

**Clinical Study Protocol with Amendment 02  
(including Statistical Analysis Plan)**

**A Multinational, Multicenter, Open-Label, Single-Assignment  
Extension of the MS-LAQ-302 (BRAVO) Study, to Evaluate the  
Long-Term Safety, Tolerability and Effect on Disease Course of  
Daily Oral Laquinimod 0.6 mg in Subjects with Relapsing Multiple**

**Study Number MS-LAQ-302E**

**NCT01047319**

**Protocol with Amendment 02 Approval Date: 25 February 2016**

**TEVA PHARMACEUTICAL INDUSTRIES LTD., ISRAEL**

**CLINICAL STUDY PROTOCOL**

**Study Title:** A Multinational, Multicenter, Open-Label, Single-Assignment Extension of the MS-LAQ-302 (BRAVO) Study, to Evaluate the Long-Term Safety, Tolerability and Effect on Disease Course of Daily Oral Laquinimod 0.6 mg in Subjects with Relapsing Multiple Sclerosis

**Protocol No:** MS-LAQ-302E

**EudraCT/IND No:** 2009-015815-42 / 071287

**Clinical Phase:** III Open-Label Extension Study

**Protocol Version Date:** September 16, 2009

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

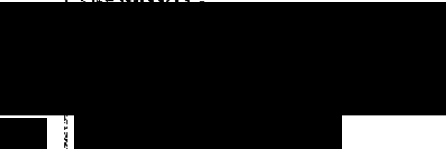
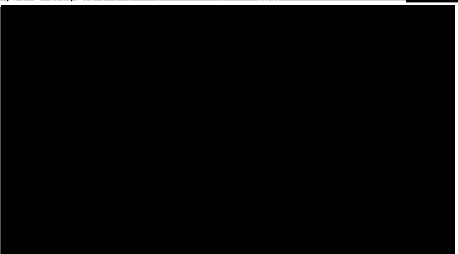
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### PROTOCOL REVIEW & APPROVAL

PROTOCOL No. MS-LAQ-302E  
BRAVO OPEN-LABEL EXTENSION STUDY  
Protocol Version: September 16, 2009  
Including Global Amendments No. 1 and 2

Sponsor's Authorized Representative	Signature: 	Date: <i>25 FEB 2016</i>
 Teva Pharmaceutical Industries, Ltd		

Study Principal Investigator	Signature: 	Date: <i>26 Feb 2016</i>
		

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**1. SYNOPSIS**

<b>Protocol Number:</b>	MS-LAQ-302E
<b>Eudract/IND Numbers:</b>	2009-015815-42 / 071287
<b>Study Title:</b>	A multinational, multicenter, open-label, single-assignment extension of the MS-LAQ-302 (BRAVO) study, to evaluate the long-term safety, tolerability and effect on disease course of daily oral laquinimod 0.6 mg in subjects with relapsing multiple sclerosis
<b>Number of Centers:</b>	All centers that randomized subjects in the MS-LAQ-302 study
<b>Clinical Phase:</b>	III, open-label extension study
<b>Study Duration:</b>	Treatment phase: starting from completion of the MS-LAQ-302E study (Termination visit), and may continue to participate in the MS-LAQ-302E study as long as the Sponsor continues the development of laquinimod 0.6 mg for relapsing remitting multiple sclerosis (RRMS).
<b>Study Population:</b>	Subjects who completed the Termination visit of the MS-LAQ-302 double-blind treatment phase according to the MS-LAQ-302 protocol, signed an informed consent form for the open-label extension study and met all eligibility criteria for this study.
<b>Study Objective(s):</b>	To make laquinimod 0.6 mg available for all subjects who completed the placebo-controlled MS-LAQ-302 study according to the protocol and to evaluate the long-term safety, tolerability and effect on disease course of daily oral laquinimod 0.6 mg in subjects with relapsing multiple sclerosis.
<b>Study Design:</b>	<p>This is a multinational, multicenter, open-label, single-assignment extension of the MS-LAQ-302 study, to evaluate the long-term safety, tolerability and effect on disease course of daily oral laquinimod 0.6 mg in subjects with relapsing multiple sclerosis.</p> <p>Eligible subjects will be treated with laquinimod 0.6 mg capsules once daily.</p> <p>Subjects completing the full-duration of the double-blind MS-LAQ-302 study (completion of Termination visit) according to the MS-LAQ-302 protocol will be offered the opportunity to enter the MS-LAQ-302E study. In this open-label study, the subjects will be treated with laquinimod 0.6 mg (regardless of their initial treatment assignment during the MS-LAQ-302 study, whether oral or injectable) as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS.</p> <p>Scheduled in-clinic visits will be conducted at Baseline (Month 0E) (the Termination visit of MS-LAQ-302 will serve as the baseline visit of MS-LAQ-302E) and at months 1E, 2E, 3E, 6E and every 6 months thereafter, until Termination/early discontinuation.</p> <p>The following assessments will be performed at the specified time points:</p> <ul style="list-style-type: none"> <li>• Vital signs will be measured at each study visit. At month 0E [Baseline (Termination visit of the MS-LAQ-302 study)] vital signs will be measured also 30 and 60 minutes after the administration of the first dose of laquinimod 0.6 mg.</li> <li>• Weight will be measured at all visits until Termination/Early discontinuation.</li> <li>• A physical examination will be performed at months 0E [Baseline (Termination visit of the MS-LAQ-302 study)], 6E, 12E and then every 12 months (every other scheduled visit) thereafter, until Termination/Early discontinuation visit.</li> </ul>

	<ul style="list-style-type: none"> <li>● The following safety clinical laboratory tests will be performed: <ul style="list-style-type: none"> <li>– Complete blood count (CBC) with differential – at all scheduled visits</li> <li>– Serum chemistry (including electrolytes, liver enzymes, direct and total bilirubin, pancreatic amylase, creatine phosphokinase [CPK], and estimated glomerular filtration rate) – at all scheduled visits</li> <li>– Hematology.</li> <li>– A urine dipstick beta-human Chorionic Gonadotropin (<math>\beta</math>-hCG) test will be performed in women of child-bearing potential (at site) - at all scheduled visits except Termination/Early discontinuation visit</li> <li>– Serum <math>\beta</math>-hCG in women of child-bearing potential - at all scheduled study visits</li> <li>– Starting after visit Month 3E a urine dipstick <math>\beta</math>-hCG test will be performed at home in women of child-bearing potential every 28 (<math>\pm</math>2) days. The subject will be contacted by telephone within 72 hours after the test is scheduled to be performed and will be asked specific questions regarding the test. In case of suspected pregnancy (positive urine <math>\beta</math>-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.</li> <li>– Serum conventional high-sensitivity C-reactive protein (hs-CRP) and fibrinogen at all scheduled visits</li> <li>– In case of abnormal CPK result: troponin and CPK-MB will be tested. In case of CPK &gt;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.</li> <li>– Lipase will be tested in case of abnormal pancreatic amylase results</li> </ul> </li> <li>● The use of effective contraception will be ascertained at every visit.</li> <li>● Following Visit Month 6E, all subjects will be regularly contacted by telephone every 3 months between the scheduled visits and asked a general question regarding their well-being (for women of child-bearing potential, there is no need to perform a separate call, as this question will be a part of the monthly pregnancy urine test call)</li> <li>● Electrocardiography (ECG), neurological evaluations, including Expanded Disability Status Scale (EDSS), 25 foot walk test/Ambulation Index (AI), Functional systems (FS), MS Functional Composite (MSFC), subject-reported fatigue as assessed by the Modified Fatigue Impact Scale (MFIS), general health status and quality of life parameters will be assessed by the Short-Form general health survey (SF-36) subject-reported questionnaire and Binocular low-contrast visual acuity using the 100%, 2.5% and 1.25% contrast level charts [Sloan letter or Tumbling-E] will be performed at months 0E [Baseline (Termination visit of the MS-LAQ-302 study)], 6E and then at every scheduled study visit thereafter, until Termination/early discontinuation visit</li> <li>● Adverse events (AEs) will be monitored throughout the study</li> </ul>
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	<ul style="list-style-type: none"> <li>● Concomitant medications will be monitored throughout the study</li> <li>● Relapses will be confirmed/monitored throughout the study</li> </ul> <p>The allowed treatment for a relapse will be intravenous Methylprednisolone 1 g/day or oral steroids for up to 5 consecutive days.</p> <p>Subjects who discontinue treatment for any reason will continue follow-up according to scheduled visits.</p> <p><u>Ancillary studies:</u></p> <ul style="list-style-type: none"> <li>● The effect of general health and symptom severity on work will be assessed by the work productivity and activities impairment General Health (WPAI-GH) questionnaire at months 0E [Baseline (Termination visit of the MS-LAQ-302 study)], 6E and then at every scheduled study visit thereafter, until Termination/Early discontinuation visit (this assessment will be performed in all subjects from US sites only).</li> </ul> <p>As of the implementation of Protocol Amendment #1, all neurological/medical assessments may be performed by a single Study Physician/Neurologist since all the sites are now in Period 2 of the study.</p> <p>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.</p>
<b>Number of Subjects:</b>	One thousand, three hundred and thirty two subjects were randomized to the MS-LAQ-302 study. One thousand forty seven subjects who completed the Termination visit of the MS-LAQ-302 study according to the MS-LAQ-302 protocol, signed an informed consent form for the open-label extension study and met all eligibility criteria for this study enrolled to the MS-LAQ-302E study.
<b>Inclusion/Exclusion Criteria:</b>	<p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> <li>1. Subjects must have completed the Termination visit of MS-LAQ-302 (completion of all Termination visit activities) according to the MS-LAQ-302 protocol.</li> <li>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)].</li> <li>3. Subjects must be willing and able to comply with the protocol requirements for the duration of the study.</li> <li>4. Subjects must be able to comprehend, sign and date a written informed consent prior to entering the MS-LAQ-302E study.</li> </ol> <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> <li>1. Premature discontinuation from the MS-LAQ-302 study, for any reason.</li> </ol>

	<ol style="list-style-type: none"> <li>2. Pregnancy [according to urine dipstick <math>\beta</math>-hCG test performed at Baseline (Month 0E) visit] or breastfeeding.</li> <li>3. Subjects with clinically significant or unstable medical or surgical condition detected or worsened during the MS-LAQ-302 study, which preclude safe participation and completion of the MS-LAQ-302E study. Acute exacerbation of MS will not exclude participation in the MS-LAQ-302E study.</li> <li>4. Use of inhibitors of cytochrome P450 (CYP) 3A4 within 2 weeks prior to baseline visit (VOE, Month 0E).</li> </ol>
<b>Route and Dosage Form:</b>	One capsule containing 0.6 mg laquinimod to be administered orally once daily.
<b>Outcome Measures:</b>	<p>To assess the long-term safety and tolerability of daily oral laquinimod 0.6 mg in subjects with relapsing multiple sclerosis.</p> <p>Safety and Tolerability Outcome Measures:</p> <p><b>Safety:</b></p> <ul style="list-style-type: none"> <li>• AEs</li> <li>• Vital signs</li> <li>• ECG findings</li> <li>• Clinical laboratory parameters</li> </ul> <p><b>Tolerability:</b></p> <ul style="list-style-type: none"> <li>• Proportion of subjects (%) who prematurely discontinued from the study, reason of discontinuation and the time to withdrawal.</li> <li>• Proportion of subjects (%) who prematurely discontinued from the study due to AEs and the time to withdrawal</li> </ul> <p>To assess the long-term effect of laquinimod 0.6 mg on disease course, as assessed by several parameters:</p> <ul style="list-style-type: none"> <li>• Number of confirmed relapses</li> <li>• Progression of disability as measured by the EDSS score (including FS and AI)</li> <li>• Progression of disability as measured by the MSFC score</li> <li>• Binocular low-contrast visual acuity using the 100%, 2.5% and 1.25% contrast level charts [Sloan letter or Tumbling-E]</li> <li>• Subject-reported fatigue as assessed by the MFIS General health status and quality of life parameters as assessed by the SF-36</li> </ul>
<b>Statistical Considerations:</b>	An estimate of sample size is not applicable, since it is an active extension study. Summary statistics will be prepared for demographic, safety and efficacy variables.

**2. LIST OF ABBREVIATIONS**

9-HPT	9-Hole Peg Test
ACTH	Adrenocorticotrophic Hormone
ADME	Absorption/Distribution/Metabolism/Elimination
AE	Adverse Event
AhR	Aryl Hydrocarbon Receptor
AI	Ambulation Index
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (SGPT)
ARR	Annualized Relapse Rate
AST	Aspartate Aminotransferase (SGOT)
AUC	Area Under the Concentration by Time Curve
BP	Blood Pressure
β-hCG	Beta-human Chorionic Gonadotropin
CA	Competent Authority
CAB	Clinical Advisory Board
CBC	Complete Blood Count
CCSVI	Chronic Cerebrospinal Venous Insufficiency
CHMP	Committee for Medicinal Product for Human Use
C <sub>max</sub>	Maximum Plasma Concentration
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSU	Clinical Supplies Unit
CT	Computed Tomography
CYP	Cytochrome P450
DLC	Dioxin-like Compound
DM	Data Management
DMC	Data Monitoring Committee
EAE	Experimental Autoimmune Encephalomyelitis
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
EU	European Union
FDA	Food and Drug Administration
FS	Functional Systems
GCP	Good Clinical Practice
g	gram
GdE	Gadolinium Enhancing

GFR	Glomerular filtration rate
GGT	Gamma Glutamyl Transpeptidase
HAV	Hepatitis A Virus
HBc	Hepatitis B core antigen
HCV	hepatitis C Virus
HDL	High Density Lipoprotein
hs-CRP	High-sensitivity C-reactive Protein
I3C	Indole-3-Carbinol
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IFN- $\beta$	Interferon-beta
Ig	Immunoglobulin
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-To-Treat
IV	Intravenous
IVIG	Intravenous Immunoglobulin
IVRS/ IWRS	Interactive Voice/Web Response System
L	Liter
LCM	Local Clinical Management
LDL	Low Density Lipoprotein
LKM	Liver Kidney Microsome
LSO	Local Safety Officer
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MFIS	Modified Fatigue Impact Scale
mg	Milligram
ml	Milliliter
MOA	Mechanism of Action
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
PASAT	Paced Auditory Serial Addition Task
PK	Pharmacokinetics
QA	Quality Assurance
RBC	Red Blood Cell (Count)
RDC	Remote Data Capture
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SF-36	Short-Form General Health Survey



Amended Protocol 02

SOP	Standard Operating Procedures
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TCDD	Tetrachloro-p-dibenzodioxin
T <sub>max</sub>	Time to Maximum Plasma Drug Concentration
ULN	Upper Limit of the Normal Range
US	United States
WBC	White Blood Cell
WPAI-GH	Work Productivity and Activities Impairment – General Health

### 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 MS 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-beta (IFN- $\beta$ ) 1a (Avonex<sup>®1</sup>, Rebif<sup>®2</sup>) or 1b (Betaseron<sup>®3</sup>, Extavia<sup>®4</sup>), glatiramer acetate (Copaxone<sup>®5</sup>), mitoxantrone (Novantrone<sup>®6</sup>), natalizumab (Tysabri<sup>®7</sup>; for patients non-responsive to other medications), and alemtuzumab (Lemtrada<sup>™8</sup>). Oral disease modifying treatments for RRMS include fingolimod (Gilenya<sup>®9</sup>), teriflunomide (Aubagio<sup>®10</sup>), and dimethyl fumarate (Tecfidera<sup>®11</sup>). Oral symptomatic treatment with dalfampridine (Ampyra<sup>®12</sup>) 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,

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<sup>1</sup> Avonex is a registered trademark of Biogen Idec

<sup>2</sup> Rebif is a registered trademark of EMD Serono, Inc

<sup>3</sup> Betaseron is a registered trademark of Bayer

<sup>4</sup> Extavia is a registered trademark of Novartis Pharmaceuticals

<sup>5</sup> Copaxone<sup>®</sup> is a registered trademark of Teva Pharmaceutical Industries Ltd.

<sup>6</sup> Novantrone is a registered trademark of Serono Inc.

<sup>7</sup> Tysabri is a registered trademark of Biogen Idec.

<sup>8</sup> Lemtrada is a registered trademark of Genzyme corporation

<sup>9</sup> Gilenya is a registered trademark of Novartis Pharmaceuticals

<sup>10</sup> Aubagio is a registered trademark of Genzyme corporation

<sup>11</sup> Tecfidera is a registered trademark of Biogen Idec

<sup>12</sup> Ampyra is a registered trademark of Acorda therapeutics

pericarditis and pleuritis) occurring during Phase 3 studies led to early termination of these studies.

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

Laquinimod demonstrates a predictable and linear pharmacokinetics (PK) profile (see Section 3.3.1) characterized by high plasma protein binding (>98%), high oral bioavailability (~90%), low oral clearance (~0.09 L/h), low apparent volume of distribution (~10 L) and long half-life (~80 h). 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- $\kappa$ B 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 CYP3A4-mediated biotransformation, resulting in a few hydroxylated and dealkylated minor metabolites which could undergo further glucuronidation. All circulating plasma human metabolites were formed in animal test species at adequate exposure levels. Laquinimod was shown to cause a marked decrease of CYP3A4 activity and is a strong inducer of CYP1A enzymes. CYP1A induction is a biomarker of activation of the Aryl

Hydrocarbon Receptor (AhR) transcription factor; activation of this pathway by laquinimod has been demonstrated.

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

### 3.2.3. Toxicology

The nonclinical safety program of laquinimod has encompassed separate investigations on vital organ systems, single and repeat dose toxicity in mice (duration up to 13 weeks), rats (duration up to 26 weeks), and dogs (duration up to 52 weeks), genotoxicity, carcinogenicity studies in p53<sup>+/-</sup> 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 (RBC) indices. In general, the severity of these effects was dose-related and toxicity was mostly reversible upon drug discontinuation. The nature of these toxic events allows adequate monitoring in the clinical setting (for details please refer to the laquinimod IB).

Laquinimod was neither mutagenic nor clastogenic in in vitro and in vivo assays. Laquinimod treatment resulted in the formation of micronuclei in vitro and in vivo through an aneugenic mechanism, with broad safety margin (>99) above the intended clinical dose of 0.6 mg/day.

The carcinogenicity program consisted of a 26-week study in transgenic p53<sup>+/-</sup> mice and a 2-year rat study. The study in transgenic p53<sup>+/-</sup> mice did not show an increase in treatment-related neoplastic findings at any tested dose. In the 2-year rat carcinogenicity study, increased incidence of uterine adenocarcinomas was observed in high dose female rats. It is the sponsor's position that this finding is likely due to a decrease in the incidence of prolactin secreting pituitary adenomas that was observed in this study. In contrast to rodents, in humans, prolactin is not a luteinizing hormone and does not affect the estrogen:progesterone ratio; therefore the mechanism proposed by the sponsor is not considered relevant to humans. A higher incidence of thyroid follicular cell adenomas was observed in high dose male rats. This lesion is considered to be related to laquinimod's induction of liver enzymes and consequently enhanced clearance of thyroid hormones in rats, a well-characterized rat-specific mechanism proposed by the sponsor, that is not considered relevant to humans. In addition, an increase in the incidence of oral cavity tumors was noted in mid and high dose female rats (2/60 in each group). The oral effects may relate to the AhR activation properties of laquinimod since similar lesions were seen following lifelong exposure of rats to other AhR activators. However, the incidence of oral cavity tumors in rats treated with laquinimod was lower than that seen with industrial chemicals such as 2,3,7,8-tetrachloro-p-dibenzodioxin (TCDD) ([NTP TR-521 2006](#)) and dioxin-like

compounds (DLCs), and was more similar to the incidence seen with the dietary ingredient indole-3-carbinol (I3C) found in cruciferous vegetables. Of note, the oral tumors seen with I3C were considered by the US National Toxicology Program as irrelevant for I3C risk assessment (NTP TR-584 2014). No increased incidence of oral tumors was seen in humans exposed to TCDD, indicating a species specific response in rats. Therefore, oral cavity tumors induced by laquinimod in rats after a lifelong exposure do not imply an elevated carcinogenicity risk in humans. Humans, in general, also seem to be less sensitive to AhR activation by laquinimod than rats, as shown by the differential gene expression profiles discussed in the IB.

A standard pre- and post-natal toxicity study and a follow-up investigational study in rats demonstrated urogenital malformations in female rat offspring exposed in utero to laquinimod at doses similar to the clinical dose of 0.6 mg/day based on exposure. A slight delay in puberty and reduction in fertility were noted in rat offspring exposed in utero to laquinimod at doses slightly higher than the clinical dose of 0.6 mg/day in humans. The mechanism leading to the malformations in rats is unknown. Induction of urogenital malformations in rodents has been reported for a variety of agents including sex hormones and the AhR agonist TCDD. Several studies were performed to investigate the potential hormonal modulating activity of laquinimod, but no such effects were demonstrated at clinically relevant levels. An AhR mediated effect cannot be excluded since it plays a distinct role in developmental processes in many experimental animals. However, the relevance to humans of the teratogenic effects seen in rodents is questionable. In a pre- and post-natal toxicity study in monkeys, the high dose level was associated with higher incidence of prenatal loss which limited the number of monkeys that could be evaluated, but there were no treatment-related malformations at doses up to 28-fold the expected plasma exposure at intended clinical dose of 0.6 mg/day.

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

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

In the planned clinical study, potential risks will be mitigated by careful screening of subjects, frequent and proactive monitoring of subjects and appropriate stopping rules. Furthermore, an independent data monitoring committee (DMC) is assigned to assess the data (see Section 21.2).

### **3.3. Clinical Experience**

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

#### **3.3.1. Clinical Pharmacology Studies**

Laquinimod is considered to have high oral bioavailability with linear, time independent and predictable 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. Laquinimod 0.6 mg 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] T1 lesions and cumulative new T<sub>2</sub> lesions) were met (Table 1).

**Table 1: ALLEGRO: Summary of Efficacy Results**

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

<sup>a</sup> 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)
<b>ARR</b>	17.7% (0.0746)	21.3% (0.0264)	25.9% (0.0067)	28.7% (0.0021)
<b>Brain atrophy</b>	27.6% (0.0001)	27.4% (<0.0001)	-10% (0.14)	-9% (0.14)
<b>EDSS progression (3 m confirmation)</b>	31.3% (0.06)	33.5% (0.04)	25.8% (0.13)	28.7% (0.09)
<b>EDSS progression (6 m confirmation)<sup>a</sup></b>	39% (0.0423) <sup>b</sup>	40.6% (0.0423 <sup>b</sup> )	26.6% (0.1686)	28.3% (0.1426)
<b>MSFC z-score</b>	77% (0.15)	77% (0.15)	66% (0.2)	66% (0.2)
<b>Cumulative number of GdE T1 lesions<sup>c</sup></b>	21.5% (0.07)	21.7% (0.062)	61.5% (<0.0001)	60% (<0.0001)
<b>Cumulative number of new T2 lesions<sup>c</sup></b>	16.5% (0.08)	18.7% (0.037)	51.1% (<0.0001)	52.3% (<0.0001)

<sup>a</sup> Post hoc analysis

<sup>b</sup> p-value calculated based on log rank test

<sup>c</sup> 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<sup>13</sup>]. In addition, treatment with laquinimod demonstrated reduction in brain atrophy: ALLEGRO: 32.8% [p<0.0001], BRAVO<sup>13</sup> : 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

<sup>13</sup> Results corrected for two MRI parameters found to be imbalanced at baseline. Original results were: EDSS: 31.3%, p=0.0628; Brain Atrophy: 27.6%, P=0.0001



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 (WBC) count increased, platelets decreased) and elevation of blood C-reactive protein (CRP) or fibrinogen levels; these laboratory changes are generally mild and asymptomatic.

