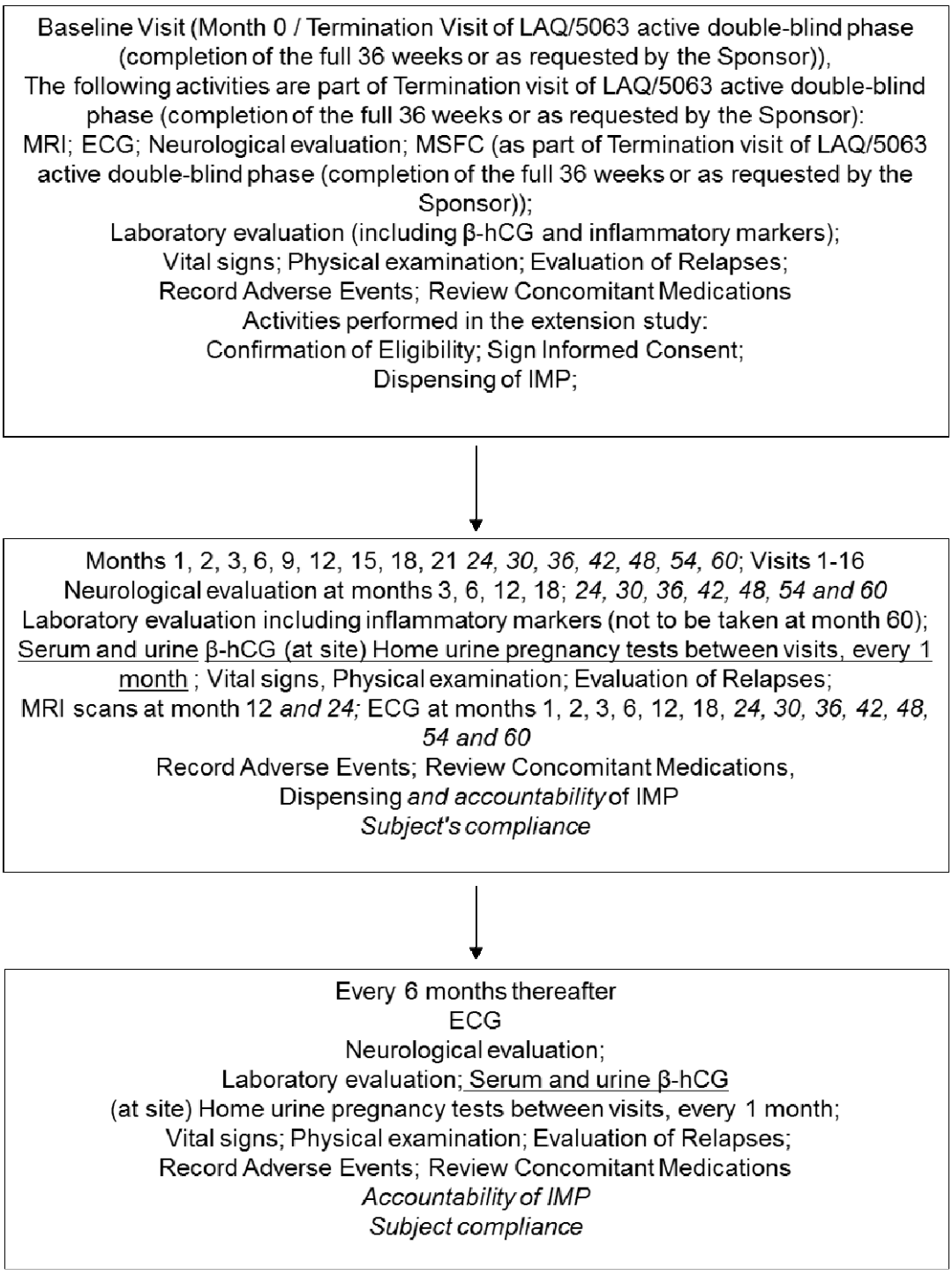


Figure 3: Study Flowchart for Open-Label Phase of LAQ/5063 Extension Study



5.2. Number of Subjects

Subjects who successfully completed the LAQ/5062 study and wished to continue to the extension study (approximately 264 subjects).

Subjects who completed LAQ/5063 phase double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), will be invited to continue to the open-label phase (LAQ/5063 OL).

5.3. Inclusion Criteria

Subjects must meet all inclusion criteria in order to be eligible for Study 5063:

1. Subjects must have completed 36 weeks of treatment in the LAQ/5062 study and all termination visit activities in accordance with the 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 give signed, written informed consent prior to entering this extension study.

<u>Inclusion Criteria For The Open-Label Phase</u>

1. Subjects must have completed the 36 weeks of treatment (completion of the full 36 weeks or as requested by the Sponsor), of the active double-blind phase.

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 open-label phase (LAQ/5063 OL).

4. Subjects must give signed, written informed consent prior to entering the open-label phase (LAQ/5063 OL).

Inclusion Criteria for the LAQ/5063 OL open-label phase - further extension (after visit Month 24)

1. Subjects must have completed the 24 months of treatment of the first period of the open label phase

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)].

5.4. Exclusion Criteria

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

1. Premature discontinuation from core study LAQ/5062 for any reason.

2. Pregnancy or breastfeeding.

3. Subjects with clinically significant or unstable medical or surgical condition detected or worsened during the core study, which would preclude safe and complete study participation.

Exclusion Criteria For The Open-Label Phase

1. Premature discontinuation from LAQ/5063 active double-blind phase for any reason other than sponsor's request.

2. Pregnancy or breastfeeding.

3. Subjects with clinically significant or unstable medical or surgical condition, detected or worsened during the active double-blind phase of LAQ/5063, which would preclude safe and complete study participation.

4. Use of experimental drugs, immunosuppressive drugs, and/or participation in clinical studies within the period from termination of LAQ/5063 active double-blind phase to the open-label phase (LAQ/5063 OL).

5. Previous treatment with immunomodulators with the exception of laquinimod (including IFN 1a and 1b, Glatiramer Acetate and intravenous [IV] immunoglobulin [IG]) within 2 months prior to entering the open-label phase for those subjects who have a time gap between termination of LAQ/5063 active double-blind phase to the open-label phase (LAQ/5063 OL).

6. Use of corticosteroids within 30 days prior to entering the open-label phase, except for IV methylprednisolone 1 g/day for a maximum of 3 days, in the period from termination of LAQ/5063 active double-blind phase to the open-label phase (LAQ/5063 OL).

7. Use of potent inhibitors of CYP3A4 within 2 weeks prior to open label phase (LAQ/5063 OL) and/or use of fluoxetine one month prior entering the open label phase (LAQ/5063 OL), in the period from termination of LAQ/5063 active double-blind phase to the open-label phase (LAQ/5063 OL) (see list in Appendix 5).

8. Use of the following substrates of CYP1A2: theophylline and/or warfarin within 2 weeks prior to entering the open-label phase (LAQ/5063 OL), in the period from termination of LAQ/5063 active double-blind phase to the open-label phase (LAQ/5063 OL).

9. Use of amiodarone in the period from termination of LAQ/5063 active double-blind phase to the open-label phase (LAQ/5063 OL).

10. Following the switch to new formulation (capsules), hypersensitivity to: mannitol, meglumine or sodium stearyl fumarate.

Exclusion Criteria for the LAQ/5063 OL open-label phase- further extension (after visit Month 24)

1. Premature discontinuation from LAQ/5063 OL phase prior to completion of 24 months of treatment period.

2. Pregnancy or breastfeeding

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 (see Appendix 10). 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 (see Appendix 10).

6. CONCOMITANT MEDICATIONS

6.1. Allowed Concomitant Medications

Symptomatic MS agents, such as anti-cholinergic and anti-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 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 6.2, may be given concomitantly as needed for the subject's welfare.

Topical and inhaled steroids are allowed at the discretion of the Investigator 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 case report form (CRF).

Unless clinically indicated, any concomitant therapy should remain stable during the study; changes to the concomitant therapy must be recorded in the source document file as well as in the CRF.

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 6) 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 6) should be advised that plasma levels of these drugs could increase when combined with laquinimod.

6.2. Disallowed Medications (During Study)

- Natalizumab (Tysabri®)
- Fingolimod (Gilenya)

- IFN-β 1a or 1b
- Dimethyl fumarate (Tecfidera)
- Glatiramer Acetate
- Teriflunomide (Aubagio)
- Alemtuzumab (Lemtrada)
- Cladribine
- Rituximab
- Ocrelizumab
- Atacicept
- Belimumab
- Ofatumumab
- Inducers of CYP3A4 such as rifampin and carbamadizepine (for more examples see Appendix 5). Use of CYP3A4 inducers may result in reduced laquinimod plasma concentrations and may reduce its effectiveness.
- Moderate/strong inhibitors of CYP3A4; for example, ketoconazole and erythromyicin (see full list in Appendix 5) 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 relapse; see Section 6.1)
- Adrenocorticotrophic hormone (ACTH)
- Chemotherapeutic agents
- Cytotoxic agents
- Cyclophosphamide
- IV immunoglobulin (IVIG)

- Plasmapheresis
- Any other experimental agents
- Other immunosuppressive or immunomodulating agents

7. STUDY CONDUCT

The study assessments will be performed according to the summary of the Study Task Flow Sheet (see Table 5). For the open-label phase the study assessments will be performed according to the summary of the Study Task Flow Sheet (see Table 6 and Table 7).

7.1. Study Period

This is a continuation of the LAQ/5062 study as a multinational, multicenter, randomized, double-blind, parallel group study, assessing the safety, tolerability and efficacy of two doses of laquinimod in subjects with RRMS, followed by an open-label phase of laquinimod 0.6 mg daily (LAQ/5063 OL).

Subjects will enter this randomized, two active arms study immediately after completion of the LAQ/5062 core study. The blinding in both, core study (LAQ/5062) and its extension, will be maintained. Subjects will enter the open-label phase after completion of the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor).

The study duration is 36 weeks of double blind treatment (Week 0 [baseline] to Week 36 [termination]) or until the Sponsor's request. The duration of the open-label phase is as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS.

Subjects will be evaluated at study sites at Baseline (Week 0 / Termination (Week 36) of Core Study LAQ/5062), at Weeks 4, 8, 12, 16, 24, and 36 (Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor).

For the Study 5063 open label extension phase, the visits will be at monthly intervals for the first 3 months and at three months intervals for the period of 24 months. Upon completion of the 24 month treatment period visits will be performed at 6 months intervals thereafter, where, for the purpose of this study, a month is 30 days and a visit is defined as X months ± 7 days.

During the open label phase subjects will be evaluated at study sites for the following scheduled visits:

Baseline (Month 0 / Termination visit of LAQ/5063 active double-blind phase [completion of the full 36 weeks or as requested by the Sponsor]), Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 30, Month 36, Month 42, Month 48, Month 54, Month 60 and every 6 months thereafter, until termination (as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS) or early discontinuation.

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

7.2. Study Task Flow Sheets

Table 5: Study Task Flow Sheet for Study 5063 (Double-Blind Active Extension Phase)

Procedure/Visit Number	**Baseline[a] V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**Termination / V4**	Unscheduled Visit[b]
Weeks	**0**	**4**	**8**	**12**	**16**	**24**	**36 / Early Discontinuation**	
Informed Consent Signature	X							
Eligibility Criteria	X							
Concomitant Medications	X	X	X	X	X	X	X	X
ECG	X	X	X	X	X	X	X	X
Neurological Examination[c]	X			X		X	X	X
MSFC	X						X	
Evaluation of Relapse[d]	X	X	X	X	X	X	X	X
Serum β-hCG[e]	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
MRI (T_1, T_2)	X						X[f]	X
Vital Signs[g]	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X
Safety Laboratory Tests	X	X	X	X	X	X	X	X
Samples for inflammatory markers	X	X	X	X	X	X	X	X
First IMP Administration[h]	X[i]							
PK sampling (sub-group)	X[j]						X[k]	
PPK Sampling (Ancillary study)							X	
Laquinimod Dispensing, & Accountability	X	X	X	X	X	X	X[l]	X
Subject Compliance		X	X	X	X	X	X	X
Termination Documentation & Notification of Early Termination							X	

[a] At Baseline of this extension study only Eligibility, Informed Consent and Drug Dispensing are performed. All other tasks are part of the activities of Termination of the Core study.

[b] Assessments during an unscheduled visit will be performed as deemed necessary by the Investigator, except for vital signs and adverse events, which are mandatory at each visit. Relapse evaluation will be conducted when the visit is due to subject's complaint of possible relapse.

[c] 25-foot walk is performed with each neurological evaluation

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

[e] For women of child-bearing potential

[f] MRI scan will be performed within 4 days prior to the visit date.

[g] Weight will be measured at baseline and termination visits only.
[h] At home except for subjects participating in PK sub-study.
[i] One day post-baseline visit.
[j] One day post-baseline visit
[k] PK sampling will be performed in a sub-group of subjects following the last dose of treatment period on days: 1, 3, 6, 10, 14 after visit 6 (Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor))
[l] Accountability only

Subjects participating in the PK sub-study will have a gap of at least 14 days between Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), and Baseline Visit of the open-label phase (LAQ/5063 OL) in order to complete with the required assessments.

Table 6: Study Task Flow Sheet for Study 5063 OL (up to Month 24)

Procedure/Visit Number	**Baseline [a] V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**Termination / V10**	**Unscheduled Visit[b]**
Months	**0**	**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24/Early Discontinuation**	
Informed Consent Signature	X											
Eligibility Criteria	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X[c]	X	X	X	X		X		X		X	X
Neurological Examination[d]	Xc			X	X		X		X		X	X
Evaluation of Relapse[d]	X	X	X	X	X	X	X	X	X	X	X	X
Serum and urine β-hCG [e](on site)	X[f]	X	X	X	X	X	X	X	X	X	X	X
Urine β-hCG[e] (self check, at home); Pregnancy tests mandatory phone calls[g]	EVERY 1 MONTH BETWEEN VISITS											
Ascertaining use of effective contraception	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
MRI (T_1, T_2)	X[h]						X				X[i]	X
Vital Signs[j]	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X[c]	X	X	X	X	X	X	X	X	X	X	X
Safety Laboratory Tests[k]	X[f]	X	X	X	X	X	X	X	X	X	X	X
Samples for inflammatory markers	Xf	X	X	X	X	X	X	X	X	X	X	X
First IMP Administration	X[l]											
Laquinimod Dispensing, & Accountability		X	X	X	X	X	X	X	X	X	X[m]	X
Subject Compliance		X	X	X	X	X	X	X	X	X	X	X

Procedure/Visit Number	**Baseline [a] V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**Termination / V10**	**Unscheduled Visit[b]**
Months	**0**	**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24/Early Discontinuation**	
Termination Documentation & Notification of Early Termination											X	

[a] At Baseline of the open label phase only Eligibility, Informed Consent and Drug Dispensing are performed. For most of the subjects all other tasks are part of the activities of Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor). For subjects who have a gap from termination of LAQ/5063 active double-blind phase and open-label phase the baseline visit should include all the assessments as stated in the above Task Flow Sheet

[b] Assessments during an unscheduled visit will be performed as deemed necessary by the Investigator, except for vital signs, which are mandatory at each visit. Relapse evaluation will be conducted when the visit is due to subject's complaint of possible relapse.

[c] Subjects who performed the test evaluation within a window of ≤ 30 days, as part of the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), will not need to undergo another test evaluation

[d] Relapse evaluation will be performed in scheduled as well as unscheduled visits as deemed necessary by the Investigator/Coordinator. 25-foot walk is performed with each neurological evaluation

[e] For women of child-bearing potential

[f] Subjects who performed the test evaluation within a window of ≤ 14 days, as part of the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), will not need to undergo another test evaluation

[g] Mandatory phone calls will be performed within 72 hours of the scheduled home pregnancy test

[h] A MRI performed within 14 days as part of the termination visit of LAQ/5063 active double-blind phase (completion of full 36 weeks or as requested by the Sponsor) will not need to undergo another MRI scan for Baseline visit of LAQ/5063 OL.

[i] MRI scan will be performed within 4 days prior to the visit date.

[j] Weight will be measured at baseline and termination visits only.

[k] Testing for Factor V Leiden Mutation will be performed within scheduled or unscheduled visits during the open label phase. Carriers. of the mutation will be discontinued from the study

[l] All subjects will take the first IMP administration one day post-baseline visit.

[m] Accountability only

Table 7: Study Task Flow Sheet for Study 5063 OL (Months 24 onwards)

Procedure/Visit Number	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Every 6 months**	**Termination**	**Unscheduled Visit**
Months	**24**	**30**	**36**	**42**	**48**	**54**	**60**		**Early Discontinuation**	**Unscheduled visit[a]**
Informed Consent [b] Signature	X						X			
Inclusion/Exclusion criteria	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Cardiovascular risk factor assessment and management[c]	X		X		X		X	Every 12 months from Month 72		
ECG	X	X	X	X	X	X	X	X	X	X
Neurological Examination	X	X	X	X	X	X	X	X	X	X
Evaluation of Relapse[d]	X	X	X	X	X	X	X	X	X	X
Ascertaining the use of Effective contraception	X	X	X	X	X	X	X	X	X	X
Serum and urine β-hCG[e] (on site)	X	X	X	X	X	X	X	X	Serum test only	X
Urine β-hCGc (self check, at home); Pregnancy tests mandatory phone calls[f]	EVERY 1 MONTH BETWEEN VISITS									
Adverse Events	X	X	X	X	X	X	X	X	X	X
MRI (T_1, T_2)	X									
Vital Signs [g]	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X
Safety Laboratory Tests (including inflammatory markers, GFR estimation)	X	X	X	X	X	X	X[h]	X[h]	X[h]	X[h]
Laquinimod Dispensing, & Accountability	X	X	X	X	X	X	X[i]	X	X[i]	X
Subject Compliance	X	X	X	X	X	X	X	X	X	X
Termination Documentation & Notification of Early Termination									X	

Procedure/Visit Number	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Every 6 months**	**Termination**	**Unscheduled Visit**
Months	**24**	**30**	**36**	**42**	**48**	**54**	**60**		**Early Discontinuation**	**Unscheduled visit[a]**
Unscheduled samples										X[j]

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]).

