

**Clinical Study Protocol with Amendment 04**

**A Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled,  
Parallel-Group Study to Evaluate the Efficacy and Safety of Laquinimod (0.5,  
1.0 and 1.5 mg/day) as Treatment in Patients with Huntington's Disease**

**Phase II**

**Study TV5600-CNS-20007**

**(LEGATO-HD - Laquinimod Efficacy and Safety in a Global Trial Of HD)**

**IND 120331**

**EudraCT number: 2014-000418-75**

**Global Protocol Amendment 04 Approval Date: 16 February 2016**

**Sponsor (and Monitor)**

Teva Branded Pharmaceutical Products R&D, Inc.  
41 Moores Rd.  
Frazer, PA 19355  
USA

**Authorized Representative (Signatory)**

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

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**PROTOCOL AMENDMENTS****A Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled,  
Parallel-Group Study to Evaluate the Efficacy and Safety of Laquinimod (0.5,  
1.0 and 1.5 mg/day) as Treatment in Patients with Huntington's Disease****Study TV5600-CNS-20007****(LEGATO-HD - Laquinimod Efficacy and Safety in a Global Trial Of HD)**

The original protocol for study TV5600-CNS-20007 (dated 27 May 2014) has been amended and reissued as follows:

Global Protocol Amendment 04	16 February 2016 (123 patients randomized to date)
Administrative Letter 07	05 November 2015
Administrative Letter 06	22 October 2015
Global Protocol Amendment 03	24 September 2015 (75 patients randomized to date)
Administrative Letter 05	29 April 2015
Administrative Letter 04	21 April 2015
Administrative Letter 03	18 February 2015
Global Protocol Amendment 02	16 February 2015 (6 patients enrolled to date)
Protocol Amendment (Local EC UK 02)	25 January 2015
Administrative Letter 02	14 November 2014
Protocol Amendment (Local EC UK 01)	30 September 2014 (0 patients enrolled to date)
Global Protocol Amendment 01	10 September 2014 (0 patients enrolled to date)
Administrative Letter 01	18 July 2014
Protocol Approval Date	27 May 2014

**INVESTIGATOR AGREEMENT**

**Clinical Study Protocol with Amendment 04**

**Original Protocol Dated 27 May 2014**

**IND Number: 120331; EudraCT Number: 2014-000418-75**

**A Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Laquinimod (0.5, 1.0 and 1.5 mg/day) as Treatment in Patients with Huntington's Disease**

**Principal Investigator:** \_\_\_\_\_

**Title:** \_\_\_\_\_

**Address of Investigational Center:** \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_


**Tel:** \_\_\_\_\_

I have read the protocol with Amendment 04 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes approval of this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

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

<b>Principal Investigator</b>	<b>Signature</b>	<b>Date</b>

**SPONSOR PROTOCOL APPROVAL**

<b>Sponsor's Authorized Representative</b>	<b>Signature</b>	<b>Date</b>
Spyros Papapetropoulos, MD, PhD Global Head, Neurodegeneration, Clinical Development		Feb-16-2016

**COORDINATING INVESTIGATOR AGREEMENT**

**Clinical Study Protocol with Amendment 04**

**Original Protocol Dated 27 May 2014**

**IND Number: 120331; EudraCT Number: 2014-000418-75**

**A Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Laquinimod (0.5, 1.0 and 1.5 mg/day) as Treatment in Patients with Huntington's Disease**

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**Coordinating Investigator:** Ralf Reilmann, MD, PhD

**Title:** Founding Director and CEO, George Huntington Institute; Chair - EHDN Huntington Center, University of Munster; Chair - Laboratory of Biomarkers and Neurodegeneration, University of Munster

**Address of Investigational Center:**

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Technology-Park - Deilmann Building IV J  
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<p><b>Coordinating Investigator</b> Ralf Reilmann, MD, PhD</p>	<p><b>Signature</b> </p>	<p><b>Date</b> 16 FEB 2016</p>
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## **CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS**

### **Central Clinical Laboratory**

Quest Diagnostics Clinical Laboratories, Inc.  
27027 Tourney Road  
Suite 2E Valencia, CA 91355  
USA

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Middlesex TW5 9QA  
UK

Quest Diagnostics Nichols Institute  
33608 Ortega Highway  
San Juan Capistrano, CA 92675-2042  
USA

### **Central Electrocardiogram Evaluation**

Biomedical Systems Corporation  
77 Projgress Parkway  
St. Louis, MO 63053  
USA

### **Web and Phone Integrated Interactive Response Technology**

PAREXEL International  
Lady Bay House  
Meadow Grove  
Nottingham  
NG2 3HF  
UK

### **Computer-Based Rating System**

QuantiMedis GmbH  
Marientalstrasse 43  
48149 Münster  
Germany

Stout Neuropsych Pty Ltd  
44 Stewart Street  
Ormond VIC 3204  
Australia

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**Bioanalytical Laboratory**

Teva Pharm. Works Private Ltd. Co (TPW)  
Pallagi St 13  
4042 Debrecen  
Hungary

**Central MRI Vendor**

IXICO Technologies Limited  
4<sup>th</sup> Floor, Griffin Court  
15 Long Lane  
London  
EC1A 9PN  
United Kingdom

**Scale Management**

Bracket  
575 E. Swedesford Road, Suite 200  
Wayne, PA 19087  
USA

**MRS Analysis**

University of British Columbia MRI Research Centre  
Room M10 Purdy Pavilion  
2221 Wesbrook Mall  
Vancouver  
British Columbia  
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CANADA

**PET Substudy**

Imperial College London  
Hammersmith Hospital, Neurology Imaging Unit  
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W12 0NN  
United Kingdom

**Collaborator**

Huntington Study Group  
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University of Ulm  
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D-89081 Ulm  
Germany

## **CLINICAL STUDY PERSONNEL CONTACT INFORMATION**

**For medical issues, contact the physician listed below:**

**Global/EU :**

Marianne Giuffra, MD  
(Located in Germany)  
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**US:**

Margaret Zalewski, MD  
(Located in the East Coast of US)  
Office Phone (between 9-5 EST): +1 215 616 4969  
e-mail: Margaret.Zalewski@iconplc.com

In a study-related medical emergency situation, when assigned Medical Monitors for a study cannot be reached, an on-call Physician can be reached 24 hours per day, 7 days per week via an ICON Call-Center: Telephone: +1 919 674 5468

[Toll (not free of charge) telephone number allowing a global reach from both landlines and mobile phones]

On the following internet page (<https://icophone.iconplc.com>), a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the toll (not free of charge) number as indicated above. Toll-free numbers are unfortunately not available from mobile phones.

**For operational issues, contact the operational lead listed below:**

Montserrat Sanz Gomez  
Project Manager, Clinical Research Service  
External Tel: +44 162 849 6339  
Mobile: +44 782 438 2575  
e-mail: Montserrat.SanzGomez@iconplc.com

**For serious adverse events:**

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

## CLINICAL STUDY PROTOCOL SYNOPSIS

**Sponsor:** Teva Branded Pharmaceutical Products R&D, Inc.

**Title of Study:** A Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Laquinimod (0.5, 1.0 and 1.5 mg/day) as Treatment in Patients with Huntington's Disease

**Study Number:** TV5600-CNS-20007 (LEGATO-HD - Laquinimod Efficacy and Safety in a Global Trial Of HD)

**EudraCT/IND Number(s):** 2014-000418-75/120331

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

**Name of Investigational Product:** Laquinimod (TV-5600 or ABR-215062)

**Phase of Clinical Development:** II

**Number of Investigational Centers Planned:** Approximately ~51 centers

**Countries Planned:** North America, Europe and Russia

**Number of Patients Planned:** Approximately 300 patients (100 patients within each study arm) plus the 30 patients that were already randomized to the laquinimod 1.5 mg treatment arm.

**Study Population:** The study population will be comprised of patients with adult onset Huntington's disease, with a cytosine-adenosine-guanine (CAG) repeat length between 36 and 49, inclusive. The basic eligibility criteria will select a population with symptoms of Huntington's disease (HD), as assessed by a Unified Huntington's Disease Rating Scale – Total Motor Score (UHDRS-TMS) >5, but with a largely retained functional capacity, as assessed with a Unified Huntington's Disease Rating Scale – Total Functional Capacity (UHDRS-TFC) score ≥ 8.

**Planned Study Period:** Q4 2014 – Q1 2018

**Primary Study Objective:** The primary objective of this study is to assess the efficacy of laquinimod (0.5 mg and 1.0 mg qd) in patients with HD after 12 months of treatment using the UHDRS-TMS.