The safety profile of laquinimod is provided in detail below.

Table 3 presents the list of possible adverse drug reactions.

The following definitions apply to the frequency terminology used hereafter:

- very common ( $\geq 1/10$ )
- common ( $\geq 1/100$  to  $< 1/10$ )
- uncommon ( $\geq 1/1000$  to  $< 1/100$ )
- rare ( $\geq 1/10000$  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**

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

<sup>a</sup> For liver enzyme elevations and anemia - see below.

<sup>b</sup> 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**

The percentages listed in the table below refer to all patients with normal values at baseline Test	Range of Increase	Placebo	Laquinimod 0.6 mg
<b>AST (IU/L)</b>		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%)
<b>ALT (IU/L)</b>		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%)
<b>GGT(IU/L)</b>		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%)

ULN = Upper limit of normal range; AST = aspartate aminotransferase; ALT = alanine aminotransferase ; GGT= Gamma Glutamyl 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 2.5x>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**

- Hemoglobin decrease/Anemia: Treatment with laquinimod has been associated with a mild, asymptomatic, non-progressive decrease of the hemoglobin level, which occurred early after initiation of treatment and was usually transient without cessation of therapy or need for anti-anemic therapy.
- Decreased platelets: Treatment with laquinimod has been associated with a generally mild decrease of the platelet count, without clinical manifestations.
- Increased WBC: Treatment with laquinimod has been associated with a generally mild increase of the total WBC count that was consistent across WBC subtypes, without clinical manifestations.

### **3.4.1.7. 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.

#### **Exposure to laquinimod during pregnancy must be avoided.**

To prevent such exposure, women who are of childbearing potential (for example women who are not postmenopausal or surgically sterilized) must practice an acceptable method of birth control (Section 8.2.6.2) 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 should be ascertained at every study visit.

In addition, regular pregnancy testing is required during the study. If pregnancy is suspected despite all recommended precautions (e.g., positive urine beta-human chorionic gonadotropin [ $\beta$ -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 two 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.

#### **4. STUDY OBJECTIVES**

- To make treatment with oral laquinimod 0.6 mg available to all subjects who participated in the MS-LAQ-302 study (regardless of their treatment assignment, whether oral or injectable) and who completed the Termination visit of this study according to the MS-LAQ-302 protocol as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS.
- To assess the long-term safety and tolerability of laquinimod 0.6 mg once daily in subjects with relapsing MS.
- To assess the long-term effects of laquinimod 0.6 mg on the disease course, as measured by clinical efficacy outcomes, which were evaluated in the MS-LAQ-302 study in this subject population.

##### **4.1. Ancillary Studies**

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

- The effect of general health and symptom severity on work will be assessed by the work productivity and activities impairment will be assessed by the General Health (WPAI-GH) questionnaire (see [Appendix J](#)) at months 0E [Baseline (Termination visit of the MS-LAQ-302 study)], 6E and then at every scheduled study visit thereafter, until Termination/Early discontinuation visit (this assessment will be performed in all subjects from United States [US] sites only).

## 5. STUDY DESIGN

### 5.1. Overview And Plan

This is a multinational, multicenter, open-label, single-assignment extension of the MS-LAQ-302 study, to evaluate the long-term safety, tolerability and effect on disease course of daily oral laquinimod 0.6 mg in subjects with relapsing MS.

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

Subjects completing the full duration of the double-blind MS-LAQ-302 study (completion of the Termination visit) (regardless of their treatment assignment in this study, oral or injectable treatment) according to the MS-LAQ-302 protocol will be offered the opportunity to enter into the open label extension MS-LAQ-302E study. In this open-label study they will be treated with laquinimod 0.6 mg once daily.

Scheduled in-clinic visits will be conducted at Baseline (month 0E; the Termination visit of MS-LAQ-302 will serve as the baseline visit of MS-LAQ-302E) and at months 1E, 2E, 3E, 6E and every 6 months thereafter, as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS. At this time point, subjects will be invited to attend a Termination visit.

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

As of the implementation of Protocol Amendment #1, the medical/neurological assessments of the subjects at each clinical site will no longer be performed differently since all the sites are now in study period 2. In this period, there will be no need for 2 separate physicians to assess the subjects in the MS-LAQ-302E study. Subjects participating in the MS-LAQ-302E study will be assessed by a single physician/Neurologist ("Study Physician/ Neurologist").

### 5.2. Revealing the MS-LAQ-302 Study Treatment Assignment during the Open-Label Study

The investigator may request the Sponsor to provide the original treatment allocation of the subject in the MS-LAQ-302 study (laquinimod 0.6mg or placebo, in case the subject was assigned to oral treatment). This will be possible only after transition to Period 2.

### 5.3. Rationale for Study Design, Dose and Population

The open-label extension MS-LAQ-302E study is designed to:

- Provide laquinimod 0.6 mg once daily to all subjects who successfully complete the double-blind, placebo-controlled MS-LAQ-302 study for as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS.



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

The 0.6 mg daily dose was selected, since this was the dose used in the double-blind, placebo-controlled MS-LAQ-302 study.

## 6. STUDY POPULATION

One thousand, three hundred and thirty-two (1332) subjects were randomized to the MS-LAQ-302 study. All subjects who complete the Termination visit of the MS-LAQ-302 study (according to the MS-LAQ-302 protocol), meet the eligibility criteria and sign an informed consent form will be enrolled to the MS-LAQ-302E study.

### 6.1. Inclusion Criteria

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

1. Subjects must have completed the Termination visit of MS-LAQ-302 (completion of all Termination visit activities) according to the MS-LAQ-302 protocol.
2. Women of child-bearing potential (for example women who are not postmenopausal or surgically sterilized) must practice two acceptable methods of birth control for the duration of the study and until 30 days after the last dose of study medication [acceptable methods of birth control in this open label extension phase include: intrauterine devices, barrier methods (condom or diaphragm with spermicide), and hormonal methods of birth control (e.g. oral contraceptive, contraceptive patch, and long-acting injectable contraceptive)].
3. Subjects must be willing and able to comply with the protocol requirements for the duration of the study.
4. Subjects must be able to comprehend, sign and date a written informed consent prior to entering the MS-LAQ-302E study.

### 6.2. Exclusion Criteria

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

1. Premature discontinuation from the MS-LAQ-302 study, for any reason.
2. Pregnancy [according to urine dipstick  $\beta$ -hCG test performed at Baseline (Month 0E) visit] or breastfeeding.
3. Subjects with clinically significant or unstable medical or surgical condition detected or worsened during the MS-LAQ-302 study, which preclude safe participation and completion of the MS-LAQ-302E study. Acute exacerbation of MS will not exclude participation in the MS-LAQ-302E study.
4. Use of inhibitors of CYP3A4 within 2 weeks prior to baseline visit (V0E, Month 0E).

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

may be able to re-enroll in the study after meeting inclusion/exclusion criteria in [Appendix E](#). 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 E](#)).

## 7. MEDICATIONS/THERAPIES – ALLOWED AND DISALLOWED

### 7.1. Allowed Concomitant Medications/Therapies

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

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

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

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

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

Clinical studies have shown laquinimod 0.6 mg to be a strong inducer of CYP1A2. Subjects taking drugs that are metabolized by CYP1A2 (examples listed in [Appendix D](#)) 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 D](#)) should be advised that plasma levels of these drugs could increase when combined with laquinimod.

### 7.2. Disallowed Concomitant Medications During Study

- Natalizumab (Tysabri<sup>®</sup>)
- Fingolimod (Gilenya)
- IFN- $\beta$  1a or 1b
- Dimethyl fumarate (Tecfidera)
- Glatiramer Acetate (Copaxone<sup>®</sup>)

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- Teriflunomide (Aubagio)
- Alemtuzumab (Lemtrada)
- Cladribine
- Rituximab
- Ocrelizumab
- Atacicept
- Belimumab
- Ofatumumab
- Inducers of CYP3A4 such as rifampin and carbamazepine (for more examples see [Appendix C](#)). Use of CYP3A4 inducers may result in reduced laquinimod plasma concentrations and may reduce its effectiveness.
- Moderate or strong inhibitors of CYP3A4; for example, ketoconazole and erythromycin (as listed in [Appendix C](#)) 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<sup>®</sup>)
- Oral and parenteral steroids (except if given as defined by protocol for treatment of a relapse as specified in Section 7.1)
- Adrenocorticotrophic hormone (ACTH)
- Chemotherapeutic agents
- Cytotoxic agents
- Cyclophosphamide
- IV Immunoglobulin (Ig)
- Plasmapheresis
- Any other experimental agents
- Other Immunosuppressive or immunomodulating agents

## **8. STUDY CONDUCT**

### **8.1. Study Period**



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

A month in the treatment period is defined as 30 days  $\pm$  4 days.

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

**Table 5: Study Task Flow Chart for Extension Phase**

Visit	V0E <sup>a</sup>	V1E	V2E	V3E	V4E	Every 6 months	Every 12 months	Every 24 months	Termination / Early Discontinuation	Unscheduled Visit <sup>b,c</sup>
Month	0E	1E	2E	3E	6E					
Informed Consent	X									
Eligibility Criteria	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Cardiovascular risk factor assessment and management <sup>d</sup>							X	X		
First Dose at Site	X <sup>e</sup>									
Physical Examination	X				X		X	X	X	X
Vital Signs	X <sup>f</sup>	X	X	X	X	X <sup>g</sup>	X <sup>g</sup>	X <sup>g</sup>	X <sup>g</sup>	X
ECG	X				X	X	X	X	X	X
Safety Laboratory Evaluation (CBC, Chemistry, markers of inflammation, estimated GFR)	X	X	X	X	X	X	X	X	X	X
Serum $\beta$ -hCG <sup>h</sup>	X				X	X	X	X	X	X
Urine $\beta$ -hCG <sup>h</sup> (on site)	X	X	X	X	X	X	X	X		X
Ascertaining use of effective contraception	X	X	X	X	X	X	X	X	X	X
Urine $\beta$ -hCG <sup>h</sup> (self check, at home)						EVERY 1 MONTH BETWEEN SCHEDULED VISITS				
Adverse Events	X	X	X	X	X	X	X	X	X	X
Neurological examination (EDSS/FS/AI/ 25 foot walk)	X				X	X	X	X	X	X
Evaluation of Relapse <sup>i</sup>	X	X	X	X	X	X	X	X	X	X
MSFC <sup>j</sup>	X				X	X	X	X	X	
Binocular Low-Contrast Visual Acuity	X				X	X	X	X	X	

Visit	V0E <sup>a</sup>	V1E	V2E	V3E	V4E	Every 6 months	Every 12 months	Every 24 months	Termination / Early Discontinuation	Unscheduled Visit <sup>b, c</sup>
Month	0E	1E	2E	3E	6E					
MFIS	X				X	X	X	X	X	
SF-36	X				X	X	X	X	X	
WPAI-GH (ancillary study, US sites only)	X				X	X	X	X	X	
Mandatory phone calls (pregnancy tests) <sup>k</sup>						 EVERY 1 MONTH BETWEEN SCHEDULED VISITS				
Mandatory phone call (general well-being, all subjects) <sup>l</sup>						 EVERY 3 MONTHS BETWEEN SCHEDULED VISITS				
Drug Compliance & Dispensing	X	X	X	X	X	X	X	X	X <sup>m</sup>	X
Termination Documentation and Notification of Early Termination									X	
Unscheduled Samples										X <sup>n</sup>

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]).

<sup>a</sup> The Termination visit of the MS-LAQ-302 study will serve as the Baseline visit of the MS-LAQ-302E study. Therefore, all activities, excluding Urine  $\beta$ -hCG (on site), informed consent, eligibility criteria and first dose at site are a part of the Termination visit of the MS-LAQ-302 study and therefore should not be repeated. However, in case there is a gap of more than 3 days between Termination visit day of the MS-LAQ-302 study and day on which the first dose of laquinimod 0.6mg is administered in the MS-LAQ-302E study, **all** baseline activities/assessment described above (those that should have been a part of the MS-LAQ-302 study Termination visit as well as the new ones) will have to be repeated in an unscheduled visit (on the day the subject will receive the first dose).

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

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

<sup>d</sup> In addition, an evaluation should take place as soon as possible for subjects already in the study, following approval of Amendment #2

<sup>e</sup> In case the subject took the last dose of the MS-LAQ-302 study on the Termination visit day, the first dose of the MS-LAQ-302E study will be taken at the site within 3 days from baseline visit day. The rest of the baseline visit activities will be performed at the original baseline visit day (Termination visit day of the MS-LAQ-302 study).

<sup>f</sup> Post-dose vital signs will be measured at Baseline and after 30 and 60 minutes, where as the pre-dose vital signs will be taken from the last measurement in the MS-LAQ-302 study. In case the subject takes the first dose of the MS-LAQ-302E study NOT at the Termination visit of the MS-LAQ-302 study, pre-dose vital signs should be measured as well. This is not relevant for the Termination/Early discontinuation visit.



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<sup>g</sup> Weight will be measured at all visits until Termination/Early discontinuation.

<sup>h</sup> For women of childbearing potential

<sup>i</sup> Relapse evaluation will be performed in scheduled as well as unscheduled visits as deemed necessary by the Investigator/Coordinator

<sup>j</sup> Within the MSFC evaluation, the PASAT and 9-HOLE Peg tests will be performed at months 0E (Baseline; Termination visit of the MS-LAQ-302 study), 6E and every 6 months, while the Timed 25-foot walk test will be performed each time a neurological evaluation is performed

<sup>k</sup> For women of child-bearing potential; to be performed within 72 hours after the scheduled home pregnancy test. The call will be documented in the source documents

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

<sup>m</sup> Only drug retrieval

<sup>n</sup> 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.

AE = adverse event, AI = ambulation index,  $\beta$ -hCG = beta-human chorionic gonadotropin, CBC = complete blood count, ECG = electrocardiogram, EDSS = Kurtzke's expanded disability status scale, FS = functional systems, GFR = glomerular filtration rate, MFIS = modified fatigue impact scale, MSFC = multiple sclerosis functional composite, PASAT: Paced Auditory Serial Addition Task, SF-36 = Short-Form General Health Survey, US = United States, WPAI-GH = Work Productivity and Activities Impairment – General Health

## 8.2. Detailed Study Plan

### 8.2.1. Baseline Visit (Month 0E) (Visit 0E) (Termination visit of the MS-LAQ-302 study) Procedures:

After completion of all procedures of the Termination visit of the MS-LAQ-302 study according to the MS-LAQ-302 protocol, and placing a call to the interactive voice response system (IVRS) to notify the subject's completion of the MS-LAQ-302 study, the subject will be offered to participate in the MS-LAQ-302E study. The subject will be informed about all aspects of the study, including scheduled study visits and activities, and must sign and date the informed consent form. A copy of the informed consent form must be given to the subject. Eligibility for participation in the MS-LAQ-302E study will be established by the investigator.

The Baseline visit of the MS-LAQ-302E open-label extension study will occur at the Termination visit of the MS-LAQ-302 study. Therefore, many of the activities/assessments of the Termination visit of the MS-LAQ-302 study will serve as the Baseline visit (Month 0E) procedures of the MS-LAQ-302E study.

The following list includes all Baseline (Month 0E) activities. These activities were performed under the scope of the Termination visit of the MS-LAQ-302 study and therefore should not be repeated, unless otherwise specified.

- Vital signs (temperature, pulse, blood pressure [BP] and weight)
- Physical examination
- Complete neurological examination including functional systems (FS), ambulation index (AI), 25 foot walk, EDSS
- Multiple Sclerosis Functional Composite (MSFC)
- The general health status and MS-related quality of life, will be assessed using the Short-Form general health survey (SF-36) subject-reported questionnaire (see [Appendix K](#))
- The effect of general health and symptom severity on work will be assessed using the WPAI-GH questionnaire (see [Appendix J](#)) (This assessment will be performed in all subjects from US sites only).
- Evaluation of a relapse
- Electrocardiogram (ECG)
- Review of concomitant medications
- AE recording

- Safety laboratory tests including:
  - Serum pregnancy test ( $\beta$ -hCG) for women of child-bearing potential. In case of positive result, the subject will not be eligible to participate in the extension and will be considered a screening failure for the extension phase.
  - Urinalysis
  - Hematology (Complete blood count [CBC], including differential)
  - Serum chemistry (including electrolytes, liver enzymes, direct and total bilirubin, pancreatic amylase and creatine phosphokinase [CPK]).
  - Markers of inflammation (serum conventional CRP and fibrinogen)
  - Subject-reported fatigue will be assessed by the Modified Fatigue Impact Scale (MFIS) (see [Appendix F](#))

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

New activities to be performed at Baseline<sup>a, b, c</sup> visit (Month 0E, Visit 0E) (not part of the MS-LAQ-302 Termination visit) are:

- Subjects will be given all the necessary supplies and detailed instructions for administration of IMP, which will be reviewed with the subject during the visit. In addition, subjects will be instructed to contact the study center if any questions or problems arise.
- Urine pregnancy test ( $\beta$ -hCG) for all women of child-bearing potential. In case of positive result, the subject will not be eligible to participate in the study.
- For all subjects who are female of child-bearing potential:
  - The use of effective contraception will be ascertained at each study visit (should be recorded in the source documents).

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<sup>a</sup> In case the subject took the last dose of the MS-LAQ-302 study on the Termination visit day, the first dose of the MS-LAQ-302E study will be taken at the site within 3 days from baseline visit day. The rest of the baseline visit activities will be performed at the original baseline visit day (Termination visit day of the MS-LAQ-302 study).

<sup>b</sup> In case the subject does NOT take the first dose of the MS-LAQ-302E study at the Termination visit of the MS-LAQ-302 study, pre-dose vital signs should be measured as well

<sup>c</sup> In case there is a gap of more than 3 days between Termination visit day of the MS-LAQ-302 study and day on which the first dose of laquinimod 0.6mg is administered in the MS-LAQ-302E study, **all** baseline activities/assessment described above (those that should have been a part of the MS-LAQ-302 study Termination visit as well as the new ones) will have to be repeated in an unscheduled visit (on the day the subject will receive the first dose).

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

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

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

Following approval of Global Amendment #2, 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 each scheduled visit:

- Vital signs (temperature, pulse, BP).
- Review concomitant medications (ensuring no disallowed medication is being used).
- Record of AEs.
- Evaluation of relapse.
- Subject compliance (IMP accountability).
- Review instructions on IMP administration and dispensing.
- For all subjects who are female of child-bearing potential:

- The use of effective contraception will be ascertained at each study visit (should be recorded in the source documents)
- Subjects will be instructed during each visit about the teratogenicity and potential delayed risks for a child exposed in uterus to laquinimod
- Subjects will be reminded about (should be recorded in the source documents) importance of stopping the study drug and informing the site in any case of suspected pregnancy (positive home urine test result, delay of menstruation or any other reason suggesting pregnancy) and importance of performing the home pregnancy urine tests every one month (starting after visit Month 3E)
- Safety laboratory tests:
  - Serum pregnancy test ( $\beta$ -hCG) for women of child-bearing potential
  - Urine pregnancy test ( $\beta$ -hCG) for women of child-bearing potential. In case of positive result, study drug should not be dispensed, until results of serum  $\beta$ -hCG test is available and pregnancy is either confirmed or excluded (see [Appendix E](#)). In case of suspected pregnancy, the rest of the visit activities should be performed as well
  - Hematology (CBC with differential)
  - Serum chemistry (including electrolytes, liver enzymes, direct and total bilirubin, pancreatic amylase, CPK, and estimated GFR)
  - Markers of inflammation (serum conventional high-sensitivity C-reactive protein [hs-CRP] and fibrinogen).
- IVRS call to obtain pack number.

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

- Complete neurological examination including FS, EDSS, AI and Timed 25 Foot walk.
- MSFC.
- Binocular low-contrast visual acuity assessment, using 100%, 2.5% and 1.25% contrast charts [Sloan letter or Tumbling E (see [Appendix H](#) and [Appendix I](#))].
- Subject-reported fatigue will be assessed by the MFIS (see [Appendix F](#)).
- The general health status and MS-related quality of life, will be assessed using the SF-36 subject-reported questionnaire (see [Appendix K](#)).

- The effect of general health and symptom severity on work will be assessed using the WPAI-GH questionnaire (see [Appendix J](#)) (This assessment will be performed in all subjects from US sites only).

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

- Physical examination will be performed at months 6E (Visit 4E), 12E (Visit 5E) and then every 12 months thereafter (every other scheduled visit).
- ECG will be performed at month 6E (visit 4E) and at every scheduled visit thereafter.
- Weight will be measured at all visits.
- Evaluation and management of major modifiable cardiac risk factors (eg, diabetes, high blood pressure, hyperlipidemia, tobacco smoking) will be performed every 12 months, with referral to treatment and follow-up in a suitable clinic if needed. In addition, an evaluation should take place as soon as possible for subjects already in the study, following approval of Amendment #2.
- The sequence of assessments should be as follows:
  - SF-36 subject-reported questionnaire (see [Appendix K](#))
  - MFIS (see [Appendix F](#))
  - WPAI-GH questionnaire (see [Appendix J](#)) (This assessment will be performed in all subjects from US sites only)
  - The 9-Hole Peg Test (9-HPT) and Paced Auditory Serial Addition Task (PASAT) components of the MSFC (Timed 25 Foot walk may be performed later) (see [Appendix G](#))
  - The rest of the visit activities, as depicted above.
- Starting from Month 3E (Visit 3E), the following actions will be taken for female subjects of child-bearing potential:
  - The subject will be provided with home pregnancy urine  $\beta$ -hCG test kits and will be guided how to perform the test. The site staff will schedule the home test to be performed every  $28 \pm 2$  days.
  - In order to verify whether the test has been performed and to record the result of the test (see [Appendix E](#)), a mandatory phone call will be performed by the Study Neurologist/ Physician or by the site's nurse/ study coordinator within 72 hours after the test was scheduled to be performed. In case of a suspected pregnancy, 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.

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

### **8.2.3. Termination/ Early Discontinuation**

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

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

Early discontinuation is defined as any withdrawal from the study prior to the completion of the treatment period. The treatment period is defined between Month 0E visit (Visit 0E, Baseline) (Termination visit of the MS-LAQ-302 study) (after administration of the first dose) and Termination visit, included. Subjects who are discontinued from study treatment will be encouraged to continue all scheduled visits and procedures until completion of the study (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, and GFR estimation [including body weight measurement]).

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

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

- Termination/ Early discontinuation visit form
- Last visit that the subject attended

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

- Vital signs (temperature, pulse, BP, weight)
- Physical examination
- Safety laboratory tests:
  - Serum pregnancy test ( $\beta$ -hCG) for women of child-bearing potential
  - Hematology (CBC with differential)

- Serum chemistry (including electrolytes, liver enzymes, direct and total bilirubin, pancreatic amylase, CPK, and estimated GFR)
- Markers of inflammation (serum conventional hs-CRP and fibrinogen)
- ECG
- Review concomitant medications. Note: moderate/strong CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered. For information on the use of CYP1A2 substrates following laquinimod cessation, please refer to the laquinimod IB.
- Record of AEs
- If an AE is still ongoing, or a new AE is present at the termination visit, it will be followed until resolution or until it is considered stable or chronic and will be recorded in the subject's source documents and in the eCRF.
- Complete neurological examination including FS, AI, EDSS and Timed 25 Foot walk
- MSFC
- For all subjects who are female of child-bearing potential:
  - The use of effective contraception will be ascertained (should be recorded in the source documents) and 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 teratogenicity and potential delayed risks for a child exposed in uterus to laquinimod
  - Subjects will be reminded about (should be recorded in the source documents) importance of stopping the study drug and informing the site in any case of suspected pregnancy (positive home urine test result, delay of menstruation or any other reason suggesting pregnancy)
- Binocular low-contrast visual acuity assessment, using 100%, 2.5%, and 1.25% contrast charts [Sloan letter or Tumbling E (see [Appendix H](#) and [Appendix I](#))]
- Evaluation of relapse
- Subject-reported fatigue will be assessed by the MFIS (see [Appendix F](#))
- The general health status and MS-related quality of life, will be assessed using the SF-36 subject-reported questionnaire (see [Appendix K](#))



- The effect of general health and symptom severity on work will be assessed using the WPAI-GH questionnaire (see [Appendix J](#)) (This assessment will be performed in all subjects from US sites only)
- Subject compliance (IMP accountability)
- IVRS call to report subject's Termination/Early discontinuation

#### **8.2.4. Early Treatment Discontinuation**

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

An early termination visit should be completed for all subjects who prematurely discontinue from the study and do not agree to or cannot continue all scheduled visits and procedures. It includes subjects who took at least one dose in the MS-LAQ-302E study.