[a] Assessments during an unscheduled visit will be performed as deemed necessary by the Investigator, except for vital signs and adverse events, which are mandatory at each visit

[b] At Month 24 (visit 10) of the open label phase Informed Consent will be signed for the extended open label period of 36 months. At Month 60 (visit 16) of the open label phase an Informed Consent will be signed for the additional extension as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS

[c] In addition, an evaluation should take place as soon as possible for subjects already in the study, following approval of Amendment #10

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

[e] For women of child-bearing potential

[f] Mandatory phone calls will be performed within 72 hours of the scheduled home pregnancy test

[g] Weight will be measured at all visits

[h] Inflammatory markers will not be collected from Month 60 and onwards

[i] Only drug retrieval

j 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.

7.3. Detailed Study Plan

The subject will attend the study site at scheduled visits as follows: Week 0 (baseline); and at Weeks 4, 8, 12, 16, 24 and 36 (Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), the subject will attend the study site at scheduled visits as follow: Month 0 (baseline / Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), and at Months 1, 2, 3, 6, 9, 12, 15, 18, 21 24, 30, 36, 42, 48, 54, 60 and every 6 months thereafter, until termination (as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS) or early discontinuation.

Two different neurologists/physicians will assess the subjects. 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 (Section 6)**.** For the open-label phase there is no requirement to have two different neurologists/physicians to perform the neurological examination.

7.3.1. Baseline Visit (Week 0)

The baseline (Week 0) visit will occur on Week 36 (termination) of the core study LAQ/5062. For the open-label phase the baseline visit (Month 0) will occur at the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor). In case of a time gap between both phases, the baseline procedures carried out for LAQ/5063 OL open-label phase will be the same as for the LAQ/5063 active double-blind unless it is specified otherwise.

7.3.1.1. Baseline Visit Procedures

After completion of all procedures and activities of the termination visit of the core study (LAQ/5062), and placing a call to the IVRS to notify the subject's termination from the core study, the investigator will establish eligibility of subjects willing to continue in the extension study. For the open-label phase, after completion of all procedures of the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), and placing a call to the IVRS to notify the subject's termination of the LAQ/5063 active double-blind phase, the investigator will establish the eligibility of subjects willing to continue in the open-label phase (LAQ/5063 OL). Eligible subjects will be informed about all aspects of the study, including scheduled study visits and activities, and must sign and date the informed consent. Same procedure should be performed, separately for the open-label phase. A copy of the informed consent must be given to the subject. Same procedure should be performed, separately for the open-label phase. A call to the IVRS will be made in order to allocate the subjects to their treatment group according to a computer-generated randomization list produced by Teva Global BioStatistics and Global BioMedical Informatics units. For the open-label phase the IVRS will not be used as all subjects will be on the same treatment group.

The IVRS will assign a pack number and the subject will be supplied and treated with the medication labeled with the same pack number. This is for LAQ/5063 active double-blind phase only.

For the open-label phase subjects who participate in the PK sub-study and/or have a time gap between Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor) and baseline visit of the open-label phase the first administration of the IMP will be taken at the site.

The following activities are part of termination visit of core study (LAQ/5062) and Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor).

The following activities will be performed as part of the baseline visit for the open-label phase (LAQ/5063 OL) unless it is specified otherwise.

- Vital signs (temperature, pulse, blood pressure and weight)
- ECG
- Complete physical examination
- Neurological evaluation including Functional System (FS) score, Ambulation Index (AI) score and EDSS, and 25 foot walk test
- Multiple Sclerosis Functional Composite (MSFC) (This is relevant for LAQ/5063 active double-blind phase only)
- MRI
  - T_1-weighted scan after administration of gadolinium-gadopentetic acid (Gd-DTPA)
  - T_2-weighted scan
- Laboratory tests including:
  - Urinalysis
  - Hematology
  - Serum chemistry
  - Serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) for women of child-bearing potential
  - Samples for inflammatory markers (e.g. CRP, fibrinogen)

- 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 potential teratogenicity and 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)
- Evaluation of a relapse (if relevant)
- Review concomitant medications (ensuring no disallowed medication is being used).
- Record of AEs

7.3.1.2. Randomization

Assignment of subject to treatment group (randomization) will be performed at baseline visit of the extension study for eligible subjects. Randomization will be determined according to a computer-generated randomization list produced by Teva Global BioStatistics and Global BioMedical Informatics units, and the IVRS procedure will be used to allocate the subject to the treatment group. The IVRS will assign a pack number and the subject will be supplied and treated with the medication labeled with the same pack number. This is relevant for LAQ/5063 active double-blind phase only.

7.3.1.3. Post Randomization

The following procedures will be performed:

- 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.
- Subjects will be instructed to administer the IMP once daily at approximately the same time of the day. The first administration of IMP in the extension study (LAQ/5063 active double-blind phase) and the open-label phase (LAQ/5063 OL), including subjects participating in the PK sub-study and/or have a time gap as well between termination of the active double-blind phase and baseline visit of the open-label phase will be the following day at the subject's home. However, subjects participating in PK sub-study will come for a visit on the next day, and will administer the IMP at the site following the blood drawing.

- 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 or a relapse.

7.3.1.4. Day 1 PK Visit

Subjects participating in the PK sub-study will come for a visit one day following randomization, which was performed on Visit 0, for blood sampling before first administration of IMP at the site. This is relevant for LAQ/5063 active double-blind phase only.

7.3.2. Scheduled Treatment Visits

Following the baseline visit, subjects will return to the study center for 5 treatment visits at Weeks 4, 8, 12, 16 and 24 ± 3 days unless decided otherwise by the Sponsor. For the open-label phase following the baseline visit, subjects will return to the study center for additional 16 visits at Months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 ± 7 days. For the additional extension period (i.e., as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS), visits will be performed every 6 months thereafter. Subjects who discontinue treatment for any reason will continue follow-up according to scheduled visits.

Following approval of Global Amendment #10, subjects continuing on laquinimod 0.6 mg will be re-consented with information about the cardiovascular risk seen in higher doses (see Section 3.4.1.7).

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

- Call IVRS to obtain kit number(s). This is relevant for LAQ/5063 active double-blind phase only.
- Reviewing inclusion/ exclusion criteria
- Signing appendix to informed consent
- Vital signs (temperature, pulse, blood pressure weight will be measured at all visits)
- Complete physical examination
- Laboratory tests including:
  - Hematology
  - Serum chemistry (including glomerular filtration rate [GFR] estimation)
  - 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 (see Appendix 10). The rest of the visit activities should be performed

- Samples for inflammatory markers– e.g. high-sensitivity C-reactive protein [hs-CRP] and fibrinogen-

- 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 potential teratogenicity and 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)
  - 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 10), a mandatory phone call will be performed by the Treating 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.
  - Complete neurological examinations including FS, AI, EDSS (Weeks 12 and 24 only) and 25 foot walk test. For the open-label phase LAQ/5063 OL) this examination will be performed at Months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 and every 6 months thereafter for the additional extension period (i.e., as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS).

- ECG. For the open-label phase (LAQ/5063 OL) ECG will be performed at Months 1, 2, 3, 6, 12 ,18, and every 6 months thereafter

- Evaluation of relapses (if applicable)

- Review concomitant medication (ensuring no disallowed medication is being used)

- Record of AEs
- IMP capsules accountability and dispensing Subject compliance
- Review instructions on IMP capsules administration (following the switch from tablets to capsules).
- 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 #10.

7.3.2.1. Additional Pregnancy Detection Measures

- All female subjects of child bearing potential will be invited to the site for an unscheduled visit as soon as the site's Principal Investigator receives and signs Amendment #5.
- The subject should be informed of the new safety issue regarding pregnancy. The issue of contraception should be reminded and emphasized.
- The Appendix to the Informed Consent should be signed.
- All female subjects of child bearing potential will be provided with home urine pregnancy test kits.

7.3.3. Termination Visit

Termination Visit (6) / (Week 36 ± 3 days) of LAQ/5063 Active Double-Blind Phase (Completion of the full 36 weeks or as requested by the sponsor), or any Termination or Early Discontinuation visit occurring as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS.

In the event of early discontinuation, standard termination procedures will be followed.

Early discontinuation is defined as withdrawal from the study prior to the completion of the full study period:

- Withdrawal prior to completion of 24 months of the first period of open label phase.
- Subjects that chose to continue to the second period of open label phase (additional 36 months), and did not complete this period.
- Subjects that chose to continue treatment from Month 60 as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS and did not complete this period.

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]).

Subjects who have completed 24 months of open label phase and chose not to continue to further extension of open label phase will be regarded as completers.

Subjects who have completed 60 months of the extension open label phase and chose not to continue to further extension of open label phase (as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS) will be regarded as completers.

The reason for discontinuation of therapy will be documented in the source documents and captured on the CRF. If there are several reasons for early discontinuation, the more severe will be chosen as the primary reason. In the event that laquinimod is discontinued early, an early termination visit should be completed as close to the last dosing date as possible.

Subjects who did not complete the 36 weeks of treatment of LAQ/5063 active double-blind phase until approval of amendment No 2 will be called for an a termination visit of the active double-blind phase as requested by the Sponsor to be switched to the open-label phase (LAQ/5063 OL)

In case a subject completed the 60 months OL period, but decided not to proceed with the further extension, he/she will be considered as completer.

The following will be performed at the Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), and/or at any early discontinuation visit occurring as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS:

- Vital signs, including weight
- Complete physical examination
- Record of AEs: If an AE is still ongoing, or a new AE is present at the termination visit, it will be followed according to the discretion of the Investigator and recorded in the subject's source documents and in the CRF (see Section 7.3.4).
- IMP accountability
- Subject compliance
- Review concomitant medication. 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.

- ECG
- Complete neurological examination, including FS, AI, and EDSS, and 25 foot walk test
- MSFC (this is relevant for LAQ/5063 active double-blind phase only)
- Evaluation of relapses (if applicable). If a relapse is confirmed or ongoing at the termination visit, it will be followed until relapse stabilization. All follow-up evaluations must be documented in the source documents and the CRF.
- Laboratory tests
  - Hematology
  - Serum chemistry (including GFR estimation)
  - Serum pregnancy test (β-hCG) for women of child-bearing potential
  - Blood sampling for PK study (ancillary study in sub-group of subjects. For subjects participating in this study, the IMP will be administered at the site. This is relevant for LAQ/5063 active double-blind phase only)
  - Blood sampling for PPK study (ancillary study in all subjects). (This is relevant for LAQ/5063 active double-blind phase only)
  - For a detailed sampling plan for PK and PPK studies refer to Section 8.4. (This is relevant for LAQ/5063 active double-blind phase only)
- 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 all subjects will be reminded to continue using 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 potential teratogenicity and 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)
- Call IVRS for update on subject's termination (This is relevant for LAQ/5063 active double-blind phase only)

Notification of the Sponsor in the event of early discontinuation including the reason for termination (see Section 7.3.4)

7.3.4. Criteria for Early Termination

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 LAQ-5063 OL study.

Every attempt should be made to follow the early discontinued subjects. Subjects who prematurely discontinue the study should be followed and treated by the Site Investigator in a customary manner. For subjects who decide not to continue with any further visits, termination visit evaluations/procedures should be performed and completed before discontinuation. A subject may withdraw or be withdrawn from the study for the following reasons:

1. Subject withdrew consent (specify)
2. Teva requested that subject be withdrawn (specify)
3. Request of Investigator or Primary Care Physician (specify)
4. Non-compliance
5. Protocol violation
6. Loss to follow-up/failure to return
7. AE (specify primary AE)
8. Death
9. Pregnancy
10. Planned pregnancy
11. Lack of efficacy
12. Other (specify)

If a subject is withdrawn due to AEs, the appropriate AE sections of the CRF should be fully completed. The local clinical management (LCM)/Monitor should immediately be informed of any withdrawal. The primary AE that caused early discontinuation should be specified in the appropriate section in the CRF.

If an AE is present at the last visit, it will be followed until the medical condition returns to baseline or is considered stable or chronic.

All efforts should be made to follow a subject who prematurely discontinues the study due to ongoing AE. In case of manifestation of a severe degree of intolerance to IMP and/or ongoing exacerbation, the subject may be prematurely discontinued at the discretion of the Investigator.

Laboratory tests demonstrating clinically significant changes should be repeated and followed up until they return to normal or baseline levels, or are stabilized.

7.3.4.1. Safety Stopping Rules

7.3.4.1.1. Liver Enzymes

In any increase of ALT or AST to ≥ 2 times ULN the "Guidance on Safety Monitoring" (see Appendix 10) should be thoroughly followed.

In the following circumstances, study drug will be discontinued immediately and liver enzymes will be monitored according the guidance in Appendix 10:

- Any increase in ALT or AST to ≥3 times ULN, combined with 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 10)

7.3.4.1.2. Pregnancy

To further emphasize the importance of use of effective contraception and avoidance of pregnancy under laquinimod exposure, 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 childbearing potential will be instructed about the potential teratogenicity and delayed risks for a child exposed in uterus to laquinimod.

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 stopping treatment immediately if

pregnancy is suspected (positive urine β-hCG 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 LSO/CRO with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a SAE (see Section 10).

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.

7.3.4.1.3. Cancer

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

7.3.4.1.4. 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.

7.3.4.1.5. 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.

7.3.5. Temporary Discontinuation of IMP

Temporary discontinuation is defined as a missing of more than three consecutive doses.

IMP may be temporarily discontinued for either of the following reasons:

- The subject develops an intolerable AE, which is perceived by the Site Investigator to be potentially related to IMP.
- The subject is temporarily unable to take IMP due to a medical condition (concurrent illness or surgery, etc.).
- The reasons for IMP temporary discontinuation should be recorded in the appropriate section of the IMP dispensing and compliance log in the CRF and the LCM should be notified.
- The subject will report any discontinuation/delay to the Investigator and will be instructed by the Investigator regarding continuation of treatment.

7.3.5.1. Rescheduling of Missed Dose

In the event of up to 3 consecutive days of missed doses of the once-daily IMP treatment, the subject will administer IMP immediately and continue with the previous treatment scheduling. This is not defined as temporary discontinuation.

In the event of more than 3 consecutive days of missed doses of the once-daily IMP treatment, the subject will administer IMP on the following day. This is defined as temporary discontinuation.

7.3.6. Unscheduled Visit

An unscheduled visit may be performed at any time during the study as deemed necessary by the Investigator. The date and reason for an 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
- IMP dispensing, accountability and/or replacement
- Subject compliance
- Other, specify

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

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

Mandatory Unscheduled Visit Procedures

- Vital signs
- Evaluation of AEs
- Evaluation of a suspected relapse/follow-up
- Ascertain use of effective contraception

Optional Unscheduled Visit Procedures

- ECG
- Physical examination
- Neurological examination (by the Study Neurologist/Physician)
- Laboratory tests (including estimation of GFR)
- IMP accountability
- Subject compliance

- Review of concomitant medications
- For women of child bearing potential, serum or urine β-hCG test may be performed

7.3.6.1. 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 8.2.5.1)
- pharmacokinetic blood sample
- sample for potential biomarker analysis

7.3.6.1.1. 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.

7.3.6.1.2. 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.

7.3.7. Visits during Relapses (Scheduled and Unscheduled)

Subjects will be instructed to contact their study site immediately should any symptoms suggestive of a relapse occur (see Section 8.1.4).

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

The relapse assessment will be documented in the source documents and in the CRF accordingly. A complete neurological assessment, including FS, AI and EDSS, 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 1.

Corticosteroids therapy (as described in Section 6.1) may be given for a confirmed relapse at the discretion of the Treating Neurologist/Physician and must be recorded in the CRF.

7.3.7.1. Blinding

The randomization code for each subject will be delivered to the investigator via the IVRS. The subjects, investigators and site personnel, MRI personnel, and the personnel involved in subject assessment, monitoring, analysis and data management (excluding the Clinical Supplies Unit [CSU] personnel), are blinded to the subject assignment. In order to ensure that information, which could potentially bias handling, is not disclosed, the following precautions will be practiced:

- 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.

- MRI scan evaluation will be performed at a central reading center by staff that does not have access to the clinical data.

This section is relevant for LAQ/5063 active double-blind phase only.

7.3.7.2. Emergency Code Breaking

Only in case of a serious adverse event (SAE), when the blinded information is urgently needed for the treatment of the subject, should the investigator reveal the relevant subject's treatment allocation. The sponsor Local Clinical Trial Manager should be notified of the event prior to breaking of the code or immediately afterwards, without revealing the subject's group assignment.

On completion of the study, record of un-blinding events of the emergency code breaking system will be generated and checked by the sponsor or by the sponsor's authorized representative

This section is relevant for LAQ/5063 active double-blind phase only

8. ASSESSMENT METHODS

8.1. Efficacy Assessment Methods

8.1.1. MRI Evaluations

The subjects will undergo MRI at Baseline (Week 0 / Termination (Week 36) of Core Study), and at Week 36 (termination)/early discontinuation visit.

The following parameters will be assessed:

- Number of T_1 GdE 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")

Steroid treatment for relapse (see Section 6.1) will not affect the schedule of MRI scans.

All MRI data will be interpreted by the MRI-Analysis Center (MRI-AC).