**Secondary Study Objectives:**

- To assess the effect of laquinimod on brain atrophy in patients with HD after 12 months of treatment using MRI measures of caudate volume.
- To assess the effect of laquinimod on the cognitive capacity in patients with HD after 12 months of treatment using the cognitive assessment battery (CAB) for patients with HD [comprised of: Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLTR), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version)].
- To assess the effect of laquinimod on the clinical global impression in patients with HD after 12 months of treatment using the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-Plus)
- To assess the effect of laquinimod on the functional capacity in patients with HD after 12 months of treatment using the UHDRS-TFC scale



**Exploratory Study Objectives:**

- To assess the effect of laquinimod on brain atrophy in patients with HD after 12 months of treatment using MRI measures of whole brain volume, white-matter volume and ventricular volume.
- To assess the effect of laquinimod on the functional capacity in patients with HD after 12 months of treatment using the UHDRS-functional assessment (FA) scale
- To assess the effect of laquinimod on motor function in patients with HD after 12 months of treatment using the objective instrument Q-Motor
- To assess the effect of laquinimod on physical performance in patients with HD after 12 months of treatment using the modified Physical Performance Test (mPPT).
- To assess the effect of laquinimod on the quality of life in patients with HD after 12 months of treatment using the Huntington's Disease Quality of Life (HD-QoL) and EQ-5D-5L instruments
- To assess the effect of laquinimod on work productivity in patients with HD after 12 months of treatment.
- To assess the effect of laquinimod on functional impairment due to cognitive decline in patients with HD after 12 months of treatment using the Clinical Dementia Rating – Sum of Boxes (CDR-SB)
- To assess the effect of laquinimod on depression and anxiety in patients with HD after 12 months of treatment using the Hospital Anxiety and Depression Scale (HADS)
- To assess the effect of laquinimod on behavioral signs and symptoms in patients with HD after 12 months of treatment using the Problem Behaviors Assessment-Short form (PBA-s)
- To evaluate the pharmacokinetics of laquinimod and its metabolites in patients with HD
- To investigate the relationship between exposure to laquinimod and its metabolites and outcome measures (e.g., clinical effect and toxicity parameters).

**Safety and Tolerability Study Objectives:**

- To evaluate safety and tolerability of laquinimod in patients with HD during 12 months of treatment by evaluating adverse events (AEs), electrocardiography (ECG), and clinical laboratory parameters, vital signs, physical examinations, and premature discontinuations from the study.

**Ancillary Study Objectives (substudies):**

- To explore potential correlation between genetic polymorphisms in deoxyribonucleic acid (DNA) and pharmacokinetics, clinical response to laquinimod, and/or adverse drug reactions, if these occur
- To explore potential correlation between ribonucleic acid (RNA) expression profile in blood cells and clinical response to laquinimod
- To explore changes in blood cell gene expression profile following treatment with laquinimod as potential biomarkers for laquinimod mechanism of action
- To evaluate changes in cytokines and other soluble protein levels following treatment with laquinimod as potential biomarkers for laquinimod mechanism of action and/or response predictive factors
- To explore gene expression and/or protein profile in monocytes in response to laquinimod treatment
- To explore change in microglial activation state in response to treatment with laquinimod
- To explore the potential effect on metabolic changes in the putamen and frontal white matter that are associated with the earliest stages of Huntington's Disease.

**Criteria for Inclusion:**

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

- a. **[New criterion]** Documentation of prior positive genetic testing for HD, or a clinical diagnosis of symptomatic HD (Diagnostic Confidence Level 4).
- b. **[Revision 1]** Presence of 36-49 CAG repeats, inclusive, in the huntingtin gene based on centralized CAG testing during screening.
- c. Male or female between 21-55 years of age, inclusive, with an onset of HD at or after 18 years of age.
- d. **[Revision 1]** Women of child-bearing potential (women who are not post-menopausal or who have not undergone surgical sterilization) must practice an acceptable method of birth control for 30 days before taking the study treatment, and 2 acceptable methods of birth control during all study duration and until 30 days after the last dose of treatment was administered. Acceptable methods of birth control in this study include: Intrauterine device, barrier method (condom or diaphragm with spermicide) and hormonal methods of birth control (e.g., oral contraceptive, contraceptive patch, long-acting injectable contraceptive).
- e. A sum of >5 points on the UHDRS-TMS at the screening visit
- f. UHDRS- TFC  $\geq$  8 at the screening visit.
- g. Able and willing to provide written informed consent prior to any study related procedure being performed at the screening visit. Patients with a legal guardian should be consented according to local requirements.
- h. Willing to provide a blood sample for genomic CAG analysis at the screening visit.
- i. Willing and able to take oral medication and able to comply with the study specific procedures.
- j. Ambulatory, being able to travel to the study centre, and judged by the investigator as likely to be able to continue to travel for the duration of the study
- k. Availability and willingness of a caregiver, informant, or family member to provide input at study visits assessing CIBIC-Plus, CDR-SB, PBA-s, and HD-QoL. A caregiver is recommended to be someone who attends to the patient at least 2 to 3 times per week for at least 3 hours per occasion, and the suitability of the caregiver should be judged by the investigator.
- l. For patients taking allowed antidepressant medication, the dosing of medication must have been kept constant for at least 30 days before baseline and must be kept constant during the study.

**Criteria for Exclusion:**

Patients are excluded from participating in this study if 1 or more of the following criteria are met:

- a. Use of immunosuppressive agents, or cytotoxic agents, including cyclophosphamide and azathioprine within 12 months prior to screening
- b. Previous use of laquinimod

- c. Use of moderate/strong inhibitors of cytochrome P450 (CYP)3A4 within 2 weeks prior to randomization.
- d. Use of inducers of CYP3A4 within 2 weeks prior to randomization.
- e. Pregnant or breastfeeding.
- f. **[Revision 1]** Serum levels  $\geq 2$ x upper limit of the normal range (ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at screening.
- g. **[Revision 1]** Serum direct bilirubin which is  $\geq 1.5$ xULN at screening.
- h. **[Revision 2]** Estimated creatinine clearance  $< 60$  mL/min at screening, calculated using the Cockcroft Gault equation:  $(140 - \text{age}) \times \text{mass (kg)} \times [0.85 \text{ if female}] / 72 \times \text{serum creatinine (mg/dL)}$
- i. **[Revision 1]** Subjects with a clinically significant or unstable medical or surgical condition that may put the patient at risk when participating in the study or may influence the results of the study or affect the patient's ability to take part in the study, as determined by medical history, physical examinations, ECG, or laboratory tests. Such conditions may include:
  - 1. A major cardiovascular event (e.g. myocardial infarction, acute coronary syndrome, decompensated congestive heart failure, pulmonary embolism, coronary revascularization, angina) that occurred prior to randomization.
  - 2. Significant cardiovascular risk factors (such as, but not limited to, uncontrolled hypertension, uncontrolled diabetes), per investigator discretion.
  - 3. Any acute pulmonary disorder
  - 4. A central nervous system (CNS) disorder other than HD that may jeopardize the subject's participation in the study, including such disorders that are demonstrated on the baseline magnetic resonance imaging (MRI) (based on local read).
  - 5. A gastrointestinal disorder that may affect the absorption of study medication.
  - 6. Acute or chronic renal disease including acute kidney injury (AKI).
  - 7. Any form of acute or chronic liver disease.
  - 8. Known human immunodeficiency virus (HIV) positive status. Patients will undergo an HIV test at screening per local requirements, if applicable.
  - 9. Any malignancies, excluding basal cell carcinoma, in the 5 years prior to randomization.
- j. Any clinically significant, abnormal, screening laboratory result which in the opinion of the investigator, affects the patients' suitability for the study or puts the patient at risk if he/she enters the study
- k. Unsuitable for MRI (e.g., claustrophobia, metal implants)
- l. Alcohol and/or drug abuse within the 12 months prior to screening, as defined by Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition Text Revision (DSM-IV TR) criteria for substance abuse. For former alcohol and/or drug abusers, the abstinence should be confirmed by laboratory tests (drug testing and/or carbohydrate deficient transferrin (CDT) level in blood).

- m. Patients with active suicidal ideation during the past month as measured by a most severe suicide ideation score of 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or 5 (Active Suicidal Ideation with Specific Plan and Intent) on the baseline screening Columbia-Suicide Severity Rating Scale (C-SSRS) or subjects who answer “Yes” on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) if the attempt or acts were performed within 1 year of screening, or subjects who, in the opinion of the investigator, present a serious risk of suicide.
- n. Patients with known intracranial neoplasms, vascular malformations, or intracranial hemorrhage
- o. Known drug hypersensitivity that would preclude administration of laquinimod or placebo, such as hypersensitivity to mannitol, meglumine or sodium stearyl fumarate.
- p. Swallowing difficulties that would preclude administration of laquinimod or placebo capsules.
- q. [Revision 1] Treatment with any investigational product within 30 days of screening or patients planning to participate in another clinical study assessing any investigational product during the study. Patients in non-interventional and/or observational studies will not be excluded from participating in this study.
- r. Treatment with tetrabenazine within 30 days of the study baseline visit
- s. Treatment with antipsychotic medication within 30 days of the study baseline visit

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

**Investigational Product:**

The dose levels of laquinimod are 0.5, 1.0, and 1.5 mg qd. Every patient will take 3 capsules once daily, at the same time of day, during the entire study period.

- Patients randomized to the laquinimod 1.5 mg qd treatment arm will receive 3 capsules of 0.5 mg laquinimod. (Note: the treatment of this high dose arm was discontinued as of 10 January 2016)
- Patients randomized to the laquinimod 1.0 mg qd treatment arm will receive 2 capsules of 0.5 mg laquinimod and 1 capsules of matching placebo.
- Patients randomized to the laquinimod 0.5 mg qd treatment arm will receive 1 capsule of 0.5 mg laquinimod, and 2 capsules of matching placebo.