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

##### **8.2.4.1. Criteria for Early Treatment Discontinuation**

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

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

## 10. Death

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

### **8.2.5. Post Early Discontinuation Follow-Up Visit**

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

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

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

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

The following procedures will be performed during this visit:

- Mandatory procedures:
  - Vital signs
  - Review of concomitant medications
  - Evaluation of AEs
  - Pregnancy test (serum hCG test only; for women of child bearing potential)
- Optional procedures:
  - Evaluation of a suspected relapse/follow-up
  - ECG
  - Physical examination
  - Neurological examination
  - Safety laboratory tests
  - Chest X-ray

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## 8.2.6. Safety Stopping Rules

### 8.2.6.1. Liver Enzymes

In any increase of ALT or AST to  $\geq 2$  times ULN the “Guidance on Safety Monitoring” (see [Appendix E](#)) 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 E](#):

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

### 8.2.6.2. Pregnancy

Pregnancy reports should be forwarded to the Pharmacovigilance for data-entry to the global safety database. This includes also normal pregnancies without AE. The pregnancies reporting procedure should be the same as the SAE reporting procedure.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defect, congenital abnormalities or maternal and newborn complications. Pregnancy follow-up should be recorded on a specific eCRF provided by Local Clinical Trial Management.

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.

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 beta  $\beta$ -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 (based on a positive pregnancy test, delay of menstruation or any other reason to suspect 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  $\beta$ -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 20 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 11).

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

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

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

### **8.2.6.3. Cancer**

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

#### **8.2.6.4. Liver Impairment**

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

#### **8.2.6.5. 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<sup>2</sup>, 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<sup>2</sup>), the subject should stop study medication permanently.

#### **8.2.7. Replacement of Withdrawn Subjects**

Not applicable.

#### **8.2.8. Temporary Discontinuation of Study Drug Treatment**

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

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

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

#### **8.2.9. Unscheduled Visit**

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

The reasons for the unscheduled visit may be:

- Appearance of a new AE or an AE follow-up
- Change in concomitant medications
- Possible relapse
- Relapse follow-up
- Laboratory follow-up

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- Post early-discontinuation follow-up visit (see Section 8.2.5)
- IMP dispensing, accountability and/or replacement
- Subject compliance
- Delayed baseline visit
- Other (should be specified)

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

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

- Mandatory Unscheduled Visit Procedures
  - Vital signs
  - Evaluation of AEs
- Optional Unscheduled Visit Procedures
  - Evaluation of a suspected relapse/follow-up
  - ECG
  - Physical examination
  - Neurological examination
  - Safety laboratory tests (including estimation of GFR)
  - In case of drug dispensing/replacement call IVRS to obtain a pack number
  - IMP accountability
  - Subject compliance
  - Review of concomitant medications
  - For female subjects of child-bearing potential, serum or urine  $\beta$ -hCG test may be performed

- Female subjects of child-bearing potential will be questioned to ascertain use of effective contraception and will be reminded about (should be recorded in the source documents):
  - The importance of contraception
  - Importance of stopping the study drug and informing the site in any case of suspected pregnancy (positive urine  $\beta$ -hCG test result, delay of menstruation or any other reason suggesting pregnancy)
  - Importance of performing the home pregnancy urine tests every one month (starting after visit Month 3E)

### **8.2.9.1. Unscheduled Samples**

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

- urgent safety laboratory test panel (see Section [10.2.3.1](#))
- pharmacokinetic blood sample
- sample for potential biomarker analysis

#### **8.2.9.1.1. Unscheduled Pharmacokinetic Samples**

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

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

#### **8.2.9.1.2. Unscheduled Biomarker Samples**

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

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

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

**8.2.9.2. Visits during Relapses (Scheduled and Unscheduled)**

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

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

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

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

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

**8.2.9.2.1. Relapse Follow-up:**

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

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

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



## **9. INVESTIGATIONAL MEDICINAL PRODUCTS/STUDY DRUGS**

### **9.1. Treatment Administered**

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

Capsules should be swallowed with a glass of water.

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

### **9.2. Method of Assigning Subjects Numbers**

The same randomization number which was used to identify a certain subject in the MS-LAQ-302 study will serve this purpose in the MS-LAQ-302E study as well. At baseline (month 0E, visit 0E) (Termination visit of the MS-LAQ-302 study), the investigator will enter the subject's number (the same as was used in the MS-LAQ-302 study) to the IVRS in order to dispense the study drug.

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

### **9.3. Description of Investigational Medicinal Product/Study Drug**

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

### **9.4. Packaging and Labeling**

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

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

- Each bottle will be identified by a unique bottle number.
- The label on the bottles will include a fixed information section (to include the product name, storage conditions, instructions etc.) and variable information section.

- For all countries except Germany, the fixed information section will be a multi lingual booklet fixed on the bottle. It will bear information such as the study number, dosage, and directions for use, storage conditions and precautions. This part will be translated to all languages and meet all regulatory demands required for all participating countries. The front cover will contain an index to guide the subject to the relevant page.
- Due to local regulatory requirements, for Germany only, this section will be a single panel label in German that will contain a fixed part and a tear off section.
- The variable information section will include 3 parts: One detachable part, which will be attached to the subject's file upon bottle dispensing, one part to remain on the bottle and the third may be used according to local needs (pharmacy, prescription, etc). The variable information section will include the following variable data: batch number, bottle number, and expiration date (all to be pre-printed) and blank fields for the dispensing investigator's name, visit number and subject number. These blank fields will be manually filled-in by the Investigator upon provision of bottle to the subject.

## **9.5. Distribution and Shipment**

Distribution and shipment of IMPs will be performed by a Contract Research Organization (CRO), according to the distribution guidelines. IVRS will manage supply at depots and sites for all countries except Germany. For Germany, the IVRS will not be used and each site's clinical research associate (CRA) will request supplies for initial and re supply shipments. The supplies will be ordered in accordance with the 'Guidelines for demands planning and inventory management policy at site.

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

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

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

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

## **9.6. Storage, Dispensing and Return**

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

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

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

Apart of Termination visit, the IMP bottles will be dispensed to the subject at the study site at each study visit starting at baseline visit (Month 0E; Termination visit of the MS-LAQ-302 study). The bottles will be assigned to subjects by using an IVRS/IWRS. After assigning a bottle number to the subject, the site personnel should fill in the subject's number, the visit number and the dispensing investigator's name on the label of the dispensed bottle as well as on the detachable parts that would be attached to the subject's file.

At each visit from baseline (Month 0E; Termination visit of the MS-LAQ-302 study) to Month 3E visit the subject will receive 1 bottle of IMP (baseline, Month 1E and Month 2E). At visit month 3 the subject will receive 3 bottles of IMP. From visit month 6 onward the subject will receive 6 IMP bottles according to visit duration, an amount that will suffice until the following scheduled dispensing visit.

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

### **9.7. Verification of Compliance With Treatment Regimen**

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

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

### **9.8. Accountability and Compliance**

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

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

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

## 10. ASSESSMENT METHODS

### 10.1. Efficacy Assessment Methods

#### 10.1.1. On-Study Relapse Evaluation & Determination

- Subjects will be instructed to telephone their study site within 48 hours should any symptoms suggestive of a relapse appear.
- The Study Neurologist/Physician will evaluate the subject once any symptom suggestive of a relapse occurs.
- In case of a suggestive relapse during a scheduled or unscheduled visit in:
  - The evaluation of symptoms as well as the neurological evaluations/ EDSS will be made by the Study Physician/Neurologist.
  - Based on the assessment of symptoms and the EDSS/FS evaluation, the Study Physician/Neurologist will decide whether a subject experienced a relapse and will treat the subject as needed.
- In any case, the neurological evaluation of the subject by the Study Physician/Neurologist will be performed within 7 days of symptoms onset, conditional upon a symptomatic period of  $\geq 48$  hours.
- In the case of an ongoing or just-started relapse at the study Termination/Early discontinuation visit, subjects will be followed up until relapse stabilization (see Section 8.2.9.2.1).

#### 10.1.2. Neurological Evaluations

A complete neurological assessment will be performed at Months 0E [Baseline (Termination visit of the MS-LAQ-302 study)], 6E and every 6 months thereafter until Termination/Early discontinuation of the study. Every effort should be made to ensure that the same Neurologist/Physician performs the neurological assessment at all visits for a particular subject.

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

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

**10.1.3. MSFC**

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

The PASAT and 9-HPTs will be performed at Months 0E [Baseline (Termination visit of the MS-LAQ-302 study)], 6E and every 6 months (every scheduled visit) thereafter, until Termination/Early discontinuation visit.

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

[Appendix G](#) presents the instructions for administering the MSFC.

**10.1.4. Modified Fatigue Impact Scale (MFIS)**

Subject-reported fatigue will be assessed by the MFIS at months 0E [Baseline (Termination visit of the MS-LAQ-302 study)], 6E and every 6 months (every scheduled visit) thereafter, until Termination/Early discontinuation visit.

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

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

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

**10.1.5. Binocular Low- Contrast Visual Acuity**

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

The low-contrast visual acuity will be assessed binocularly at Months 0E [Baseline (Termination visit of the MS-LAQ-302 study)], 6E and every 6 months (every scheduled visit) thereafter, until Termination/Early discontinuation visit, along with the MSFC assessments. At each visit, the letter acuity will be captured using 100%, 2.5% and 1.25% contrast charts, from a distance of 2

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

[Appendix H](#) and [Appendix I](#) present the instructions for administering the binocular low-contrast visual acuity test.

#### **10.1.6. The General Health Status: Short-Form General Health Survey (SF-36)**

The general health status will be assessed by the SF-36 (see [Appendix K](#)) subject-reported questionnaire at months 0E [Baseline (Termination visit of the MS-LAQ-302 study)], 6E and every 6 months (every scheduled visit) thereafter, until Termination/Early discontinuation visit. The SF-36 is a generic, self-administered health-related quality of life instrument. In this study the instrument will be self-administered during the visit.

The SF-36 has been proven to be valid and reliable in a large number of indications (e.g., cardiovascular disease, low back pain, diabetic foot ulcers, total knee replacement and dialysis) and subject populations. It was developed in the US and was constructed such that its 36 questions represent 8 of the most important health concepts. The 8 domains of the SF-36 are: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. In addition, a single question assesses reported health transition. In addition to the 8 SF-36 domains, 2 summary scores can be evaluated: the physical health component summary score and the mental health component summary score. The SF-36 is the most widely used measure of health-related quality of life in relapsing-remitting MS and can usually be completed in 5 to 10 minutes.

#### **10.1.7. Ancillary Study: Economic Impact: The Work Productivity and Activities Impairment (WPAI-GH) Questionnaire (Ancillary Study, US sites only):**

The WPAI-GH was developed for assessing productivity losses by measuring the effect of general health and symptom severity on work as well as usual activity productivity. The WPAI-GH instrument consists of 6 questions that ask the subject the number of hours missed from work and usual activities as well as the number of hours in which work or usual activities were limited over the past 7 days. The instrument is self-interview and takes about 5 minutes to complete.

This questionnaire will be administered at months 0E [Baseline (Termination visit of the MS-LAQ-302 study)], 6E and every 6 months (every scheduled visit) thereafter, until Termination/Early discontinuation visit. This assessment will be performed in all subjects from US sites only.

## **10.2. Safety Parameters**

### **10.2.1. Adverse Events**

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

**10.2.1.1. Protocol-Defined Adverse Events for Expedited Reporting**

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

**10.2.2. Abdominal Computed Tomography Scan**

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

**10.2.3. Safety Laboratory Evaluations**

Unless specified otherwise all laboratory testing will be performed by a central laboratory facility. The following tests will be performed: (except the tests requiring close follow up due to safety stopping rules specified in Section 8.2.6 and in the Safety Monitoring Guidance [Appendix E](#)).

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

- Serum Chemistry
  - Glucose
  - Creatinine (including estimation of GFR)
  - Bilirubin (direct and total)
  - Urea
  - AST (SGOT)
  - ALT (SGPT)
  - GGT
  - Total Protein
  - Albumin
  - hs-CRP
  - CPK
    - In case of abnormal CPK result: troponin and CPK-MB will be tested



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- In case of CPK > 2000 U/L urine myoglobin will be tested and the following tests will be repeated: CPK, CPK-MB, blood urea nitrogen, creatinine, electrolytes including potassium, calcium, phosphate, hs-CRP and fibrinogen
- Alkaline Phosphatase (ALP)<sup>a</sup>
- Pancreatic Amylase
- Lipase will be tested in case of abnormal pancreatic amylase results (see [Appendix E](#) for guidance on monitoring subjects with elevated pancreatic amylase levels)
- Electrolytes
  - Sodium
  - Potassium
  - Calcium
  - Phosphorous
- Coagulation
  - Fibrinogen

INR (to be performed in local laboratory, only if required according to Safety Monitoring Guidance, [Appendix E](#)).

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

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

- Hematology
  - Hemoglobin

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<sup>a</sup> Those tests may also be performed in a local lab according to the Safety Monitoring Guideline.

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- Mean Corpuscular Hemoglobin (MCH)
- Mean Corpuscular Volume (MCV)
- MCHC
- Hematocrit
- RBC count
- WBC count + differential
- Platelet count
- Serology (to be performed only in a confirmed abnormality of liver enzymes, according to [Appendix E](#)):
  - Anti-hepatitis A virus (HAV) IgM antibodies
  - Hepatitis B Surface antigen
  - Anti- hepatitis B core antigen (HBc) IgM antibodies
  - Anti- hepatitis C virus (HCV) IgG antibodies
  - Anti-nuclear antibodies
  - Anti-Smooth Muscle (Sm) antibodies
  - Anti-Liver-Kidney Microsomes (LKM)-1 antibodies

**10.2.3.1. Urgent Safety Laboratory Panel**

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

The following tests (and others, if required) will be performed on these samples:

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

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#### **10.2.4. Vital Signs and Weight**

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

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

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

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

#### **10.2.5. ECG**

ECG will be performed at months 0E [Baseline (Termination visit of the MS-LAQ-302 study)] and every 6 months thereafter, until Termination/Early discontinuation visit.

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

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

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

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

#### **10.2.6. Physical Examination**

Physical examination will be performed at months 0E [Baseline (Termination visit of the MS-LAQ-302 study)], 6E, 12E and then every 12 months thereafter, until Termination/Early discontinuation visit.

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

#### **10.2.7. Glomerular Filtration Rate Estimation**

Significant changes in laquinimod exposure, in particular in terms of unbound drug fraction, are predicted in patients with moderate and severe renal impairment (see Section 3.3.1).

Consequently, GFR will be estimated at all visits to monitor renal function in the study in order to identify subjects with potentially impaired laquinimod clearance. Subjects with a confirmed

GFR  $\leq 60$  mL/min/1.73 m<sup>2</sup> 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<sup>2</sup>), the subject should stop study medication permanently (see Section 8.2.6.5).

#### **10.2.8. Cardiovascular Risk Assessment and Management**

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

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

## 11. SAFETY AND PHARMACOVIGILANCE

### 11.1. Adverse Event

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

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

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

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

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

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

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

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

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

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

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

TERM	DEFINITION	CLARIFICATION
No Reasonable Possibility	This category applies to those adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those adverse events, which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	<p>An adverse event may be considered as “No Reasonable Possibility” if it is clearly due to extraneous causes or when (must have two):</p> <p>It does not follow a reasonable temporal sequence from the administration of the test drug.</p> <p>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.</p> <p>It does not follow a known pattern of response to the test drug.</p> <p>It does not reappear or worsen when the drug is re-administered.</p>
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.	<p>An adverse event may be considered as “Reasonable Possibility” if or when (at least two of the following):</p> <p>It follows a reasonable temporal sequence from administration of the drug.</p> <p>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.</p> <p>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.</p> <p>It follows a known pattern of response to the test drug.</p>

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.

## 11.2. Serious Adverse Event

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

- death
- life-threatening
- requires hospitalization or prolongs existing inpatients’ hospitalization
- results in persistent or significant disability or incapacity

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- results in a congenital abnormality or birth defect
- an important medical event which requires medical intervention to prevent any of the above outcomes

**Important medical events** are those which may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; resulting in an AE will normally be considered serious by this criterion.

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

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

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

### **11.2.1. SAE Reporting**

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

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

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**SAE originated 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



**SAE originated in Canada will be sent to:**

Teva Canada safety mailbox



**SAE originated in Germany will be sent to:**

Teva Germany safety mailbox



Only in the event of difficulty transmitting the form via email, send the form via fax, or contact the sponsor's study personnel identified above for further instruction. Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the site within 24 hours of the information becoming available to the CRO.

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

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

1. Investigator Name and Center Number
2. Subject Number
3. Clinical Event
  - a. description
  - b. date of onset
  - c. severity
  - d. treatment



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- e. relationship to study drug (causality)
  - f. action taken regarding study drug
4. If the AE results in Death
    - a. cause of death (whether or not the death was related to study drug)
    - b. autopsy findings (if available)
  5. Medical History case report form (CRF) (copy)
  6. Concomitant Medication CRF (copy)
  7. Any relevant reports (laboratory, discharge, X-ray, etc)

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

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

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

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

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

## **12. STATISTICAL METHODOLOGY**

A total of up to 1332 subjects, who were enrolled in study MS-LAQ-302 are expected to be recruited into this study.

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

### **12.1. Sample Size Rationale**

Subjects that completed the full double-blind treatment period of protocol MS-LAQ-302 will be eligible for inclusion in this trial. MS-LAQ-302 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 1332 subjects.

### **12.2. Randomization Procedure**

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

### **12.3. Subjects Analysis Sets**

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

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

### **12.4. Definition of baseline values**

The last observed values from study MS-LAQ-302 will serve as the baseline values for this study.

### **12.5. Efficacy Assessment**

The statistical analyses of this study will be exploratory in nature. Continuous variables will be presented by descriptive statistics (mean, standard deviation, minimum, median and maximum values), for the whole study population, as well as by original treatment group in study MS-LAQ-302. For categorical variables, counts and percentage from total subject population will be tabulated, as well as counts and percentages by original treatment group in study MS-LAQ-302.

## **12.6. Safety And Tolerability Assessments**

### **12.6.1. Data presentation**

All data summary tables will be presented for the whole study population, as well as by original treatment group in study MS-LAQ-302.

### **12.6.2. 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 gender, maximal severity, maximal outcome and maximal relationship to the tested drug.

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

### **12.6.3. Laboratory Data**

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

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

### **12.6.4. ECG**

Distribution of Subjects by Investigators ECG Interpretation will be presented.

The ECG interpretation of the investigators will be individually listed.

### **12.6.5. Vital Signs**

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

Incidence of measurements of potential clinical significance will be provided.

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

### **12.6.6. Drug Tolerability & Drop-Out Assessment**

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

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

## **13. REGULATORY AND ETHICAL ISSUES**

### **13.1. Compliance with Regulations Applicable to Clinical Trials**

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

### **13.2. Informed Consent**

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

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

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

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

### **13.3. Subject Confidentiality**

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

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

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

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

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

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

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

### **13.5. Protocol Amendments**

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

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

### **13.6. Declaration of the End of the Clinical Trial**

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

For those countries outside EU local regulations will be followed.

### **13.7. Liability And Insurance**

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

## **14. DOCUMENTATION**

### **14.1. Study File and Site Documents**

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

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

### **14.2. Study Documents Supplied by the Sponsor**

The Sponsor will supply the investigator with the following items:

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

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

### **14.3. Maintenance and Retention of Records**

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

- Investigators will be instructed to retain all study records required by Teva and regulatory authorities in a secure and safe facility with limited access for one of the following time periods based on notification from Teva
- A period of at least two years from last marketing authorization and notification from Sponsor
- Or a period of at least two years after discontinuation of clinical development of the investigational product as confirmed by Teva
- Or longer if required by local regulations

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

## 15. DATA HANDLING

### 15.1. Data Collection via Remote Data Capture (RDC)

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

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

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

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

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

Each entered CRF must be approved by the Site Investigator on a per-visit basis and verified against the subject's source documents by the CRA/monitor. Each entry will be monitored by the CRAs and the DM personnel. Once all the CRFs for a subject have been approved, verified, reviewed and cleaned, the subject's CRFs will be locked. Site Investigators, Site Coordinators, CRAs, DM personnel, Medical Monitors and quality assurance (QA) personnel will be trained by authorized Teva staff on the use of the RDC<sup>®</sup> 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.
- DM: data updating, discrepancy handling, data locking



- QA: read only for data audit
- Read Only: browsing of data only

## 15.2. Discrepancy Handling

The internal consistency and data integrity of the study database are defined by a validated set of rules. A deviation from this set of pre-defined computerized rules creates a database discrepancy which can be handled using the RDC<sup>®</sup> application DM 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<sup>®</sup> application discrepancy management facility is fully supported by an accepted regulatory audit trail of procedures and logs.

## 15.3. Data Correction

Data correction can also be performed using the validated RDC<sup>®</sup> 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.

## 15.4. Data Extract

The Oracle Clinical<sup>®</sup> system stores the data in generic tables. The data is extracted from Oracle Clinical<sup>®</sup> to SAS<sup>®</sup> 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 DM and data analysis purposes.

## 15.5. Source Documents

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

## 15.6. Electronic CRF

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

## **15.7. Additional Documents and Records**

Subject Screening and Assignment Log – A listing of all subjects who signed the informed consent and entered the MS-LAQ-302E study.

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

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

## **16. QUALITY ASSURANCE AUDITS**

### **16.1. Good Clinical Practice**

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

### **16.2. Quality Laboratory Standards**

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

### **16.3. Quality Assurance Program**

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

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

### **16.4. Regulatory Inspections**

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

## **17. STUDY MONITORING**

### **17.1. Monitors/CRAs and Monitoring Visits**

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

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

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

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

### **17.2. Primary Source Documents**

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

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

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

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

## 18. 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.

### 18.1. 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.

## **18.2. 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.

## **18.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint**

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

## **18.4. 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.

## **19. USE OF INFORMATION AND PUBLICATION**

### **19.1. 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 (sixty) 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.



## **20. STUDY PERSONNEL**

### **20.1. Investigative Site**

#### **20.1.1. The Principal Investigator**

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

#### **20.1.2. The Study Physician/Neurologist**

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

#### **20.1.3. Study Coordinator or Designee**

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

### **20.2. The Sponsor**

#### **20.2.1. Global Clinical Leader**

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

#### **20.2.2. Clinical Operations Manager**

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

#### **20.2.3. Data Management & Biostatistics**

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

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

#### **20.2.4. Local Clinical Management**

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

#### **20.2.5. Clinical Research Associate/Monitor**

The CRA/monitor is responsible for monitoring the conduct of the study at the study centers. Monitoring visits will be arranged in advance, at a mutually acceptable time, with site personnel. Refer to Section 17.1 in this protocol for detailed monitoring activities.