MRI scans can be performed within 4 days of each visit except for Week 36/ (termination) where the MRI scans are performed 4 days prior to this visit. For the MRI Protocol, see Appendix 3.

This section is relevant only for the LAQ/5063 double-blind phase and the first 24 months of the LAQ/5063 Open-Label phase.

8.1.2. Neurological Evaluations

A complete neurological assessment will be performed at Baseline (Week 0 / Termination (Week 36) of Core Study LAQ/5062), and at Weeks 12, 24 and 36 (Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor)/early discontinuation visit. For the open-label phase a complete neurological assessment will be performed at baseline (Month 0 / Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor), Months 3, 6, 12, 18 and 24. Following completion of month 24, the neurological evaluations will be performed every 6 months thereafter. Every effort should be made to ensure that the same Study 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 10/2002). The results will be recorded on standardized and validated examination forms (see Appendix 2) as well as in the CRF.

The footnote in Appendix 2 page 75 should be disregarded for this study in cases where Functional System Score for fatigue is 1 ("Mental Functions grade 1 does not contribute to EDSS – step definition".). That is, when fatigue score=1, it does contribute both to Functional System Score and to the converted EDSS score (page 74, Appendix 2).

8.1.3. MSFC

The MSFC consists of 3 clinical examinations, the results of which are combined using z-scores. The three clinical examinations include the Paced Auditory Serial Addition Task (PASAT), Timed 25 foot walk and 9-Hole Peg Test.

The tests will be performed at Baseline (Week 0 / Termination (Week 36) of Core Study), and Week 36 (termination)/early discontinuation visit.

Appendix 4 presents the instructions for administering the MSFC.

The 25 foot walk test will be performed each time neurological evaluation is performed (baseline, Weeks 12, 24 and 36).

This section is relevant for LAQ/5063 active double-blind phase only

8.1.4. On-Study Relapse Evaluation Procedures

The subject will be examined within 7 days of the telephone contact, conditional upon a symptomatic period of ≥ 48 hours.

For the open-label phase (LAQ/5063 OL) only one neurologist/physician is required (Study Neurologist/Physician) to perform a neurological examination and treat the subject as needed.

Relapse Determination

The Study Neurologist/Physician will make the decision as to whether the neurological change is considered a relapse, based on EDSS/FS scores (see Relapse Definition, Appendix 1).

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

In the case of an ongoing or just-started relapse at the study termination visit (Week 36)/early discontinuation visit, subjects will be followed up until the end of the relapse, wherever possible (see Section 7.3.3).

8.2. Safety Assessment Methods

8.2.1. Physical Examination

The Study Neurologist/Physician will perform a full examination at every visit.

8.2.2. Emphasis on Physical Examination

In light of the potential proinflammatory effect of laquinimod, and to appropriately monitor its early manifestations, physical examinations will be conducted on a regular basis with emphasis on clinical clues of proinflammatory manifestations.

8.2.3. Vital Signs and Weight

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

Blood pressure and pulse will be recorded in a sitting position after resting for 5 minutes. If the result appears not to be logical, the measurement will be repeated after an additional 5 minutes of resting and the result will be recorded in the CRF.

All measurements and times of measurements will be recorded on the source document.

Body weight will be measured at baseline (termination visit of core study LAQ/5062) and at Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor) /early discontinuation visit. For the open-label phase weight will be measured at all visits, and as long as the subject continues study drug treatment.

8.2.4. ECG

ECGs will be performed at each study visit. For the open-label phase (LAQ/5063 OL) ECG will be performed at Months 1, 2, 3, 6, 12, 18 and 24. Following completion of Month 24, ECGs will be performed every 6 months.

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 (PCS) 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.

8.2.5. 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 Appendix 10, 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 GFR estimation)
  - Bilirubin (direct and total)*
  - Urea
  - AST (SGOT)*
  - ALT (SGPT)*
  - GGT*
  - Lipid profile (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL], triglycerides) under fasting conditions.
  - Pancreatic Amylase
  - Lipase will be tested in case of abnormal pancreatic amylase result (see Appendix 10 for guidance on monitoring subjects with elevated pancreatic amylase levels)
  - Total Protein*
  - Albumin*
  - Alkaline Phosphatase*
  - 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

- 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.

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.

- Electrolytes
  - Sodium
  - Potassium
  - Phosphorous
  - Calcium
- Coagulation
  - Fibrinogen
  - INR (to be performed in local laboratory, only if required according to Safety Monitoring Guidance, in Appendix 10
- Hematology
  - Hemoglobin
  - MCH
  - MCV
  - MCHC
  - Hematocrit
  - Red Blood Cells (RBC)

  - White Blood Cells + differential count*
  - Platelets count

- Serology (to be performed only in a confirmed abnormality of liver enzymes, according to Appendix 10):
  - Anti-HAV IgM antibodies
  - Hepatitis B Surface antigen
  - Anti-HBc IgM antibodies
  - Anti- HCV IgG antibodies
  - Anti-nuclear antibodies
  - Anti-Smooth Muscle (Sm) antibodies
  - Anti-Liver-Kidney Microsomal (LKM)-1 antibodies

Same laboratory evaluations will be performed for LAQ/5063 OL phase.

8.2.5.1. 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

8.2.6. Adverse Events

At each study visit, all AEs will be identified and documented as detailed in Section 10 of this protocol.

8.2.7. 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.

8.2.8. 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 7.3.4.1.5).

8.2.9. 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 7. In addition, an evaluation should take place as soon as possible for subjects already in the study, following approval of Amendment #10.

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.

8.3. Assessment of Subject Compliance

At each study visit, the Investigator, Site Coordinator and/or pharmacist will assess the subject's compliance with the study requirements. This will include checks of protocol compliance and use of laquinimod.

The subject will return all unused tablets and/or capsules (following the switch to capsules) in their original packages, blisters/bottles and all used partially empty and empty blisters/bottles and unused IMP at each visit to the study. Compliance with the dosing regimen will be determined by performing IMP accountability of returned blisters/bottles of the IMP used and unused. The number of unused tablets/capsules will be recorded on the CRF by site personnel. Percent compliance will be calculated as the number of used tablets/capsules divided by the number of total tablets/capsules expected to be used, multiplied by 100.

Subjects with less than 75% overall compliance during the entire study will be considered non-compliant, although they will continue to be followed-up and included in the intent-to-treat (ITT) cohort. Subjects who fail to comply with the study requirements may be withdrawn from the study, following consultation with the Sponsor.

8.4. Ancillary Studies

The Ancillary studies are relevant for LAQ/5063 active double-blind phase only.

8.4.1. Pharmacokinetic Sub-Study

Blood samples for of PK evaluation will be performed in a sub-set of countries and sites.

For PK evaluation blood sample (2 mL/each) will be collected from subjects at one time point prior to first administration of the IMP (one day after randomization into LAQ/5063), and on Week 36 at the following time points: pre-dose and at 10, 30, 45, 90 minutes, 3, 6, 24 hours and 72 hours (day 3 post-study termination), 144 hours (day 6 post-study termination), 240 hours (day 10 post-study termination) and at 336 hours (day 14 post-study termination). The blood samples will be collected into tubes containing sodium heparin. All participants in this study should administer the IMP dose at the same time in the morning.

8.4.2. Population Pharmacokinetic (PPK) Study

Blood samples for PPK study will be collected in all study sites. Subjects participating in PPK study are not necessarily participating in PK sub-study.

For PPK evaluation, 1 blood sample (2 mL/each) will be collected from subjects Week 36/Early Termination. The date and time of the blood sample, as well as the date and time of the last dose prior to the sample will be recorded on the CRF. A review of the treatment compliance will include information on the last week compliance regarding tablets intake. The blood samples will be collected into tubes containing sodium heparin.

8.4.3. Samples Handling for PK and PPK studies

Plasma will be separated by centrifugation at nominally +4°C. Deviations from the blood sampling times will be recorded in the appropriate CRFs. Samples will be prepared by the site and sent frozen to the central laboratory for storage at -70°C. Samples for PK evaluation will be sent periodically to an analytical facility for analysis. The analytical facility is:

Teva Pharmaceutical Works Co. Ltd.
Innovative R&D
Bioanalytical Laboratory
Pallagi St. 13
Debrecen
4042 Hungary

8.4.4. Bioanalysis

The concentrations of laquinimod will be determined in blood plasma using LC-MS/MS (Liquid Chromotography Tandem Mass Spectrometry) in accordance with the ABR-method M-0085A. Quantitation will be based on an internal standard, a stable isotope of laquinimod containing six ^{13}C atoms. The plasma will be prepared for injection onto the LC-MS/MS system by protein precipitation.

8.4.5. Pharmacokinetic Calculation

For calculation of the PK parameters, WinNonlin professional will be used. The PK parameters for each individual will be determined. The maximum plasma concentration (C_{max}) and the time to maximum plasma concentration (t_{max}) values will be determined from the observed plasma concentration-time curve as the maximum concentration and the corresponding time after each sampling period. The elimination rate constant (λ) at steady rate will be estimated by linear regression analysis of the terminal slope of the logarithmic plasma concentration-time curve. The area under the plasma concentration-time curve will be calculated by using the linear/logarithmic trapezoidal rule. Time dependency will be evaluated by fitting a compartmental model to the data for each subject. An additional analysis will be performed by fitting a population model to the data and possible time, dose and sex dependencies will be investigated.

9. INVESTIGATIONAL MEDICINAL PRODUCT

9.1. Description

Laquinimod 0.3 mg tablets and/or matching placebo tablets will be administered to the subjects.

Laquinimod 0.3 mg tablets are white to off-white round biconvex tablets.

The active tablets contain laquinimod sodium salt equivalent to 0.3 mg laquinimod. All inactive ingredients (excipients) are pharmaceutically acceptable. Matching placebo tablets contain no active ingredients. The matching placebo tablets will be identical in color and appearance to the tablets containing 0.3 mg of laquinimod.

Study drugs will be supplied to the study sites by Teva Pharmaceutical Industries, Ltd., through a distribution center.

The placebo paragraph is relevant for LAQ/5063 active double-blind phase only.

Upon approval of the Global Amendment # 4 to Protocol LAQ/5063 the IMP were switched from laquinimod tablets 0.3 mg, administered as two tablets once daily, to laquinimod capsules 0.6 mg. The clinical dosage remains unchanged at 0.6 mg of laquinimod, administered orally once a day.

9.2. Assignment of Treatment

At baseline (termination visit of core study), after meeting the inclusion/exclusion criteria, assignment of a subject to a treatment group will be performed by the Interactive Voice Response system (IVRS) according to the randomization scheme produced by Teva Global BioStatistics and Global BioMedical Informatics units. The subject number remains as in the core study.

The assignment of treatment is relevant for LAQ/5063 active double-blind phase only.

9.3. Investigational Medicinal Product Manufacturing

Siegfried Ltd., is the manufacturer of laquinimod tablets. Manufacturing was carried out in accordance with GMP applicable to IMPs.

The new study drug, laquinimod capsules 0.6 mg, which will be introduced during the open label phase of LAQ/5063 OL upon approval of Amendment # 4, is manufactured in compliance with current GMP standards by Teva Pharmaceutical Industries Ltd. Israel.

9.4. Packaging And Labeling

Laquinimod 0.3 mg tablets and their matching placebo will be packaged into PVC-PVDC blisters. The blisters will be packed into monthly packs which will be assigned to subjects by using an IVRS.

The CSU at Teva Pharmaceutical Industries, Ltd., Israel, will be responsible for secondary packaging, labeling and distributing of study drugs, according to EU regulations. These activities will be carried out by a sub-contracted company (Clinical Research Organization [CRO]).

Study drugs will be packed and labeled in a way that meets the regulatory requirements and maintains the blinded nature of the study.

The label of the monthly pack will include fixed information section to include for example 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 source document upon pack dispensing, 1 part will be attached to the prescription form (where applicable) and 1 part to remain on the pack. The variable information section will include the following variable data: batch code, pack number, and expiration date (all to be pre-printed) and blank fields for investigator name, visit number and subject number. These blank fields will be manually filled-in by the Investigator upon provision of pack to the subject.

At each scheduled visit (except for termination visit), the subject will receive one or more monthly pack/s (according to visit duration). The amount of study drugs dispensed will suffice until the following dispensing visit.

The placebo, IVRS and blinding paragraphs are relevant for LAQ/5063 active double-blind phase only. For the open-label phase (LAQ/5063 OL) a batch number will be allocated instead of a batch code number.

The replacement of the current drug supply, laquinimod tablets 0.3 mg, with laquinimod capsules 0.6 mg during the open label phase of LAQ/5063 OL, the process of packaging and labeling will be changed to the following:

The study drugs will be 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 at a Teva Pharmaceutical Industries Ltd. plant. The secondary packaging and labeling for subjects is performed under the responsibility of the Clinical Supply Unit of Teva Pharmaceutical Industries Ltd, according to European Union (EU) regulations and International Conference on Harmonization (ICH) guidelines as adopted by the FDA – Good Clinical Practice (GCP) (E6).

Each bottle will be identified by a unique bottle number that will be defined by sequential lists produced by Teva.

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: 2 detachable parts, which will be attached to the subject's file upon bottle dispensing and 1 part to remain on the bottle. 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 investigator 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

Export and import of IMPs will be carried out according to the provisions of Directive 2001/20/EC, Article 13.

Distribution and shipment of IMPs will be performed by a sub-contracted distribution CRO in appropriate shippers to maintain the required storage conditions of the study drugs. For the laquinimod capsules, bottles will be packed and shipped at room temperature in appropriate storage boxes.

Each shipment of IMPs supplies for the study will contain a shipment form describing the contact of shipment. This form will assist in maintaining current and accurate inventory records. When a shipment is received, the Investigator/Coordinator/pharmacist will acknowledge receipt of the IMPs supply by making 'Shipment Activation Call' (via the IVRS) and by signing on the shipment form and faxing it back to the distribution center (where applicable). For the open-label phase (LAQ/5063 OL) IVRS will not be used. Laquinimod 0.6 mg daily dose will be available at the sites.

If, upon arrival at the investigational site, the IMPs supplies appear to be damaged, the CSU should be contacted immediately.

9.6. Storage, Dispensing and Return

IMP supplies must be kept in a secure, limited-access, refrigerated (2° -8°C) and controlled storage area.

Only authorized personnel will have access to the IMP supplies.

The study site personnel at each site will be responsible for correct storage and handling of the study products. The IMPs supplies will be stored safely and properly in a temperature-controlled refrigerator (2°- 8°C), and must be kept under the prescribed conditions. The subjects should be instructed to store the IMPs (in their original package) in a refrigerator.

The IMP pack/s will be dispensed to the subject at the study site at each study visit starting at baseline visit (except for termination visit). The subjects will be instructed to administrate the study drugs once daily at approximately the same time of the day. The packs will be assigned to subjects by using an IVRS (this is relevant for LAQ/5063 active double-blind phase only). After assigning a pack number to the subject, the Investigator/Pharmacist/Coordinator should fill in manually the subject's number and investigator's name on the label of the dispensed monthly

pack, as well as on the detachable parts, which will be attached to the source document and prescription form (where applicable).

Subjects will be instructed to return all the empty blisters and unused study drugs in their original packs.

Upon approval of the Amendment #4 to LAQ/5063 the process will be changed to the following:

The IMP supplies which will be supplied in bottles must be stored at room temperature (15-25ºC) in a limited access secured storage area.

The IMP bottles will be dispensed to the subject at the study site at each study visit following the approval of this amendment and the supply process which will follow the approval. The bottles will be assigned to subjects by the site personnel. 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 the subject will receive the amount of bottles of IMP according to visit interval, 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. Route And Dosage Form

The following will be administered for each treatment group **during the double blind phase**:

- 0.3 mg group one white to off-white round biconvex tablet of 0.3 mg of laquinimod and one matching placebo tablet to be administered orally once daily.

- 0.6 mg group: two white to off-white round biconvex tablets of 0.3 mg of laquinimod tablets to be administered orally once daily.

For the open label phase (LAQ/5063 OL) all subjects will receive 0.6 mg of laquinimod: two white to off-white round biconvex tablets each of 0.3 mg of laquinimod to be administered orally once daily. Upon approval of Amendment # 4 for (LAQ/5063 OL) 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.

9.8. Verification of Compliance With Treatment Regimen

The subject will be requested to return all IMPs unused tablets/capsules (upon the switch to capsules following Amendment # 4 to LAQ/5063 protocol) in the original *packages (blisters or bottles)* to the study site at every visit.

Compliance with the dosing regimen will be determined by performing accountability of returned IMPs. The number of returned tablets **(until the switch** to capsules will occur)/capsules will be counted and recorded in the CRF by site personnel.

The subject number, pack number, batch code number, quantity of IMPs returned by the subject and visit date will be recorded by the site personnel. After the switch to the capsule formulation, batch number will be allocated instead of a batch code number.

The IMPs accountability records must be maintained at the site at all times.

Compliance will be calculated as a percentage by calculating the number of used capsules/tablets (tablets compliance will be calculated until the last tablets will be returned) divided by the number of total capsules/tablets(tablets compliance will be calculated until the last tablets will be returned) multiplied by 100.

Subjects with less than 75% overall compliance during the entire study will be considered non-compliant (see Section 8.3).

9.9. Accountability

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, pack number, batch code number, quantity of IMPs returned by the subject and the date of accountability should be recorded on the appropriate accountability forms, to be provided by the CSU.

The IMPs accountability records must be maintained at the site at all times.

After accountability of returned study drugs is performed and recorded, all IMPs unused tablets (all tablets should be returned upon the switch to capsules) /capsules must be returned by the monitor to the Sponsor or Sponsor's designee for destruction.