**Placebo:** Patients randomized to the placebo treatment arm will receive 3 capsules of matching placebo.

The capsules will be taken orally and must be swallowed whole with a glass of water. The capsule should not be opened. Laquinimod can be taken with or without food.

**Method of Blinding and Randomization:**

Prior to 10 January 2016, patients were randomly assigned to receive treatment with laquinimod at a dosage of 0.5, 1.0, or 1.5 mg qd or a matching placebo in a 1:1:1:1 ratio.

As of 10 January 2016, following the decision to discontinue treatment of the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1:1 ratio to receive treatment with laquinimod at a dosage of 0.5, 1.0 mg qd or a matching placebo. No change was performed to the original randomization list except that the patient numbers assigned to laquinimod 1.5 mg/day were removed from the list by the interactive response technology (IRT) vendor.

Patients and investigators will remain blinded to treatment assignment during the study.

The randomization code will be generated by the Clinical Supply Chain (CSC) department following specifications from the Biostatistics Department.

In addition, the sponsor's clinical personnel involved in the study will be blinded to the study drug identity until the database has been locked for analysis and the treatment assignment revealed.

### **Duration of Participation:**

Total study participation will be up to 14 months:

- Screening period of 2 weeks up to 5 weeks
- 12 months double-blind, placebo-controlled treatment period
- Safety follow-up period 1 month following the last dose of study medication.

### **General Design and Methodology:**

This is a multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled study, to evaluate the efficacy and safety of daily oral administration of laquinimod (0.5 mg and 1.0 mg) in patients with HD. Prior to 10 January 2016, eligible patients were randomly assigned to receive treatment with laquinimod at a dosage of 0.5 mg, 1.0 mg, or 1.5 mg/day or a matching placebo in a 1:1:1:1 ratio.

As of 10 January 2016, treatment with laquinimod was discontinued for all patients in the 1.5 mg dose group, and future patients will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day or 1.0 mg/day or matching placebo for 52 weeks.

It is planned to randomize a total of 300 patients (100 patients within each study arm), plus the 30 patients that were already randomized to the laquinimod 1.5 mg treatment arm. Patients will be treated with investigational product or matching placebo for 12 months, and efficacy and safety will be assessed after 1, 3, 6, 9 and 12 months of treatment.

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

- Eligibility criteria will be reviewed and confirmed at screening and baseline.
- Vital signs will be measured at each study visit.
- A physical examination will be performed at each study visit (including weight).
- Cardiovascular risk assessment and management (including smoking history) at screening and as soon as possible for patients already in the study, following approval of Global Amendment 04.
- The following safety clinical laboratory tests will be performed:
  - When applicable per local requirements, patients will undergo an HIV test at screening.
  - Complete blood count (CBC) with differential at each study visit.
  - Anemia panel (blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, interleukin [IL]-1, IL-6, interferon [IFN]- , tumor necrosis factor [TNF]- , and hepcidin) and B12 at baseline.
  - Serum chemistry (including electrolytes, liver enzymes, urea, creatinine, glucose, total protein, albumin, total bilirubin, Creatine phosphokinase (CPK), serum conventional C-reactive protein (CRP), fibrinogen and pancreatic amylase) – at all scheduled visits.
  - Estimated creatinine clearance will be calculated at all study visits.
  - Lipid profile [total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides] – at baseline and Month 12.
  - Serum thyroid-stimulating hormone (TSH), T3 and Free T4 at baseline (Month 0), Month 6 and Month 12
  - Urinalysis at the screening visit.

Serum beta human chorionic gonadotropin ( -hCG) in women of child-bearing potential will be performed at each scheduled study visit.

Urine -hCG test will be performed in women of child-bearing potential at baseline and at each scheduled study visit thereafter.

Starting after visit Month 3 a urine -hCG test will be performed at home in women of child-bearing potential every 28 ( $\pm 2$ ) days. The patient will be contacted by telephone within 72 hours after the scheduled test is to be performed and asked specific questions regarding the test. In case of suspected pregnancy (positive urine -hCG test result), 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 (within 10 days) with all remaining study drugs capsules.

- When applicable, patients will be screened for drug substances in urine and/or CDT level in blood at screening to confirm abstinence in former (more than 12 months from screening) alcohol and/or drug abusers.
- Blood for analysis of cytokines and other soluble proteins will be collected at baseline, and at Months 6 and 12, concomitant with other blood draw procedures.
- ECG will be performed at screening, baseline, and at Months 1, 3, 6, and 12, and will be centrally evaluated.
- Blood sample for genomic analysis and CAG repeat length determination will be drawn at screening.
- Adverse Events (AEs) will be monitored throughout the study.
- Suicidality will be monitored throughout the study through administration of the C-SSRS
- Concomitant medications will be monitored throughout the study.
- All subjects will undergo MRI scans at baseline and Month 12.
- Motor function evaluations (UHDRS-TMS and Q-Motor) will be performed at screening, baseline and at Months 1, 3, 6 and 12.
- Functional capacity evaluations (UHDRS-TFC and mPPT) will be performed at baseline and at Months 6 and 12. The UHDRS-TFC is also performed at screening.
- Clinical global impression will be evaluated by an independent rater using the Clinician's Interview-Based Impression of Severity (CIBIS) process at baseline and CIBIC-Plus at Months 6 and 12
- Psychiatric and behavioral evaluations (PBA-s and HADS) will be done at baseline and at Month 12.
- Cognitive capacity will be evaluated at screening, baseline and at Months 6 and 12, by administration of the HD-CAB (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS).
- A reduced battery comprised of the SDMT and Trail Making Test will be performed at Months 1 and 3.
- Cognitive functional capacity will be assessed at baseline and at Month 12, by clinician rating of the CDR-SB scale including information from the patient and the informant, and the sum of boxes score will be calculated
- Quality of life will be assessed by the administration of the HD-QoL questionnaire to the patient and the informant at baseline and Month 12. The patient will also complete the EQ-5D-5L and work limitations questionnaire (WLQ) at baseline and Month 12.
- Population Pharmacokinetic (PPK) study: Blood samples for analysis of laquinimod plasma concentrations will be collected from all subjects at Months 1, 3, 6 and 12.

For patients participating in the ancillary studies:

- Blood will be collected for 24-h pharmacokinetic (PK) profiling at selected sites at Month 1 from approximately 15 patients per each of the three continuing treatment groups, for a total of approximately 45 patients. Additionally, PK samples were collected from 2 patients in the laquinimod 1.5 mg/day treatment group when the treatment was stopped; no further PK samples will be collected from the laquinimod 1.5 mg/day treatment group.
- Blood for monocyte gene expression and protein profile will be collected in a subgroup of patients at baseline and Month 12.
- PET scan in a subgroup of patients at baseline and Month 12.
- MRI scans for MRS evaluation will be done in a subgroup of patients at baseline and Month 12.

An independent data safety monitoring board (DSMB) will oversee the study. The DSMB will review unblinded accumulating safety data on a regular basis to ensure the continuing safety of the study patients and study conduct issues.

### **Efficacy Variables and Endpoints:**

#### **Primary Efficacy Variable and Endpoint**

The primary efficacy variable and endpoint for this study is change from baseline in the UHDRS-TMS (defined as the sum of the scores of all UHDRS-TMS subitems) at Month 12/ ET (evaluated at baseline and Months 1, 3, 6 and 12).

#### **Secondary Efficacy Variables and Endpoints**

The secondary efficacy variables and endpoints for this study are:

- Percent change from baseline in caudate volume at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in HD-CAB total score (sum of the standardized sub-components) at Month 12/ET (evaluated at baseline and Months 6 and 12)
- CIBIC-Plus global score at Month 12/ET (evaluated at Months 6 and 12) as compared to baseline (rated by an independent rater)
- Change from baseline in UHDRS- TFC at Month 12/ET (evaluated at baseline, Months 6 and 12)

#### **Exploratory Efficacy Variables and Endpoints**

The exploratory efficacy variables and endpoints for this study are:

- Change from baseline in brain atrophy as defined by the percentage change in volume in: whole brain volume and white-matter volume at Month 12/ET and absolute change in ventricular volume at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in UHDRS- FA at Month 12/ET (evaluated at baseline and Months 6 and 12)
- Change from baseline in Q-Motor assessments at Month 12/ET (evaluated at baseline and Months 1, 3, 6 and 12)
- Change from baseline in mPPT at Month 12/ET (evaluated at baseline and Months 6 and 12)
- Change from baseline in HD QoL and EQ-5D-5L at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in WLQ at Month 12/ET (evaluated at baseline and Month 12)

- Change from baseline in HD-CAB sub-components at Month 12/ET (evaluated at baseline and Months 6 and 12):  
Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLTR), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version)
- Change from baseline in CDR-SB at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in HADS at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in PBA-s at Month 12/ET (evaluated at baseline and Month 12)

### **Safety Variables and Endpoints:**

Safety variables and endpoints will include the following:

- Adverse events reports throughout the study
- ECG findings throughout the study
- Clinical safety laboratory tests throughout the study
- Vital signs measurements throughout the study
- Physical examination findings throughout the study
- Changes from baseline suicidality (C-SSRS) scores throughout the study

Tolerability variables and endpoints:

- Proportion of subjects (%) who prematurely discontinued from the study, reason of discontinuation and the time to ET
- Proportion of subjects (%) who prematurely discontinued from the study due to AEs and the time to ET

### **Pharmacogenomic Sub-Study:**

Pharmacogenomic (PGx) assessment will include DNA variations and RNA, gene expression pattern potentially associated with clinical treatment responses to laquinimod (e.g. clinical effect, Q-Motor, pharmacokinetics, tolerability, and safety features or disease susceptibility and severity features). Samples for DNA analysis will be collected at screening (or if not possible, at the next possible visit). Samples for RNA analysis will be collected at baseline, Month 6 and 12.