#### **20.2.6. Global Drug Safety and Pharmacovigilance**

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

#### **20.2.7. Medical Monitor**

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

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

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

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

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

## **21. STUDY COMMITTEES**

### **21.1. Steering Committee**

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

### **21.2. Data Monitoring Committee (DMC)**

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

The DMC responsibilities are:

- To review the progress of the trial and the accumulation of data, both periodically and on an ad-hoc basis, in order to ensure subjects' welfare.
- To oversee the emerging safety data of the study.
- To review efficacy data, as deemed necessary.
- To assess whether there is any basis upon which to recommend modification or premature termination of the study.

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

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

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

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

Amended Protocol 02

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

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

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

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

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

### **21.3. Clinical Advisory Board (CAB)**

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

The committee's responsibilities will include involvement in:

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

### **21.4. Publication Committee**

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

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

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

This plan will determine the publication policy of the study outcomes and recommend on the main publishers. The plan will be consistent with Teva policy on use of confidential information (see Section 19.1).

## 22. INVESTIGATOR'S AGREEMENT

**TEVA Pharmaceutical Industries, Ltd.**

**Protocol No. MS-LAQ-302E**

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

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

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

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

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Principal Investigator's name

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Teva Representative's name

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Signature

---

Signature

---

Date

---

Date

---

Institution

## 23. REFERENCES

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

Neuhaus O, Archelos JJ, Hartung HP. Immunomodulation in multiple sclerosis: from immunosuppression to neuroprotection. *Trends Pharmacol Sci* 2003;24:131-138.

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

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

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

## **24. RATIONALE FOR PROTOCOL AMENDMENT AND SUMMARY OF CHANGES**

### **24.1. Global Amendment #2**

At the time of issuance of this amendment there are 714 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 re-consented 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

Amended Protocol 02

- 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, ascertaining use of effective contraception at termination/early discontinuation has been added to make consistent with the text

These changes did not alter the study population or endpoints.

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

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



Original text with changes shown	New wording	Reason/Justification for change
<b>TITLE PAGE</b>		
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
<b>Section 3.1.1. General</b>		
Authorized disease-modifying drugs for Relapsing Remitting Multiple Sclerosis (RRMS) given by injection include interferon-beta (IFN-β) 1a (Avonex <sup>®</sup> , Rebif <sup>®</sup> ) or <del>interferon-beta</del> 1b (Betaseron <sup>®</sup> , Extavia <sup>®</sup> ), glatiramer acetate (Copaxone <sup>®</sup> ), mitoxantrone (Novantrone <sup>®</sup> ), <del>and</del> natalizumab (Tysabri <sup>®</sup> ; for patients non-responsive to other medications), and alemtuzumab (Lemtrada <sup>™</sup> ). Oral disease modifying treatments for RRMS include fingolimod (Gilenya <sup>®</sup> ), teriflunomide (Aubagio <sup>®</sup> ), <del>and</del> dimethyl fumarate (Tecfidera <sup>®</sup> ) <del>and alemtuzumab (Lemtrada<sup>™</sup>)</del> .	Authorized disease-modifying drugs for Relapsing Remitting Multiple Sclerosis (RRMS) given by injection include interferon-beta (IFN-β) 1a (Avonex <sup>®</sup> , Rebif <sup>®</sup> ) or 1b (Betaseron <sup>®</sup> , Extavia <sup>®</sup> ), glatiramer acetate (Copaxone <sup>®</sup> ), mitoxantrone (Novantrone <sup>®</sup> ), natalizumab (Tysabri <sup>®</sup> ; for patients non-responsive to other medications), and alemtuzumab (Lemtrada <sup>™</sup> ). Oral disease modifying treatments for RRMS include fingolimod (Gilenya <sup>®</sup> ), teriflunomide (Aubagio <sup>®</sup> ), and dimethyl fumarate (Tecfidera <sup>®</sup> ).	Correction; Lemtrada is not administered orally.
<b>Section 3.1.2. Study Drug</b>		
(new text)	<u>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.</u>	Additional information added to give context.
<b>Section 3.2.2. Metabolism and Pharmacokinetics</b>		
Laquinimod was shown to cause a marked decrease of CYP3A4 activity and is a <del>potent</del> strong inducer of CYP1A	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

Original text with changes shown	New wording	Reason/Justification for change
enzymes.		IB
<b>Section 3.2.3. Toxicology</b>		
<p><del>Finally, a small increase in the incidence of oral cavity squamous cell carcinomas</del> <u>In addition, an increase in the incidence of oral cavity tumors was noted in mid and high dose female rats (2/60 in each group). The oral effects may relate to the AhR activation properties of laquinimod since similar lesions were seen following lifelong exposure of rats to other AhR activators. However, the incidence of oral cavity tumors in rats treated with laquinimod was lower than that seen with industrial chemicals such as 2,3,7,8-tetrachloro-p-dibenzodioxin (TCDD) (NTP TR-521) and dioxin-like compounds (DLCs), and was more similar to the incidence seen with the dietary ingredient indole-3-carbinol (I3C) found in cruciferous vegetables. Of note, the oral tumors seen with I3C were considered by the US National Toxicology Program as irrelevant for I3C risk assessment (NTP TR-584). No increased incidence of oral tumors was seen in humans exposed to TCDD, indicating a species specific response in rats. Therefore, oral cavity tumors induced by laquinimod in rats after a lifelong exposure do not imply an elevated carcinogenicity risk in humans. Humans, in general, also seem to be less sensitive to AhR activation by laquinimod than rats, as shown by the differential gene expression profiles discussed in the IB 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</u></p>	<p>In addition, an increase in the incidence of oral cavity tumors was noted in mid and high dose female rats (2/60 in each group). The oral effects may relate to the AhR activation properties of laquinimod since similar lesions were seen following lifelong exposure of rats to other AhR activators. However, the incidence of oral cavity tumors in rats treated with laquinimod was lower than that seen with industrial chemicals such as 2,3,7,8-tetrachloro-p-dibenzodioxin (TCDD) (NTP TR-521) and dioxin-like compounds (DLCs), and was more similar to the incidence seen with the dietary ingredient indole-3-carbinol (I3C) found in cruciferous vegetables. Of note, the oral tumors seen with I3C were considered by the US National Toxicology Program as irrelevant for I3C risk assessment (NTP TR-584). No increased incidence of oral tumors was seen in humans exposed to TCDD, indicating a species specific response in rats. Therefore, oral cavity tumors induced by laquinimod in rats after a lifelong exposure do not imply an elevated carcinogenicity risk in humans. Humans, in general, also seem to be less sensitive to AhR activation by laquinimod than rats, as shown by the differential gene expression profiles discussed in the IB.</p>	<p>Updated for consistency with the IB</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>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.</p>		
<b>Section 3.3.1. Clinical Pharmacology Studies</b>		
<p>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. Laquinimod 0.6 mg is a weak inhibitor of CYP3A4 and a strong inducer of CYP1A2. For additional information, please refer to the IB.</p> <p><u>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</u></p>	<p>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. Laquinimod 0.6 mg is a weak inhibitor of CYP3A4 and a strong inducer of CYP1A2. For additional information, please refer to the IB.</p> <p>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.</p>	<p>Updated for consistency with the IB</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><u>laquinimod is maintained in subjects with hepatic impairment (mild to severe) and renal impairment (moderate to severe) across this dose range.</u></p>		
<p><b>Section 3.3.2. Clinical Safety and Efficacy Studies</b></p>		
<p>(new text)</p>	<p><u>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.</u> <u>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.</u></p>	<p>Information regarding safety findings in the CONCERTO and ARPEGGIO studies</p>
<p><b>Section 3.4. Known and Potential Risks and Benefits to Human Subjects</b></p>		
<p>Note: the table has been updated in line with the updated <u>Reference Safety Information; myocardial infarction and cerebrovascular accident are now included.</u> <u>Table 3: Tabulated List of Adverse Reactions in the Pooled ALLEGRO and BRAVO Studies</u> ... <u>Cardiac disorders</u> Uncommon: Myocardial infarction ... Nervous system disorders Very Common: Headache Rare: Cerebrovascular accident</p>	<p>Note: the table has been updated in line with the updated Reference Safety Information; myocardial infarction and cerebrovascular accident are now included. <u>Table 3: Tabulated List of Adverse Reactions</u> ... Cardiac disorders Uncommon: Myocardial infarction ... Nervous system disorders Very Common: Headache Rare: Cerebrovascular accident</p>	<p>Update to Reference Safety Information</p>
<p><b>Section 3.4.1.7. Cardiovascular Events (Laquinimod 1.2 and 1.5 mg)</b></p>		
<p>(new section)</p>	<p><u>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</u></p>	<p>Information regarding safety findings in the CONCERTO and</p>

Original text with changes shown	New wording	Reason/Justification for change
	<p><u>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.</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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.</u></p>	<p>ARPEGGIO studies</p>
<p><b>Section 3.4.2.2. Cancer</b></p> <p>It is the sponsor’s position that these findings are likely related to <del>the administration procedure</del> or to species-specific mechanisms</p>	<p>It is the sponsor’s position that these findings are likely related to species-specific mechanisms</p>	<p>Administration procedure no longer considered a factor</p>

Original text with changes shown	New wording	Reason/Justification for change
<b>Section 3.4.2.3. Cardiotoxicity and Systemic Inflammation</b>		
<p><del>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.</del>  <u>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.</u> 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 <u>similar potential these safety issues.</u> <u>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.</u><del>This analysis showed that none of these safety issues constitute a signal of concern for laquinimod.</del></p>	<p>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.</p>	<p>Information added on safety of 0.6 mg dose</p>
<b>Section 5.1. Overview And Plan (Other sections affected by this change: Section 8.1. Study Period; Section 8.2.2. Scheduled Treatment Visits [Months 1E (Visits 1E) and Onwards]; Section 8.2.6.1. Liver Enzymes)</b>		
(new text)	<u>Subjects who discontinue treatment for any reason will continue follow-up according to scheduled visits.</u>	Additional follow-up added for safety reasons
<b>Section 7.1. Allowed Concomitant Medications/Therapies</b>		
Short-term treatment with corticosteroids will be allowed during <del>acute</del> 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 <del>potent</del> <u>strong</u> inducer of CYP1A2. Subjects taking drugs that are metabolized by CYP1A2 (examples listed in Appendix D) should be advised that plasma levels of these drugs could decrease when combined with laquinimod. <u>In general, as a precautionary measure, it is recommended to avoid the use of</u>	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 D) 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	Wording made consistent with IB

Original text with changes shown	New wording	Reason/Justification for change
<p><u>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.</u> <del>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.</del></p>	<p>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.</p>	
<p><b>Section 7.2. Disallowed Concomitant Medications During Study (Other sections affected by this change: Section 8.2.3. Termination/ Early Discontinuation)</b></p>		
<p><u>Interferons IFN-β 1a or 1b</u> ... Moderate or strong inhibitors of CYP3A4; for example, ketoconazole and erythromycin (as listed in Appendix C) <u>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.</u></p>	<p>IFN-β 1a or 1b ... Moderate or strong inhibitors of CYP3A4; for example, ketoconazole and erythromycin (as listed in Appendix C) 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.</p>	<p>Clarification</p>
<p><b>Section 8.2.3. Termination/ Early Discontinuation</b></p>		
<p>(new text)</p>	<p><u>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]).</u></p>	<p>Additional follow-up added for safety reasons</p>
<p>– 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) <del>and importance of performing the home pregnancy urine tests every one month (starting after visit Month 3E)</del></p>	<p>– 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)</p>	<p>Pregnancy tests not required in this context.</p>

Original text with changes shown	New wording	Reason/Justification for change
<b>Section 8.2.4. Early Treatment Discontinuation (Other sections affected by this change: Section 10.2.3. Safety Laboratory Evaluations; APPENDIX E. GUIDANCE ON SAFETY MONITORING)</b>		
<p><u>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]).</u></p> <p>An early termination visit should be completed for all subjects who prematurely discontinue from the study <u>and do not agree to or cannot continue all scheduled visits and procedures.</u> It includes subjects who took at least one dose in the MS-LAQ-302E study.</p>	<p>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]).</p> <p>An early termination visit should be completed for all subjects who prematurely discontinue from the study and do not agree to or cannot continue all scheduled visits and procedures. It includes subjects who took at least one dose in the MS-LAQ-302E study.</p>	Clarification
<b>Section 8.2.5. Post Early Discontinuation Follow-Up Visit</b>		
(new text)	<u>Note: This section specifically pertains to subjects that discontinue treatment early but do not agree to continue follow up.</u>	Clarification
<p><del>In case of early termination of the study AE for which the relationship with the study drug is characterized as ‘Reasonable Possibility’,</del> Moderate and strong CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered.</p>	Moderate and strong CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered.	Text removed as this restriction is more general
<b>Section 8.2.6.2. Pregnancy</b>		
<p><del>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.</del></p>	(text deleted)	Text removed as was specific to a previous amendment
<p>Additionally, monthly pregnancy tests (urine dipstick and/or serum pregnancy <math>\beta</math> hCG test, as applicable per the relevant time point) will be performed <u>(except for where subjects have discontinued study drug but are continuing to attend study visits for follow up).</u></p>	<p>Additionally, monthly pregnancy tests (urine dipstick and/or serum pregnancy <math>\beta</math> 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).</p>	Clarification
<b>Section 8.2.6.3. Invasive Cancer (Other sections affected by this change: APPENDIX E. GUIDANCE ON SAFETY MONITORING)</b>		
<p>Subjects that are diagnosed with a <u>malignant solid or liquid tumor</u> <del>invasive cancer</del> while participating in the study should stop study medication and discontinue their study participation <u>drug.</u></p>	Subjects that are diagnosed with a malignant solid or liquid tumor while participating in the study should stop study drug.	Correction of terminology; also, subjects diagnosed with a tumor should only be



Original text with changes shown	New wording	Reason/Justification for change
		discontinued from the study drug, not from the study.
<b>Section 8.2.6.4. Liver Impairment</b>		
(new section)	<u>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.</u>	New stopping rule to avoid higher exposures to laquinimod
<b>Section 8.2.6.5. Renal Impairment</b>		
(new section)	<u>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) <math>\leq 60</math> mL/min/1.73 m<sup>2</sup>, while participating in the study should stop study medication temporarily and the GFR assessment should be repeated. If the renal impairment is confirmed (GFR <math>\leq 60</math> mL/min/1.73 m<sup>2</sup>), the subject should stop study medication permanently.</u>	New stopping rule to avoid higher exposures to laquinimod
<b>Section 8.2.9. Unscheduled Visit</b>		
(new text)	– <u>For female subjects of child-bearing potential, serum or urine <math>\beta</math>-hCG test may be performed</u>	Urine test was included in flow chart but not in text, so has been added to text for consistency. Serum test has been added to flow chart and text.
<b>Section 8.2.9.1. Unscheduled Samples</b>		
(new section)	<u>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:</u> <ul style="list-style-type: none"> <li>• <u>urgent safety laboratory test panel (see Section 10.2.3.1)</u></li> <li>• <u>pharmacokinetic blood sample</u></li> <li>• <u>sample for potential biomarker analysis</u></li> </ul>	Additional samples can be collected

Original text with changes shown	New wording	Reason/Justification for change
<b>Section 8.2.9.1.1. Unscheduled Pharmacokinetic Samples</b>		
(new section)	<u>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.</u>	Additional samples can be collected
<b>Section 8.2.9.1.2. Unscheduled Biomarker Samples</b>		
(new section)	<u>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.</u>	Additional samples can be collected
<b>Section 10.2.1.1. Protocol Defined Adverse Events for Expedited Reporting</b>		
(new section)	<u>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 CRE.</u>	Due to cardiovascular findings at higher dose levels, adverse events for expedited reporting have been identified.
<b>Section 10.2.2. Abdominal Computed Tomography Scan</b>		
(new section)	<u>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.</u>	Added for consistency with other laquinimod protocols

Original text with changes shown	New wording	Reason/Justification for change
<b>Section 10.2.3. Safety Laboratory Evaluations (Other sections affected by this change: Section 8.2.2. Scheduled Treatment Visits [Months 1E (Visits 1E) and Onwards]; Section 8.2.3. Termination/ Early Discontinuation)</b>		
<ul style="list-style-type: none"> <li>● <u>hs-CRP</u></li> </ul>	<ul style="list-style-type: none"> <li>● hs-CRP</li> </ul>	It is specifically hs-CRP that should be measured
<ul style="list-style-type: none"> <li>○ In case of abnormal CPK result: troponin <del>or</del> <u>and</u> CPK-MB will be tested</li> </ul>	<ul style="list-style-type: none"> <li>○ In case of abnormal CPK result: troponin and CPK-MB will be tested</li> </ul>	Both troponin and (not or) CPK MB will be measured
<p><del>In case of new hemoglobin decrease of &gt; 1g/dL from the subject's hemoglobin level at Baseline, subjects will be re-tested to ascertain true decrease. If true decrease, a thorough anemia work up will be done including:</del></p> <ul style="list-style-type: none"> <li>○ <del>direct medical history and physical examination</del></li> <li>○ <del>blood smear, serum iron, ferritin, total iron binding capacity, folic acid, B12, haptoglobin, IL-1, IL-6, IFN-γ, TNF-α, and hepcidin.</del></li> <li>○ <del>additional investigations and follow up per Investigator's discretion or Sponsor's request</del></li> </ul>	(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)
<ul style="list-style-type: none"> <li>● <del>Urinalysis</del> <ul style="list-style-type: none"> <li><del>pH</del></li> <li><del>Glucose</del></li> <li><del>Ketones</del></li> <li><del>Erythrocytes, Leukocytes</del></li> <li><del>Protein</del></li> </ul> </li> </ul>	(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.
<b>Section 10.2.3.1. Urgent Safety Laboratory Panel</b>		
(new section)	<p><u>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.</u></p> <p><u>The following tests (and others, if required) will be performed on these samples:</u></p>	Unscheduled samples can be collected for further investigation of clinical events of interest

Original text with changes shown	New wording	Reason/Justification for change
	<ul style="list-style-type: none"> <li>• <u>serum chemistry panel, including fibrinogen and hs-CRP</u></li> <li>• <u>hematology panel</u></li> <li>• <u>CPK-MB</u></li> <li>• <u>troponin I</u></li> </ul>	
<b>Section 10.2.4. Vital Signs <u>and Weight</u> (Other sections affected by this change: Section 8.2.2. Scheduled Treatment Visits [Months 1E (Visits 1E) and Onwards])</b>		
Body weight will be measured at <del>Month 0E [Baseline (Termination visit of the MS LAQ 302 study)]</del> and every 12 months thereafter, <u>all visits until Termination/Early discontinuation, and as long as the subject continues study drug treatment.</u>	Body weight will be measured at all visits until Termination/Early discontinuation, and as long as the subject continues study drug treatment.	Weight will now be measured at all visits
<b>Section 10.2.7. Glomerular Filtration Rate Estimation (Other sections affected by this change: Section 8.2.2. Scheduled Treatment Visits [Months 1E (Visits 1E) and Onwards]; Section 10.2.3. Safety Laboratory Evaluations)</b>		
(new section)	<u>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 &lt;60 mL/min/1.73 m<sup>2</sup> should stop study medication temporarily and the GFR assessment should be repeated. If the renal impairment is confirmed (GFR &lt;60 mL/min/1.73 m<sup>2</sup>), the subject should stop study medication permanently (see Section 8.2.6.5).</u>	GFR estimation added to monitor renal function
<b>Section 10.2.8. Cardiovascular Risk Assessment and Management (Other sections affected by this change: Section 8.2.2. Scheduled Treatment Visits [Months 1E (Visits 1E) and Onwards])</b>		
(new section)	<u>Evaluation and management of major modifiable cardiac risk factors (eg, diabetes, high blood pressure, hyperlipidemia, tobacco smoking) will be performed at the time points indicated in Table 5. In addition, an evaluation should take place as soon as possible for subjects already in the study, following approval of Amendment #2. 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.</u>	Additional safety precautions for cardiovascular risks

Original text with changes shown	New wording	Reason/Justification for change
<b>Section 11.2.1. SAE Reporting (Other sections affected by this change: Section 13.3. Subject Confidentiality; Section 15.1. Data Collection via Remote Data Capture (RDC))</b>		
The following information should be provided to accurately and completely record the event: 1. Investigator Name and Center Number 2. Subject Number 3. <del>Subject initials</del> 4. <del>Subject Demographics</del>	The following information should be provided to accurately and completely record the event: 1. Investigator Name and Center Number 2. Subject Number	Subject initials and demographics should no longer be recorded
<b>Section 13.2. Informed Consent (Other sections affected by this change: Section 8.2.2. Scheduled Treatment Visits [Months 1E (Visits 1E) and Onwards])</b>		
(new text)	<u>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).</u>	Subjects continuing on the study with this amendment will be re consented.
<b>Section 18. CLINICAL PRODUCT COMPLAINTS</b>		
(new section)	<p><u>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:</u></p> <ul style="list-style-type: none"> <li>• <u>suspected contamination</u></li> <li>• <u>questionable stability (eg. color change, flaking, crumbling, etc)</u></li> <li>• <u>defective components</u></li> <li>• <u>missing or extra units (eg. primary container is received at the investigational center with more or less than the designated number of units inside)</u></li> <li>• <u>incorrect packaging, or incorrect or missing labeling/labels</u></li> <li>• <u>unexpected or unanticipated taste or odor, or both</u></li> <li>• <u>device not working correctly or appears defective in some manner</u></li> </ul> <p><u>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.</u></p>	Section added for consistency with sponsor’s current protocol template

Original text with changes shown	New wording	Reason/Justification for change
	<p><u>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.</u></p>	
<p><b>Section 18.1. Product Complaint Information Needed from the Investigational Center</b></p>		
<p>(new section)</p>	<p><u>In the event that the product complaint form cannot be completed, the investigator will obtain the following information, as available:</u></p> <ul style="list-style-type: none"> <li>• <u>investigational center number and principal investigator name</u></li> <li>• <u>name, phone number, and address of the source of the complaint</u></li> <li>• <u>clinical protocol number</u></li> <li>• <u>subject identifier (subject study number) and corresponding visit numbers, if applicable</u></li> <li>• <u>product name and strength for open-label studies</u></li> <li>• <u>subject number, bottle, and kit numbers (if applicable) for double-blind or open-label studies</u></li> <li>• <u>product available for return Yes/No</u></li> <li>• <u>product was taken or used according to protocol Yes/No</u></li> <li>• <u>description or nature of complaint</u></li> <li>• <u>associated serious adverse event Yes/No</u></li> <li>• <u>clinical supplies unblinded (for blinded studies) Yes/No</u></li> <li>• <u>date and name of person receiving the complaint</u></li> </ul> <p><u>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.</u></p>	<p>Section added for consistency with sponsor’s current protocol template</p>
<p><b>Section 18.2. Handling of Study Drug at the Investigational Center</b></p>		
<p>(new section)</p>	<p><u>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</u></p>	<p>Section added for consistency with sponsor’s current protocol template</p>

Original text with changes shown	New wording	Reason/Justification for change
	<p><u>study monitor or designee will provide the information needed for returning the study drug.</u>  <u>If it is determined that the investigational center must return all study drug, the sponsor will provide the information needed to handle the return.</u>  <u>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.</u></p>	
<b>Section 18.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint</b>		
(new section)	<p><u>If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 11).</u></p>	Section added for consistency with sponsor's current protocol template
<b>Section 18.4. Documenting a Product Complaint</b>		
(new section)	<p><u>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.</u></p>	Section added for consistency with sponsor's current protocol template
<b>APPENDIX C. MODERATE/STRONG CYP3A4 INHIBITORS AND CYP3A4 INDUCERS</b>		
(section, including tables, updated to make consistent with current IB)	(see Appendix C for new wording)	Updated for consistency with current IB
<b>APPENDIX D. LIST OF MEDICATIONS THAT SHOULD BE USED WITH CAUTION</b>		
(section, including tables, updated to make consistent with current IB)	(see Appendix D for new wording)	Updated for consistency with current IB
<b>APPENDIX E. GUIDANCE ON SAFETY MONITORING</b>		
(new text)	<p><u>4. Guidance on Monitoring Subjects with Elevated Pancreatic Amylase Levels</u>  <u>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</u></p>	Guidance updated for consistency with body of the protocol

Original text with changes shown	New wording	Reason/Justification for change
	<p><u>severity of this condition. An MRI may be performed as an alternative to the CT scan.</u></p> <p><u>5. Liver Impairment</u>  <u>Subjects who develop any chronic liver disease associated with liver functional impairment while participating in the study should stop study medication.</u></p> <p><u>6. Renal Impairment</u>  <u>Subjects who develop renal disease associated with moderate or severe functional impairment, defined as glomerular filtration rate (GFR) &lt;60 mL/min/1.73 m<sup>2</sup>, 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<sup>2</sup>), the subject should stop study medication permanently.</u></p>	



## **24.2. Global Amendment #1**

At the time of issuance of this amendment there were 822 ongoing subjects 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 listed in the summary table below.