Accountability forms, filled in by the Study Monitor, must be sent with the returned IMPs for verification and a copy is left at the site in the Investigator's file.

10. 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 evaluation of conditions suggestive of 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 labeling reference of this study is the IB.

The relationship to study treatment is characterized as in the below table until Month 60, inclusive:

TERM	DEFINITION	CLARIFICATION
Unrelated	This category applies to those AEs which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)	
Unlikely	In general, this category can be considered applicable to those AEs, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP.	An AE may be considered unlikely related if or when at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the IMP. • 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 IMP. • It does not reappear or worsen when the IMP is re-administered.
Possibly	This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the IMP administration appears unlikely but cannot be ruled out with certainty.	An AE may be considered possibly related if or when at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP. • It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • It follows a known pattern of response to the IMP.
Probably	This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the IMP.	An AE may be considered probably related if or when at least 3 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP. • 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 AE does not disappear upon discontinuation of the IMP, yet IMP-relatedness clearly exists. • It follows a known pattern of response to the IMP.

The relationship to study treatment from Month 60 and thereafter is characterized as in the below table:

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 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 Reasonable Possibility related 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

A 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.

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 should be recorded and reported immediately (cross reference to the Pharmacovigilance section). 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 last dose).

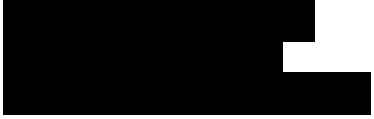
SAE Reporting

In order to satisfy regulatory requirements, any SAE, whether deemed IMP-related or not, must be reported to the contract research organization (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 Local Safety Officer who will forward the SAE report to the Global Pharmacovigilance Unit:

SAEs originating in Europe and rest of the world should be sent to:

Global Drug Safety and Pharmacovigilance Unit (Israel)



SAE originated in USA will be sent to:

Teva USA clinical safety mailbox

[redacted]

SAE originated in Canada will be sent to:

Teva Canada safety mailbox

[redacted]

SAEs originating 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 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 contract research organization / Local Safety Officer for local submission to the regulatory authorities (competent authorities [CA]) and Ethics Committee (EC)/Institutional Review Board (IRB) and investigators according to regulations.

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

1. Investigator name and site number
2. Subject number
3. Clinical event:
    a. description
    b. date of onset
    c. severity
    d. treatment (including hospitalization)
    e. relationship to IMP (causality)
    f. action taken regarding IMP
4. If the AE was fatal:

a. cause of death (whether or not the death was related to the IMP)
b. autopsy findings (if available)

5. Medical History (copy)

6. Concomitant Medication (copy)

7. Any relevant reports (laboratory, discharge, x-Ray, etc)

This information should be sent to the LCM/ Local Safety Officer 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.

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.

10.1. 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.

11. STATISTICAL METHODOLOGY

A total of up to 264 subjects, randomized to treatment with 0.3 mg or 0.6 mg of laquinimod, are expected to be recruited into this double-blind, multi-national trial. The trial is planned for 36 weeks of double-blind treatment.

All data summaries in this trial will be presented by treatment group.

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.

11.1. Sample Size Rationale

Subjects that completed protocol LAQ/5062 will be eligible for inclusion in this trial. LAQ/5062 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 264 subjects.

11.2. Randomization Procedure

The randomization scheme for this trial is based on the randomization scheme of protocol LAQ/5062, where each subject was allocated to one of the 3 treatment groups: Laquinimod 0.6 mg, Laquinimod 0.3 mg or placebo.

In this trial the subjects allocated to Laquinimod 0.6 mg and Laquinimod 0.3 mg groups will continue to receive the same treatment, while the subjects allocated to the placebo group will be randomized to receive either Laquinimod 0.6 mg or Laquinimod 0.3 mg.

The randomization scheme for LAQ/5062 placebo group, employing a 1:1 treatment assignment ratio, using blocks stratified by centers, will be prepared by Teva Global BioStatistics and Global BioMedical Informatics units. The scheme will be generated using SAS® PLAN procedure. The randomization list and the seed used to generate it will be kept sealed in a fire-protected safe.

This randomization process generates a new 2:2:1:1 treatment assignment ratio, where the assignments are:

- Subjects who were treated by Laquinimod 0.6 mg in both LAQ/5062 and LAQ/5063 studies.
- Subjects who were treated by Laquinimod 0.3 mg in both LAQ/5062 and LAQ/5063 studies.
- Subjects who were treated by placebo in study LAQ/5062 and by Laquinimod 0.6 mg in study LAQ/5063.

- Subjects who were treated by placebo in study LAQ/5062 and by Laquinimod 0.3 mg in study LAQ/5063.

Because there is no obligation of LAQ/5062 subjects to enter this study, there is no guaranty that the 2:2:1:1 randomization scheme will be kept.

In the open-label phase, all subjects will receive laquinimod 0.6 mg daily

11.3. Subjects Cohorts

A single data cohort is defined for this clinical trial. This cohort is:

ITT: Consists of all subjects who have been randomized 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.

11.4. Efficacy Assessment

11.4.1. Number of enhancing lesions on T_1-weighted images taken on Week 36

Descriptive statistics of the number of enhancing lesions on T_1-weighted images taken on Week 36 and change from LAQ/5062 baseline and LAQ/5063 baseline to Week 36 will be presented by treatment group.

11.4.2. The number of new T_2 lesions on scan taken on Week 36

Descriptive statistics of new T_2 lesions measured on Week 36, with reference to the previous visit performed under LAQ/5062 protocol, will be presented by treatment group.

11.4.3. The volume of T_2 lesions on scan taken on Week 36

This endpoint will be analyzed using the same methodology outlined for the number of enhancing lesions on T_1-weighted images taken on Week 36 (see Section 11.4.1).

11.4.4. The number of new hypointense lesions on enhanced T_1 scans taken on Week 36

Descriptive statistics of the number of new hypointense lesions on enhanced T_1 scans taken on Week 36, with reference to the previous visit performed under LAQ/5062 protocol will be presented by treatment group.

11.4.5. The proportion of subjects with no enhancing lesions on Week 36

The counts and percentages of subjects with no enhancing lesions on Week 36 will be presented by treatment group.

11.4.6. The total number of confirmed relapses

Descriptive statistics of the total number of confirmed relapses will be presented by treatment group.

11.4.7. The proportion of relapse-free subjects

A subject that did not experience any relapse during the treatment period will be considered as a responder for the purpose of this analysis.

The counts and percentages of relapse-free subjects will be presented by treatment group.

11.4.8. EDSS scores

Descriptive statistics of the EDSS scores, will be presented by treatment group and visit.

11.4.9. Categorical change from baseline in EDSS Score

A subject's EDSS change is defined as the difference between the subject's EDSS score at Baseline, and his or her last non-Baseline recorded EDSS score. EDSS changes will be classified as "Worsening", "Unchanged" or "Improvement".

The counts and percentages of subjects in each category will be presented by treatment group and visit.

In addition, counts and percentages of the categorical change from study LAQ/5062 baseline will be presented.

11.5. Safety And Tolerability Assessments

11.5.1. Adverse Events

The incidence and frequency of AEs will be presented by System Organ Class and preferred terminology according to the 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 treatment group, gender, age, maximal severity, maximal outcome, maximal action taken and maximal relationship to the tested drug.

SAEs and seriousness criteria will be listed and discussed on a case by case basis.

11.5.2. Laboratory Data

The incidence of laboratory tests outside the normal range and the incidence of measurements of potential clinical significance will be presented by treatment group. Shift analysis of these counts from LAQ/5062 baseline and LAQ/5063 baseline will also be provided. Descriptive statistics as well as their changes from LAQ/5062 baseline and LAQ/5063 baseline, will also be presented by study group.

11.5.3. ECG

The incidence of abnormal measurements will be presented by treatment group. Shift analysis from LAQ/5062 baseline and LAQ/5063 baseline will be provided as well. Descriptive statistics, as well as, their changes from LAQ/5062 baseline and LAQ/5063 baseline, will also be presented by study group.

11.5.4. Vital Signs

Incidence of measurements of potential clinical significance will be presented by study group. Shift analysis from LAQ/5062 baseline and LAQ/5063 baseline will be provided as well. Descriptive statistics of vital signs, as well as, their changes from LAQ /5062 baseline and LAQ/5063 baseline, will be presented by study group.

11.5.5. Drug Tolerability & Drop-Out Assessment

The number and percentage of subjects who failed to complete the study will be presented by treatment groups.

The number and percentage of subjects who prematurely discontinued from the study due to AEs will be presented by treatment groups.

12. REGULATORY AND ETHICAL ISSUES

12.1. 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 directives, including Directive 2001/20/EC of the European Parliament and the Council of the EU.

12.2. Informed Consent

The principles of Informed Consent, according to the ICH step 5 guidelines on GCP, and/or EU Directives, will be followed. A subject should not enter a clinical study or perform any study-related procedures 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 approved informed consent form.

A signed copy of the consent form will be given to the subject and the original will be maintained at the site following the signing and dating by the person administering the consent and witness (where appropriate).

A copy of the proposed consent form must be submitted to the EC, together with the protocol, and approved prior to study start.

Subjects continuing on laquinimod 0.6 mg will be re-consented with information about the cardiovascular risk seen in higher doses (see Section 3.4.1.7).

12.3. Ethics Committee

The EC has to issue a favorable opinion in order to allow the start of the clinical trial. Teva must receive, prior to site initiation, a copy of the written EC opinion which contains specific identification of the documents approved.

Any substantial[m] 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 sent to the EC and written opinion has to be provided to Teva. Records of the EC review and opinion of all documents pertaining to this study must be kept on file by the Investigator and are subject to regulatory authority and/or Sponsor inspection during or after completion of the study. SAEs must be reported to the EC by the Sponsor.

[m] as defined in the EU in the "Detailed guidance for the request for authorization of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial" (ENTR/CT April 2004)

Periodic status reports must be submitted to the EC 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 must be sent to the Sponsor.

12.4. Protocol Amendments

For clinical trial sites located in EU member states, the procedures outlined in Directive 2001/20/EC, Article 10(a), are applicable. Elsewhere, the country regulations apply.

12.5. Declaration Of The End Of The Clinical Trial

For clinical trial sites located in EU member states, 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). Elsewhere, the country regulations apply.

12.6. Subject Confidentiality

The Sponsor is concerned about the individual subject's privacy; therefore, all subject data will be identified by a subject identification number. The data will be blinded correspondingly in all data analyses. However, after receiving the subject's approval (by signing the Informed Consent), it is required that the Investigator permit the Study Monitor, independent auditor or regulatory agency personnel (with or without the Investigator) 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 test result reports; admission/ discharge summaries for hospital admissions occurring while the subject is in the study; and autopsy reports for deaths occurring during the study (where applicable).

The subject's authorization allows Teva to receive and review the subject's protected health information which may be re-disclosed to any authorized representative of Teva or central laboratory facility for review of subject medical records in the context of the study.

12.7. Liability And Insurance

A Certificate of Clinical Trials Insurance will be provided to the study sites by Teva Pharmaceutical Industries, Ltd in addition to the local certificate, as per local regulations.

13. DOCUMENTATION

13.1. Study File And Site Documents

Prior to the initiation of the study, the following documents must be provided to Teva Pharmaceutical Industries, Ltd.:

1. Confidentiality Agreement signed by Principal Site Investigator (PSI)
2. Copy of the protocol, amendments and notifications (if applicable), signed by the PSI
3. The PSI's curriculum vitae
4. Signed Clinical Study Agreement with site
5. EC written opinion for the protocol, amendments, informed consent, subject information sheet (if applicable), advertisements (if applicable) and membership list
6. CA written opinion (if applicable)
7. Hospital Management opinion (if applicable)
8. PSI’s financial disclosure information

13.2. Site Documents/Equipment Supplied By The Sponsor

Prior to the initiation of the study, the Sponsor will supply the Site Investigator with the following items, in addition to the protocol:

- Current version of the IB
- Central Laboratory certification and normal range values
- Portable Computer for Data Capturing (including Oracle Clinical Remote Data Capture [RDC®] application; see Section 13.4)
- A hard copy of the electronic CRF in PDF format
- User Manual for the RDC®
- Regulatory Binder
- Informed Consent Template
- Insurance Certificate

- Subjects study binder, including source pages to be used during the study if hospital clinic office records are not used.

13.3. Maintenance And Retention Of Records

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

Site 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:

- at least 2 years from the last marketing approval worldwide, or for at least 15 years, whichever is the greater; or

- longer if required by local regulations

The Site Investigator will be instructed to consult with Teva before disposal of any study records and to notify Teva of any change in the location, disposition or custody of the study files.

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

13.4. Data Handling

13.4.1. Electronic Case Report Form

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

Data will be entered at the site by the Site Investigator, Study Coordinator or the Site Coordinator, using the validated Oracle Clinical RDC® application, which provides a framework for entering clinical data on a CRF. The RDC® application is integrated with the Teva clinical data management validated system that is 21 CFR part 11 compliant (Oracle Clinical®).

The electronic CRFs 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 subject screened or enrolled 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 and addresses (i.e., Subject Identification Record, see Section 13.5).

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, Clinical Data Quality Control (CDQC) and the Data Management (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, CDQC personnel, 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 (SITE): data entry
- Study Coordinator (COOR): 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.
- CDQC and DMs: data updating, discrepancy handling, data locking
- QA: read only for data audit

13.4.2. Coding

AEs and Medical History that are entered into the clinical data management systems will be coded using MedDRA. Medications that are entered into the clinical data management systems will be coded using the World Health Organization Drug Dictionary (WHO Drug).

13.4.3. 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.

13.4.4. 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.

13.4.5. 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.

13.4.6. Source Documents

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

13.5. Additional Documents And Records

Subject Screening and Assignment Log – reflects any subject who has signed the informed consent.

Subject Identification Record – allows linking of subject's study number, name and date of birth for those subjects who were randomized to the study - to be kept only at the Site Investigator's site.

IMP Inventory/Shipment Form – reflects the total amount of IMP shipped to the site and received and acknowledged by the Site Investigator, pharmacist or designee.

IMP Accountability Log – reflects the total amount of IMP dispensed to and returned by each subject.

Informed Consent Forms – must be available for each subject and verified for proper documentation.

13.6. Protocol Modification

The procedures defined in the protocol and in the CRF will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. In order to ensure the validity of the data, with minimal exceptions, no deviations from the protocol may be made unless the issue is broad enough to warrant changes in writing from the Sponsor and the EC/IRB prior to implementation.

14. QUALITY ASSURANCE AUDITS/INSPECTIONS

14.1. Good Clinical Practice

The study described in this protocol will be carried out according to internationally accepted standards of GCP.

Laboratory tests/evaluations described in this protocol will be conducted in accordance with quality laboratory standards.

14.2. Quality Assurance Program

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

The purpose of these audits is to determine whether or not the study is being conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and 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 arranged and conducted within a reasonable time frame.

14.3. Regulatory Inspections

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

The CA of the EU member states concerned may request verification of compliance with GCP and GMP. In accordance with the provisions of Directive 2001/20/EC, Article 15, inspections by the CA may be conducted at the trial sites, the manufacturing site of the IMP, any laboratory used for analyses and/or the Sponsor's premises.

15. STUDY MONITORING

15.1. Monitors And Monitoring Visits

The Study Monitor/CRA will be responsible for ensuring adherence to local regulations, EU Directives (where applicable), ICH guidelines and the Sponsor's SOPs. Study Monitors for this trial will be provided by the Sponsor or Sponsor's designee (in Germany, Spain, Czech Republic and Russia). The Monitors will operate according to the EU Directives and in compliance with ICH guidelines, as well as local regulations and Sponsor's SOPs.

Sponsor Monitors and/or Monitors from CROs will be trained to monitor the study. They will be trained on ICH GCP guidelines, the Sponsor's SOPs, study protocol, the use of RDC® and the study monitoring conventions.

Regular monitoring of study data at each site will be performed in accordance with applicable regulations. Individual sites will be monitored to ascertain that enrollment rate, data recording and protocol adherence are satisfactory. The frequency of monitoring individual sites may fluctuate depending upon enrollment rate and the quantity of data collected and will be documented in the monitoring plan.

These monitoring visits will be performed for the purposes of verifying adherence to the protocol and the completeness and exactness of data entered on the CRFs. 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 IMP accountability. The Monitor will review the progress of the study with the Site 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 or resolve data clarifications. Adequate time and space for these visits will be made available by the Site Investigator.

15.2. Primary Source Documents

The Site Investigator must maintain primary source documents supporting CRF data entries. These documents, which are considered "source data," should include documentation of:

- 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 Site Investigator(s); occurrence (or lack) of AEs; and changes in medication usage, including the date the IMP was commenced and completed
- 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 Site Investigator must also retain all subject-specific printouts, reports of tests and procedures performed as a requirement of the study. During monitoring visits, the Monitor will need to verify data in the CRFs against these source data.

16. 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.

16.1. 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.

16.2. 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.

16.3. 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 10).

16.4. 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.

17. USE OF INFORMATION AND PUBLICATIONS

17.1. 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.

18. STUDY PERSONNEL

A complete list of contact details of all study personnel and sites will be supplied to the Sponsor.

18.1. Study Principal Investigator

The Study Principal Investigator is the head of the Clinical Steering Committee (CSC) and, as such, acts as the primary consultant on issues of safety, protocol adherence, study conduct and special cases regarding subject eligibility. He/she also motivates sites regarding recruitment.

18.2. Country Principal Investigator

The Country Principal Investigator fulfills the same functions as the Study Principal Investigator, for his/her particular country.