### **Other Ancillary Studies:**

- Microglial activation state will be investigated in selected patients (N=aiming at 10 per treatment arm). Positron emission tomography (PET) scans and imaging analysis of microglial activation marker translocator protein (TSPO) will be performed at baseline and Month 12.
- Change in putaminal and frontal white matter markers of neuronal integrity (N-acetyl-aspartate (NAA)) and astrocytosis (myo-inositol) will be investigated at selected sites using magnetic resonance spectroscopy (MRS) (N=aiming at 20 per treatment arm) at baseline and Month 12.
- Monocyte gene expression and/or protein profile in response to treatment with laquinimod will be analyzed at selected sites and patients (N=aiming at 25 per treatment arm). Monocytes will be separated from isolated peripheral blood mononuclear cells (PBMC) and be analyzed for gene expression and/or protein profile at baseline and Month 12.
- Peripheral cytokine and proteomic analysis in response to treatment with laquinimod will be investigated in a subgroup of patients at selected sites at baseline and Months 6 and 12.



## **Statistical Considerations:**

### Sample Size

The study aims to detect potential beneficial effects in deteriorating clinical signs and symptoms. Based on previous studies in patients with HD, the UHDRS-TMS has been shown to be one of the more sensitive clinical measures to detect decline in symptoms of HD. It is estimated that approximately 100 patients per arm will enable a power of 80% to detect a beneficial effect of 2.5 points or more in the change from baseline in UHDRS-TMS of an active laquinimod arm compared to placebo, assuming standard deviation (SD) of 6.2 and type I error of 5%.

As the intention is to investigate laquinimod as a treatment with the potential to slow disease progression and prohibit neuronal death in the CNS, the study should also be sized to be able to detect changes in brain atrophy rate after treatment with laquinimod. One of the most sensitive measures to detect brain atrophy over time in patients with HD is change in the caudate volume. It is estimated that approximately 100 patients per arm will also enable a power of 80% to detect a beneficial effect of 0.95 (30% of the estimated decline in placebo) or more in the percent change from baseline in caudate brain atrophy of an active laquinimod arm compared to placebo, assuming SD of 2.36 and type I error of 5%.

### Statistical Analyses

Due to the decision from 10 January 2016 to discontinue treatment of the laquinimod 1.5 mg dose arm, and the low number of enrolled patients compared to the target at this time, data from the laquinimod 1.5 mg treatment arm will be presented descriptively only, and will not be included in any inferential analyses for efficacy or safety.

### Control of Type I Error Rate

The Hochberg's Step-Up method for multiple comparisons between treatment arms in combination with the hierarchical method between the primary efficacy endpoint and the secondary efficacy endpoints, will be used to maintain the experiment wise type I error of 5% level.

### Primary Efficacy Endpoint Analysis

The change from baseline in UHDRS-TMS will be analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical week in trial by treatment interaction, center, and UHDRS-TMS at baseline. The unstructured covariance matrix for repeated observations within patients will be used. In case that the model will not converge, the Maximum-Likelihood (ML) estimation method will be used instead of the default Restricted ML (REML). If the model still does not converge then a simpler covariance structures with less parameters will be used, according to the following order: Heterogeneous Autoregressive(1) [ARH(1)], Heterogeneous Compound Symmetry (CSH), Autoregressive(1) [AR(1)], and Compound Symmetry (CS). The estimated means at the Month 12 visit will be compared between the active treatment arms and the placebo arm.

The Hochberg's Step-Up method for multiple comparisons between treatment arms will be used to control inflation in type I error rate.

### Secondary Efficacy Endpoints Analyses

According to the hierarchical method to control inflation in type I error rate for multiple endpoints, any statistically significant dose that will be observed in the primary analysis will continue to be tested for the secondary endpoints at an alpha level of 5%, according to the secondary endpoints order.

The secondary efficacy endpoints: change from baseline in HD-CAB total score and change from baseline in UHDRS- TFC, will be analyzed in the same way as the primary efficacy endpoint except that the efficacy endpoint evaluation at baseline will be included in the model instead of baseline UHDRS-TMS.

The CIBIC-Plus will be analyzed in the same way as the primary efficacy endpoint except that the baseline CIBIS (Clinician's Interview-Based Impression of Severity) will be included in the model as the efficacy measure at baseline.

The percent change from baseline to Month 12/Early Termination in caudate volume will be analyzed using an Analysis Of Covariance (ANCOVA) model (SAS® MIXED procedure). The model will include the following fixed effects: treatment, center, and caudate volume at baseline. The estimated means at the Month 12 visit will be compared between the active treatment arms and the placebo arm. Early terminated patient observation will have their Last Observation Carried Forward (LOCF).

#### Exploratory Efficacy Endpoints Analyses

The exploratory efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint except that the efficacy endpoint evaluation at baseline will be included in the model instead of baseline UHDRS-TMS.

The change from baseline to Month 12/Early Termination of continuous efficacy endpoints that are measured at baseline and at month 12 only, will be analyzed using an ANCOVA model (SAS® MIXED procedure). The model will include the following fixed effects: treatment, center, and the efficacy measure at baseline. The estimated means at the Month 12 visit will be compared between the active treatment arms and the placebo arm. Early terminated patient observation will have their Last Observation Carried Forward (LOCF).

#### Safety Analyses

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term (PT) or system organ class (SOC) category for the analyses of safety. Summaries will be presented for all AEs, AEs determined by the investigator to be related to study treatment, serious AEs, and AEs causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of SAEs and AEs leading to withdrawal will be presented.

Changes in laboratory and vital signs measurement data will be summarized descriptively. All values will be compared with prespecified boundaries to identify potentially clinically significant changes or values, and such values will be listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with study drug.

For continuous variables, descriptive statistics (n, mean, SD, standard error, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of SAEs, patient withdrawals due to AEs, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will also be provided.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation</b>	<b>Term</b>
βHCG	beta human chorionic gonadotropin
AD	Alzheimer's disease
ADME	Absorption, distribution, metabolism, and excretion
AhR	Aryl Hydrocarbon Receptor
AKI	Acute kidney injury
ALT	alanine aminotransferase (SGPT)
ALS	amyotrophic lateral sclerosis
ANCOVA	analysis of covariance
AR(1)	Autoregressive(1)
ARH(1)	Heterogeneous Autoregressive(1)
AST	aspartate aminotransferase (SGOT)
AUC	area under the plasma drug concentration by time curve
AUC <sub>0-τ</sub>	area under the plasma drug concentration by time curve for 1 dosing interval of a multiple-dose regimen
BMI	body mass index
BSI	Boundary Shift Integral
BBSI	Brain Boundary Shift Integral
BUN	Blood urea nitrogen
CAB	Cognitive Assessment Battery
CAG	cytosine-adenosine-guanine repeat
CBC	Complete Blood Count
CBSI	Caudate Boundary Shift Integral
CD	Crohn's Disease
CDMS	clinical data management system
CDR-SB	Clinical Dementia Rating - Sum of Boxes
CDT	Carbohydrate deficient transferrin
CFR	Code of Federal Regulations
CIBIC	Clinician's Interview-Based Impression of Change
CIBIS	Clinician's Interview-Based Impression of Severity
CIOMS	Council for International Organizations of Medical Sciences

<b>Abbreviation</b>	<b>Term</b>
Cmax	maximum observed plasma drug concentration
Cmin	minimum observed plasma drug concentration
CNS	Central nervous system
CPK	Creatine phosphokinase
Cr	Creatine
CrCl	Creatinine Clearance
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CRP	C-reactive Protein
CS	Compound Symmetry
CSC	Clinical Supply Chain
CSH	Heterogeneous Compound Symmetry
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed tomography
CYP	Cytochrome P450
DLCs	Dioxin-like compounds
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DSM–IV	Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition Text Revision
DSMB	Data and Safety Monitoring Board
EAE	experimental autoimmune encephalomyelitis
ECG	electrocardiography, electrocardiogram
EHDN	European Huntington's Disease Network
EQ VAS	EQ visual analogue scale
ET	Early Termination
EU	European Union
FAS	full analysis set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
Glu	Glutamate
HAB	High affinity binding