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

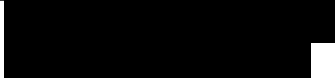
Previous approved wording	Amended or new wording	Rationale
<b>Section 3 INTRODUCTION</b>		
-	See section	The section has been greatly revised to bring in line with current experience. Please see section for full details.
<b>Synopsis AND Section 4: Study objectives AND Section 5.1: Overview and plan AND Section 5.3: Rationale for study design, dose and population AND Section 8.1: Study period</b>		
<p><del>.....until laquinimod 0.6 mg is commercially available for the treatment of MS patients or until its development for MS has been stopped</del></p>	<p><u>..... as long as the Sponsor continues the development of laquinimod 0.6 mg for RRMS.</u></p>	<p>The Sponsor reasoned that the long term follow-up for safety and efficacy is of utmost importance and would like to maintain the subjects under this clinical protocol. The Sponsor would like to prolong the study as long as the Sponsor continues the development of laquinimod 0.6 mg for RMMS patients. Therefore, the duration of the study will no longer be dependent on commercial availability of laquinimod 0.6mg.</p>
<b>Synopsis</b>		
<p><del>For purposes of neurological/medical assessments, the study will be divided into 2 periods:</del></p> <p><del><b>Period 1:</b> in which all subjects will continue to be evaluated by 2 distinct physicians — a Treating and an Examining Neurologists/ Physician (as in the MS LAQ 302 study).</del></p> <p><del><b>Period 2:</b> in which all subjects will be assessed by a single Study Physician/ Neurologist.</del></p> <p><del>The Sponsor will inform the sites when to change from Period 1 to Period 2</del></p>	<p><u>As of the implementation of Protocol Amendment #1, all neurological/medical assessments may be performed by a single Study Physician/Neurologist since all the sites are now in Period 2 of the study.</u></p>	<p>Distinction of Period 1/2 – there is no longer need to distinguish between study period 1 and 2 since all the subjects are now in the study period 2. Similarly there is no need for distinction between the Treating and the Examining Physicians/ Neurologists.</p>

Previous approved wording	Amended or new wording	Rationale
<b>Section 5.1: Overview and plan</b>		
<p><b>5.2 Study Periods</b></p> <p>The medical/neurological assessments of the subjects at each clinical site will be performed differently <del>in each of the following study periods:</del></p> <p><u>Period 1:</u>  <del>In this period, either two separate Neurologists or two Physicians will continue to assess the subjects in the MS LAQ 302E study (as in the MS LAQ 302 study). An Examining Neurologist/Physician will assess the subject's neurological status, unaware of subject's well being and a Treating Neurologist/Physician will decide whether a subject experienced a relapse and will treat the subject as needed (in addition to his/her responsibility for subject eligibility evaluation, the supervision of the study drug administration, the recording and treating of adverse events and the monitoring of safety assessments, including routine laboratory parameters).</del>  <del>In order to maintain reliable evaluation and reduce the potential for bias the following actions will be undertaken:</del>  <del>The Examining Neurologist/Physician will be the only one to evaluate the subject neurologically.</del>  <del>The Examining Neurologist/ Physician will have no access to the subject's file, including previous neurostatus forms, RDC system and adverse events. A decision as per treatment of a relapse will be under the sole responsibility of the Treating Neurologist/Physician.</del></p> <p><u>Period 2:</u>            In this period, there will be no need for 2 separate physicians to assess the subjects in the MS-LAQ-302E study. <del>From that moment,</del> subjects participating in the MS-LAQ-302E study will be assessed by a</p>	<p>The medical/neurological assessments of the subjects at each clinical site will <u>no longer</u> be performed differently <u>since all the sites are now in study period 2.</u> <del>In each of the following study periods.</del> In this period, there will be no need for 2 separate physicians to assess the subjects in the MS-LAQ-302E study. <del>From that moment,</del> <u>Subjects participating in the MS-LAQ-302E study will be assessed by a single physician/Neurologist ("Study Physician/ Neurologist").</u></p>	

Previous approved wording	Amended or new wording	Rationale
<p>single physician/Neurologist ("Study Physician/Neurologist").</p> <p><del>The study will begin with medical/neurological assessments which will be performed as described in Period 1 (identical to the assessment methods in the MS-LAQ-302 study)</del></p> <p><del>The sponsor will inform the sites when to change the method of medical/neurological assessments from Period 1 to Period 2</del></p>		
<p><b>Section 8.2.1 Baseline Visit (Month 0E) (Visit 0E) (Termination visit of the MS-LAQ-302 study) Procedures</b></p>		
<p>Serum pregnancy test (<math>\beta</math>-hCG) for women of child-bearing potential.</p>	<p>. Serum pregnancy test (<math>\beta</math>-hCG) for women of child-bearing potential. <u>In case of positive result, the subject will not be eligible to participate in the extension and will be considered a screening failure for the extension phase.</u></p>	
<p><b>Section 10.1.2 Neurological Evaluations</b></p>		
<p>At each of the study Periods, every effort should be made to ensure that the same Neurologist/Physician performs the neurological assessment at all visits for a particular subject.</p>	<p><del>At each of the study Periods.</del> Every effort should be made to ensure that the same Neurologist/Physician performs the neurological assessment at all visits for a particular subject.</p>	
<p><b>Section 8.2.9.1: Visits during relapses (scheduled and unscheduled)</b></p>		
<p>The Examining Neurologist/Physician (or Study Physician/Neurologist, where applicable, see Section 5.1.1)</p> <p>the Treating Neurologist/Physician [or by the Study Physician, where applicable (see Section 5.1.1),</p>	<p><del>The Examining Study Neurologist/Physician (or Study Physician/Neurologist, where applicable, see Section 5.1.1)</del></p> <p>the <u>Treating Study Neurologist/Physician</u> [or by the <u>Study Physician</u>, where applicable (see Section 5.1.1)</p>	
<p><b>Section 10.1.1: On-study Relapse Evaluation and Determination</b></p>		
<ul style="list-style-type: none"> <li>Subjects will be instructed to telephone their study site within 48 hours should any symptoms suggestive of a relapse appear.</li> <li><del>The Treating Neurologist/Physician (or the Study Physician/Neurologist, where applicable) (see Section 5.1.1 and Section 18.1.2)</del> will</li> </ul>	<ul style="list-style-type: none"> <li>Subjects will be instructed to telephone their study site within 48 hours should any symptoms suggestive of a relapse appear.</li> <li><u>The Study Neurologist/Physician</u> will evaluate the subject once any symptom suggestive of a relapse occurs.</li> </ul>	

Previous approved wording	Amended or new wording	Rationale
<p>evaluate the subject once any symptom suggestive of a relapse occurs.</p> <ul style="list-style-type: none"> <li>• In case of a suggestive relapse during a scheduled or unscheduled visit in <u>Period 1</u> (see Section 5.1.1):               <ul style="list-style-type: none"> <li>— <del>The Treating Neurologist/Physician will refer the subject to the Examining Neurologist/Physician for performance of neurological evaluations and obtain EDSS score (see Section 18.1.3).</del></li> <li>— <del>An Examining Neurologist/Physician will assess the subject’s neurological status, unaware of subject’s well being and a Treating Neurologist/Physician will decide whether a subject experienced a relapse and will treat the subject as needed.</del></li> </ul> </li> <li>• <del>In case of a suggestive relapse during a scheduled or unscheduled visit in <u>Period 2</u> (see Section 5.1.1):</del> <ul style="list-style-type: none"> <li>• The evaluation of symptoms as well as the neurological evaluations/ EDSS will be made by the Study Physician (see Section 19.1.2).</li> <li>• Based on the assessment of symptoms and the EDSS/FS evaluation, the Study Physician will decide whether a subject experienced a relapse and will treat the subject as needed.</li> <li>• In any case, the neurological evaluation of the subject (by <del>The Examining Neurologist in <u>Period 1</u></del> or by the Study Physician/Neurologist in <u>Period 2</u>) will be performed within 7 days of symptoms onset, conditional upon a symptomatic period of <math>\geq 48</math> hours.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• In case of a suggestive relapse during a scheduled or unscheduled visit:               <ul style="list-style-type: none"> <li>– The evaluation of symptoms as well as the neurological evaluations/ EDSS will be made by the <u>Study Physician/Neurologist</u>.</li> <li>– Based on the assessment of symptoms and the EDSS/FS evaluation, the <u>Study Physician/Neurologist</u> will decide whether a subject experienced a relapse and will treat the subject as needed.</li> </ul> </li> <li>• In any case, the neurological evaluation of the subject by the Study Physician/<u>Neurologist</u> will be performed within 7 days of symptoms onset, conditional upon a symptomatic period of <math>\geq 48</math> hours.</li> <li>• In the case of an ongoing or just-started relapse at the study Termination/Early discontinuation visit, subjects will be followed up until relapse stabilization</li> </ul>	

Previous approved wording	Amended or new wording	Rationale
<ul style="list-style-type: none"> <li>In the case of an ongoing or just-started relapse at the study termination/early discontinuation visit, subjects will be followed up until relapse stabilization</li> </ul>		
<b>Section 11.2.1: SAE Reporting</b>		
<p>In order to satisfy regulatory requirements, any Serious Adverse Event, whether deemed IMP-related or not, must be reported to the <del>Local Clinical Management</del> 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.</p> <p>The SAE should be submitted within 24 hours of becoming aware of the event to the <del>Local Clinical Management</del>. The <del>local Clinical Management</del> will forward the report to the Local Safety Officer who will forward the SAE report to the <del>Global</del> Pharmacovigilance Unit:</p> <p>SAE originated in Europe and rest of the world should be sent to: Global Drug Safety and Pharmacovigilance Unit (Israel)</p> <p>[REDACTED]</p> <p>SAE originated in USA will be sent to: [REDACTED]</p>	<p>In order to satisfy regulatory requirements, any SAE, whether deemed IMP-related or not, must be reported to the <u>Contract Research Organization (CRO)</u> 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.</p> <p>The SAE should be submitted within 24 hours of becoming aware of the event to the <u>CRO</u>. The <u>CRO</u> will forward the report to the <u>appropriate Pharmacovigilance unit at Teva or the Local Safety Officer (LSO)</u> who will forward the SAE report to the <u>appropriate Pharmacovigilance unit at Teva</u>:</p> <p><b>SAE originated in Europe and rest of the world should be sent to:</b> Global Drug Safety and Pharmacovigilance Unit (Israel)</p> <p>[REDACTED]</p> <p><b>SAE originated in USA will be sent to:</b> Teva USA clinical safety mailbox [REDACTED]</p> <p><b>SAE originated in Canada will be sent to:</b> Teva Canada safety mailbox [REDACTED]</p> <p><b>SAE originated in Germany will be sent to:</b> Teva Germany safety mailbox [REDACTED]</p>	

Previous approved wording	Amended or new wording	Rationale
	<p>  <u>Only in the event of difficulty transmitting the form via email, send the form via fax, or contact the sponsor's study personnel identified above for further instruction.</u></p>	
<p><del>In Period 1, blinding will be maintained for the people who are involved directly in the study, therefore in case of a SUSAR case only the Local Safety Officer will receive the un-blinded report for regulatory submission, while the others will receive a blinded report (Teva S.O.P 50.11.16). This precaution is not relevant for Period 2.</del></p>	<p>None</p>	
<p><b>Section 19.1.1: The Principal Investigator</b></p>		
<p><del>The Treating Neurologist/Physician (applicable in Period 1)</del>  <del>The Treating Neurologist/Physician will be responsible for subject eligibility evaluation, the supervision of the study drug administration, the recording and treating of adverse events, the monitoring of safety assessments, including routine laboratory parameters, and coordinating MRI performance. He/she will determine if a subject experiences a relapse and whether to treat the relapse or not and he/she will decide whether to treat the subject as needed.</del>  <del>The Examining Neurologist/Physician (applicable in Period 1)</del>  <del>The Examining Neurologist will be responsible for all neurological examinations. Throughout the study, the Examining Neurologist/Physician will remain unaware of the safety profile. For each subject, the same Examining Physician should be used for all neurological exams performed throughout the study. It is particularly important that:</del></p> <ul style="list-style-type: none"> <li><del>• The Treating Neurologist/Physician and the</del></li> </ul>	<p>None</p>	

Previous approved wording	Amended or new wording	Rationale
<p>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.</p> <ul style="list-style-type: none"> <li>• The Treating Neurologist/Physician will inform the subject of the importance of not discussing safety issues with the Examining Neurologist/Physician.</li> </ul>		
<b>Section 19.1.2: The Study Physician/Neurologist</b>		
<p>Section 18.1.2 The Study Physician/ Neurologist (applicable in Period 2)  <del>In case where there is no need for distinction between the Treating and the Examining Physicians/ Neurologists (Period 2) (to be communicated to the clinical sites by the Sponsor, or Sponsor's designee),</del> the Study Physician/ Neurologist will be responsible for the general medical evaluations as well as the neurological assessments. The Study Physician will make the decision as to whether the neurological change is considered a relapse, based on EDSS/FS scores obtained by him/her.</p>	<p>Section 19.1.2 The Study Physician/Neurologist  The Study Physician/Neurologist will be responsible for the general medical evaluations as well as the neurological assessments. The Study Physician will make the decision as to whether the neurological change is considered a relapse, based on EDSS/FS scores obtained by him/her.</p>	
<b>Section 20.2: Data Monitoring Committee</b>		
<p><del>During Period 1, the DMC Chairperson will interact with the Sponsor's statistician. Within this work frame, the study un blinded statistician, will produce and distribute reports to the DMC members. The statistician of the DMC will address any statistical question raised by the DMC during data review, and will perform data analyses according to the DMC's request. During Period 2, this interaction may be done via the Global Clinical Leader.</del></p>	None	
<b>Appendix B: Definitions</b>		
<p><del>In Period 1 (see Section 5.1.1), the subjects' general medical evaluations will be assessed separately from their neurological assessment evaluations by two</del></p>	<p>In Period 2, there will be no distinction between the Treating Neurologist/ Physician and the Examining Neurologist/ Physician. In such cases, a single Study</p>	



Previous approved wording	Amended or new wording	Rationale
<p><del>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.</del></p> <p><del>The Treating Neurologist/Physician will make the decision as to whether the neurological change is considered a relapse, based on EDSS/FS scores as assessed by the Examining Neurologist/ Physician (see Relapse Definition, above).</del></p> <p><del>Follow up visits to monitor the course of the relapse until stabilization will be made at the Treating Neurologist/Physician discretion, in addition to the assessment at the next scheduled visit.</del></p> <p><del>In Period 2 (see Section 5.1.1), there will be no distinction between the Treating Neurologist/ Physician and the Examining Neurologist/ Physician. In such cases, a single Study Physician will be responsible for the general medical evaluations as well as the neurological assessments. The Study Physician will make the decision as to whether the neurological change is considered a relapse, based on EDSS/FS scores obtained by him/her. The Study Neurologist/ Physician will follow-up on the subject during the course of a relapse, until stabilization.</del></p> <p><del>Relapse Evaluation Procedures</del>  <del>Subjects will be instructed to telephone their study site within 48 hours should any symptoms suggestive of a relapse appear.</del></p> <p><del>In Period 1, the Examining Neurologist/ Physician will evaluate the subject within 7 days of symptoms onset, conditional upon a symptomatic period of <math>\geq 48</math> hours:</del></p>	<p>Physician/Neurologist will be responsible for the general medical evaluations as well as the neurological assessments. The Study Physician/Neurologist will make the decision as to whether the neurological change is considered a relapse, based on EDSS/FS scores obtained by him/her. The Study Neurologist/ Physician will follow-up on the subject during the course of a relapse, until stabilization.</p> <p>Relapse Evaluation Procedures          Subjects will be instructed to telephone their study site within 48 hours should any symptoms suggestive of a relapse appear.</p> <p>The <u>Study</u> Neurologist/ Physician will evaluate the subject within 7 days of symptoms onset, conditional upon a symptomatic period of <math>\geq 48</math> hours:</p> <ul style="list-style-type: none"> <li>The <u>Study</u> Neurologist/Physician will evaluate and treat the subject once any symptom suggestive of a relapse occurs.</li> </ul> <p>In Period 2, all of the above mentioned relapse evaluation activities will be performed by the Study Neurologist/ Physician.</p>	

Previous approved wording	Amended or new wording	Rationale
<ul style="list-style-type: none"> <li>The <del>Treating</del> Neurologist/Physician will evaluate the subject once any symptom suggestive of a relapse occurs.</li> <li>In case of a suggestive relapse during a scheduled or unscheduled visit, the Treating Neurologist/Physician will refer the subject to the Examining Neurologist/Physician.</li> </ul> <p>In Period 2, all of the above mentioned relapse evaluation activities will be performed by the Study Neurologist/ Physician.</p>		
<b>Synopsis AND Section 8.2: Detailed Study Plan</b>		
In case of suspected pregnancy, .....	In case of suspected pregnancy ( <u>positive urine <math>\beta</math>-hCG test result, delay of menstruation or any other reason suggesting pregnancy</u> ), .....	Teva considers the prevention of exposure to laquinimod during pregnancy to be of great importance, and
<b>Table 5 Study Task Flow Chart AND Section 8.2: Detailed Study Plan AND Appendix E (Study task flow chart for returning subjects)</b>		
None.		following consultation with the CHMP and Data Safety Committee (DMC) has
<b>Section 8.2: Detailed Study Plan</b>		
<p>–Female subjects of child-bearing potential will be reminded about (should be recorded in the source documents) the importance of stopping the study drug and informing the site in any case of suspected pregnancy (positive home urine test result, absence of menstruation or any other reason suggesting pregnancy)</p>	<ul style="list-style-type: none"> <li><u>For all subjects who are female of child-bearing potential:</u> <ul style="list-style-type: none"> <li><u>The use of effective contraception will be ascertained at each study visit (should be recorded in the source documents).</u></li> <li><u>Subjects will be instructed during each visit about the teratogenicity and potential delayed risks for a child exposed in uterus to laquinimod</u></li> <li><del>Female subjects of child-bearing potential</del> will be reminded about (should be recorded in the source documents) the importance of stopping the study drug and informing the site in</li> </ul> </li> </ul>	<p>decided to introduce additional language and measures for pregnancy prevention in this amendment and in a revised informed consent form. To strengthen the preventative measures, the 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 randomization. Furthermore a</p>

Previous approved wording	Amended or new wording	Rationale
	any case of suspected pregnancy (positive home urine test result, delay of menstruation or any other reason suggesting pregnancy)	serum beta HCG test prior to enrollment and additional follow up measures and clarifications are added.
<b>Section 8.2.3: Termination/ early discontinuation</b>		
Female subjects of child-bearing potential will be reminded to continue using an acceptable method of contraception up to 30 days from the date of the last dose of the IMP	<u>The use of effective contraception will be ascertained (should be recorded in the source documents) and 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</u>	
<b>Synopsis AND Section 6.2 Exclusion Criteria</b>		
None	Female subjects of childbearing potential who may want to get pregnant in the future, and are interested in re-starting laquinimod treatment following delivery and cessation of breastfeeding may be able to re-enroll in the study after meeting inclusion/exclusion criteria 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 ( <u>see Appendix E</u> ).	The Sponsor realizes that there might be female subjects of childbearing potential who are participating in this long-term study that might want to get pregnant in the future, and might be interested in continuing taking Laquinimod after giving birth. The Sponsor would like to assure that these women do not conceive during treatment with laquinimod and are given the opportunity to return to the study, if they wish, following childbirth and lactation. Therefore, the protocol has been amended to say that these subjects may be re-enrolled after meeting inclusion/exclusion criteria.
<b>Section 7.1: Allowed Concomitant Medication/Therapies</b>		
Short-term treatment with IV corticosteroids will be allowed during acute relapses; Allowed treatment for relapses is a fixed dose of IV methylprednisolone 1 g/day or oral steroids for a maximum of five	Short-term treatment with <del>IV</del> corticosteroids will be allowed during acute relapses; Allowed treatment for relapses is a fixed dose of <del>IV</del> -methylprednisolone 1 g/day <u>or oral steroids</u> for a maximum of five	In order to align the protocol with more recent clinical study protocols with laquinimod, allowed treatment for relapses

Previous approved wording	Amended or new wording	Rationale
<p>consecutive days. No tapering off is allowed.</p> <p>Other medications, excluding those mentioned in Section 7.2 may be given concomitantly as needed for the subject's welfare.</p> <p>Topical and inhaled steroids are allowed at the discretion of the Treating Physician/Neurologist for indications other than MS.</p> <p>Administration of all medications, including indication, dose, frequency, and route of administration will be recorded in the source documentation file and in the electronic Case Report Form (eCRF).</p>	<p>consecutive days. No tapering off is allowed.</p> <p>Other medications, excluding those mentioned in Section 7.2 may be given concomitantly as needed for the subject's welfare.</p> <p>Topical and inhaled steroids are allowed at the discretion of the Study Physician/Neurologist (or <del>the Study Physician, were applicable, see Section 5.1.1</del>) for indications other than MS.</p> <p>Administration of all medications, including indication, dose, frequency, and route of administration will be recorded in the source documentation file and in the electronic Case Report Form (eCRF).</p>	<p>include a short course of glucocorticosteroids (e.g., IV methylprednisolone 1g/day for up to 5 consecutive days or oral steroids). Extended courses of steroids beyond 5 days constitute a protocol violation. No tapering off is allowed.</p>
<b>Section 7.1: Allowed Concomitant Medication/ Therapies</b>		
<p><del>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.</del></p>	<p><u>Clinical studies have shown laquinimod 0.6 mg to be a potent inducer of CYP1A2. Subjects taking drugs that are metabolized by CYP1A2 (examples listed in Appendix F) should be advised that plasma levels of these drugs could decrease when combined with laquinimod. Physicians should consider increasing the dose of such medications upon initiation of laquinimod treatment; in this case, dose reduction of the CYP1A2 inhibitor should be considered if laquinimod is stopped. Drug-Drug interaction studies have been performed with laquinimod doses of 0.6 mg and 1.2 mg. These studies show that laquinimod at both doses is a weak inhibitor of CYP3A4. Subjects taking drugs that are metabolized by CYP3A4 (specifically those with a Narrow Therapeutic Index listed in Table 6) should be advised that plasma levels of these drugs could increase when combined with laquinimod.</u></p>	<p>Laquinimod is a potent inducer of CYP1A2. A recently completed drug-drug interaction study confirmed that laquinimod at the dose of 1.2 mg is also a weak CYP3A4 inhibitor. Therefore, these paragraphs were included to emphasize the risk related to the concomitant use of laquinimod and drugs that are metabolized by CYP1A2 or CYP3A4.</p> <p>In addition, a new appendix (Appendix D) has been added to present partial lists of CYP3A4 substrates with a narrow therapeutic index and of drugs known to be metabolized by CYP1A2.</p>
<b>Appendix D: List of Allowed Medications During the Study That Should Be Used with Caution</b>		
None	<p><b><u>A partial list Of CYP3A4 substrates with a narrow therapeutic index</u></b></p> <p><u>alfentanil</u></p> <p><u>cyclosporine</u></p>	