18.3. Investigative Site Personnel

At each study site, the staff will consist of a minimum of two neurologists/physicians, MRI radiologist, MRI technician and a Clinical Coordinator (who can be a nurse or a physician). One of the neurologists will serve as the PSI. His/her responsibilities are described below. For the open-label phase (LAQ/5063 OL) only one neurologist/physician is required and the other neurologist/physician will serve as back-up.

18.3.1. Principal Site Investigator

At each investigation site, a neurologist will be appointed to serve as the PSI 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 PSI will oversee the accrual of appropriate subjects, the conduct of the study according to the trial protocol, communication with the EC and collection of required data. The PSI may function as either the Treating or Examining Neurologist (see below).

18.3.2. The Neurologist/Physician

For the open-label phase (LAQ/5063 OL) only one neurologist/physician is required (Study Neurologist/Physician).

18.3.3. The MRI Radiologist and Technician

Applicable only for the LAQ/5063 study and the first 24 months of the open-label phase of the LAQ/5063 study.

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

18.3.4. The Clinical Coordinator

A nurse or physician will be responsible for subject scheduling. He/she will instruct the subject on proper laquinimod administration; collect and forward blood samples and requests to the appropriate laboratories; obtain and forward laboratory results; and assist all site study staff.

18.4. The Sponsor

The list of Sponsor Personnel and Sponsor Representatives is no longer applicable see Section 21 and Appendix 8.

18.4.1. Corporate Clinical Study Leader

The Corporate Clinical Study Leader is responsible for the day-to-day study activities at a corporate level; for ensuring good conduct and adequate resources; and for providing high-quality study management and data management.

18.4.2. BioStatistics and BioMedical Informatics

Global BioStatistics and Global BioMedical Informatics Units are responsible for the randomization scheme, adequate performance of the data management application (RDC); 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.

18.4.3. Clinical Operations (Corporate Coordination Center)

Teva Clinical Operations will manage the day-to-day operations of the trial at a corporate level. Teva will also be responsible for, among other things, 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.

18.4.4. Local Clinical Management (LCM)

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.

18.4.5. Clinical Research Associate (CRA)

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 15.1 in this protocol for detailed monitoring activities.

18.4.6. 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.

18.4.7. Medical Monitor

The Medical Monitor is responsible for periodically reviewing the safety data to include AEs and laboratory values.

18.4.8. Global Operations Manager

Will manage the day-to-day operations of the trial and will also be responsible 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. STUDY COMMITTEES

19.1. 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 Appendix 9. 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

19.2. Clinical Steering Committee (CSC)

The CSC members (see Appendix 7) will consist of all Country Principal Investigators and will be responsible for day-to-day study conduct issues in their relevant countries:

- Assist in selection of qualified and experienced sites
- Assist in design of protocol, CRF and other documents
- Review subject eligibility criteria if needed
- Follow-up enrollment rate
- Assist sites for protocol adherence
- Assist in regulatory submissions
- Assist in review of publication

19.3. Data Safety Monitoring Board (DSMB)

This section is no longer applicable - see Section 21.

20. INVESTIGATOR'S AGREEMENT

I have read this clinical protocol, number LAQ-5063 and the Amendments 1 to 10:

An active extension of LAQ/5062 study- multinational, multi-center, randomized, double-blind, parallel-group study, to evaluate the safety, tolerability and efficacy of two doses (0.3 mg and 0.6 mg) of laquinimod, orally administered in relapsing remitting (R-R) MS subjects, followed by an open-label phase of laquinimod 0.6 mg daily (LAQ/5063 OL).

I agree that it contains all the necessary details for conducting this study.

I will conduct the study as outlined therein. I will provide copies of the protocol and all information regarding LAQ-5063 active double-blind phase and open-label phase as stated in the Investigator's Brochure, furnished to me by the Sponsor, to all relevant staff/members. I will discuss this material with them to ensure they are fully informed regarding LAQ-5063 active double-blind phase and open-label phase and the conduct of the study. I agree to keep records on all subject information (Case Report Forms and subject's Informed Consent statement), LAQ-5063 active double-blind phase and open-label phase shipment and return forms, and all other information collected during the study for a minimum period of 2 years or otherwise as instructed by Teva or local regulatory authorities.

Investigator's Name : _____

(printed)

Date : _____ Signature : _____

(dd/mm/yy)

On behalf of Teva:

Name : _____ Title : _____

Date : _____ Signature :_____

(dd/mm/yy)

21. RATIONALE FOR PROTOCOL AMENDMENT AND SUMMARY OF CHANGES

21.1. Global Amendment #10

This is the 10th amendment to protocol LAQ/5063. At the time of issuance of this amendment there are 110 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 3.4.1.7). 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 do not alter the study population or endpoints.

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

Deletions are indicated with a ~~strikethrough~~, additions with an underline.

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 3.1.2. 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
Section 3.2.3. Toxicology		
In addition, an ~~Finally, a small~~ increase in the incidence of oral cavity ~~squamous cell carcinomas~~tumors was noted in mid and high dose female rats (2/60 in each group). The oral effects may relate to the AhR activation properties of laquinimod since similar lesions were seen following lifelong exposure of rats to other AhR activators. However, the incidence of oral cavity tumors in rats treated with laquinimod was lower than that seen with industrial chemicals such as 2,3,7,8-tetrachloro-p-dibenzodioxin (TCDD) (NTP TR−521) and dioxin-like compounds (DLCs), and was more	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	Updated for consistency with the IB

Original text with changes shown	New wording	Reason/Justification for change
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~~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~~.	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.	
Section 3.3.1. Clinical Pharmacology Studies		
Laquinimod PK is 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.	Laquinimod PK is 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.	Updated for consistency with the IB

Original text with changes shown	New wording	Reason/Justification for change
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.	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.	
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	Information regarding safety findings in the CONCERTO and ARPEGGIO studies

Original text with changes shown	New wording	Reason/Justification for change
	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 3.4.1.7.	
Section 3.4. Known and Potential Risks and Benefits to Human Subjects		
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
Section 3.4.1.7. Cardiovascular Events (Laquinimod 1.2 and 1.5 mg)		
(new section)	On 30 December 2015, a DMC review of 8 unblinded cases from the CONCERTO and 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	Information regarding safety findings in the CONCERTO and ARPEGGIO studies

Original text with changes shown	New wording	Reason/Justification for change
	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.	
Section 3.4.2.2. 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 3.4.2.3. 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 similar potential ~~these~~ 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,	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,	Information added on safety of 0.6 mg dose

Original text with changes shown	New wording	Reason/Justification for change
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~~This analysis showed that none of these safety issues constitute a signal of concern for laquinimod~~.	laquinimod manifested clinical evidence of myocardial infarction.	
Section 5.1. Overview and Plan		
(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 6.1. Allowed Concomitant Medications		
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 metabolized by CYP1A2 (examples listed in Appendix 6) 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.~~	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 6) 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.	Wording made consistent with IB
Section 6.2. Disallowed Medications (During Study) (Other sections affected by this change: Section 7.3.3. Termination Visit)		
• ~~IFNs~~ IFN-β 1a or 1b ... • Moderate/strong inhibitors of CYP3A4; for example, ketoconazole and erythromyicin (see full list in Appendix 5) 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	• IFN-β 1a or 1b ... • Moderate/strong inhibitors of CYP3A4; for example, ketoconazole and erythromyicin (see full list in Appendix 5) 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	Clarification

Original text with changes shown	New wording	Reason/Justification for change
laquinimod exposure, respectively.	in laquinimod exposure, respectively.	
Section 7.1. Study Period (Other sections affected by this change: Section 7.3.2. Scheduled Treatment Visits; Section 7.3.4.1.1. 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 7.3.3. Termination Visit		
(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.
Section 7.3.4. Criteria for Early Termination		
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 LAQ-5063 OL study.	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 LAQ-5063 OL study.	Clarification
Section 7.3.4.1.2. Pregnancy		
~~Teva considers the prevention of exposure to laquinimod during pregnancy to be of great importance, and following consultation with the CHMP and 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

Original text with changes shown	New wording	Reason/Justification for change
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 7.3.4.1.3. ~~Invasive~~ Cancer (Other sections affected by this change: APPENDIX 10. 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 ~~medication and discontinue their participation in the study~~ drug.	Subjects who are diagnosed with a malignant solid or liquid tumor while participating in the study should stop drug.	Correction of terminology
Section 7.3.4.1.4. 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 in the study should stop study medication.	New stopping rule to avoid higher exposures to laquinimod
Section 7.3.4.1.5. 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 7.3.6. Unscheduled Visit		
(new text)	• For women of child bearing potential, serum or urine β-hCG test may be performed	Added to make consistent with study flow chart
Section 7.3.6.1. 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 8.2.5.1) • pharmacokinetic blood sample	Additional samples can be collected

Original text with changes shown	New wording	Reason/Justification for change
	• sample for potential biomarker analysis	
Section 7.3.6.1.1. 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 7.3.6.1.2. 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 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.	Additional samples can be collected
Section 8.2.3. Vital Signs and Weight (Other sections affected by this change: Section 7.3.2. Scheduled Treatment Visits)		
Body weight will be measured at baseline (termination visit of core study LAQ/5062) and at Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor) /early discontinuation visit. For the open-label phase weight will be measured at all visits, and as long as the subject continues study drug treatment.	Body weight will be measured at baseline (termination visit of core study LAQ/5062) and at Termination visit of LAQ/5063 active double-blind phase (completion of the full 36 weeks or as requested by the Sponsor) /early discontinuation visit. For the open-label phase weight will be measured at all visits, and as long as the subject continues study drug treatment.	Weight will be measured at all visits
Section 8.2.5. Safety Laboratory Evaluations (Other sections affected by this change: Section 7.3.2. Scheduled Treatment Visits; Section 7.3.3. Termination Visit)		
– hs-CRP	– hs-CRP	It is specifically hs-CRP that should be measured

Original text with changes shown	New wording	Reason/Justification for change
○ 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 new hemoglobin decrease of >1g/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, interleukin (IL)-1, IL-6, IFN γ, TNF α, and hepcidin~~ ~~○ Additional investigations and follow-up per the 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~~ – ~~Glucose~~ – ~~Ketones~~ – ~~Blood, Erythrocytes, Leukocytes~~ – ~~Protein~~ – ~~Nitrite~~	(text deleted)	Urinalysis will no longer be performed for consistency with other laquinimod studies and because the clinical information gained from such a test would be minimal in this study.
Section 8.2.5.1. 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	Unscheduled samples can be collected for further investigation of clinical events of interest

Original text with changes shown	New wording	Reason/Justification for change
	• troponin I	
Section 8.2.7. 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 8.2.8. Glomerular Filtration Rate Estimation (Other sections affected by this change: Section 7.3.2. Scheduled Treatment Visits; Section 8.2.5. 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 ≤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 7.3.4.1.5).	GFR estimation added to monitor renal function
Section 8.2.9. Cardiovascular Risk Assessment and Management (Other sections affected by this change: Section 7.3.2. Scheduled Treatment Visits)		
(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 7. In addition, an evaluation should take place as soon as possible for subjects already in the study, following approval of Amendment #10. 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 10. SAFETY AND PHARMACOVIGILANCE (Other sections affected by this change: Section 12.6. Subject Confidentiality; Section 13.4.1. Electronic Case Report Form; APPENDIX 3. MRI PROTOCOL)		
The following information should be provided to accurately and completely record the event: 1. Investigator name and site number 2. Subject number ~~3. Subject initials~~	The following information should be provided to accurately and completely record the event: 1. Investigator name and site number 2. Subject number	Subject initials and demographics should no longer be recorded

Original text with changes shown	New wording	Reason/Justification for change
~~4. Subject demographics~~		
Section 10.1. 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 12.2. Informed Consent (Other sections affected by this change: Section 7.3.2. Scheduled Treatment Visits)		
(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 3.4.1.7).	Subjects continuing on the study with this amendment will be re consented.
Section 16. 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: • 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	Section added for consistency with sponsor's current protocol template

Original text with changes shown	New wording	Reason/Justification for change
	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 16.1. 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 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 added for consistency with sponsor's current protocol template
Section 16.2. 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	Section added for consistency with

Original text with changes shown	New wording	Reason/Justification for change
	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.	sponsor's current protocol template
Section 16.3. 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 10).	Section added for consistency with sponsor's current protocol template
Section 16.4. 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 3. MRI PROTOCOL		
• Check that the subject can successfully undergo MRI examination, including GFR estimation.	• Check that the subject can successfully undergo MRI examination, including GFR estimation.	Added requirement for GFR estimation
APPENDIX 5. MODERATE/STRONG CYP3A4 INHIBITORS AND CYP3A4 INDUCERS		
(section, including tables, updated to make consistent with current IB)	(see Appendix 5 for new wording)	Updated for consistency with current IB
APPENDIX 6. LIST OF MEDICATIONS THAT SHOULD BE USED WITH CAUTION		
(section, including tables, updated to make consistent with current IB)	(see Appendix 6 for new wording)	Updated for consistency with current IB
APPENDIX 10. GUIDANCE ON SAFETY MONITORING		
(new text)	4. Guidance on Monitoring Subjects with Elevated Pancreatic Amylase Levels	Guidance updated for consistency with body of

Original text with changes shown	New wording	Reason/Justification for change
	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 level. 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 m2, 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 m2), the subject should stop study medication permanently.	the protocol

21.2. Global Amendment #9

This was the ninth amendment to protocol LAQ/5063. At the time of issuance of this amendment 117 subjects had taken part in this 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 below and all substantive changes are listed in the summary table below.

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

Previous approved wording	Amended or new wording	Reason/Justification for change
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 5.1: Overview and plan AND Section 7.1: Study Period AND Section 7.3: Detailed Study Plan		
… until ~~laquinimod 0.6 mg is commercially available for the treatment of MS or until~~ the development of laquinimod 0.6 mg for MS is stopped by the Sponsor.	…. as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS.	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 0.6 mg.
Section 5.1: Overview and plan		
Figure 4: Study Flowchart Figure 5: Study Flowchart For Open_Label Phase	Addition of Figure 1: Treatment Groups in MS-LAQ/5062 (Core Study) and the Double Blind and Open Label Phases of LAQ/5063 (Extension Study) Table 5: Study Task Flow Sheet for Study 5063 (Double-Blind Active Extension Phase) Table 6: Study Task Flow Sheet for Study 5063 OL (up to Month 24) Study Task Flow Sheet for Study 5063 OL (Months 24 onwards)	Figure 1 was added to clarify the relationship between the core study (MS-LAQ/5062) and the extension study (LAQ/5063). The titles of Tables 5-7 were changed to clarify which study phase they correspond to.
Section 7.3: Detailed Study Plan		
None	• 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 all subjects will be reminded to continue using 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 potential teratogenicity and delayed risks for a child exposed	Teva considers the prevention of exposure to laquinimod during pregnancy to be of great importance, and following consultation with the CHMP and Monitoring Committee (DMC) has decided to introduce additional language and measures for pregnancy prevention in this amendment and in a revised informed consent form.

Previous approved wording	Amended or new wording	Reason/Justification for change
	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)	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 randomization, furthermore a serum beta hCG test prior to randomization. In addition a new Section (Section 11.5.6 – Pregnancy) was added to include more data on the potential delayed risks following *in utero* exposure to laquinimod, subjects' counselling and assuring of subjects' understanding and ability to follow the required preventive pregnancy measures.
Table 6 AND Table 7 AND Section 7.3: Detailed Study Plan		
None.	*Activity added to all study visits:* - Ascertaining the use of effective contraception	
Section 7.3.4.1.2: Pregnancy		
None.	See Section 7.3.4.1.2.	
Synopsis AND Section 7.3.2: Scheduled treatment visits AND Appendix 10: Guidance on safety monitoring		
In case of suspected pregnancy (positive urine β-hCG test result)	In case of suspected pregnancy (positive urine β-hCG test result, delay of menstruation or any other reason suggesting pregnancy)	
Synopsis AND Section 2: Exclusion Criteria AND Appendix 10: Guidance on safety monitoring		
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. A new informed consent form should be signed before re-enrollment	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. 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.	
Synopsis AND Section 6.1: Allowed concomitant medications		
….IV methylprednisolone for 3 days…..	…..IV methylprednisolone 1 g/day or oral steroids for ~~3~~ a maximum of 5 consecutive days…..	In order to comply with Standard of Care, the protocol now states that treatment for acute relapse may include

Previous approved wording	Amended or new wording	Reason/Justification for change
		short term treatment with oral steroids.
Section 6.1: Allowed concomitant medications		
~~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 6) 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 6) 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 DDI 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 6) has been added to present partial lists of CYP3A4 substrates with a narrow therapeutic index and of drugs known to be metabolized by CYP1A2. Laquinimod is mainly metabolized by the CYP3A4 P450 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 leads to an approximately 80% reduction in the plasma levels of laquinimod, as measured by the area under the plasma concentration-time curve (AUC). Therefore, strong inducers of CYP3A4 (Carbamazepine, Phenytoin, Phenobarbital, St. John's Wort) have been added as disallowed medications in all clinical studies with Laquinimod. Use of CYP3A4 inducers may result in reduced laquinimod plasma concentrations and reduced effectiveness. The Laquinimod Investigator's Brochure has been updated with the above information in
Section 6.2: Disallowed medications (during the study)		
▪ Interferons ▪ Natalizumab (Tysabri®) ▪ Mitoxantrone (Novantrone®) ▪ Glatiramer Acetate ▪ Inhibitors of CYP3A4; for example, ketoconazole and erythromyicin (see full list in Appendix 5) ▪ Parenteral steroids (except if given as defined by protocol for acute relapse; see Section 6.1) ▪ Oral steroids ▪ Chemotherapeutic agents ▪ Immunosuppressive or immunomodulating agents ▪ Experimental agents ~~(including aminopyridine)~~ IV Immunoglobulin (Ig) and any other IV experimental agents	▪ Natalizumab (Tysabri®) ▪ Fingolimod (Gilenya) ▪ IFNs ▪ Dimethyl fumarate (Tecfidera) ▪ Glatiramer Acetate ▪ Teriflunomide (Aubagio) ▪ Alemtuzumab (Lemtrada) ▪ Cladribine ▪ Rituximab ▪ Ocrelizumab ▪ Atacicept ▪ Belimumab ▪ Ofatumumab ▪ Inducers of CYP3A4 such as rifampin and carbamadizepine (for more examples see Appendix 5). Use of CYP3A4 inducers may result in reduced	