<b>Abbreviation</b>	<b>Term</b>
HADS	Hospital Anxiety and Depression Scale
HCG	human chorionic gonadotropin
HD	Huntington's Disease
HD- CAB	Huntington's Disease Cognitive Assessment Battery
HDL	High density lipoprotein
HDPE	High-density polyethylene
HD-QoL	Huntington's Disease Quality of Life
Hgb	haemoglobin
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
HVLT-R	Hopkins Verbal Learning Test, revised
IB	Investigator's Brochure
iCRO	Imaging Contract Research Organization
I3C	Indole-3-carbinol
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
INR	International Normalized Ratio
IOI	Inter onset intervals
IPI	Inter peak intervals
IRB	Institutional Review Board
IRT	interactive response technology
ISCED	International Standard Classification of Education
ITI	Inter tap intervals
ITT	intent-to-treat
LAB	Low affinity binding
LDL	Low density lipoprotein
LOCF	Last Observation Carried Forward
LSO	local safety officer
MAB	Mixed affinity binding
Max	maximum
mPPT	Modified Physical Performance Test

<b>Abbreviation</b>	<b>Term</b>
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myo-inositol
ML	Maximum Likelihood
MoA	Mechanism of action
MPV	Mean platelet volume
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MS	Multiple Sclerosis
MTD	Maximal Tolerated Dose
Na2EDTA	Disodium ethylenediamine tetraacetate
NAA	N-acetyl-aspartate
NF- B	Nuclear Factor-KappaB
OTC	over-the-counter
OTS	One Touch Stockings of Cambridge
PBA-s	Problem Behaviors Assessment-Short form
PBMC	Peripheral Blood Mononuclear Cells
PD	Parkinson's disease
PET	Positron Emission Tomography
PGx	pharmacogenomic(s)
PK	Pharmacokinetic(s)
PPK	Population Pharmacokinetics
PT	Preferred Term
qd	once daily
Q-Motor	Quantitative Motor Assessments
QoL	Quality of Life
RBC	red blood cell
RDW	Red Cell Distribution Width
REML	Restricted Maximum-Likelihood
RNA	Ribonucleic Acid
RRMS	Relapsing-Remitting Multiple Sclerosis
SAP	Statistical Analysis Plan



<b>Abbreviation</b>	<b>Term</b>
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SDV	source document verification
SLE	Systemic lupus erythematosus
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
Tmax	time to maximal plasma drug concentration
tCho	total Choline
TCDD	2,3,7,8-Tetrachlorodibenzo-p-dioxin
TD	Tap duration
TE	Echo Time
TF	Tapping forces
TNF	Tumor Necrosis Factor
TR	Repetition Time
TSH	thyroid stimulating hormone
TSPO	Translocator Protein
UHDRS-FA	Unified Huntington's Disease Rating Scale Functional Assessment
UHDRS-TFC	Unified Huntington's Disease Rating Scale Total Functional Capacity
UHDRS-TMS	Unified Huntington's Disease Rating Scale Total Motor Score
ULN	upper limit of the normal range
US(A)	United States (of America)
VBSI	Ventricular Boundary Shift Integral
WBC	white blood cell
WHO	World Health Organization
WHO Drug	World Health Organization (WHO) drug dictionary
WLQ	Work Limitations Questionnaire

## 1. BACKGROUND INFORMATION

### 1.1. Introduction

The aim of this clinical study is investigate the efficacy and safety of laquinimod as a potential treatment for patients with Huntington's disease (HD).

Laquinimod is developed by Teva Pharmaceutical Industries, Ltd. for Multiple Sclerosis (MS) and HD. The mechanism of action (MoA) of laquinimod includes modulation of the peripheral inflammation and central nervous system (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 inflammation, CNS inflammation, tissue damage, and neurodegeneration in CNS diseases that involve microglia and astrocytic activation, like MS and HD. Recently performed studies show that the aryl hydrocarbon receptor (AhR) pathway is involved in the efficacy of laquinimod in the experimental autoimmune encephalomyelitis (EAE) model. Further investigations are ongoing, assessing the role of AhR in the MoA of laquinimod.

Further, laquinimod was shown to cause a weak decrease of CYP3A4 activity and is a strong inducer of CYP1A enzymes. CYP1A induction is a biomarker of activation of the AhR transcription factor; activation of this pathway by laquinimod has been demonstrated.

Given laquinimod's suggested mode of action as an immunomodulator, its penetrance to the CNS in animals with an intact blood-brain-barrier, and its downregulation of activated microglia and astrocytes in the cuprizone induced demyelination model, its potential as a drug slowing disease progression in HD is being explored by Teva.

Huntington's disease is a hereditary disorder causing degeneration of neurons in the brain leading to uncontrolled movements, progressive loss of controlled motor function, cognitive decline, and emotional disturbance. The onset and progression varies but the most common age of onset is between 30 and 40 years. The illness generally lasts 15-20 years, and has fatal outcome.

HD manifests in 4 domains; motor impairment, cognitive decline, psychiatric problems, and loss of function, all assessed by various rating scales. A number of medications are used off-label to control motor and emotional problems arising from HD. The scientific evidence for these drugs in HD is poor and most of these drugs have significant side effects. None of the drugs used today has an effect on disease progression. One drug, tetrabenazine, is approved to treat chorea associated with HD.

It is believed that inflammatory processes in the CNS contribute to the pathogenesis of HD, via neuronal disturbances and cell death. Microglia, the major intrinsic immunocompetent cell in the CNS, are normally present in a quiescent state. Upon exposure to neuronal insults such as infection, ischaemia or the presence of abnormal protein aggregations (including mutant huntingtin aggregation), microglia become activated and release pro-inflammatory cytokines and cytotoxic mediators. In addition, it has been shown that microglia hyperreactivity is an autonomous feature in HD, as the expression of mutant Huntingtin in microglia promotes pro-inflammatory transcriptional activity in the absence of proinflammatory stimuli. (Crotti et al, 2014). This inflammatory activation may contribute to neuronal death. Microglia activation was

evident post-mortem in HD patients (Sapp et al, 2001) as well as in-vivo in pre-symptomatic and symptomatic HD gene carriers, demonstrated by positron emission tomography (PET) tracer ligands to activation markers on microglia (Tai et al, 2007). In-vivo microglia activation was shown in correlation with striatal neuronal dysfunction. These findings indicate that microglial activation is an early event in the pathogenic processes of HD and is associated with subclinical progression of disease. Elevated levels of inflammatory cytokines have been detected both in serum and cerebral spinal fluid in patients with HD. Specifically interleukin (IL)-6 levels were increased in the plasma of premanifest HD gene carriers. In addition, monocytes from HD patients as well as macrophages and microglia from the YAC128 HD model, were hyperactive in response to stimulation. In in vitro experiments, utilizing monocytes from patients with HD and microglia cells from YAC128 mice, reduced levels of this aberrant IL-6 production was observed after incubation with laquinimod.

Moreover, in a post-mortem analysis of HD patients striatum, RNA Levels of IL-6, IL-8, and tumor necrosis factor (TNF- $\alpha$ ) were significantly increased (Björkqvist et al, 2008). IL-6 release is triggered by activation of the NF- $\kappa$ B pathway. The increased cytokine release, in particular IL-6, correlates with the interesting finding that the NF- $\kappa$ B activity is upregulated in several HD cell models and transgenic mouse models, possibly by direct interaction of mutant htt and IKK (Khoshnan et al, 2004).

Further, cleavage of the mutant huntingtin protein by caspase-6 is believed to contribute to the pathogenesis of HD (Graham et al, 2011). In vitro studies have indicated that primary cortical neurons show reduced caspase 6 activity when treated with laquinimod, and laquinimod showed protective effects on axonal degeneration driven by caspase 6 activity.

In human HD studies, astrocytosis is observed in affected regions of the brain of patients with HD. The mutated huntingtin protein co-localizes with these reactive astrocytes in specific regions (Singhrao et al, 1998). Astrocytes from HD mice has been shown to have an aberrant activation of NF- $\kappa$ B, and peripheral monocytes from HD patients express a hyper-reactive phenotype. Investigation on the effect of laquinimod on human activated astrocytes demonstrates that laquinimod inhibits astrocyte morphological changes in response to inflammatory cytokines and decreases their production of pro-inflammatory compounds.

No clinical studies with laquinimod in patients with HD have been performed, and the potential benefits of laquinimod treatment for individual patients participating in this study is not known. The study is designed to investigate potential beneficial effects after treatment with laquinimod in patients with HD. The rationale for this is based on the immunomodulatory effects in CNS associated with treatment with laquinimod, findings indicating that laquinimod downregulates aberrant cytokine production from HD monocytes and microglia, and reports in the scientific literature that aberrant inflammatory phenotypic changes are an intrinsic feature in patients with HD and animal models for HD.

## 1.2. Name and Description of Investigational Product

Laquinimod (International Non-proprietary Name), also known by the laboratory code TV-5600 or ABR-215062 sodium salt, is a quinoline-3-carboxamide derivative. It is a novel chemical compound with the International Union of Pure and Applied Chemistry name sodium 5-chloro-3-(ethyl(phenyl)carbamoyl)-1-methyl-2-oxo-1,2-dihydroquinolin-4-olate.

The laquinimod investigational medicinal product is available as capsules containing laquinimod sodium equivalent to 0.5 mg laquinimod.