Previous approved wording	Amended or new wording	Rationale
	<u>diergotamine</u> <u>ergotamine</u> <u>fentanyl</u> <u>pimozide</u> <u>quinidine</u> <u>sirolimus</u> <u>tacrolimus</u> <b><u>A partial list of drugs known to be metabolized by CYP1A2:</u></b> <u>clozapine</u> <u>duloxetine</u> <u>theophylline</u> <u>tizanidine</u> <u>alosetron</u> <u>ramelteon</u> <u>tacrine</u>	
<b>Section 7.2: Disallowed Concomitant Medications During Study</b>		
<ul style="list-style-type: none"> <li>• Interferons</li> <li>• Glatiramer Acetate (Copaxone<sup>®</sup>)</li> <li>• Natalizumab (Tysabri<sup>®</sup>)</li> <li>• Inhibitors of CYP3A4; for example, ketoconazole and erythromycin (as listed in Appendix C)</li> <li>• Mitoxantrone (Novantrone<sup>®</sup>)</li> <li>• Oral steroids</li> <li>• Parenteral steroids (except if given as defined by protocol for treatment of an acute relapse as specified in Section 7.1)</li> <li>• Chemotherapeutic agents</li> <li>• 4-amino pyridine or 3,4 diaminopyridine</li> <li>• IV Immunoglobulin (Ig) and any other experimental agents</li> <li>• Other Immunosuppressive or immunomodulating agents</li> </ul>	<ul style="list-style-type: none"> <li>• Natalizumab (Tysabri<sup>®</sup>)</li> <li>• Fingolimod (Gilenya)</li> <li>• Interferons</li> <li>• Dimethyl fumarate (Tecfidera)</li> <li>• Glatiramer Acetate (Copaxone<sup>®</sup>)</li> <li>• Teriflunomide (Aubagio)</li> <li>• Alemtuzumab (Lemtrada)</li> <li>• Cladribine</li> <li>• Rituximab</li> <li>• Ocrelizumab</li> <li>• Atacicept</li> <li>• Belimumab</li> <li>• Ofatumumab</li> <li>• Inducers of CYP3A4 such as rifampin and carbamazepine (for more examples see Appendix C). Use of CYP3A4 inducers may result in reduced laquinimod plasma</li> </ul>	<p>Laquinimod is mainly metabolized by the CYP3A4 P450 isoenzyme. Following an 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</p>

Previous approved wording	Amended or new wording	Rationale
	<p>concentrations and may reduce its effectiveness.</p> <ul style="list-style-type: none"> <li>• Moderate or strong inhibitors of CYP3A4; for example, ketoconazole and erythromycin (as listed in Appendix C)</li> <li>• Mitoxantrone (Novantrone®)</li> <li>• Oral steroids</li> <li>• Parenteral steroids (except if given as defined by protocol for treatment of an acute relapse as specified in Section 7.1)</li> <li>• Adrenocorticotrophic hormone (ACTH)</li> <li>• Chemotherapeutic agents</li> <li>• Cytotoxic agents</li> <li>• Cyclophosphamide</li> <li>• IV Immunoglobulin (Ig)</li> <li>• Plasmapheresis</li> <li>• Any other experimental agents</li> <li>• Other Immunosuppressive or immunomodulating agents</li> </ul>	<p>Wort) may result in reduced laquinimod plasma concentrations and reduced effectiveness. Therefore CYP3A4 inducers have been added as disallowed medications in all clinical studies with laquinimod. The Laquinimod Investigator's Brochure Edition 7 has been updated with the above information in Section 6.7.1. The disallowed use of CYP3A4 inducers has been added to Section 7.2 (Disallowed concomitant medications during the study) and Appendix C 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 7.2 Disallowed concomitant medications during the study):                      Fingolimod (Gilenya)                      Dimethyl fumarate (Tecfidera)                      Teriflunomide (Aubagio)                      Alemtuzumab (Lemtrada)                      The medication 4-amino pyridine (Ampyra, Fampyra)</p>

Previous approved wording	Amended or new wording	Rationale																		
		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).																		
<b>Section 8.2.5: Post Early Discontinuation Follow-Up Visit</b>																				
In case of early termination of the study due to an AE for which the relationship with the study drug is characterized as ‘Reasonable Possibility’, CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered.	In case of early termination of the study due to an AE for which the relationship with the study drug is characterized as ‘Reasonable Possibility’, <u>moderate and strong</u> CYP3A4 inhibitors are disallowed during the 30 days after the last dose has been administered.																			
<b>Appendix C List of Systemically-administered CYP3A4 Inhibitors which are Disallowed Prior and During Study</b>																				
<p>Cardiac drugs/antiarrhythmic agents amiodarone diltiazem nifedipine verapamil mibefradil</p> <p>Antimicrobial agents Erythromycin Clarithromycin Troleandomycin Telithromycin</p> <p>Antifungals/Imidazoles Fluconazole Itraconazole Ketoconazole Miconazole Voriconazole</p>	<p><b>A partial list of moderate/strong CYP3A4 inhibitors:</b></p> <table border="1" data-bbox="856 808 1516 1393"> <thead> <tr> <th data-bbox="856 808 1136 846">Medication class</th> <th data-bbox="1136 808 1516 846">Drug name</th> </tr> </thead> <tbody> <tr> <td data-bbox="856 846 1136 980"><b>Protease inhibitors</b></td> <td data-bbox="1136 846 1516 980">indinavir, saquinavir, lopinavir, nelfinavir, amprenavir, atazanavir, darunavir, ritonavir</td> </tr> <tr> <td data-bbox="856 980 1136 1018"><b>Antivirals:</b></td> <td data-bbox="1136 980 1516 1018">boceprevir, telaprevir</td> </tr> <tr> <td data-bbox="856 1018 1136 1117"><b>Antifungals:</b></td> <td data-bbox="1136 1018 1516 1117">Ketoconazole, Itraconazole, voriconazole, posaconazole, fluconazole</td> </tr> <tr> <td data-bbox="856 1117 1136 1222"><b>Antibiotics</b></td> <td data-bbox="1136 1117 1516 1222">troleandomycin, clarithromycin, telithromycin, ciprofloxacin, erythromycin</td> </tr> <tr> <td data-bbox="856 1222 1136 1260"><b>Antidepressant</b></td> <td data-bbox="1136 1222 1516 1260">nefazodone</td> </tr> <tr> <td data-bbox="856 1260 1136 1323"><b>Calcium channel blocker</b></td> <td data-bbox="1136 1260 1516 1323">Diltiazem, verapamil, mibefradil</td> </tr> <tr> <td data-bbox="856 1323 1136 1360"><b>Antiemetics</b></td> <td data-bbox="1136 1323 1516 1360">Aprepitant</td> </tr> <tr> <td data-bbox="856 1360 1136 1393"><b>Diuretics</b></td> <td data-bbox="1136 1360 1516 1393">Conivaptan</td> </tr> </tbody> </table>	Medication class	Drug name	<b>Protease inhibitors</b>	indinavir, saquinavir, lopinavir, nelfinavir, amprenavir, atazanavir, darunavir, ritonavir	<b>Antivirals:</b>	boceprevir, telaprevir	<b>Antifungals:</b>	Ketoconazole, Itraconazole, voriconazole, posaconazole, fluconazole	<b>Antibiotics</b>	troleandomycin, clarithromycin, telithromycin, ciprofloxacin, erythromycin	<b>Antidepressant</b>	nefazodone	<b>Calcium channel blocker</b>	Diltiazem, verapamil, mibefradil	<b>Antiemetics</b>	Aprepitant	<b>Diuretics</b>	Conivaptan	
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<b>Antiemetics</b>	Aprepitant																			
<b>Diuretics</b>	Conivaptan																			

Previous approved wording	Amended or new wording		Rationale
<p>HIV drugs: Protease Inhibitors, such as indinavir, ritonavir and others Delavirdine</p> <p>Antidepressants fluoxetine fluvoxamine nefazodone</p> <p>Others/antituberculosis and antimalarial isoniazid quinine emetidine zileuton aprepitant</p> <p>* This is a partial list only ** Systemic drugs only. Topical preparations (vaginal preparations, creams, etc) are allowed. *** In case of early termination of the study due to AE which is considered as 'Reasonable Possibility' related to the study drug, CYP3A4 inhibitors are disallowed during 30 days after the last dose of the study drug was taken.</p>	<p><b>Antineoplastic agents</b></p>	<p>Imatinib</p>	<p><b>Note:</b> 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 * This is a partial list only ** Systemic drugs only. Topical preparations (vaginal preparations, creams, etc) are allowed.</p>
<p><b>Synopsis AND Table 5: Study Flow Chart AND Section 8.2.1: Baseline visit AND Section 8.2.2: Scheduled Treatment Visits [Months 1E (Visits 1E) and onwards] AND Section 8.2.3: Termination/ early discontinuation</b></p>			
<p>Safety laboratory test: serum levels of TSH, T3 and free T4</p>			<p>Monitoring of thyroid function tests was relevant during the core study treatment with Avonex. Currently, there are no subjects in the open label extension phase treated with Avonex. No safety signal for</p>
<p><b>Section 10.2.2: Safety Laboratory Evaluations</b> <input type="checkbox"/> T3, Free T4, TSH only at months 0E [Baseline (Termination visit of the MS LAQ 302 study)], 6E and then at every scheduled study visit thereafter, until Termination/Early discontinuation</p>			



Previous approved wording	Amended or new wording	Rationale
<del>visit.</del>		hypo- and hyperthyroidism, or abnormal thyroid function tests has been detected with laquinimod use. If a diagnosis of hypo- or hyperthyroidism is established, the subject should be treated according to best medical practice.
<b>Section 8.2.4.1: Criteria for Early Treatment Discontinuation</b>		
None	8). <u>Planned pregnancy</u> 9). <u>Lack of efficacy (according to the Investigator's decision).</u>	Two additional criteria for early treatment discontinuation have been included: pregnancy (due to fact that laquinimod is contraindicated in pregnancy) and lack of efficacy.
<b>Section 10.2.2: Safety laboratory evaluations</b>		
[...] CPK <input type="checkbox"/> CPK [...]	[...] <ul style="list-style-type: none"> <li>- CPK</li> <li>- <u>In case of abnormal CPK result: troponin or CPK-MB will be tested</u></li> <li>- <u>In case of CPK &gt; 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</u></li> <li>[...]</li> <li>- <u>Lipase will be tested in case of abnormal pancreatic amylase results</u></li> <li>[...]</li> <li>- Hemoglobin. <u>In case of new hemoglobin decrease of &gt; 1 g/dL from the subject's hemoglobin level at Baseline, subject will be re-tested to ascertain true decrease. If true</u></li> </ul>	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 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 low hemoglobin

Previous approved wording	Amended or new wording	Rationale
	<p><u>decrease, a thorough anemia work-up will be done including:</u></p> <ul style="list-style-type: none"> <li>- <u>Directed medical history and physical examination</u></li> <li>- <u>Blood smear, serum iron, ferritin, total iron binding capacity, folic acid, B12, haptoglobin, IL-1, IL-6, IFN-<math>\gamma</math>, TNF-<math>\alpha</math>, and hepcidin.</u></li> <li>- <u>Additional investigations and follow-up per the Investigator's discretion or Sponsor's request.</u></li> </ul>	<p>levels, a thorough anemia work-up will be done.</p>
<b>Section 8.2.6: Safety Stopping rules</b>		
<p><u>Inflammatory Events:</u> The subject's participation in the study will be discontinued immediately upon meeting either one of the following criteria:</p> <p><input type="checkbox"/> <del>A combination of elevated CRP (<math>\geq 3 \times</math>ULN) or WBC (<math>\geq 2 \times</math>ULN) or fibrinogen (<math>\geq 3 \times</math> ULN) with significant signs/symptoms suggestive of inflammation of non-infectious origin (e.g. arthralgia, chest pain, chest discomfort or edema).</del></p> <p><input type="checkbox"/> <del>An established diagnosis of either of the following: pericarditis, pleuritis, pleural effusion, newly diagnosed non-infectious arthritis or primary peritonitis.</del></p> <p><u>Thromboembolic events:</u> <del>In any suspicion for thrombotic events, all measures should be taken in order to establish or to exclude the diagnosis. The decision as per the continuation of the study drug will be made on a case by case basis.</del></p> <p><u>Pancreatitis:</u> <del>Any subject with an established diagnosis (radiographically/sonographically based) of acute pancreatitis will be immediately withdrawn from the study.</del></p>	<p>New subsections added; see Section 8.2.6.2 and Section 8.2.6.3 <u>for full text</u></p>	<p>The Sponsor has decided to remove the stopping rules of monitoring of inflammatory conditions, monitoring the potential of developing thrombosis and monitoring of serum pancreatic amylase based on the updated safety analyses and to align the protocol with more recent clinical study protocols with laquinimod.</p> <p>Complete blood count, amylase, CRP and fibrinogen are routinely monitored during scheduled visits. The subjects with these laboratory abnormalities should be managed and treated according to best medical practice.</p> <p>In addition: A new serum chemistry evaluation should</p>

Previous approved wording	Amended or new wording	Rationale
		<p>be performed in case of CPK &gt; 2000 U/L (i.e. urine myoglobin and troponin) to complete safety assessments in case of abnormally high CPK levels. In addition, in case of abnormal pancreatic amylase results, lipase will be tested. Laboratory tests to be performed in case of abnormal CPK, and elevated p-amylase were added to the relevant sections dealing with safety laboratory evaluations. 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)</p>
<b>Synopsis AND Section 10.1.7: Economic Impact</b>		
Section deleted	None	The Sponsor has decided not to perform Termination/Early discontinuation visit MRI assessments for all subjects in the study. No change in the MRI assessments for the MRI ancillary study.
<b>Section 19.1.2: The Study Physician/ Neurologist</b>		
Section deleted	None	
<b>Section 19.2.2: Clinical Operations Manager</b>		
The Global Operations Manager is responsible for day-to-day operations of the study.....	The <del>Global</del> <u>Clinical</u> Operations Manager is responsible for day-to-day operations of the study.....	

Previous approved wording	Amended or new wording	Rationale
<b>Section 19.2.6: Global Drug Safety and Pharmacovigilance</b>		
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. <del>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 DMC (see details below).</del>	Global Drug Safety & Pharmacovigilance is responsible for: reviewing safety issues that arise during the study, assessing and evaluating <u>the causality</u> 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.
<b>Appendix E: Guidance on Safety Monitoring</b>		
-	See Appendix E	The section has been greatly revised to bring in line with current experience. Please see section for full details.
<b>Appendix K: The SF-36v2™ Health Survey</b>		
None	None	A typo was corrected in Question 9 of the survey
<b>Entire Document</b>		
-	Numbering of Appendices from 6 to 11 has been changed throughout the text. In addition, appendices are now numbered from A to K.	Updated cross-references to appendices (due to addition of a new Appendix D). In addition, literature references have been changed to reflect the changes in the protocol

**25. CHANGES TO PATIENT ENTRY CRITERIA**

Not applicable.

## APPENDIX A. 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"<sup>a</sup>. Since "in study" relapse definition must be supported by an objective neurological evaluation (see next paragraph), a neurological deficit must sustain long enough to eliminate pseudo-relapses.

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

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

The EDSS/FS/AI (in the first visit indicative for a relapse, as well as in follow up visits) will be a part of a complete neurological assessment performed by the Examining Neurologist/ Physician (or the Study's Neurologist/ Physician, in case all subjects in the MS-LAQ-302 double-blind placebo-controlled study have completed (or early terminated) their treatment period).

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

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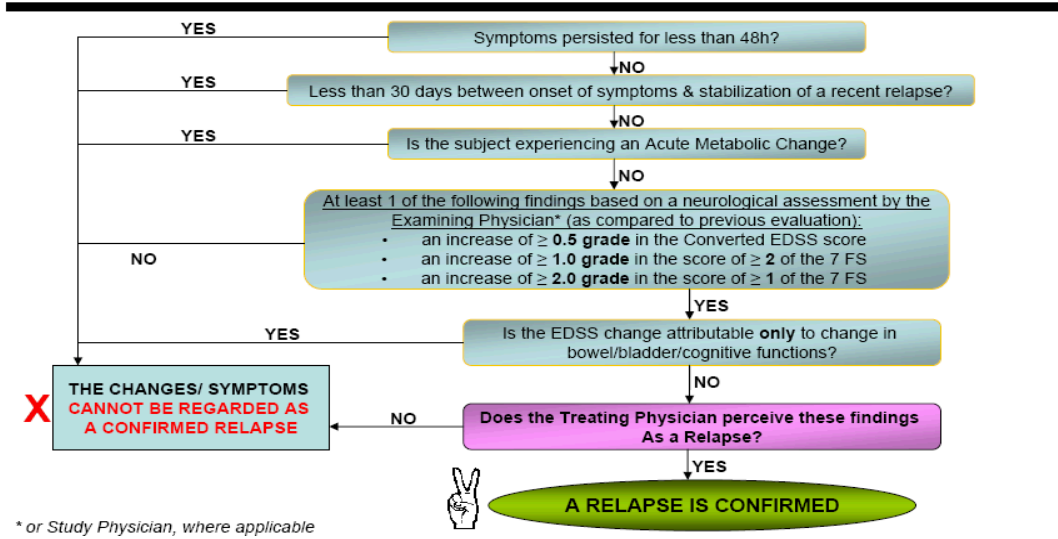
<sup>a</sup> Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis (McDonald, Ann. Neurol. 2001;50:121-127)

**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.



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

#### Relapse Evaluation Procedures

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

The Study Neurologist/ Physician will evaluate the subject within 7 days of symptoms onset, conditional upon a symptomatic period of  $\geq 48$  hours:

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

In Period 2, all of the above mentioned relapse evaluation activities will be performed by the Study Neurologist/ Physician.

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

R-R MS is characterized by clearly defined acute attacks with full recovery or with sequelae and residual deficit upon recovery, periods between disease relapses characterized by a lack of disease progression (Lublin 1996)<sup>a</sup>.

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<sup>a</sup> Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis. *Neurol* 1996;46:907-911.



## **APPENDIX B. NEUROSTATUS**

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

## NEUROSTATUS

### DEFINITIONS

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

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

### GENERAL GUIDELINES

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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)

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

#### FUNCTIONAL SYSTEMS (FS)

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A score of 1 in a Functional System implies that the patient is not aware of the deficit and that the deficit or sign does not interfere with normal daily activities. However, this general rule does not apply to the Visual, Bowel/Bladder and Cerebral FS.

#### EXPANDED DISABILITY STATUS SCALE (EDSS)

---

The EDSS step should not be lower than the score of any individual FS, with the exception of the Visual and Bowel/Bladder FS. Signs or symptoms that are not due to multiple sclerosis will not be taken into consideration for assessments, but should be noted.

**1 VISUAL (OPTIC) FUNCTIONS**

---

**VISUAL ACUITY**

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

**VISUAL FIELDS**

---

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

**SCOTOMA**

---

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

**\*DISC PALLOR**

---

- 0 not present
- 1 present

**NOTE**

---

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

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

---

\*optional

**FUNCTIONAL SYSTEM SCORE**

---

- 0 normal
- 1 disc pallor and/or mild scotoma and/or visual acuity (corrected) of worse eye less than 20/20 (1.0) but better than 20/30 (0.67)
- 2 worse eye with large scotoma and/or maximal visual acuity (corrected) of 20/30 to 20/59 (0.67–0.34)
- 3 worse eye with large scotoma or moderate decrease in fields and/or maximal visual acuity (corrected) of 20/60 to 20/99 (0.33–0.2)
- 4 worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20/100 to 20/200 (0.2–0.1); grade 3 plus maximal acuity of better eye of 20/60 (0.3) or less
- 5 worse eye with maximal visual acuity (corrected) less than 20/200 (0.1); grade 4 plus maximal acuity of better eye of 20/60 (0.3) or less
- 6 grade 5 plus maximal visual acuity of better eye of 20/60 (0.3) or less

**2 BRAINSTEM FUNCTIONS**

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**EXTRAOCULAR MOVEMENTS (EOM) IMPAIRMENT**

---

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

**NYSTAGMUS**

---

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

**TRIGEMINAL DAMAGE**

---

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

**FACIAL WEAKNESS**

---

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

**HEARING LOSS**

---

- 0 none
- 1 **signs only**
- 2 **mild**
- 3 **moderate:** cannot hear finger rub and/or misses several whispered numbers
- 4 **marked:** misses all or nearly all whispered numbers

**DYSARTHRIA**

---

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

**DYSPHAGIA**

---

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

**OTHER BULBAR FUNCTIONS**

---

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

**FUNCTIONAL SYSTEM SCORE**

---

- 0 normal
- 1 **signs only**
- 2a moderate nystagmus
- 2b other mild disability
- 3a severe nystagmus
- 3b marked extraocular weakness
- 3c moderate disability of other cranial nerves
- 4a marked dysarthria
- 4b other marked disability
- 5 **inability to swallow or speak**

**3 PYRAMIDAL FUNCTIONS****REFLEXES**

0	absent	Cutaneous Reflexes
1	diminished	0 = normal
2	normal	1 = weak
3	exaggerated	2 = absent
4	nonsustained clonus (a few beats of clonus)	* Palmomental Reflex
5	sustained clonus	0 = absent 1 = present
		Plantar Response
		0 = flexor
		1 = neutral or equivocal
		2 = extensor

**LIMB STRENGTH**

The weakest muscle in each group defines the score for that muscle group. Use of functional tests, such as hopping on one foot and walking on heels/toes, are recommended in order to assess BMRC grades 3-5.

**BMRC RATING SCALE**

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

**FUNCTIONAL TESTS**

\* Pronator Drift (upper extremities) Pronation and downward drift:

- 0 none
- 1 mild
- 2 evident

\* Position Test (lower extremities – ask patient to lift both legs together, with legs fully extended at the knee) Sinking:

- 0 none
- 1 mild
- 2 evident
- 3 able to lift only one leg at a time (grade from the horizontal position at the hip joints...)
- 4 unable to lift one leg at a time

\* Walking on heels/toes

- 0 normal
- 1 impaired
- 2 not possible

\* Hopping on one foot

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

**LIMB SPASTICITY (AFTER RAPID FLEXION OF THE EXTREMITY)**

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

**GAIT SPASTICITY**

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

\*optional

**FUNCTIONAL SYSTEM SCORE**

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

**4 CEREBELLAR FUNCTIONS**

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**HEAD TREMOR**

---

- 0 none
- 1 mild
- 2 moderate
- 3 severe

**TRUNCAL ATAXIA**

---

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

**LIMB ATAXIA****(TREMOR/DYSMETRIA AND RAPID ALTERNATING MOVEMENTS)**

---

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

**TANDEM (STRAIGHT LINE) WALKING**

---

- 0 normal
- 1 impaired
- 2 not possible

**GAIT ATAXIA**

---

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

**ROMBERG TEST**

---

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

**OTHER CEREBELLAR TESTS**

---

- 0 normal
- 1 mild abnormality
- 2 moderate abnormality
- 3 severe abnormality

**NOTE**

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The presence of severe gait ataxia alone (without severe truncal ataxia and severe ataxia in three or four limbs) results in a Cerebellar FS score of 3.