<table>
<tr><th>Previous approved wording</th><th>Amended or new wording</th><th>Reason/Justification for change</th></tr>
<tr><td></td><td>laquinimod plasma concentrations and may reduce its effectiveness.
▪ Moderate/strong inhibitors of CYP3A4; for example, ketoconazole and erythromyicin (see full list in Appendix 5)
▪ Mitoxantrone (Novantrone®)
▪ Oral steroids
▪ Parenteral steroids (except if given as defined by protocol for acute relapse; see Section 6.1)
▪ Adrenocorticotrophic hormone (ACTH)
▪ Chemotherapeutic agents
▪ Cytotoxic agents
▪ Cyclophosphamide
▪ IV immunoglobulin (IVIG)
▪ Plasmapheresis
▪ Any other experimental agents
▪ Other immunosuppressive or immunomodulating agents</td><td rowspan="3">Section 6.7.1.
The disallowed use of CYP3A4 inducers has been added to Section 6.2 (Disallowed concomitant medications during the study) and Appendix 5 has been updated with the list of disallowed medications.
Recently several drugs have been approved for use in RRMS. The amended protocol has been updated to include the following drugs in the disallowed medication during study (Section 6.2 Disallowed concomitant medications during the study):
Fingolimod (Gilenya)
Dimethyl fumarate (Tecfidera)
Teriflunomide (Aubagio)
Alemtuzumab (Lemtrada)

The medication 4-amino pyridine (Ampyra, Fampyra) is now allowed during the study since it is no longer an experimental drug (has received FDA approval and indicated to improve walking in adult patients with multiple sclerosis (MS) who have walking disability).</td></tr>
<tr><td colspan="2">Appendix 5 – List* of systematically administered** CYP3A4 inhibitors which are disallowed prior and during the study</td></tr>
<tr><td>~~Cardiac drugs/antiarrhythmic agents~~
~~amiodarone~~
~~diltiazem~~
~~nifedipine~~
~~verapamil~~
~~mibefradil~~

~~Antimicrobial agents~~
~~Erythromycin~~
~~Clarithromycin~~
~~Troleandomycin~~
~~Telithromycin~~

~~Antifungals/Imidazoles~~
~~Fluconazole~~
~~Itraconazole~~
~~Ketoconazole~~</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><tr><td>Antidepressant</td><td>nefazodone</td></tr><tr><td>Calcium channel blocker</td><td>Diltazem, verapamil, mibefradil</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>~~Miconazole~~
~~Voriconazole~~

~~HIV drugs:~~
~~Protease Inhibitors, such as indinavir, ritonavir and others~~
~~Delavirdine~~

~~Antidepressants~~
~~fluvoxamine~~
~~nefazodone~~

~~Others/antituberculosis and antimalarial~~
~~isoniazid~~
~~aprepitant~~</td><td><table><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 7.3.4: Criteria for early termination</td></tr>
<tr><td>None</td><td><u>10. Planned pregnancy</u>
<u>11. Lack of efficacy</u></td><td rowspan="3">Two new criteria for early termination were added and new stopping rules were implemented following CHMP opinion, two new conditions were included among the stopping rules (women who become pregnant during the study and subjects diagnosed with invasive cancer)</td></tr>
<tr><td colspan="2">Section 7.3.4.1: Safety Stopping Rules AND Appendix 10: Guidance for Safety Monitoring</td></tr>
<tr><td>None</td><td><u>New subsections added: see Section 7.3.4.1.2</u>and Section 7.3.4.1.3for full text.</td></tr>
<tr><td colspan="3">Section 8.1.4: On-study Relapse Evaluation Procedures</td></tr>
<tr><td>None</td><td><u>For the open-label phase (LAQ/5063 OL) only one neurologist/physician is required (Study Neurologist/Physician) to perform a neurological examination and treat the subject as needed.</u></td><td rowspan="3">In the open label extension there is no need for distinction between the Treating and the Examining Physicians/ Neurologists.</td></tr>
<tr><td colspan="2">Section 7.3: Detailed Study Plan AND Section 8: Assessment Methods</td></tr>
<tr><td>…Examining neurologist/ physician…..</td><td>….Study neurologist/ physician……</td></tr>
</table>

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 17.3 Investigative Site Personnel AND Section 7.3: Detailed Study Plan		
~~**The Treating Neurologist/Physician**~~ ~~Will be responsible for subject eligibility evaluation, the supervision of the study drug administration, the recording and treating of adverse experiences, the monitoring of safety assessments, including routine laboratory parameters, and coordinating MRI performance. He will determine if a subject experiences a relapse (based on the evaluation performed by the Examining Neurologist/Physician) and whether to treat the relapse or not.~~ ~~**The Examining Neurologist/Physician**~~ ~~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.~~ ~~Note: 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.~~ ~~For the open-label phase (LAQ/5063-OL) only one neurologist/physician is required~~.	**The Neurologist/Physician** For the open-label phase (LAQ/5063 OL) only one neurologist/physician is required (Study Neurologist/Physician).	
Section 8.2.5: Safety Laboratory Evaluations		
• Cholesterol […] • CPK […]	• Lipid profile (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL], triglycerides) under fasting conditions. Only at baseline and every 12 months during Periods 1 and 2. […] • CPK • In case of abnormal CPK result: troponin or	Laboratory tests to be performed in case of abnormal CPK were added to the relevant sections dealing with safety laboratory evaluations. 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

Previous approved wording	Amended or new wording	Reason/Justification for change
	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, CRP and fibrinogen […] • Lipase will be tested in case of abnormal pancreatic amylase results […] • Hemoglobin. In case of new 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 and haptoglobin – Additional investigations and follow-up per the Investigator's discretion or Sponsor's request.	requirement for testing urine myoglobin in case of CPK>2000 U/L, was added. In addition, lipase will be tested in case of abnormal pancreatic amylase results. In case of new hemoglobin decrease of > 1 g/dL, a thorough anemia work-up will be done. Lipid profile added to align with other similar protocols.
Appendix 10: Guidance on Safety Monitoring		
-	See section	The section has been greatly revised to bring in line with current experience. Please see section for full details.
Section 10: Safety and Pharmacovigilance		
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	In order to satisfy regulatory requirements, any Serious Adverse Event, whether deemed IMP-related or not, must be reported to the Contract Research Organization (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	

Previous approved wording	Amended or new wording	Reason/Justification for change
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]	becoming aware of the event to the CRO. The CRO will forward the report to the appropriate Pharmacovigilance unit at Teva or 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:** Teva USA clinical safety mailbox [redacted] **SAE originated in Canada will be sent to:** Teva Canada 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.	
SYNOPSIS AND Section 5.3 Inclusion Criteria		
2. Women of child- bearing potential must practice ~~a reliable method~~ of birth control. (Acceptable methods of birth control in this ~~study~~ include: ~~double barrier methods such as diaphragms with spermicide, condoms and spermicide. Also intrauterine devices; hormonal contraception must be accompanied by an additional method of birth control.)~~.	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)].	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 10 SAFETY AND PHARMACOVIGILANCE		
Pregnancy reports: Pregnancy reports should be forward to the Pharmacovigilance for data-entry to the global	Pregnancy reports: Pregnancies should be reported throughout the study. This includes also normal	Text brought up to date with current procedures.

Previous approved wording	Amended or new wording	Reason/Justification for change
safety database. This includes also normal pregnancies without AE. 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 CRF provided by Local Clinical Management. The pregnancies reporting procedure should be the same as the SAE reporting procedure.	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.	
Section 11.2 Randomization Procedure		
-	In the open-label phase, all subjects will receive laquinimod 0.6 mg daily	Clarification added.
Section 17.4.6 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 Director is 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 by the external data monitoring committee (DMC see details below).~~	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.
Entire Document		
-	Numbering of Appendices from has been changed throughout the text and are now numbered from 1 to 10	Updated cross-references to appendices (due to addition of a newAppendix 6). In addition, literature references have been changed to reflect the changes in the protocol

22. CHANGES TO PATIENT ENTRY CRITERIA

Not applicable.

APPENDIX 1. 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[n]". 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.

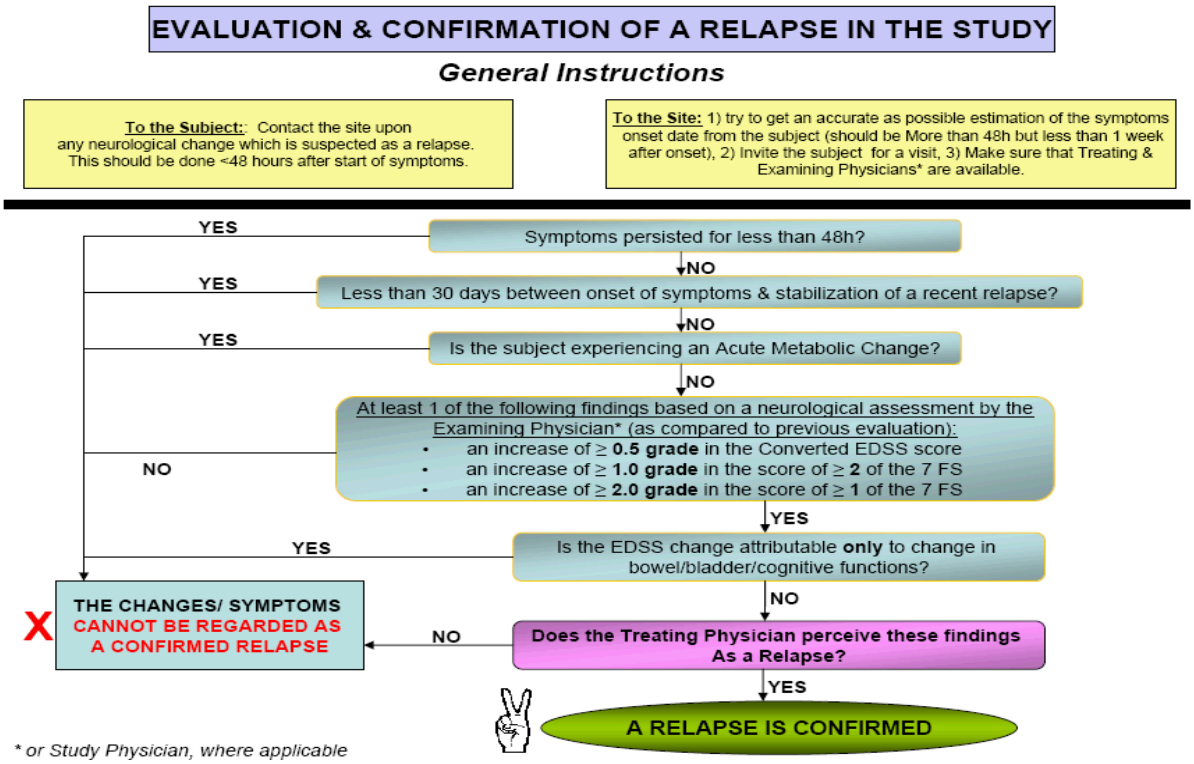
An event will be counted as a relapse only when the subject's symptoms are accompanied by observed objective neurological changes, consistent with at least one of the following:

- 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 are in the LAQ/5063 open label phase).

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 confirmation of a relapse.

[n] 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

APPENDIX 2. NEUROSTATUS

Standardized Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status

neurostatus

Standardised Neurological Examination and Assessment of Kurtzke's *Functional Systems*[1] and *Expanded Disability Status Scale*[1]

SOURCE DOCUMENT

SUBJECT NO/SUBJECT INITIALS

COUNTRY/CENTRE NO

NAME OF EDSS RATER

DATE OF EXAMINATION

[1] slightly modified from J. F. Kurtzke, Neurology 1983;33,1444-52

1 neurostatus

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 the Functional Systems implies that the patient is not aware of the deficit and that the deficit or sign does not interfere with normal daily activities (with the exceptions of optic, vegetative and cerebral functions).

EXPANDED DISABILITY STATUS SCALE (EDSS)
EDSS should not be lower than the highest score of the FS. Symptoms which are not MS-related will not be taken into consideration for assessments, but should be noted.

2 neurostatus

VISUAL (OPTIC) FUNCTIONS

Definitions

Visual acuity

The visual acuity score is based upon the line on the Snellen chart at 20 feet (5 m) 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 done during follow up.

Fields

0 = normal
1 = signs only, deficits present only on formal 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

OPTIC FUNCTIONS	OD	OS
Visual acuity (corrected)		
Visual fields		
Scotoma		
Disc pallor		

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = disc pallor and/or mild scotoma and/or visual acuity of worse eye (corrected) less than 30/30 (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 (0.1–0.2); 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

3 neurostatus

BRAINSTEM FUNCTIONS

Definitions

Assessment of impairment/disability

0 = normal

1 = signs only: clinically detectable numbness, facial weakness, or cranial nerve deficit of which patient is not aware

2 = mild: clinically detectable numbness, facial weakness, dysarthria or cranial nerve deficits of which patient is aware

3 = moderate: diplopia with incomplete paralysis of any eye movement, impaired discrimination of sharp/dull in 1 or 2 trigeminal branches, trigeminal neuralgia (at least one attack in the last 24 hours), weakness of eye closure, cannot hear finger rub and/or misses several whispered numbers, obvious dysarthria during ordinary conversation impairing comprehensibility

4 = severe (marked): complete loss of movement of either eye in one direction, impaired discrimination of sharp/dull or complete loss of sensation in the entire distribution of one or both trigeminal nerves, unilateral or bilateral facial palsy with lagophthalmus or difficulty with liquids, sustained difficulty with swallowing, incomprehensible voice

CRANIAL NERVE EXAMINATION	
EOM (extra ocular movements) impaired	
Nystagmus	
Trigeminal damage	
Facial weakness	
Hearing loss	
Dysarthria	
Dysphagia	
Other bulbar signs	

Nystagmus

0 = normal

1 = signs only

2 = gaze evoked nystagmus below limits of "moderate" (usual equivalent is grade one in FS score)

3 = moderate, sustained nystagmus on 30° horizontal or vertical gaze, but not in primary position, patient may or may not realize disturbance (usual equivalent is grade 2 in FS score)

4 = severe, sustained nystagmus in primary position or coarse persistent nystagmus in any direction interfering with visual acuity, complete internuclear ophthalmoplegia with sustained nystagmus of abducting eye, oscillopsia

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = signs only
	2a = moderate nystagmus or/and
	2b = other mild disability
	3a = severe nystagmus or/and
	3b = marked extraocular weakness or/and
	3c = moderate disability of other cranial nerves
	4a = marked dysarthria or/and
	4b = other marked disability
	5 = inability to swallow or speak

4 neurostatus

PYRAMIDAL FUNCTIONS

Definitions * = optional

REFLEXES

0 = absent, 1 = weak, 2 = normal, 3 = exaggerated, 4 = cloniform, 5 = inexhaustible (indicate difference between R & L by < or >)

Plantar response

0 = flexor, 1 = neutral, 2 = extensor

Cutaneous reflexes

0 = normal, 1 = weak, 2 = absent

***Palmomental reflex**

0 = absent, 1 = present

LIMB STRENGTH

The weakest muscle in each group defines the score for that group. Use of functional tests like jumping with one foot, walking on toes or heels are recommended in order to assess grades 3-5 BMRC.

BMRC Rating scale

0 = no activity, 1 = visible contraction without visible joint movement, 2 = visible movements with elimination of gravity, 3 = movements against gravity possible but impaired, 4 = movements against resistance possible but impaired, 5 = normal strength

FUNCTIONAL TESTS

* Position test UE (upper extremities)

Sinking, 0 = none, 1 = mild, 2 = evident

***Position test LE (lower extremities)**

Sinking, 0 = none, 1 = mild, 2 = evident

1 = only separate lifting possible (grades from horizontal position in hip joints...°)

2 = even separate lifting not possible

***Walking on heels/tiptoes**

0 = normal, 1 = impaired, 2 = not possible

***Monopedal hopping**

0 = normal, 1 = 6–10 times, 2 = 1–5 times, 3 = not possible

LIMB SPASTICITY

0 = normal, 1 = mild, barely increased muscular tone after rapid flexion of an extremity, 2 = moderate, 3 = severe, barely surmountable increased spastic tonus after rapid flexion of an extremity, 4 = contracted

Gait spasticity

0 = normal, 1 = barely perceptible, 2 = evident, minor interference with function, 3 = permanent shuffling, major interference with function

REFLEXES	R	><	L
Biceps			
Triceps			
Radial			
Knee			
Ankle			
Plantar response			
Cutaneous reflexes			
*Palmomental reflex			

LIMB STRENGTH		
Shoulder		
Elbow flexors		
Elbow extensors		
Hand/finger flexors		
Hand/finger extensors		
Hip flexion		
Knee flexors		
Knee extensors		
Foot/toe flexors		
Foot/toe extensors		
*Position test UE, pronation		
*Position test UE, sinking		
*Position test LE, sinking		
only lifting of single leg possible	°	°
*Walking on heels		
*Walking on tiptoes		
*Hopping on one foot		

SPASTICITY		
Arm		
Leg		
Gait		

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = abnormal signs without disability
	2 = minimal disability, patient complains about fatiguability in 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) movements against gravity are possible 3b = severe monoparesis, refers to BMRC grade 2 or less in one muscle group
	4a = marked paraparesis or hemiparesis (usually BMRC grade 2 in 2 limbs) 4b = moderate tetraparesis (refers to BMRC grade 3 in 3 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 3 or more limbs)
	6 = Tetraplegia (grade 0 or 1 in all muscle groups of upper and lower limbs)

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CEREBELLAR FUNCTIONS

Definitions
UE = upper extremities
LE = lower extremities
EO = eyes open
EC = eyes closed

Head tremor, rebound
0 = normal
1 = mild abnormality
2 = moderate abnormality
3 = severe abnormality

Truncal ataxia
0 = none
1 = signs only
2 = mild, swaying with EC
3 = moderate, swaying with EO
4 = severe, unable to sit without assistance

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

Gait ataxia
0 = none
1 = signs only
2 = mild, abnormal balance only on heel or toe walking, or walking along a line
3 = moderate, abnormal balance on ordinary walking or while seated
4 = severe, unable to walk more than a few steps or requires support by another person or walking aid because of ataxia

Romberg test
0 = normal
1 = mild, mild insecurity with EC
2 = moderate, not stable with EC
3 = severe, not stable with EO

Straight line walking
0 = without problems
1 = impaired
2 = not possible

Note
The presence of severe gait ataxia alone results in a grade of 3 in the cerebellar FS. If weakness interferes with the testing of ataxia, score the patient's actual performance, but also indicate the possible role of weakness by marking the box marked 'X'.