Laquinimod capsules and corresponding placebo are supplied as white opaque cap and body, hard gelatine capsules filled with white to off-white granulate. The capsules are packed in high-density polyethylene (HDPE) bottles equipped with child-resistant caps and should be stored at room temperature (+15°C to +25°C).

A more detailed description of the product is given in Section 3.4.

### **1.3. Findings from Nonclinical and Clinical Studies**

#### **1.3.1. Nonclinical Studies**

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

Laquinimod metabolism is mostly Cytochrome P450 (CYP) 3A4-mediated biotransformations 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 weak 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, and excretion (ADME)-pharmacokinetic (PK) program of laquinimod, please refer to the Laquinimod Investigator's Brochure (IB).

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

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

Overall, the non-clinical safety program identified several safety issues. Specifically, the toxicities identified are pro-inflammatory effects (including thyroiditis), mild liver toxicity, and mild reductions of red blood cell 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 current edition of the laquinimod Investigator's Brochure).

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

The carcinogenicity program consisted of a 26-week study in transgenic p53+/- mice and a 2-year rat study. The study in transgenic p53+/- mice did not show an increase in treatment-related neoplastic findings at any tested dose. In the 2-year rat carcinogenicity study, increased incidence of uterine adenocarcinomas was observed in high dose female rats. It is the sponsor's position that this finding is likely due to a decrease in the incidence of prolactin secreting pituitary adenomas that was observed in this study. In contrast to rodents, in humans, prolactin is not a luteinizing hormone and does not affect the estrogen/progesterone ratio; therefore the mechanism proposed by the sponsor is not considered relevant to humans. A higher incidence of thyroid follicular cell adenomas was observed in high dose male rats. This lesion is considered to be related to laquinimod's induction of liver enzymes and consequently enhanced clearance of thyroid hormones in rats, a well-characterized rat-specific mechanism proposed by the sponsor, that is not considered relevant to humans.

In addition, an increase in the incidence of oral cavity tumors was noted in mid and high dose females (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<sup>1</sup>) 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<sup>2</sup>). 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 0.5 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

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<sup>1</sup> 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.

<sup>2</sup> 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.

higher than the originally intended clinical dose of 1.5 mg/day in humans. The mechanism leading to the malformations in rats is unknown. Induction of urogenital malformations in rodents has been reported for a variety of agents including sex hormones and the AhR agonist TCDD. Several studies were performed to investigate the potential hormonal modulating activity of laquinimod, but no such effects were demonstrated at clinically relevant levels. In a pre- and post-natal toxicity study in monkeys, the high dose level was associated with higher incidence of prenatal loss which limited the number of monkeys that could be evaluated, but there were no treatment-related malformations at doses up to 9-fold the expected plasma exposure at the originally intended clinical dose of 1.5 mg/day.

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

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

In the planned clinical study, potential risks will be mitigated by careful screening of patients and monitoring of patients and appropriate stopping rules for certain potential AEs related to the toxicology target organs. Furthermore, an independent data safety monitoring board (DSMB) will be assigned to assess the data in an unblinded manner (see Section 7). The body of existing clinical safety data for the doses studied to date suggests that laquinimod is safe and well-tolerated.

### **1.3.2. Clinical Studies**

#### **1.3.2.1. Clinical Pharmacology Studies**

Laquinimod is considered to have high oral bioavailability with linear, time independent and predictable PK that is 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 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 and moderate hepatic impairment. Studies have shown that laquinimod is a strong inducer of CYP1A2 and a weak inhibitor of CYP3A4. Therefore, co-administration of laquinimod may affect the systemic exposure of drugs metabolized by CYP450 1A2 or CYP3A4.

Plasma levels of drugs that are CYP1A2 substrates may decrease when combined with laquinimod and within 30 days after the last laquinimod dose, rendering these drugs less effective.

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

For additional information on concomitant use of laquinimod with CYP1A2 substrates, please refer to Section 5.3.2.

Studies in subjects with mild or 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 with 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 0.6mg 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 or severe hepatic impairment (3.41- and 6.51-fold, respectively) or 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 1.5mg dose range following single- or multiple dose administration, demonstrating that the doseproportional pharmacokinetics of laquinimod is maintained in subjects with hepatic impairment (mild to severe) and renal impairment (moderate to severe) across this dose range.

#### **1.3.2.2. Clinical Safety and Efficacy Studies**

No clinical data on the effects of laquinimod in patients with HD is available. However, clinical data from patients with relapsing remitting MS show a benefit of laquinimod treatment on brain atrophy and disability progression after 1 year of treatment, also in patients without relapses during this period. A disproportionately large effect on disability compared to relapses was also observed. The results suggest that in addition to peripheral inflammatory modulating effects, laquinimod could also have neuroprotective effects, and a mode of affecting CNS inflammatory processes beyond the classical MS dogma of active T cell driven lesions.

Detailed information concerning all clinical studies with laquinimod is presented in the IB. For a brief overview on these studies, see also Section 1.5.

### **1.4. Known and Potential Risks and Benefits to Human Subjects**

#### **1.4.1. Known and Potential Risks and Benefits for Laquinimod**

##### **1.4.1.1. Potential Risk Based on Non Clinical Safety Findings**

Laquinimod has been extensively studied in a battery of non clinical safety studies. The data and major findings have been described in Section 1.3.1, and in the current IB. The toxicities identified are pro-inflammatory effects (including thyroiditis), mild liver toxicity, and mild reductions of red blood cell indices. The severity of these effects was dose-related and toxicity was mostly reversible upon drug discontinuation.

As these events are addressed in the clinical setting by frequent monitoring of relevant clinical laboratory assessments (described in Section 7.3), and were all reversible, it is judged that these non-clinical findings should not preclude administration of laquinimod to patients with HD as described in this protocol. Careful screening of patients and appropriate stopping rules for

specific AEs related to the toxicology target organs, as described in [Appendix A](#), will further minimize any potential risk.

#### **1.4.1.2. Potential Risk Based on Clinical Safety Findings**

This is the first clinical study with laquinimod in HD. Therefore, no clinical data on the effects of laquinimod in patients with Huntington's disease is available, and a wide dose range exploration is warranted.

Unless noted otherwise, characterization of the safety profile (important risks and ADRs) 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 haematological changes [Hemoglobin (Hgb) decreased/anaemia, white blood cells (WBC) 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 1](#) presents the list of 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 1: 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: Anaemia* 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*: (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>Renal and urinary disorders</u> Uncommon: Micturition urgency
<u>Reproductive system and breast disorders</u> Common: Menstruation disorders and uterine bleeding
<u>General disorders and administration site conditions</u> Common: Peripheral oedema
<u>Investigations</u> Common: Blood fibrinogen increased*, C-reactive protein (CRP) increased *, blood amylase increased, creatinine decreased

\* An asterisk (\*) indicates that additional information is provided under section Description of Selected Adverse Reactions below.

**Description of selected adverse drug reactions:**

**1.4.1.2.1. Liver enzyme elevations:**

Treatment with laquinimod has been associated with mostly mild, reversible, asymptomatic liver enzyme elevations that generally occur within 6 months after initiation of treatment (see [Table 2](#)).

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 2: ALLEGRO and BRAVO: Shift from Normal Test at Baseline to Highest Value for ALT, AST and GGT Tests**

Test	Range of Increase	Placebo	Laquinimod 0.6 mg
<b>AST (IU/L)</b>		Subjects with Normal Test at Baseline: N = 977	Subjects 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>		Subjects with Normal Test at Baseline: N = 930	Subjects 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>		Subjects with Normal Test at Baseline: N = 930	Subjects with Normal Test at Baseline: N = 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; IU/L = international units/L

#### 1.4.1.2.2. Elevated blood fibrinogen level

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

#### 1.4.1.2.3. Elevated blood CRP 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 phase III 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.

#### **1.4.1.2.4. Back and neck pain**

Treatment with laquinimod has been associated with an increased incidence of back and neck pain. Back and neck pains usually occur during the first three months of treatment, are generally of mild severity, but may sometimes occur at a later time point, be of longer duration or require symptomatic treatment.

#### **1.4.1.2.5. Appendicitis**

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

#### **1.4.1.2.6. Haematological changes**

##### Hgb decrease/Anaemia:

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

##### Decreased platelets:

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

##### Increased white blood cells:

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

As per the current protocol, regular monitoring of liver enzymes, complete blood count (CBC), blood fibrinogen and CRP levels will be performed (described in Section 7.3), and patients will be followed regularly for adverse events. The sponsor considers these means as adequate to address laquinimod-related safety concerns. To further mitigate any potential risks, patients with unstable medical conditions will be excluded from the study. In addition, an independent DSMB will be assigned to assess the data in unblinded manner (see Section 7).

#### **1.4.1.2.7. Cardiovascular Events (in the high-dose treatment arms of the ongoing MS studies)**

In December 2015, the Data Monitoring Committee (DMC) for the Teva-sponsored MS studies, LAQ-MS-305 (CONCERTO) and TV5600-CNS-20006 (ARPEGGIO), found an imbalance in serious cardiovascular events in the high-dose treatment arms of these studies (1.2 mg in CONCERTO, 1.5 mg in ARPEGGIO). Six cases of myocardial infarction occurred in the CONCERTO 1.2 mg treatment arm, compared with no events in the 0.6 mg or placebo treatment arms, along with a cerebral infarction in a 31-year-old man in the 1.2 mg treatment arm. In the ARPEGGIO study, 1 myocardial infarction event was identified in the laquinimod 1.5 mg treatment arm. The decisions were largely based on data from 15 November 2015 when total

exposure in CONCERTO was 3070 patient-years in 2199 individuals, and total exposure in ARPEGGIO was 35 patient-years in 191 individuals.