If weakness interferes with the testing of ataxia, score the patient's actual performance, but also indicate the possible role of weakness by marking an "X" after the Cerebellar FS score.

---

UE = upper extremities

LE = lower extremities

**FUNCTIONAL SYSTEM SCORE**

---

- 0 normal
- 1 abnormal signs without disability
- 2 mild ataxia
- 3a moderate truncal ataxia
- 3b moderate limb ataxia
- 3c moderate or severe gait ataxia
- 4 severe truncal ataxia and severe ataxia in three or four limbs
- 5 unable to perform coordinated movements due to ataxia
- X pyramidal weakness (BMRC grade 3 or worse in limb strength) interferes with cerebellar testing

## 5 SENSORY FUNCTIONS

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### SUPERFICIAL SENSATION (LIGHT TOUCH AND PAIN)

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

### VIBRATION SENSE (AT THE MOST DISTAL JOINT)

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

### POSITION SENSE

---

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

### \* LHERMITTE'S SIGN

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

### \* PARAESTHESIAE (TINGLING)

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

UE = upper extremities

LE = lower extremities

\*optional

## FUNCTIONAL SYSTEM SCORE

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

**6 BOWEL AND BLADDER FUNCTIONS**

**URINARY HESITANCY AND RETENTION**

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

**URINARY URGENCY AND INCONTINENCE**

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

**BLADDER CATHETERISATION**

- 0 none
- 1 intermittent self-catheterisation
- 2 constant catheterisation

**BOWEL DYSFUNCTION**

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

**\* SEXUAL DYSFUNCTION**

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

**NOTE**

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

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

\*optional

**FUNCTIONAL SYSTEM SCORE**

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



## 7 CEREBRAL FUNCTIONS

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### DEPRESSION AND EUPHORIA

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

### DECREASE IN MENTATION

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

### + FATIGUE

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

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

### NOTE

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

## FUNCTIONAL SYSTEM SCORE

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

Amended Protocol 02

**8 AMBULATION**

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**DEFINITIONS**

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

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

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

**HOWEVER, THE FOLLOWING EXCEPTIONS APPLY:**

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

**NOTE**

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

When determining the EDSS step, the Visual FS and Bowel and Bladder FS scores are converted to a lower score as follows:

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

Please enter both the actual and converted scores.

**9 KURTZKE'S EXPANDED DISABILITY STATUS SCALE****DEFINITIONS**

- EDSS steps below 4 refer to patients who are fully ambulatory (able to walk  $\geq$  500 meters). The precise step is defined by the Functional System (FS) scores.
- EDSS steps between 4.0 and 5.0 are defined by both the FS scores and the walking range. In general, the more severe parameter determines the EDSS step.
- EDSS steps 5.5 to 8.0 are exclusively defined by the ability to ambulate and type of assistance required, or the ability to use a wheelchair.
- From steps 0 to 4.0, the EDSS should not change by 1.0 step, unless there is a similar change in a FS score by 1 grade.
- The EDSS step should not be lower than the score of any individual FS, with the exception of the Visual and Bowel/Bladder FS.

**NOTE**

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

**EXPANDED DISABILITY STATUS SCALE**

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

## APPENDIX C. MODERATE/STRONG CYP3A4 INHIBITORS AND CYP3A4 INDUCERS

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

Moderate and strong CYP3A4 inhibitors are prohibited because concomitant administration is predicted to increase laquinimod exposure and may increase the likelihood of adverse events (Table 6).

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

Medication class	Drug name
<b>Protease inhibitors</b>	indinavir, saquinavir, lopinavir, nelfinavir, amprenavir, atazanavir, darunavir, ritonavir
<b>Antivirals:</b>	boceprevir, telaprevir, danoprevir, ledipasvir, elvitegravir
<b>Antifungals:</b>	Ketoconazole, Itraconazole, voriconazole, posaconazole, fluconazole
<b>Antibiotics</b>	troleandomycin, clarithromycin, telithromycin, ciprofloxacin, erythromycin
<b>Antidepressant</b>	nefazodone
<b>Calcium channel blocker</b>	Diltazem, verapamil, mibefradil
<b>Antiemetics</b>	Aprepitant, casopitant, netupitant
<b>Diuretics</b>	Conivaptan
<b>Antineoplastic agents</b>	Imatinib
<b>Antiarrhythmics</b>	dronedarone

**Note:**

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

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

**Table 7: A Partial List of CYP3A4 Inducers**

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

## APPENDIX D. LIST OF MEDICATIONS THAT SHOULD BE USED WITH CAUTION

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

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

<b>alfentanil</b>
<b>cyclosporine</b>
<b>diergotamine</b>
<b>ergotamine</b>
<b>fentanyl</b>
<b>pimozide</b>
<b>quinidine</b>
<b>sirolimus</b>
<b>tacrolimus</b>

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

In general, as a precautionary measure, it is recommended to avoid the use of CYP1A2 substrates in clinical trials of laquinimod. Therapeutic alternatives may be considered in the appropriate clinical context.

**Table 9: A Partial List of Drugs that are Mainly Metabolized by Cytochrome P450 1A2**

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

Drugs with a narrow therapeutic index appear in bolded text

## APPENDIX E. 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<sup>1</sup> will be measured at each study visit.

In any case of elevated ALT or AST to a level exceeding of  $\geq 2 \times \text{ULN}$  (including subjects whose Baseline ALT or AST levels are  $\geq 2 \times$  and  $\leq 3 \times$  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<sup>2</sup>. 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 $\geq 3 \times \text{ULN}$ :

Confirmation of the abnormality (in case the abnormality is of ALT or AST  $\geq 8$  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  $\geq 3 \times \text{ULN}$

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<sup>1</sup> In case total bilirubin is  $> \text{ULN}$ , than direct bilirubin will be checked

<sup>2</sup> 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  $\geq 2$  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 $\geq 3\times$ and $\leq 5\times$ ULN (if Baseline value is $\geq 2.5\times$ ULN, ALT or AST $\geq 3.5\times$ ULN and $\leq 5\times$ ULN)**

In addition to the above procedures required for any elevation to levels  $>3\times$ ULN:

- ALT, AST, GGT, ALP, total and direct bilirubin, CBC and differential (to assess for eosinophilia) and INR should be monitored on days 5 ( $\pm 2$ ), 8 ( $\pm 2$ ), 14 ( $\pm 2$ ), and 28 ( $\pm 2$ ). 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 ( $\geq 3\times$ ULN in case Baseline within normal range or  $\geq 2\times$ ULN in case the Baseline value was above ULN, but still  $<5\times$ ULN) 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 $\geq 5\times$ but less than $8\times$ ULN**

In addition to the above procedures required for any elevation to levels  $>3\times$ ULN:

- ALT, AST, GGT, ALP, total and direct bilirubin, CBC and differential count (to assess for eosinophilia), and INR should be monitored twice a week.

- At least for every other measurement, the tests should be sent to the central laboratory. The rest of the tests may be sent to a local laboratory. INR should always be sent to a local laboratory.

### 1.1.3 ALT or AST $\geq 8xULN$

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

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

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

## **2. Use of Moderate/Strong CYP3A4 Inhibitors**

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

## **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)  $\leq 60$  mL/min/1.73 m<sup>2</sup>, 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<sup>2</sup>), 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  $\beta$ -hCG test. In addition, a serum pregnancy  $\beta$ -hCG test will be performed at each visit to the site. Subjects who have discontinued study drug but are continuing to attend study visits for follow-up do not need to perform pregnancy tests.

1. In case the urine test is negative, study drugs will be dispensed according to planned visit tasks (see [Table 5](#)).
  - a. If the blood test is positive, the subject will be contacted immediately and instructed to stop taking the study drug. The subject should be invited to attend an early termination visit.
  - b. If the blood test is negative – study procedures will be undertaken as planned.
2. In case the urine test is positive – the study drug will not be dispensed (if this occurs at Baseline visit, the subject will not be eligible to participate in the study and will be considered as a screening failure)
  - a. If the blood test is positive, the subject will be invited to the site for an early termination visit
  - b. If the blood test is negative, the subject will be contacted and informed about the test result and the study drugs will be sent to her by courier as soon as possible.
3. Starting from visit 3 (Month 3), the following actions will be taken:
  - a. The subject will be provided with home pregnancy urine  $\beta$ -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 ( $\pm$ 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  $\beta$ -hCG pregnancy test should be performed and the rest of the activities will be as in 2.

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

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

#### **Inclusion criteria for returning subjects**

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

1. Subjects must have completed the Termination visit of MS-LAQ-302E (completion of all Termination visit activities) according to the MS-LAQ-302E 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 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).
5. Subjects must be willing and able to comply with the protocol requirements for the duration of the study.

6. Subjects must be able to comprehend, sign and date a written informed consent prior to re-enrolling into the MS-LAQ-302E study.

**Exclusion criteria for returning subjects**

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



1. Premature discontinuation from the MS-LAQ-302 study, for any reason except for planned pregnancy.
2. Subjects with progressive forms of MS or other nonRRMS 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 azathioprine within 12 months prior to re-enrollment visit.
5. Use of either of the following within 2 years prior to re-enrollment: natalizumab (Tysabri®), rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab.
6. Previous treatment with glatiramer acetate (Copaxone®), Interferon- $\beta$  (either 1a or 1b), fingolimod (Gilenya®), dimethyl fumarate (Tecfidera) or IV immunoglobulin (IVIG) within 2 months prior to re-enrollment visit.
7. Use of teriflunomide (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 patients 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  $\beta$ -hCG performed within 7 days prior to re-initiation of treatment] or breastfeeding.
17. Serum levels  $\geq 3$ xULN of either ALT or AST at re-enrollment visit.
18. Serum direct bilirubin which is  $\geq 2$ xULN at re-enrollment visit.

19. Subjects with clinically significant or unstable medical or surgical condition detected or worsened during the MS-LAQ-302E or MS-LAQ-302E study, which preclude safe participation and completion of the MS-LAQ-302E study.
20. Any malignancies, excluding basal cell carcinoma, in the 5 years prior to re-enrollment.
21. Subjects who underwent endovascular treatment for Chronic Cerebrospinal Venous Insufficiency (CCSVI) within 3 months prior to re-enrollment.

**Table 10: Study Task Flow Chart for Returning Subjects after Planned Pregnancy**

Visit	V0E1	V1E1	V2E1	V3E1	V4I	Every 6 months	Every 12 months	Every 24 months	Termination / Early Discontinuation	Unscheduled Visit <sup>a, b</sup>
Month	0E1	1E1	2E1	3E1	6E1					
Informed Consent for returning subjects	X									
Eligibility Criteria for returning subjects	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Cardiovascular risk factor assessment and management <sup>c</sup>							X	X		
Physical Examination	X				X		X	X	X	X
Vital Signs	X <sup>d</sup>	X	X	X	X	X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>	X
ECG	X				X	X	X	X	X	X
Safety Laboratory Evaluation (CBC, Chemistry, markers of inflammation, GFR estimation)	X	X	X	X	X	X	X	X	X	X
Ascertaining use of effective contraception	X	X	X	X	X	X	X	X	X	X
Serum $\beta$ hCG <sup>f</sup>	X	X	X	X	X	X	X	X	X	X
Urine $\beta$ hCG <sup>f</sup> (on site)	X	X	X	X	X	X	X	X	X	X
Discuss the importance of Contraception <sup>f</sup>	X	X	X	X	X	X	X	X	X	X
Urine $\beta$ hCG <sup>f</sup> (self check, at home)						<b>EVERY 1 MONTH BETWEEN SCHEDULED VISITS</b>				
Adverse Events	X	X	X	X	X	X	X	X	X	X
Neurological examination (EDSS/FS/AI/ 25 foot walk)	X				X	X	X	X	X	X
Evaluation of Relapse <sup>g</sup>	X	X	X	X	X	X	X	X	X	X
MSFC <sup>h</sup>	X				X	X	X	X	X	



Visit	V0E1	V1E1	V2E1	V3E1	V4E1	Every 6 months	Every 12 months	Every 24 months	Termination / Early Discontinuation	Unscheduled Visit <sup>a, b</sup>
Month	0E1	1E1	2E1	3E1	6E1					
Binocular Low-Contrast Visual Acuity	X				X	X	X	X	X	
MFIS	X				X	X	X	X	X	
Mandatory phone calls (pregnancy tests) <sup>i</sup>						 <b>EVERY 1 MONTH BETWEEN SCHEDULED VISITS</b>				
Mandatory phone calls (general well-being, all subjects) <sup>j</sup>						 <b>EVERY 3 MONTHS BETWEEN SCHEDULED VISITS</b>				
Drug Compliance & Dispensing	X	X	X	X	X	X	X	X	X <sup>k</sup>	X
Termination Documentation and Notification of Early Termination									X	
Unscheduled samples										X <sup>l</sup>

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]).

<sup>a</sup> Vital signs and AEs are mandatory activities in an unscheduled visit. All other activities are optional and may be performed as deemed necessary by the investigator. Chest X-ray may also be performed in this visit.

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

<sup>c</sup> In addition, an evaluation should take place as soon as possible for subjects already in the study, following approval of Amendment #2.

<sup>d</sup> Post-dose vital signs will be measured at Baseline and after 30 and 60 minutes.

<sup>e</sup> Weight will be measured at all visits until Termination/Early discontinuation.

<sup>f</sup> For women of childbearing potential. Serum pregnancy test (beta human chorionic gonadotropin [ $\beta$ -hCG]) for women of child-bearing potential within the 7 days prior to re-initiation of treatment

<sup>g</sup> Relapse evaluation will be performed in scheduled as well as unscheduled visits as deemed necessary by the Investigator/Coordinator

<sup>h</sup> Within the MSFC evaluation, the PASAT and 9-HOLE Peg tests will be performed at months 0E1, 6E1, and every 6 months, while the Timed 25-foot walk test will be performed each time a neurological evaluation is performed

<sup>i</sup> For women of child-bearing potential; to be performed within 72 hours of the scheduled home pregnancy test

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

<sup>k</sup> Only drug retrieval

<sup>l</sup> 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.

Amended Protocol 02

AE = Adverse Event, AI = Ambulation Index,  $\beta$ -hCG = beta-human Chorionic Gonadotropin, CBC = Complete Blood Count, ECG = Electrocardiogram, EDSS = Kurtzkle's Expanded Disability Status Scale, FS = Functional System, GFR = glomerular filtration rate, MFIS = Modified Fatigue Impact Scale, MSFC = Multiple Sclerosis Functional Composite

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Date: \_\_\_\_\_ Subject No.: \_\_\_\_\_

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**HOME PREGNANCY TEST QUESTIONNAIRE**

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Date of contacting the subject: \_\_\_\_ / \_\_\_\_ / \_\_\_\_  
DD     MM     YY

Name of site staff person to contact the subject \_\_\_\_\_

Date in which home urine pregnancy test was performed: \_\_\_\_ / \_\_\_\_ / \_\_\_\_   
DD     MM     YY     ND

Home urine pregnancy test result:  Positive/negative

IF HOME URINE PREGNANCY TEST WAS NOT PERFORMED:

Was a urine pregnancy test scheduled?    
Yes     No

If yes – specify the date for which the next contact was scheduled \_\_\_\_ / \_\_\_\_ / \_\_\_\_  
DD     MM     YY

**APPENDIX F. MODIFIED FATIGUE IMPACT SCALE (MFIS)****INSTRUCTIONS**

Following is a list of statements that describe how fatigue may affect a person. Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. In medical conditions like MS, feelings of fatigue can occur more often and have a greater impact than usual. Please read each statement carefully, and then circle the one number (0, 1, 2,...) that best indicates how often fatigue has affected you in this way during the past 4 weeks. Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you.

**Because of my fatigue  
during the past 4 weeks...**

	Never	Rarely	Sometimes	Often	Almost Always
1. <u>I have been less alert.</u>	0	1	2	3	4
2. I have had difficulty paying attention for <u>long periods of time.</u>	0	1	2	3	4
3. I have been unable to <u>think clearly</u>	0	1	2	3	4
4. I have been clumsy <u>and uncoordinated</u>	0	1	2	3	4
5. <u>I have been forgetful</u>	0	1	2	3	4
6. I have had to pace myself <u>in my physical activities</u>	0	1	2	3	4

**Because of my fatigue  
during the past 4 weeks...**

	Never	Rarely	Sometimes	Often	Almost Always
7. I have been less motivated to do anything that requires <u>physical effort</u>	0	1	2	3	4
8. I have been less motivated to participate in social <u>activities.</u>	0	1	2	3	4
9. I have been limited in my ability to do things away <u>from home.</u>	0	1	2	3	4
10. I have had trouble maintaining physical effort <u>for long periods.</u>	0	1	2	3	4
11. I have had difficulty <u>making decisions</u>	0	1	2	3	4
12. I have been less motivated to do anything that requires <u>thinking</u>	0	1	2	3	4
13. <u>my muscles have felt weak</u>	0	1	2	3	4
14. <u>I have been physically uncomfortable</u>	0	1	2	3	4
15. I have had trouble finishing <u>tasks that require thinking</u>	0	1	2	3	4

**Because of my fatigue  
during the past 4 weeks...**

	Never	Rarely	Sometimes	Often	Almost Always
16. I have had difficulty organizing my thoughts when doing things at home or at work	0	1	2	3	4
17. I have been less able to complete tasks that require physical effort.	0	1	2	3	4
18. My thinking has been slowed down	0	1	2	3	4
19. I have had trouble concentrating	0	1	2	3	4
20. I have limited my physical activities.	0	1	2	3	4
21. I have needed to rest more often or for longer periods.	0	1	2	3	4

## **APPENDIX G. 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:

Trial 1, Timed 25-Foot Walk

Trial 2, Timed 25-Foot Walk

Trial 1, Dominant Hand, 9-HPT

Trial 2, Dominant Hand, 9-HPT

Trial 1, Non-Dominant Hand, 9-HPT

Trial 2, Non-Dominant Hand, 9-HPT

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

## Amended Protocol 02

If the subject cannot complete Trial 2 of the Timed Walk after a 5-minute rest period.

If the subject cannot complete a trial in 3 minutes.

### Administration

#### Trial 1

Make sure that the stopwatch is set to 0:00. For the Timed 25-Foot Walk, the subject should be directed to one end of a clearly marked 25-Foot course (clearly defined on the floor or on the wall) and instructed to stand just behind the starting line. Point out where the 25-Foot course ends, then instruct the subject as follows: *"I'd like you to walk 25 feet as quickly as possible, but safely. Do not slow down until after you've passed the finish line. Ready? Go."*

Begin timing when the lead foot is lifted and crosses the starting line. The examiner should walk along with the subject as s/he completes the task. Stop timing when the lead foot crosses the finish line. The examiner should then record the subject's walk time to within 0.1 second, rounding as needed. Round up to the next tenth if hundredth's place is  $>$  (greater than or equal to) .05, round down if hundredth's place is  $<$ .05 (e.g., 32.45" would round to 32.5" but 32.44" would round to 32.4"). Once the time is recorded, be sure to reset the stopwatch.

#### Trial 2

After completing the first timed walk, position the subject just behind the line where s/he is not standing, repeat the same instructions, and have the subject complete the walk again.

### Assistive Devices

The goal is to have the subject use the same assistive device at each study visit. The Study Physician/Neurologist will select an assistive device at the beginning of the study for each subject that needs one, keeping in mind that the subject may deteriorate modestly during the trial.

In general, subjects should use their customary assistive device(s), NOT the least assistance possible to complete the test. For subjects with significant gait impairment, the Study Neurologist/Physician should have the subject use a rolling walker even if this is not the subject's customary device. In general, non-wheeled walkers should not be used. If a subject does use an assistive device, this should be noted on the Record Form.

### Completing the Record Form

Record any circumstances that you believe may have affected the subject's performance. These are factors that may have affected the trial but were not severe enough to necessitate repetition of the trial. Examples include, but are not limited to, the following:

- The subject had a cold or reports not feeling well.
- The subject tripped but did not fall.



If a situation arises that necessitates the repetition of a trial, indicate the reason a trial had to be repeated on the Record Form. Examples of reasons to repeat a trial include, but are not limited to, the following:

- The subject fell during the walk.
- Examiner forgot to start or stop stopwatch.
- Examiner forgot to reset stopwatch in between trials.
- The subject stopped to talk to someone while walking, or another person/thing somehow interfered with walk.

Record only the times for the two **successfully completed** trials of the Timed 25-Foot Walk. If the subject could not complete one or both of the trials of the Timed 25-Foot Walk, record this in the appropriate Section of the Record Form. For example, if the subject's disease has progressed and/or physical limitations prohibit him or her from completing the trial, you should indicate "Unable to complete trial due to physical limitations" and record any specifics that you can observe (i.e., subject in a wheelchair now and unable to walk, etc.). If the subject did not complete a trial for any other reason, specify this as well (e.g., subject fell and was too fatigued to complete another trial, subject refused to complete trial).

### **Instructions for the 9-Hole Peg Test**

#### **Description**

The 9-HPT is a quantitative measure of upper extremity (arm and hand) function. The 9-HPT is the second component of the MSFC to be administered. Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand). It is important that the 9-HPT is administered on a solid table (not a rolling hospital bedside table) and that the 9-HPT apparatus be anchored.

#### **Materials Needed**

9-HPT Apparatus, Anchor, stopwatch, clipboard, 9-HPT Record Form

#### **Time Limit per Trial**

5 minutes (300 seconds) per trial

#### **Discontinue Rules**

If the subject cannot complete one trial of the 9-HPT in 5 minutes.

If the subject cannot complete a trial with his or her dominant hand within 5 minutes, move on to the trials with the non-dominant hand.

If the subject cannot complete a trial with his or her non-dominant hand, move on to the PASAT.

## Administration

### Dominant Hand---Trial 1

Make sure that the stopwatch is set to "0:00." Introduce this Section by saying, "*Now, we're going to be measuring your arm and hand function.*" If this is the first visit, determine the dominant hand, ask, "*Are you right or left-handed?*" If the subject is not sure, then the dominant hand is determined by asking the subject which hand he/she did or does write with. Make a note of the dominant hand for subsequent instructions. Place the 9-HPT apparatus on the table, directly in front of the subject. Arrange the apparatus so that the side with the pegs is in front of the hand being tested and the side with the empty pegboard is in front of the hand not being tested. Secure with anchor.

Read the following instructions to the subject: "***On this test, I want you to pick up the pegs one at a time, using one hand only, and put them into the holes as quickly as you can in any order until all the holes are filled. Then, without pausing, remove the pegs one at a time and return them to the container as quickly as you can. We'll have you do this two (2) times with each hand. We'll start with your [DOMINANT] hand. You can hold the pegboard steady with your [NON-DOMINANT] hand. If a peg falls onto the table, please retrieve it and continue with the task. If a peg falls on the floor, keep working on the task and I will retrieve it for you. See how fast you can put all of the pegs in and take them out again. Are you ready? Begin.***"

Start timing as soon as the subject touches the first peg, and stop timing when the last peg hits the container. If a peg drops on the floor, the examiner may retrieve it and put it back in the peg box. However, if a peg drops onto the table, allow the subject to retrieve it.