CEREBELLAR EXAMINATION	
Head tremor	
Truncal ataxia, EO	
Truncal ataxia, EC	

	R	L
Tremor/dysmetria UE		
Tremor/dysmetria LE		
Rapid alternate movements impaired UE		
Rapid alternate movements impaired LE		
Gait ataxia, EO		
Straight line walking, EO		
Other, e.g. rebound		
Romberg test		

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = abnormal signs without disability
	2 = mild ataxia
	3a = moderate truncal ataxia 3b = moderate limb ataxia
	4 = severe ataxia in all limbs or trunk
	5 = unable to perform coordinated movements due to ataxia
	X = weakness (grade 3 or more on pyramidal) interferes with testing

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SENSORY FUNCTIONS

Definitions * = optional
UE = upper extremities
LE = lower extremities

Superficial sensation – Touch/pain
0 = normal
1 = signs only, patient is not aware of deficit, but slightly reduced sensation of feeling (temperature, figure writing)
2 = mild, patient is aware of impaired light touch or pain, but able to discriminate sharp/dull
3 = moderate, impaired discrimination of sharp/dull
4 = severe, no discrimination of sharp/dull and/or unable to feel light touch
5 = complete loss, anaesthesia

Vibration sense
0 = normal
1 = mild, graded tuning fork 5–7 of 8 (alternatively) detects more than 10 sec. but less than examiner
2 = moderate, graded tuning fork 1–4 of 8 (alternatively) detects more than 2 sec. but less than 11 sec.
3 = marked, complete loss of vibration sense

Position sense
0 = normal
1 = mild, 1–2 incorrect responses on testing, only distal joints affected
2 = moderate, misses many movements of fingers or toes, proximal joints affected
3 = marked, no perception of movement/astasia

***Lhermitte**
0 = negative
1 = positive

***Paraesthesia (tingling)**
(do not influence FS-score)
0 = none
1 = present

SENSORY EXAMINATION	R	L
Superficial sensation (touch/pain) UE		
Superficial sensation trunk		
Superficial sensation LE		
Vibration sense UE		
Vibration sense LE		
Position sense UE		
Position sense LE		
*Lhermitte		
*Paraesthesiae UE		
*Paraesthesiae trunk		
*Paraesthesiae LE		

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

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BOWEL/BLADDER FUNCTIONS

Definitions * = optional

BLADDER

Hesitancy/retention

0 = none
1 = mild, no major impact on lifestyle
2 = moderate, urine retention, frequent UTI
3 = severe, requires catheterisation
4 = loss of function, overflow incontinence

Urgency/incontinence

0 = none
1 = mild, no major impact on lifestyle
2 = moderate, rare incontinence, no more than once a week, must wear pads
3 = severe, frequent incontinence, several times a week up to more than once daily, must wear urinal or pads
4 = loss of function, loss of bladder control

Catheterisation

0 = none
1 = intermittent self catheterisation
2 = constant

Bowel

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

***Sexual dysfunction**

0 = none
1 = mild
2 = moderate
3 = severe
4 = loss

BLADDER AND BOWEL FUNCTIONS	
Hesitancy/retention	
Urgency/incontinence	
Catheterisation	
Bowel dysfunction	
*Sexual dysfunction	

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = mild urinary hesitancy, urgency and/or constipation
	2 = moderate urinary hesitancy and/or urgency and/or rare incontinence and/or severe constipation
	3 = frequent urinary incontinence or intermittent self catheterisation; needs constantly enemata or manual measures to evacuate bowel
	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

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CEREBRAL FUNCTIONS

Definitions
The presence of depression and/or euphoria alone results in a score of 1 on the cerebral FS, but does not affect the EDSS score.

Depression/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, difficulties apparent to patient and/or «significant other» such as impaired ability to follow a rapid course of association and of surveying complex matters, impaired judgement in certain demanding situations, able to handle the daily routine, but no tolerance for additional stressors, intermittently symptomatic to even normal levels of stress, reduced performance, tendency toward negligence due to obliviousness or fatigue. However, not apparent while taking the history or performing the routine neurological examination.
3 = moderate, definite abnormalities on formal mental status testing, but still oriented to time, place and person
4 = marked, not oriented in 1 or 2 spheres of time, place or person, marked effect on lifestyle
5 = dementia, confusion and/or complete disorientation

Fatigue*
0 = none
1 = mild, not interfering with daily activities
2 = moderate, interfering but not limiting daily activities for more than 50 %
3 = severe, significantly limiting daily activities (> 50% reduction)

*Because difficult to evaluate objectively, in some studies fatigue does not contribute to this Functional System or the EDSS Score. Please adhere to the study's specific instructions.

MENTAL STATUS EXAMINATION	
Depression	
Euphoria	
Decrease in mentation	
Fatigue	

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = mood alteration only (does not affect EDSS score)/mild fatigue
	2 = mild decrease in mentation/ moderate or severe fatigue
	3 = moderate decrease in mentation
	4 = marked decrease in mentation
	5 = dementia

AMBULATION

Definitions
Actual walking distance without assistance obligatory up to 500 m (if possible). Actual walking distance with assistance obligatory up to 150 m (if possible).

In the definitions of EDSS grades 6.0 and 6.5 both a description of assistance required and of the walking range are included. In general, the distinction of bilateral versus unilateral assistance required to walk overrules the walking range.
However, the following exceptions are suggested,
If a patient is able to walk considerably longer than 100 m (> 120) with two sticks, crutches or braces he is in grade 6.0.
If a patient is able to walk more than 10 m and up to 100 m with two sticks, crutches or braces he is in grade 6.5.
If a patient needs assistance by another person (as opposed to one stick, crutch or brace) and/or is not able to walk more than 50 m with one stick, crutch or brace he is in grade 6.5.

AMBULATION

Walking range as reported (without help or sticks)

	meters
in	min

Able to walk without rest or assistance

	≥ 100 meters, but < 200 meters
	≥ 200 meters, but < 300 meters
	≥ 300 meters, but < 500 meters
	≥ 500 meters but not unrestricted
	Unrestricted

Actual distance (obligatory up to 500 m if possible)

	meters

Unable to walk 100 m without constant assistance

Unilateral assistance		meters
	Cane/crutch	
	Other	
Bilateral assistance		meters
	Canes/crutches	
	Other	
Other person		

SYNOPSIS OF FS SCORES

	Visual [1,3]
	Brainstem
	Pyramidal
	Cerebellar
	Sensory
	Bladder/Bowel [2,3]
	Mental

[1] For calculation of the EDSS the score of the visual FS is to be converted as follows, 6 = 4; 5 = 3; 4 = 3; 3 = 2; 2 = 2; 1 = 1.

[2] Scores of the bowel / bladder FS are converted as follows: 6=5, 5=4, 4=3, 3=3, 2=2, 1=1.

[3] Please enter both the actual and the converted score.

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KURTZKE EXPANDED DISABILITY SCALE (EDSS)

EDSS steps below 4 refer to patients who are fully ambulatory (able to walk >500 m), and the precise step is defined by the functional systems (FS) score(s). EDSS steps between 4.0 and 5.0 are defined by both FS-scores and walking range. In general, the worst of both should determine
the score. Steps 5.5-8.0 are exclusively defined by ability to ambulate or use wheelchair.

Up to 4.0 EDSS should not change by 1.0 step unless there is a change in same direction of at least one step in at least one FS.
EDSS should not be lower than each of FS (excepted visual and bowel/bladder FS).

0	normal neurological exam (all grade 0 in FS)
1.0	no disability, minimal signs in one FS1 (i.e. grade 1)
1.5	no disability, minimal signs in more than one FS 1 (more than one 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) 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 grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)
4.0	ambulatory without aid or rest for > 500 m; 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 m; up and about much of the day; characterised by relatively severe disability usually consisting of one FS grade 4 or combinations of lesser grades exceeding limits of previous steps
5.0	ambulatory without aid or rest for > 200 m (usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.5)
5.5	ambulatory without aid or rest > 100 m
6.0	unilateral assistance (cane or crutch) required to walk at least 100 m with or without resting
6.5	constant bilateral assistance (canes or crutches) required to walk at least 20 m without resting
7.0	unable to walk 5 m even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 h a day
7.5	unable to take more than a few steps; restricted to wheelchair; may need some help in transfer 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

Actual EDSS

Signature

[1] Mental function's grade 1 does not contribute to EDSS-step definitions

4 neurostatus

PYRAMIDAL FUNCTIONS

Definitions * = optional

REFLEXES

0 = absent, 1 = weak, 2 = normal, 3 = exaggerated, 4 = cloniform, 5 = inexhaustible (indicate difference between R & L by < or >)

Plantar response

0 = flexor, 1 = neutral, 2 = extensor

Cutaneous reflexes

0 = normal, 1 = weak, 2 = absent

***Palmomental reflex**

0 = absent, 1 = present

LIMB STRENGTH

The weakest muscle in each group defines the score for that group. Use of functional tests like jumping with one foot, walking on toes or heels are recommended in order to assess grades 3-5 BMRC.

BMRC Rating scale

0 = no activity, 1 = visible contraction without visible joint movement, 2 = visible movements with elimination of gravity, 3 = movements against gravity possible but impaired, 4 = movements against resistance possible but impaired, 5 = normal strength

FUNCTIONAL TESTS

*Position test UE (upper extremities)

Sinking, 0 = none, 1 = mild, 2 = evident

***Position test LE (lower extremities)**

Sinking, 0 = none, 1 = mild, 2 = evident

1 = only separate lifting possible (grades from horizontal position in hip joints...°)

2 = even separate lifting not possible

***Walking on heels/tiptoes**

0 = normal, 1 = impaired, 2 = not possible

***Monopedal hopping**

0 = normal, 1 = 6–10 times, 2 = 1–5 times, 3 = not possible

LIMB SPASTICITY

0 = normal, 1 = mild, barely increased muscular tone after rapid flexion of an extremity, 2 = moderate, 3 = severe, barely surmountable increased spastic tonus after rapid flexion of an extremity, 4 = contracted

Gait spasticity

0 = normal, 1 = barely perceptible, 2 = evident, minor interference with function, 3 = permanent shuffling, major interference with function

REFLEXES	R	><	L
Biceps			
Triceps			
Radial			
Knee			
Ankle			
Plantar response			
Cutaneous reflexes			
*Palmomental reflex			

LIMB STRENGTH		
Shoulder		
Elbow flexors		
Elbow extensors		
Hand/finger flexors		
Hand/finger extensors		
Hip flexion		
Knee flexors		
Knee extensors		
Foot/toe flexors		
Foot/toe extensors		
*Position test UE, pronation		
*Position test UE, sinking		
*Position test LE, sinking		
only lifting of single leg possible	°	°
*Walking on heels		
*Walking on tiptoes		
*Hopping on one foot		

SPASTICITY		
Arm		
Leg		
Gait		

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = abnormal signs without disability
	2 = minimal disability, patient complains about fatiguability in 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) movements against gravity are possible 3b = severe monoparesis, refers to BMRC grade 2 or less in one muscle group
	4a = marked paraparesis or hemiparesis (usually BMRC grade 2 in 2 limbs) 4b = moderate tetraparesis (refers to BMRC grade 3 in 3 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 3 or more limbs)
	6 = Tetraplegia (grade 0 or 1 in all muscle groups of upper and lower limbs)

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CEREBELLAR FUNCTIONS

Definitions
UE = upper extremities
LE = lower extremities
EO = eyes open
EC = eyes closed

Head tremor, rebound
0 = normal
1 = mild abnormality
2 = moderate abnormality
3 = severe abnormality

Truncal ataxia
0 = none
1 = signs only
2 = mild, swaying with EC
3 = moderate, swaying with EO
4 = severe, unable to sit without assistance

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

Gait ataxia
0 = none
1 = signs only
2 = mild, abnormal balance only on heel or toe walking, or walking along a line
3 = moderate, abnormal balance on ordinary walking or while seated
4 = severe, unable to walk more than a few steps or requires support by another person or walking aid because of ataxia

Romberg test
0 = normal
1 = mild, mild insecurity with EC
2 = moderate, not stable with EC
3 = severe, not stable with EO

Straight line walking
0 = without problems
1 = impaired
2 = not possible

Note
The presence of severe gait ataxia alone results in a grade of 3 in the cerebellar FS. If weakness interferes with the testing of ataxia, score the patient's actual performance, but also indicate the possible role of weakness by marking the box marked 'X'.

CEREBELLAR EXAMINATION	
Head tremor	
Truncal ataxia, EO	
Truncal ataxia, EC	

	R	L
Tremor/dysmetria UE		
Tremor/dysmetria LE		
Rapid alternate movements impaired UE		
Rapid alternate movements impaired LE		
Gait ataxia, EO		
Straight line walking, EO		
Other, e.g. rebound		
Romberg test		

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = abnormal signs without disability
	2 = mild ataxia
	3a = moderate truncal ataxia 3b = moderate limb ataxia
	4 = severe ataxia in all limbs or trunk
	5 = unable to perform coordinated movements due to ataxia
	X = weakness (grade 3 or more on pyramidal) interferes with testing

6 neurostatus

SENSORY FUNCTIONS

Definitions * = optional
UE = upper extremities
LE = lower extremities

Superficial sensation – Touch/pain
0 = normal
1 = signs only, patient is not aware of deficit, but slightly reduced sensation of feeling (temperature, figure writing)
2 = mild, patient is aware of impaired light touch or pain, but able to discriminate sharp/dull
3 = moderate, impaired discrimination of sharp/dull
4 = severe, no discrimination of sharp/dull and/or unable to feel light touch
5 = complete loss, anaesthesia

Vibration sense
0 = normal
1 = mild, graded tuning fork 5–7 of 8 (alternatively) detects more than 10 sec. but less than examiner
2 = moderate, graded tuning fork 1–4 of 8 (alternatively) detects more than 2 sec. but less than 11 sec.
3 = marked, complete loss of vibration sense

Position sense
0 = normal
1 = mild, 1–2 incorrect responses on testing, only distal joints affected
2 = moderate, misses many movements of fingers or toes, proximal joints affected
3 = marked, no perception of movement/astasia

***Lhermitte**
0 = negative
1 = positive

***Paraesthesia (tingling)**
(do not influence FS-score)
0 = none
1 = present

SENSORY EXAMINATION	R	L
Superficial sensation (touch/pain) UE		
Superficial sensation trunk		
Superficial sensation LE		
Vibration sense UE		
Vibration sense LE		
Position sense UE		
Position sense LE		
*Lhermitte		
*Paraesthesiae UE		
*Paraesthesiae trunk		
*Paraesthesiae LE		

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

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BOWEL/BLADDER FUNCTIONS

Definitions * = optional

BLADDER

Hesitancy/retention

0 = none
1 = mild, no major impact on lifestyle
2 = moderate, urine retention, frequent UTI
3 = severe, requires catheterisation
4 = loss of function, overflow incontinence

Urgency/incontinence

0 = none
1 = mild, no major impact on lifestyle
2 = moderate, rare incontinence, no more than once a week, must wear pads
3 = severe, frequent incontinence, several times a week up to more than once daily, must wear urinal or pads
4 = loss of function, loss of bladder control

Catheterisation

0 = none
1 = intermittent self catheterisation
2 = constant

Bowel

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

***Sexual dysfunction**

0 = none
1 = mild
2 = moderate
3 = severe
4 = loss

BLADDER AND BOWEL FUNCTIONS	
Hesitancy/retention	
Urgency/incontinence	
Catheterisation	
Bowel dysfunction	
*Sexual dysfunction	

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = mild urinary hesitancy, urgency and/or constipation
	2 = moderate urinary hesitancy and/or urgency and/or rare incontinence and/or severe constipation
	3 = frequent urinary incontinence or intermittent self catheterisation; needs constantly enemata or manual measures to evacuate bowel
	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

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CEREBRAL FUNCTIONS

Definitions
The presence of depression and/or euphoria alone results in a score of 1 on the cerebral FS, but does not affect the EDSS score.