Due to these events, the DMC recommended stopping the high-dose treatment arms (1.2 mg/day and 1.5 mg/day) in the laquinimod MS trials. The DMC did not identify any overt cardiovascular risk in the 0.6 mg treatment arm, but felt that long term monitoring for emergence of any signal was necessary. The DMC also recommended that study subjects continuing on laquinimod 0.6 mg be reconsented with information about the cardiovascular risk seen at higher doses.

On 07 January 2016, the LEGATO-HD Data Safety Monitoring Board (DSMB) was called by Teva to review and discuss the recommendations of the DMC for the CONCERTO and ARPEGGIO MS trials and their implications on LEGATO-HD. The DSMB confirmed that no cardiovascular events had been observed to date for any dose of the LEGATO-HD trial and concurred with the Sponsor's recommendation that the high-dose (ie, 1.5 mg) arm in this trial be discontinued as a proactive safety measure. The DSMB approved the continuation of the 0.5 mg/day and 1.0 mg/day arms with enhanced monitoring and safety precautions.

Teva notified LEGATO-HD investigators on 10 January 2016 to immediately contact patients randomized to the high dose of 1.5 mg laquinimod and instruct them to discontinue study medication as a proactive measure to protect the safety of patients (endorsed by DSMB as noted above).

Currently, the mechanism of the cardiovascular events remains unknown. Although no specific time-to-event patterns have been identified in the MS studies, 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 investigations into potential predictors and the potential causality are ongoing.

### **1.4.1.3. Other Potential Safety Issues with Laquinimod**

#### **1.4.1.3.1. Pregnancy**

Studies in rats have shown reproductive toxicity including teratogenicity (urogenital malformations) at doses similar to the clinical dose of 0.5 mg/day in humans. Delay in puberty and reduced fertility were noted in rat offspring exposed to laquinimod in utero at doses slightly higher than the originally intended clinical dose of 1.5 mg/day in humans (see Section 1.3.1). 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, female patients who are of child-bearing potential (for example women who are not postmenopausal or surgically sterilized) must practice an acceptable method of birth control (see Section 7.2) for 30 days before initiation of treatment, and 2 acceptable methods of birth control throughout treatment and for 30 days after cessation of treatment. Use of acceptable contraception will be ascertained at every study visit.

In addition, regular pregnancy testing is required during the study. If pregnancy is suspected despite all recommended precautions (based on a positive pregnancy test, delay in menses or any

other reason to suspect pregnancy), treatment should be discontinued immediately. The patient will be reminded of the potential risk to the fetus, and all options, including discontinuation of pregnancy, should be discussed.

All female patients should be counseled by the investigator about the potential risks of exposure to laquinimod during pregnancy and the need to use acceptable contraception and avoid pregnancy throughout treatment with laquinimod and for 30 days after cessation of treatment.

#### **1.4.1.3.2. Cancer**

An increase in the incidence of uterine and oral cancers was observed in rats (see Section 1.3.1). It is the sponsor's position that these findings are likely related to species-specific mechanisms. While a connection to humans cannot be entirely excluded, these mechanisms are likely not relevant to humans. Currently available clinical data does not suggest that laquinimod at a dose of 0.6 mg/day is associated with an increased risk of cancer.

#### **1.4.1.3.3. Cardiotoxicity and Systemic Inflammation**

In clinical studies performed with laquinimod's predecessor, roquinimex, pericarditis/pleuritis and ischaemic 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 non-clinical findings.

A thorough analysis was done on the laquinimod safety data (which is mostly reflective of the 0.6 mg/day dose) to evaluate similar potential safety issues. Based on 2347 patients exposed to laquinimod 0.6 mg for over 10,000 MS 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 signal for laquinimod in doses up to 0.6 mg/day. However, at doses of 1.2 and 1.5 mg, laquinimod manifested a potential clinical signal of myocardial infarction in the MS trials.

#### **1.4.1.3.4. QT Prolongation**

Even though laquinimod in doses up to 1.2 mg once daily (qd) did not prolong the QTcF interval, (based on the thorough QT study TQT-LAQ-122), and pre-clinical data do not indicate a potential for laquinimod to influence the QT interval, higher doses of laquinimod have not been studied for potential QT prolongation effects. ECG monitoring is implemented in this protocol, as described in Section 7.5.

#### **1.4.1.4. Justification for Using Placebo**

There are no standard treatments in HD, and no registered drugs known to slow disease progression are available for patients with HD. The only approved drug for treatment of HD is Tetrabenazine, which is indicated for treatment of chorea in patients with HD. A number of medications are used off-label to control motor and emotional problems arising from HD. All of these drugs are symptomatic, and the scientific evidence for their use in patients with HD is poor.

In addition, many of the drugs that have been used are fraught with significant side effects, including worsening of parkinsonian symptoms, and cognitive decline. No drugs are available that target the underlying pathogenesis of HD. In this context, a placebo controlled study to investigate laquinimod's potential benefits in patients with HD is deemed acceptable.

#### **1.4.1.5. Potential Benefits**

No clinical studies with laquinimod in patients with HD have been performed, and the potential benefits of laquinimod treatment for individual patients participating in this study is not known. The study is designed to investigate potential beneficial effects after treatment with laquinimod in patients with HD. The rationale for this is based on the immunomodulatory effects in CNS associated with treatment with laquinimod, and reports in scientific literature that aberrant inflammatory phenotypic changes are an intrinsic feature in patients with HD and animal models for HD (see Section 1.1).

#### **1.4.1.6. Overall Benefit-Risk Assessment**

An imbalance in serious cardiovascular events in the high-dose treatment arms (1.2 mg/day and 1.5 mg/day) in the Teva-sponsored CONCERTO and ARPEGGIO studies in MS was identified (6 cases of myocardial infarction in the CONCERTO 1.2 mg treatment arm, compared with no events in the 0.6 mg or placebo treatment arms, along with a cerebral infarction in a 31-year-old man in the 1.2 mg treatment arm. In the ARPEGGIO study, 1 myocardial infarction event was identified in the laquinimod 1.5 mg treatment arm. Due to these events, the DMC recommended stopping higher-dose laquinimod treatment (1.2 and 1.5 mg) in the laquinimod MS trials (see Section 1.4.1.2.7).

No cardiovascular events have been observed to date for any dose in the LEGATO-HD trial.

On 07 January 2016, the LEGATO-HD DSMB met and approved the Sponsor's proposal to discontinue the 1.5 mg arm of the study as a proactive safety measure, and approved the continuation of the 0.5 mg/day and 1.0 mg/day arms with enhanced monitoring and safety precautions.

Teva notified LEGATO-HD investigators on 10 January 2016 to immediately contact patients randomized to the high dose of 1.5 mg laquinimod and instruct them to discontinue study medication as a proactive measure to protect the safety of patients currently participating in the LEGATO-HD study. This action was endorsed by the DSMB as noted above. Patients in the 1.5 mg/day (high dose) treatment arm, whose treatment with laquinimod was discontinued, were asked to continue all scheduled visits for safety assessment after study drug discontinuation.

Appropriate risk mitigation procedures have been implemented via this protocol amendment to restrict excess drug exposure due to impairment of liver or kidney function, as well as to assure evaluation and management of cardiovascular risk factors.

LEGATO-HD is the first "proof of concept" study in the HD patient population, which represents a disease with a fatal outcome and a severe unmet medical need (no current available medications). Based on data accumulated to date, the LEGATO-HD study aims for disease modification beyond symptomatic treatment.

Thus, the LEGATO study in the HD patient population represents different benefit/risk considerations.

Based on the above described risks and means for their mitigation, it is judged that potential benefit from administration of laquinimod to patients with HD outweighs the risks based on currently available information, supporting investigation of its role in the Huntington's disease patient population.

For an overall risk benefit assessment of laquinimod treatment in human patients, additional information may be found in the current Investigator's Brochure.

## **1.5. Selection of Drugs and Dosages**

The dosages of laquinimod to be evaluated in this double-blind study (i.e. 0.5, 1.0 and 1.5 mg/day) were selected on the basis of an extensive clinical program evaluating pharmacokinetics, safety, tolerability and efficacy in healthy volunteers, and patients with MS, Crohn's Disease (CD) and systemic lupus erythematosus (SLE).