Record the subject's time under "Dominant hand ---Trial 1." If the subject stops after having put all the pegs into the holes, prompt the subject to remove them as well by saying, "***And now remove them all.***" If the subject begins to remove more than one peg at a time, correct him/her by saying, "***Pick up one peg at a time.***"

### Dominant Hand ---Trial 2

After the first trial with the dominant hand, say, "*Good. Now, I'd like you to do the same thing again, once again using your [DOMINANT] hand. See how fast you can put all of the pegs in and take them out again. Ready? Begin.*" Again, start timing as soon as the subject touches the first peg, and stop timing when the last peg hits the container. Record the subject's time under "Dominant hand---Trial 2."

### Non-Dominant Hand ---Trials 1 and 2

After the second trial with the dominant hand, rotate the apparatus 180 degrees such that the side with the pegs is now in front of the non-dominant hand and the empty pegboard is in front of the dominant hand. Then say, "*OK. Now, I'd like you to switch and use your [NON-DOMINANT] hand. This time, you can use your [DOMINANT] hand to stabilize the pegboard. Ready? Begin.*" Administer, time and record the two non-dominant hand trials following the procedures described above for dominant hand trials.

### **Completing the Record Form**

Record any circumstances that you believe may have affected the subject's performance. These are factors that may have affected the trial but were not severe enough to necessitate repetition of the trial. Examples include, but are not limited to, the following:

- The subject dropped a peg.
- The subject has a cold.
- The subject forgot eyeglasses and had difficulty seeing pegs.
- The subject talked during the task.
- The subject knocked entire apparatus on the floor

If a trial is repeated, indicate this and specify the reason it had to be repeated. Examples of reasons to repeat a trial include the following:

The subject knocked entire apparatus on the floor.

- The examiner forgot to start or stop stopwatch.
- The examiner forgot to reset the stopwatch in between trials.

Record only the times for the two **successfully completed trials** for each hand on the 9-HPT. If the subject could not complete one or both of the trials for either hand of the 9-HPT, record this in the appropriate Section of the Record Form. If the subject's disease has progressed and/or physical limitations prohibit him or her from completing the trial, the examiner should mark, "Unable to complete trial due to physical limitations." and then record any specifics that can be observed (e.g., subject unable to use right hand, subject could not complete within time limit, etc.). If the subject did not complete a trial for any other reason, describe the specific circumstances (e.g., subject refused).

### **Instructions for the Paced Auditory Serial Addition Test (PASAT)**

#### **Description**

The PASAT is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. The PASAT is the last measure administered at each visit. It is presented on CD player to control the rate of stimulus presentation. Single digits are presented every 3" and the subject must add each new digit to the one immediately prior to it. The test result is the number of correct sums given (out of 60 possible). To minimize familiarity with stimulus items, two alternate forms have been developed; the order of these should be counterbalanced across testing sessions.

#### **Materials Needed**

CD player, CD with PASAT stimuli, clipboard, PASAT Record Forms

#### **Discontinue Rules**

If the subject cannot get at least two answers correct (consecutive or not) on any one of the three 3" practice sequences.

Amended Protocol 02

If the subject cannot get at least one answer correct on PASAT-3" test, this subject is considered unable to perform the test.

### **Administration**

Verify that you have the correct Record Form and CD player (Form A or B) *before* you start reading the instructions for the 3" Practice Trial to the subject.

### **PASAT-3 Practice Trial**

For Part 1 (stimuli every 3") say, "*On this CD you are going to hear a series of single digit numbers that will be presented at the rate of one every 3 seconds. Listen for the first two numbers, add them up, and tell me your answer. When you hear the next number, add it to the one you heard on the tape right before it. Continue to add the next number to each preceding one. Remember, you are not being asked to give me a running total, but rather the sum of the last two numbers that were spoken on the tape.*"

Then give the following example: "*For example, if the first two numbers were '5' and '7,' you would say '12.'* If the next number were '3,' you would say '10.' Then if the next number were '2,' you would say '5.' If the subject is having difficulty understanding these instructions, write 5, 7, 3 and 2 on a sheet of paper and repeat the instructions demonstrating how the task is done.

Then say, "*This is a challenging task. If you lose your place, just jump right back in---listen for two numbers in a row and add them up and keep going. There are some practice items at the beginning of the tape. Let's try those first.*" Play the sample items, stopping the CD after the last practice item. Repeat the practice items, if necessary, until the subject understands the instructions (up to three times). You should always administer at least one practice trial before administering the actual test. If the subject begins to give you a running total, stop the practice immediately and explain the task again, emphasizing that he/she is not to give you a running total. Then start the practice items again from the beginning. If the subject begins adding each number to the number two previous to it, again stop the practice immediately, explain the correct way to do the task, and start the practice items from the beginning. If the subject merely makes a math error, do not stop the tape; continue with the practice items. After two consecutive 'no responses,' prompt him/her to resume by saying, "*Jump back in with the next two numbers you hear.*"

Administer the practice sequence a maximum of three times. Record answers in the space provided on the back of the PASAT Record Form.

**PASAT-3**

Once it is clear that the subject possesses sufficient understanding of the task, begin Part 1. Before starting Part 1, remind him/her: "*Remember if you get lost, just jump back in because I can't stop the test once it has begun.*" Discourage talking and oral calculations during the test, only the subject's answers should be spoken out loud. The subject may need prompting to continue the test if she/he gets lost. After five consecutive 'no responses,' redirect the subject quickly by saying, "*Jump back in,*" but do not stop the tape.

**Completing the PASAT Record Form**

Circle all correct answers. Write in any incorrect responses in the space provided. Place a dash when no response was given. If the subject corrects him/herself after giving a response, count the amended answer as the response. The *amended* response is the one that will be used in determining total correct, regardless of whether it was the correct or incorrect response. *Slash through the old response and write in "SC" with a circle around it to indicate that the subject self-corrected.*

Each Section of the PASAT has a maximum of 60 correct answers (i.e., 61 digits are presented for each part). Count the total number correct (number of circled answers) for PASAT-3 and record on both the PASAT Record Form and the Summary Score Sheet.

Finally record any circumstances that you believe may have affected the subject's performance. These are factors that may have affected the trial, but were not severe enough to necessitate repetition of the trial. Examples include, but are not limited to, the following:

- Subtle noises outside of the testing room
- Subject reports frustration or mild distress
- Subject talked during test (other than to give answers)

If a trial must be repeated, indicate this and specify the reason why it had to be repeated. Examples of reasons to repeat a trial include, but are not limited to, the following:

- Test interrupted (e.g. someone walked into the room or other major disturbance)
- Examiner error, such as starting the tape in the wrong place or using the wrong form.

Record only totals for the **successfully completed** PASAT-3.

If the subject is unable to perform the PASAT (i.e., cannot get at least two correct on any 3" practice and at least one correct on the test portion), the examiner should indicate "Unable to complete due to cognitive limitations" and record any specific observations. If the subject did not complete a trial for any other reason, record the reasons for this as well (e.g., subject refused to complete test, etc.).

**Scores from the MSFC component test results will be computed by the Data Management Center. Instructions will be included in the analytical plan.**

## **APPENDIX H. LOW-CONTRAST SLOAN LETTER CHART TESTING FOR PATIENTS WITH MULTIPLE SCLEROSIS**

### **Low-Contrast Sloan Letter Chart Testing**

For Patients with Multiple Sclerosis:

Testing Protocol Manual

(BINOCULAR TESTING)

Laura J. Balcer, M.D., M.S.C.E.

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*The following are instructions for testing patients using the front illuminated Low-Contrast Sloan Letter Charts (LCSLC - Precision Vision, LaSalle, IL). The inter-rater reliability of this testing protocol has been shown to be extremely high in patients with multiple sclerosis and in visually-asymptomatic volunteers. A standardized script with instructions to be read to the patient by the examiner is included below. The examiner should read through the following instructions and practice testing prior to examining study patients.*

#### Preparation and Set-Up:

- a) Set room lighting level to 80-100 cd/m<sup>2</sup> (equivalent is about 80-100 foot-candles). This level illumination may be achieved in a bright exam room/hallway with fluorescent lighting. Having exact lighting is less important than using the same room/area for each patient/testing session.
- b) Place the charts at 2 meters distance from the patient's eyes. An artist's easel or similar device may be used, as may a ledge, stand, or chair to prop the charts perpendicular to the floor. Use a pre-measured string or tape to measure the distance from the patient's eyes (bridge of nose) to the testing charts at the beginning of each testing session (each patient).
- c) The 100%, 2.5%, and 1.25% charts will be used for testing.
- d) Patients should wear their usual distance correction for testing (glasses or contact lenses that are used for driving, etc.). The same glasses or contact lenses (same prescription) should be used for each testing session throughout the study.
- e) Patients should be asked to read the charts with both eyes open.

#### Vision Testing:

Instruct patient to read slowly, letters only, left to right, starting at the top of the chart.

Amended Protocol 02

Instruct the patient that they are not allowed to re-read any line.

The patient is allowed to correct a “mis-speak” of a single letter only if he/she does so before reading the next letter---instruct the patient of this.

During the chart reading, PUSH (encourage) the patient until he/she cannot read any letters after being told to guess.

The patient must guess at each letter, even if he/she cannot easily read it, until he/she cannot or does not correctly identify any of the 5 letters on a particular line.

Stopping Rule: Once the patient cannot or does not correctly identify any of the 5 letters on a line after attempting it, STOP. Go on to the next chart.

Test all 3 charts in the same order (100%, 2.5%, 1.25%) for each patient.

During testing, circle all letters read correctly on the data forms for each chart (with both eyes). Put an “X” through each incorrectly identified letter; leave unattempted letters unmarked.

Fill in the number of letters correct at the end of each line of 5 letters. Record the total number of letters correct for each chart at the bottom of the column. The Snellen visual acuity equivalent (i.e., 20/20 or 6/6) for the patient corresponds to the lowest line on the 100% chart (black on white) for which the patient identifies 3 or more letters correctly.

If a patient is unable to identify any of the letters correctly on the first line of any of the 3 charts, please indicate this at the top of the data collection form.



Script for Testing to be Read to Patient:

These instructions should be read to the patient once he/she is comfortably seated in front of the charts at 2 meters distance (see above for instructions on Preparation and Set-Up):

1. I am going to show you 3 different eye charts with letters on them. The letters will become increasingly lighter for each chart.
2. For each chart, please begin at the very top of the chart and read each letter slowly, from left to right on each line.
3. If you miss-speak on a letter or feel you have identified it incorrectly, you may correct your response only before you read the next letter.
4. You are not allowed to re-read an entire line.
5. Please try not to lean forward in the chair while reading the letters.

After the first chart (100% chart) has been uncovered, say:

6. You may begin reading the letters.
7. Please start at the top of the chart.

For each chart, allow the patient to continue reading letters until he/she either:

1) Does not identify any of the 5 letters on any given line correctly → say:

You may stop. We will go on to the next chart now.

OR

2) States that they are unable to read any more letters → point to the line which is next for the patient to attempt (use the yellow-tipped pointer only) and say:

Can you read any of the letters on this line?

a) If patient responds no → say: Please guess if you can.

If patient responds that they cannot → say:

You may stop. We will go on to the next chart now.

b) If patient responds yes or begins reading, then continue to record responses until the patient cannot or does not correctly identify any of the 5 letters on a given line.

Stopping Rule: For each chart, once the patient cannot or does not identify any of the 5 letters correctly on a given line, say: You may stop. We will go on to the next chart now.

Amended Protocol 02

Please use the yellow-tipped pointer only to point to the charts (pens and fingers may leave marks). The examiner may point to the chart when requested by the patient to indicate the line that they are attempting/should attempt next.

Repeat the above procedure for each of the 3 charts (100%, 2.5%, and 1.25% in that order) with both eyes open.

## APPENDIX I. LOW-CONTRAST TUMBLING-E CHART TESTING FOR PATIENTS WITH MULTIPLE SCLEROSIS

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Visual Function Test Instructions (Tumbling E Version)  
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### Low-Contrast Tumbling E Chart Testing For Patients with Multiple Sclerosis: Testing Protocol Manual (BINOCULAR TESTING)

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*The following are instructions for testing patients using the front illuminated Low-Contrast Tumbling E Charts (Precision Vision, LaSalle, IL). The inter-rater reliability of this testing protocol has been shown to be extremely high in patients with multiple sclerosis and in visually-asymptomatic volunteers. A standardized script with instructions to be read to the patient by the examiner is included below. The examiner should read through the following instructions and practice testing prior to examining study patients.*

#### Preparation and Set-Up:

1. Set room lighting level to 80-100 cd/m<sup>2</sup> (equivalent is about 80-100 foot-candles). This level illumination may be achieved in a bright exam room/hallway with fluorescent lighting. Having exact lighting is less important than using the same room/area for each patient/testing session.
2. Place the charts at 2 meters distance from the patient's eyes. An artist's easel or similar device may be used, as may a ledge, stand, or chair to prop the charts perpendicular to the floor. Use a pre-measured string or tape to measure the distance from the patient's eyes (bridge of nose) to the testing charts at the beginning of each testing session (each patient).
3. The 100%, 2.5%, and 1.25% charts will be used for testing.
4. Patients should wear their usual distance correction for testing (glasses or contact lenses that are used for driving, etc.). The same glasses or contact lenses (same prescription) should be used for each testing session throughout the study.
5. Patients should be asked to read the charts with both eyes together.

Visual Function Test Instructions (Tumbling E Version)  
Page 2 of 4**Vision Testing:**

1. Instruct patient to read slowly, left to right, starting at the top of the chart. The patient should indicate the direction that the "E" character points, that is, which direction do the 3 lines of the "E" point (i.e. **E**, **3**, **W**, **M**)? Patients can speak their native language equivalent of "right," "left," "up," or "down."
2. Instruct the patient that they are not allowed to re-"read" any line.
3. The patient is allowed to correct a "mis-speak" of the direction of a single letter "E" only if he/she does so before reading the next letter "E"---instruct the patient of this.
4. During the chart reading, **PUSH** (encourage) the patient until he/she cannot identify the direction any "E" letters after being told to guess.
5. The patient must guess at the direction of each letter "E," even if he/she cannot easily read it, until he/she cannot or does not correctly identify the directions of any of the 5 letters "E" on a particular line.
6. **Stopping Rule:** Once the patient cannot or does not correctly identify the direction of any of the 5 letters "E" on a line after attempting it, **STOP**. Go on to the next chart.
7. Test all 3 charts in the same order (100%, 2.5%, 1.25%) for each patient.
8. During testing, circle all letters "E" for which the direction is identified correctly on the data forms for each chart. Put an "**X**" through each incorrectly identified "E" direction; leave unattempted letters "E" unmarked.
9. Fill in the number of letters "E" for which the direction is identified correctly at the end of each line of 5 letters "E." Record the total number of letters correct for each chart at the bottom of the column. The **Snellen visual acuity equivalent** (i.e., 20/20 or 6/6) for the patient corresponds to the lowest line on the **100% chart** (black on white) for which the patient identifies the direction of 3 or more letters "E" correctly.
10. If a patient is unable to identify the direction of any of the letters "E" correctly on the first line of any of the 3 charts, please indicate this at the top of the data collection form.

Visual Function Test Instructions (Tumbling E Version)  
Page 3 of 4**Script for Testing to be Read to Patient:**

These instructions should be read to the patient once he/she is comfortably seated in front of the charts at 2 meters distance (see above for instructions on Preparation/Set-Up):

1. *I am going to show you 3 different eye charts with capital letters "E" on them. The letters will become increasingly lighter for each chart.*
2. *For each chart, please begin at the very top of the chart and slowly identify which direction the three straight lines of the letter "E" is pointing. For example, if the letter looks like this (show patient an example written or printed E), you would say "to the right."*
3. *Identify the direction of each letter "E" slowly, from left to right on each line.*
4. *If you mis-speak on the direction of a letter "E" or feel you have identified it incorrectly, you may correct your response only before you read the next letter "E".*
5. *You are not allowed to re-read an entire line.*
6. *Please try not to lean forward in the chair while reading the letters.*

After the first chart (100% chart) has been uncovered, say:

1. *You may begin reading the letters.*
2. *Please start at the top of the chart.*

For each chart, allow the patient to continue reading letters until he/she either:

- 1) Does not identify the direction of any of the 5 letters "E" on any given line correctly  
→ say: *You may stop. We will go on to the next chart now.*  
**OR**
- 2) States that they are unable to identify the direction of any more letters "E" → point to the line which is next for the patient to attempt (use yellow-tipped pointer only) and say:  
*Can you identify which way any of the letters "E" on this line are pointing?*
  - a) If patient responds **no** → say: *Please guess if you can.*  
If patient responds that they cannot → say:  
*You may stop. We will go on to the next chart now.*
  - b) If patient responds **yes** or begins reading, then continue to record responses until the patient cannot or does not correctly identify the direction of any of the 5 letters "E" on a given line.

**Stopping Rule:** For each chart, once the patient cannot or does not identify the direction of any of the 5 letters "E" correctly on a given line, say: *You may stop. We will go on to the next chart now.*

**Please use the yellow-tipped pointer only to point to the charts (pens and fingers may leave marks). The examiner may point to the chart when requested by the patient to indicate the line that they are attempting/should attempt next.**

Visual Function Test Instructions (Tumbling E Version)  
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**Low-Contrast Tumbling E Chart Testing – Binocular (both eyes open)**

Name of Examiner: \_\_\_\_\_

Snellen Visual Acuity Equivalent			100% Chart (2 meters)	2.5% Chart (2 meters)	1.25% Chart (2 meters)
Feet (20/x)	Meters (6/x)	Chart Line	Chart Symbols (circle correct)	Chart Symbols (circle correct)	Chart Symbols (circle correct)
20/200	6/60	20M	Э M Э W E _____	M Э E W E _____	Э W Э E M _____
20/160	6/48	16M	W E W Э M _____	W M Э E Э _____	E Э E M W _____
20/125	6/37.5	12M	E Э M W Э _____	E W M Э M _____	M E M W Э _____
20/100	6/30	10M	M E W Э W _____	Э E W M W _____	W M W Э E _____
20/80	6/24	8M	W Э M W E _____	E M Э W Э _____	E W E M Э _____
20/64	6/19.2	6M	E M W E Э _____	M E W Э W _____	W E W Э M _____
20/50	6/15	5M	Э W E Э M _____	Э W M E M _____	M Э M W E _____
20/40	6/12	4M	W E Э M Э _____	W Э E M E _____	Э M Э E W _____
20/32	6/9.6	3M	Э M E W E _____	Э M W E M _____	M Э W M E _____
20/25	6/7.5	2.5M	E W M Э W _____	W E Э M E _____	Э M E Э W _____
20/20	6/6	2M	W Э E W M _____	M W E Э W _____	W E Э W M _____
20/16	6/4.8	1.6M	M W M Э E _____	E Э M W Э _____	E W M E Э _____
			Total correct _____	Total correct _____	Total correct _____

Snellen visual acuity equivalent \_\_\_\_\_  
(Snellen equivalent (i.e., 6/6 in meters) for lowest line on 100% chart for which subject identifies 3 or more correctly)



**APPENDIX J. WORK PRODUCTIVITY AND ACTIVITIES  
IMPAIRMENT – GENERAL HEALTH V2.0 (WPAI-GH)  
QUESTIONNAIRE**

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? \_\_\_\_\_ NO \_\_\_\_\_ YES  
*If NO, check "NO" and skip to question 6.*

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

\_\_\_\_\_ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

\_\_\_\_\_ HOURS

4. During the past seven days, how many hours did you actually work?  
\_\_\_\_\_ HOURS *(If "0", skip to question 6.)*



5. During the past seven days, how much did your health problems affect your productivity while you were working?

*Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.*

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	Health problems completely prevented me from working
--	------------------------	--

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

*By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.*

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	Health problems completely prevented me from doing my daily activities
--	------------------------	--

CIRCLE A NUMBER

## APPENDIX K. THE SF-36V2™ HEALTH SURVEY

The SF-36® Health Survey asks for your views about your health in general. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully, and circle the one number that best describes your answer to each question. *Thank you for completing this survey!*

1. In general, would you say your health is:

(circle one)

- |                 |   |
|-----------------|---|
| Excellent.....  | 1 |
| Very Good ..... | 2 |
| Good .....      | 3 |
| Fair .....      | 4 |
| Poor .....      | 5 |

1. Compared to one year ago, how would you rate your health in general now?

(circle one)

- |  |   |
|--|---|
| Much better now than one year ago.....     | 1 |
| Somewhat better now than one year ago..... | 2 |
| About the same as one year ago .....       | 3 |
| Somewhat worse now than one year ago ..... | 4 |
| Much worse now than one year ago.....      | 5 |

2. The following questions are about activities you might do during a typical day.

Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

<u>Activities</u>	<b>Yes, Limited A Lot</b>	<b>Yes, Limited A Little</b>	<b>No, Not Limited At All</b>
a. <b>Vigorous activities</b> , such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. <b>Moderate activities</b> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing <b>several</b> flights of stairs	1	2	3
e. Climbing <b>one</b> flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking <b>more than a mile</b>	1	2	3
h. Walking <b>several hundred yards</b>	1	2	3
i. Walking <b>one hundred yards</b>	1	2	3
j. Bathing or dressing yourself	1	2	3

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

	<b>All of the time</b>	<b>Most of the time</b>	<b>Some of the time</b>	<b>A little of the time</b>	<b>None of the time.</b>
a. Cut down on the <b>amount of time</b> you spent on work or other activities	1	2	3	4	5
b. <b>Accomplished less</b> than you would like	1	2	3	4	5
c. Were limited in the <b>kind</b> of work or other activities	1	2	3	4	5
d. Had <b>difficulty</b> performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	All of the Time	Most of the Time	Some of the Time	A Little of the Time	None of the Time
a. Cut down the <b>amount of time</b> you spent on work or other activities	1	2	3	4	5
b. <b>Accomplished less</b> than you would like	1	2	3	4	5
c. Did work or other activities <b>less carefully than usual</b>	1	2	3	4	5

5. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one)

- Not at all .....1
- Slightly.....2
- Moderately.....3
- Quite a bit .....4
- Extremely.....5

6. How much bodily pain have you had during the past 4 weeks?

(circle one)

- None .....1
- Very mild.....2
- Mild .....3
- Moderate.....4
- Severe .....5
- Very Severe .....6

7. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

- Not at all ..... 1
- A little bit..... 2
- Moderately..... 3
- Quite a bit ..... 4
- Extremely ..... 5

8. These questions are about how you feel and how things have been with you during the past 4 weeks: For each question, please give the one answer that comes closest to the way you have been feeling: How much of the time during the past 4 weeks -

.....(circle one number on each line)

	<b>All of the Time</b>	<b>Most of the Time</b>	<b>Some of the Time</b>	<b>A little of the Time</b>	<b>None of the Time</b>
a. Did you feel full of life?	1	2	3	4	5
b. Have you been very nervous?	1	2	3	4	5
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5
d. Have you felt calm and peaceful?	1	2	3	4	5
e. Did you have a lot of energy?	1	2	3	4	5
f. Have you felt down-hearted and depressed?	1	2	3	4	5
g. Did you feel worn out?	1	2	3	4	5
h. Have you been happy?	1	2	3	4	5
i. Did you feel tired?	1	2	3	4	5

9. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one)

- All of the time ..... 1
- Most of the time ..... 2
- Some of the time ..... 3
- A little of the time ..... 4
- None of the time..... 5

10. How TRUE or FALSE is each of the following statements for you?

(circle one number on each line)

	<b>Definitely True</b>	<b>Mostly True</b>	<b>Don't Know</b>	<b>Mostly False</b>	<b>Definitely False</b>
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5