Depression/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, difficulties apparent to patient and/or «significant other» such as impaired ability to follow a rapid course of association and of surveying complex matters, impaired judgement in certain demanding situations, able to handle the daily routine, but no tolerance for additional stressors, intermittently symptomatic to even normal levels of stress, reduced performance, tendency toward negligence due to obliviousness or fatigue. However, not apparent while taking the history or performing the routine neurological examination.
3 = moderate, definite abnormalities on formal mental status testing, but still oriented to time, place and person
4 = marked, not oriented in 1 or 2 spheres of time, place or person, marked effect on lifestyle
5 = dementia, confusion and/or complete disorientation

Fatigue*
0 = none
1 = mild, not interfering with daily activities
2 = moderate, interfering but not limiting daily activities for more than 50 %
3 = severe, significantly limiting daily activities (> 50% reduction)

*Because difficult to evaluate objectively, in some studies fatigue does not contribute to this Functional System or the EDSS Score. Please adhere to the study's specific instructions.

MENTAL STATUS EXAMINATION	
Depression	
Euphoria	
Decrease in mentation	
Fatigue	

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = mood alteration only (does not affect EDSS score)/mild fatigue
	2 = mild decrease in mentation/ moderate or severe fatigue
	3 = moderate decrease in mentation
	4 = marked decrease in mentation
	5 = dementia

AMBULATION

Definitions
Actual walking distance without assistance obligatory up to 500 m (if possible). Actual walking distance with assistance obligatory up to 150 m (if possible).

In the definitions of EDSS grades 6.0 and 6.5 both a description of assistance required and of the walking range are included. In general, the distinction of bilateral versus unilateral assistance required to walk overrules the walking range.
However, the following exceptions are suggested,
If a patient is able to walk considerably longer than 100 m (> 120) with two sticks, crutches or braces he is in grade 6.0.
If a patient is able to walk more than 10 m and up to 100 m with two sticks, crutches or braces he is in grade 6.5.
If a patient needs assistance by another person (as opposed to one stick, crutch or brace) and/or is not able to walk more than 50 m with one stick, crutch or brace he is in grade 6.5.

AMBULATION

Walking range as reported (without help or sticks)

	meters
in	min

Able to walk without rest or assistance

	≥ 100 meters, but < 200 meters
	≥ 200 meters, but < 300 meters
	≥ 300 meters, but < 500 meters
	≥ 500 meters but not unrestricted
	Unrestricted

Actual distance (obligatory up to 500 m if possible)

	meters

Unable to walk 100 m without constant assistance

Unilateral assistance		meters
	Cane/crutch	
	Other	
Bilateral assistance		meters
	Canes/crutches	
	Other	
Other person		

SYNOPSIS OF FS SCORES

	Visual [1,3]
	Brainstem
	Pyramidal
	Cerebellar
	Sensory
	Bladder/Bowel [2,3]
	Mental

[1] For calculation of the EDSS the score of the visual FS is to be converted as follows, 6 = 4; 5 = 3; 4 = 3; 3 = 2; 2 = 2; 1 = 1.

[2] Scores of the bowel / bladder FS are converted as follows: 6=5, 5=4, 4=3, 3=3, 2=2, 1=1.

[3] Please enter both the actual and the converted score.

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KURTZKE EXPANDED DISABILITY SCALE (EDSS)

EDSS steps below 4 refer to patients who are fully ambulatory (able to walk >500 m), and the precise step is defined by the functional systems (FS) score(s). EDSS steps between 4.0 and 5.0 are defined by both FS-scores and walking range. In general, the worst of both should determine
the score. Steps 5.5-8.0 are exclusively defined by ability to ambulate or use wheelchair.

Up to 4.0 EDSS should not change by 1.0 step unless there is a change in same direction of at least one step in at least one FS. EDSS should not be lower than each of FS (excepted visual and bowel/bladder FS).

0	normal neurological exam (all grade 0 in FS)
1.0	no disability, minimal signs in one FS1 (i.e. grade 1)
1.5	no disability, minimal signs in more than one FS 1 (more than one 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) 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 grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)
4.0	ambulatory without aid or rest for > 500 m; 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 m; up and about much of the day; characterised by relatively severe disability usually consisting of one FS grade 4 or combinations of lesser grades exceeding limits of previous steps
5.0	ambulatory without aid or rest for > 200 m (usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.5)
5.5	ambulatory without aid or rest > 100 m
6.0	unilateral assistance (cane or crutch) required to walk at least 100 m with or without resting
6.5	constant bilateral assistance (canes or crutches) required to walk at least 20 m without resting
7.0	unable to walk 5 m even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 h a day
7.5	unable to take more than a few steps; restricted to wheelchair; may need some help in transfer 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

Actual EDSS

Signature

[1] Mental function's grade 1 does not contribute to EDSS-step definitions

APPENDIX 3. MRI PROTOCOL

Applicable only for the LAQ/5063 study and the first 24 months of the open-label phase of the LAQ/5063 study.

Post-Gd T_1-weighted and dual-echo MRI scans of the brain will be performed.

For each subject, on-treatment MRIs scans will be performed within 4 days prior to the visit at Week 36 (termination).

The same scanner, used in the core study LAQ/5062 must be used for each subject for the entire duration of the study; scanners should have at least 1.0 Tesla magnetic field strength. The MRI-AC in [redacted] will conduct the entire MRI analysis.

Scanning Requirements:

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.
- Enter the subject data into the scanner console, using:
- study number (protocol number, site number, subject number)
- date of birth/sex
- weight
- scan number
- Explain the scanning procedure to the subject and position her/him in the scanner in the most comfortable position.
- Insert an intravenous 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.

IMAGING

The following order for sequences will be kept:

- T_1-weighted axial scout
- T_1-weighted coronal scout
- T_1-weighted sagittal scout
  - Rapid T_1-weighted SE or T_2-weighted FSE/TSE axial (this is for repositioning check)
  - T_2-weighted FSE/TSE
  - T_1-weighted SE post gadolinium

Sequences from 1 to 4 will be done to obtain reference images for subject repositioning.

Sequence parameters:

T_1-weighted axial scout:

- TR: 100
- TE: 10-20
- Slice number: 3
- Slice thickness: 5mm
- Orientation: axial
- Field of view (FOV): 210-230 mm
- Matrix: 128 x 256
- Inter-slice gap: 5 mm

- Number of acquisitions: 1
- Phase encoding: 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); the acquisition parameters will be the following:

- TR: 100
- TE: 10-20
- Slice number: 1
- Slice thickness: 5 mm
- Orientation: coronal
- Field of view (FOV): 210-230 mm
- Matrix: 128 x 256
- Number of acquisitions: 1
- Phase encoding: L > R

From the coronal scout make a sagittal scout image, aligned with the falx cerebri and other midline structures, following these parameters:

- TR: 500-650
- TE: 10-20
- Slice number: 1
- Slice thickness: 5 mm
- Orientation: sagittal
- Field of view (FOV): 210-230 mm
- Matrix: 128 x 256
- Number of acquisitions: 1-3
- Phase encoding: 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 corpus callosum genu and splenium. The slice group will be positioned to include the whole brain from the vertex to the level of the foramen magnum. 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.

For T_1-weighted images, the following parameters should be used:

- TR-600
- TE: 10-20
- Slice number: 22
- Slice thickness: 3 mm
- Orientation: axial
- Field of view (FOV): 250 mm
- Matrix: 140 x 256
- Inter-slice gap: 3 mm
- Series: interleaved
- Number of acquisitions:1
- Phase encoding: L > R

For T_2-weighted images, a fast spin echo (or turbo spin echo) sequence should be used with the following parameters:

- TR: 2200-3000
- TE: either single-echo or dual-echo (according to site preference):
- TE first echo: 30-50; TE second echo: 60-100
- ETL: according to site preference
- Slice number: 22
- Slice thickness: 3 mm
- Orientation: axial

- FOV: 250 mm
- Matrix: approximately 140 x 256. The number of phase-encode lines will depend on the exact sequence used
- Inter-slice gap: 3 mm
- Series: interleaved
- Number of acquisitions: 1
- Phase-encoding: L > R

Please note that the hardcopies of this first series of T_1 or T_2 axial images should be one 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).

If possible, to speed up the examination, use a rectangular 3/4 FOV (i.e., reduce the phase-encoding matrix by 25%) when doing all the subsequent series of axial images. 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).

The scanning procedure is resumed by doing two interleaved series of fast or turbo spin-echo dual echo sequence. Conventional spin-echo sequences are allowed in case fast imaging is not available. Image parameters will be the following:

- TR: 2200-3000
- TE: 15-50/80-120
- ETL: 4-6
- Slice number: 22
- Slice thickness: 3 mm
- Orientation: axial
- Field of view (FOV): 250 mm
- Matrix: 256 x 256 (192 x 256 if RECFOV)
- Inter-slice gap: 3 mm
- Series: interleaved

- Number of acquisitions: 1
- Phase encoding: L > R
- Resaturation slab/flow compensation: Yes

The axial presaturation slab (50-80 mm) will be positioned inferior to the slice group to suppress flow-related artifacts.

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.

Some General Electric and Philips scanners allow all the 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, then this should be done.

Perform a bolus injection of Gd-DPTA using the intravenous 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). During the post-injection delay interval 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.

The following parameters should be used:

- TR: 600-650 (Keep the TR within the range and optimize the signal to noise ratio, i.e., the maximum echo time and the lowest bandwidth consistent with the TR range.)
- TE: 10-20
- Slice number: 22
- Slice thickness: 3 mm
- Orientation: axial
- Field of view (FOV): 250 mm
- Matrix: 256 x 256 (192 x 256 if RECFOV)
- Inter-slice gap: 3 mm
- Series: interleaved
- Number of acquisitions: 2
- Phase encoding: L > R
- Presaturation slab/flow compensation: yes

The second series of images will be positioned to fill the gaps of the first one. Once the two acquisitions are completed, check the image consistency in terms of both correct repositioning (when compared with "fast" T_1) and covering the whole brain as indicated above. In case of spoiled 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 Gd-DTPA injection.

Scans should be evaluated by the center radiologist and any pathological, non-MS findings should be reported to the Treating Investigator.

ELECTRONIC BACKUP PROCEDURES

Electronic backups (CD) should be prepared and archived within the sites.

Preparation of Scans:

A CD containing all sequences per visit should be prepared. All sheets should be divided into 20 images, starting in the upper left corner with the most caudal slice; use the same format for all series.

For each scan, sheets should be the following:

- One sheet divided into 4 with the axial and coronal localizers and two sagittal localizers (showing clearly how the axial slices were positioned, one with the position line alone and one with the whole slice group).
- Two sheets for T_1-weighted SE after contrast (20+20 images)
- Four sheets for PD/T_2-weighted FSE/TSE (20+20 images x 2)
- One sheet for the last 4 cranial images of all sequences (4 images per row)
- Total number of sheets for MRI scan: 8

In the event that machine constraints do not allow such image printing, the MRI-AC should be contacted and the image format negotiated on a site-by-site basis.

The site will keep its own hard copy backups only for the repositioning images of the screening (Week 4) MRI.

Electronic Data

One set of scans will be sent by courier to the MRI-AC within 3 working days from the scan date.

The center will send a copy of MRI digital images to the MRI-AC.

Different options are available as were discussed with the center prior to start of the core study to solve in advance any problem arising from the use of different media and data formats.

As a general guideline the following is a list, ordered by preference, of the acceptable media:

- Electronic tapes: 4mm DAT or 8mm video 1/4" tape digital linear tape (DLT)
- CD-ROM
- 5 1/4" Optical disks WORM or rewritable's depending on the scanner used
- Network transfer ftp

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, at the following e-mail address:

[redacted]

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.

As subjects are entered, a planned time for the following scans will be provided to the MRI-AC by each participating site study coordinator. The MRI-AC will call each site on failure to log anticipated films and/or electronic data at the MRI-AC.

Steroid Treatment and MRI Scan Schedule

It is recognized that steroid therapy strongly reduces the effect of gadolinium-enhancement and to a minor degree, the size of lesion of T_2-weighted images. However, moderate and severe MS relapses may warrant treatment with IV methylprednisolone (IVMP), as described in Section 6.1. In this study, subjects treated with IVMP will be scanned at pre-planned times, rather than to arbitrarily adjust for recent steroid use.

MRI Scan Analysis

The following analyses will be performed:

- Count of total contrast-enhancing T_1-weighted lesions
- T_2 lesions load (volume)
- Count of number of new T_2 lesions
- Count of new hypointense T_1 lesions on enhanced T_1 scans ("black holes")

The quantification of lesion load will be performed using a semi-automated segmentation technique based on local threshold.

MRI Scan Quality Control

The quality of scans will be reviewed by the MRI-AC when received. Within 3 working days of receiving the scan, the MRI-AC will fax the MRI scan acceptance form to participating sites, the local clinical management and to the Corporate Coordination Center.

In case of unsatisfactory image quality, the scans will be rejected and repeated. Rejected scans will be repeated within 2 weeks from the date of the first assessment. Repositioning will be considered acceptable when less than a 2-slice thickness difference exists for recognizable landmarks on the axial slices between MRI sessions.

APPENDIX 4. 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 > .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. 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 treating 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, ask, "*Are you right or left-handed?*" 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.

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 audiotape 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

Audiocassette tape player, audiocassette tape 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 audiocassette (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 tape 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 tape 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. Write "NR" (for "no response") 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 5. 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 8).

Table 8: 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 9).

Table 9: 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 6. 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 10) should be advised that plasma levels of these drugs could increase when combined with laquinimod.

Table 10: 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 11 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 11: 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 7. LIST OF STEERING COMMITTEE MEMBERS

APPENDIX 8. LIST OF DATA SAFETY MONITORING BOARD (DSMB) MEMBERS

It should be noted that as the study is in open label phase, the originally assigned DSMB is not operating any further.

The study is supervised by Teva's internal safety committee as well as by an external Data Monitoring Committees (DMC) of the ongoing Phase III studies MS-LAQ-301 (ALLEGRO) and MS-LAQ-302 (BRAVO).

APPENDIX 9. LIST OF CLINICAL ADVISORY BOARD (CAB) MEMBERS

APPENDIX 10. 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[o] 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[p]. 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

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

[p] 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 Smooth Muscle Antibodies), anti-LKM (Liver Kidney Microsomal) 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 4 weeks and will include measurement of liver enzymes at least QW (may be performed in a local laboratory, with at least 1 test being sent to the central laboratory).
- Every effort should be made to complete the additional tests/ evaluations, as described above.

2. Use of Moderate/Strong CYP3A4 Inhibitors

Laquinimod 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 5.

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 level. 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 childbearing 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 method (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, the subject 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 Section 7.2).

    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 LAQ/5063 OL phase (completion of all Termination visit activities) according to the LAQ/5063 OL 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 [intravenous (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 during the study and up to 30 days after the last dose of the study treatment was administered. 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, 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 LAQ/5063 OL 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 LAQ/5063 OL study, for any reason, except 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®), IFN-β (either 1a or 1b), fingolimod (Gilenya®), dimethyl fumarate (Tecfidera) or IV immunoglobulin (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 test 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 LAQ/5063 OL study, which preclude safe participation and completion of the LAQ/5063 OL 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 12: Study Task Flow Chart for Returning Subjects (Month 24 onwards)

Visit	**V10E1**	**V11E1**	**V12E1**	**V13E1**	**V14E1**	**V15E1**	**V16E1**	**Every 6 months**	**Termination/Early Discontinuation**	**Unscheduled Visit[a]**
Month	**24E1**	**30E1**	**36E1**	**42E1**	**48E1**	**54E1**	**60E1**			
Informed consent[b]	X						X			
Inclusion/exclusion criteria	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Cardiovascular risk factor assessment and management[c]	X		X		X		X	Every 12 months from Month 72		
ECG	X	X	X	X	X	X	X	X	X	X
Neurological examination	X	X	X	X	X	X	X	X	X	X
Evaluation of relapse[d]	X	X	X	X	X	X	X	X	X	X
Ascertaining the use of effective contraception	X	X	X	X	X	X	X	X	X	X
Serum and urine βhCG[e] (on site)	X	X	X	X	X	X	X	X	X	X
Urine βhCG (self check, at home); pregnancy tests mandatory phone calls[f]	**EVERY 1 MONTH BETWEEN VISITS**									
Adverse events	X	X	X	X	X	X	X	X	X	X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X
Safety laboratory evaluation (CBC, chemistry, GFR estimation, markers of inflammation)	X	X	X	X	X	X	X[h]	X[h]	X[h]	X[h]
Laquinimod dispensing and accountability	X	X	X	X	X	X	X[i]	X	X[i]	X
Subject compliance	X	X	X	X	X	X	X	X	X	X

Visit	**V10E1**	**V11E1**	**V12E1**	**V13E1**	**V14E1**	**V15E1**	**V16E1**	**Every 6 months**	**Termination/Early Discontinuation**	**Unscheduled Visit[a]**
Month	**24E1**	**30E1**	**36E1**	**42E1**	**48E1**	**54E1**	**60E1**			
Termination documentation and notification of early termination									X	
Unscheduled samples										X[j]

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

[a] Assessments during an unscheduled visit will be performed as deemed necessary by the Investigator, except for vital signs and adverse events, which are mandatory at each visit

[b] At Month 24 (visit 10) of the open label phase Informed Consent will be signed for the extended open label period of 36 months. At Month 60 (visit 16) of the open label phase an Informed Consent will be signed for the additional extension as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS

[c] In addition, an evaluation should take place as soon as possible for subjects already in the study, following approval of Amendment #10

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

[e] For women of child-bearing potential

[f] Mandatory phone calls will be performed within 72 hours of the scheduled home pregnancy test

[g] Weight will be measured at all visits

[h] Inflammatory markers will not be collected from Month 60 and onwards

[i] Only drug retrieval

[j] 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.

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

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