Two studies to evaluate the MTD of laquinimod in healthy volunteers and MS patients have been performed. One early ascending-dose study in healthy volunteers and MS patients (Study 99506202) established the dose of 1.2 mg/day as the MTD in MS patients, based solely on laboratory findings that were predefined in the protocol as dose limiting toxicity [increased levels of CRP and fibrinogen]. A subsequent ascending dose study in MS patients (Study MS-LAQ-101), in which a safety committee recommended dose escalation following data availability for each dosing cohort, did not reproduce study 99506202 results and did not reveal dose-dependent AEs, laboratory or electrocardiography (ECG) findings up to and including the dose of 2.7 mg/day. The sample size, treatment duration (4 weeks) and overall exposure were greater in study MS-LAQ-101 compared to Study 99506202, and assessment of tolerability of dose was based on a combination of clinical evaluation and laboratory parameters. Hence, the sponsor considers study MS-LAQ-101 as more adequately representing the safety profile of higher doses of laquinimod. The last cohort of patients received 2.7 mg laquinimod with no dose limiting adverse events (AEs) or laboratory findings (see Section 1.5). The study's safety committee recommended further dose escalation; however the sponsor has instead decided to perform dose escalation above 2.7 mg laquinimod, if needed, under a new, more comprehensive protocol. Hence, 2.7 mg/day is the highest multiple dose administered to humans to date.

Laquinimod 1.5 mg was selected as the maximal dose to be tested for the current study based on the existing MTD study (up to 2.7 mg).

Daily doses of 0.1 mg and 0.3 mg were originally assessed in MS patients in a phase II study (01506203), which showed that laquinimod 0.3 mg reduced the cumulative number of active lesions at week 24 while laquinimod 0.1 mg did not demonstrate an effect. A new phase II study (LAQ/5062) assessed the efficacy, tolerability, and safety of 0.3 mg/day and 0.6 mg/day of laquinimod in MS patients, and demonstrated a statistically significant effect on the primary endpoint for the laquinimod 0.6 mg dose. However, in contrast to study 01506203, a significant effect on the primary endpoint could not be demonstrated after treatment with laquinimod 0.3 mg. This discrepancy is considered by the sponsor to be likely explained by methodological differences in measuring the MS lesions. None of the studies identified significant safety or tolerability concerns.

Two Phase III studies with laquinimod 0.6 mg dose/day have been completed in patients with MS (ALLEGRO and BRAVO). Both studies used annualized relapse rate as the primary

endpoint. In ALLEGRO, significant effect of laquinimod treatment was shown on the primary endpoint and 3 key secondary endpoints. The BRAVO study did not show a statistically significant effect on the primary endpoint, but a post hoc corrected analysis showed that results were comparable to those of ALLEGRO. In addition, it was demonstrated that the suggested effect of laquinimod on disease progression and brain atrophy is consistent and robust. Both studies showed a benign safety profile of laquinimod at the dose tested.

In light of the dose-dependent clinical effect detailed above and absence of safety concerns in the MS-LAQ-101 study, the sponsor has initiated a clinical program in MS patients to investigate whether a 1.2 mg qd dose of laquinimod is associated with greater efficacy while retaining the adequate safety and tolerability profile that was evident for the 0.6 mg qd dose. This program is currently ongoing.

The safety and efficacy of laquinimod given 0.5, 1.0, 1.5, or 2.0 mg/day have been investigated in 180 patients with CD for 8 weeks (study CD-LAQ-201). Significant effect on the primary endpoint (Crohn's Disease Activity Index) was seen after treatment with laquinimod 0.5 mg/day; laquinimod 1 mg had a lower magnitude effect that was also less robust than the effect of laquinimod 0.5 mg. Laquinimod 1.5 mg and 2.0 mg did not have an overall clinical effect compared to the pooled placebo. However, when evaluating reduction in calprotectin levels, an objective marker of disease activity, similar efficacy was observed across the laquinimod doses. Laquinimod showed an overall favorable safety and tolerability profile in this study. Laquinimod is no longer being developed as a treatment for CD.

The safety and efficacy of laquinimod given 0.5 or 1.0 mg/day have also been investigated in two studies in SLE patients [with lupus nephritis (LN-LAQ-201) and with lupus arthritis (LA-LAQ-202)] for 24 and 12 weeks, respectively. In LN-LAQ-201, 46 patients were enrolled: 15 received placebo, 16 received laquinimod 0.5 mg and 15 received laquinimod 1 mg. In LA-LAQ-202, 82 patients were enrolled: 26 were randomized to receive placebo, and 28 patients were randomized to each of the laquinimod arms (0.5 mg, and 1 mg). Overall laquinimod was safe and well tolerated in these studies. No clinically meaningful effect of laquinimod treatment could be seen in patients with LA. Beneficial effect of laquinimod was seen in patients with LN with both doses investigated, with the 0.5 mg dose showing a greater improvement in several efficacy variables. Laquinimod is no longer being developed as a treatment for SLE.

The described data indicates that 0.6 mg/day is the minimal clinically effective dose in MS patients, whereas data from patients with CD and lupus nephritis indicated that also 0.5 mg/day is efficacious in treating the inflammatory condition in these diseases. The maximal tolerated dose has not formally been established, but the maximum tested repeated dosing is 2.7 mg/day in humans. Data from animal models for CNS inflammation, show a clear dose response of laquinimod's inhibition of disease (for additional information, please refer to the IB). Hence, 3 doses of laquinimod, ranging from 0.5 mg/day, believed to be a minimal effective dose, to 1.5 mg/day, providing a reasonable margin to the highest dose tested in humans over a short time period, were chosen for investigation. Also, given the available data on the 0.5 and 1.0 mg doses of laquinimod, a parallel (rather than sequential) design was deemed appropriate.

Note: 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). In CONCERTO there were 6 such cases in



the 1.2 mg arm but none in the 0.6 mg or placebo arms, along with a myocardial infarction in the ARPEGGIO 1.5 mg dose group and a cerebral infarction in a 31-year-old patient in the 1.2 mg arm of CONCERTO. Due to these events and the DMC recommendation to stop all high-dose laquinimod treatment arms (1.2 mg/day and 1.5 mg/day) in the MS trials; accordingly, the high-dose arms were discontinued in both trials as of 01 January 2016.

On 07 January 2016, the LEGATO-HD DSMB was called urgently by Teva to review and discuss new information regarding the occurrence of an imbalance in cardiovascular events from the high-dose laquinimod arms in the multiple sclerosis trials CONCERTO and ARPEGGIO (1.2 mg in CONCERTO, 1.5 mg in ARPEGGIO).

The most recent study data for LEGATO-HD were also reviewed in open and closed sessions. No cardiovascular signal was detected from the LEGATO-HD study as of 10 January 2016. The DSMB agreed with the plan to discontinue the 1.5 mg arm of the LEGATO-HD study as a proactive safety measure, and approved the continuation of the 0.5 mg/day and 1.0 mg/day arms with enhanced monitoring and safety precautions. Therefore, these treatment arms will be continued with updated informed consent and an amended protocol while the sponsor closely monitors cardiovascular events in all laquinimod studies for emergence of any potential cardiovascular signal.

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

## **1.6. Compliance Statement**

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

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

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

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

## **1.7. Population To Be Studied**

Based on the anticipated mode of action (MoA) of laquinimod in HD, an intervention to reduce CNS inflammation as early as possible would be desirable to prevent further neuronal dysfunction and death. However, the rate of progression in signs and symptoms makes it difficult to detect slowing of disease in a feasible way in terms of treatment length in patients without signs of disease. Therefore, patients with clinical symptoms that are measurable, but with a retained functional capacity will be selected. Further, concomitant medications with antipsychotic drugs may confound the data due to side effects in the motor and cognitive domain, and thus these drugs will be disallowed in the study. It is also known that cytosine-adenosine-guanine (CAG) repeat length in the mutant huntingtin gene influence disease progression and course. To reduce variability in the study, patients will be selected from a pre-defined range of CAG repeat lengths frequently observed in the clinic.

Thus, the target patient population will be adult patients, with a CAG repeat length between 36 and 49, and the basic eligibility criteria will select a patient population with symptoms of HD, as assessed by a Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) >5, but with a largely retained functional capacity, as assessed with a HDRS-Total Functional Capacity (UHDRS-TFC) score ≥ 8. This will recruit a symptomatic early HD patient population.

The criteria for study eligibility are described in Section 4.1 and Section 4.2, respectively.

## **1.8. Relevant Literature and Data**

Relevant literature is cited above. Further literature and data may be found in the current Investigator's Brochure.

## **2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES**

### **2.1. Purpose of the Study**

The purpose of this Phase II clinical study is to investigate the efficacy and safety of multiple doses of laquinimod (0.5, 1.0 and 1.5 mg/day) as a potential treatment for patients with Huntington's disease (HD).

As no drug is currently available to treat HD disease progression, the study will be placebo controlled.

Prior to 10 January 2016, a total of 400 patients were planned to be equally randomized in a 1:1:1:1 ratio (100 patients within each treatment arm) to receive laquinimod 0.5, 1.0, 1.5 mg/day, or matching placebo for 52 weeks.

As of 10 January 2016, following the decision to discontinue treatment of the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day, 1.0 mg/day, or matching placebo for 52 weeks. Approximately 300 patients (100 patients within each study arm), plus the 30 patients who were already randomized to the laquinimod 1.5 mg treatment arm, are planned to be enrolled in the study.

This is the first clinical study with laquinimod in HD. Therefore, no clinical data on the effects of laquinimod in patients with Huntington's disease is available, and a wide dose range exploration is warranted.

Clinical data from patients with relapsing remitting multiple sclerosis (RRMS) show a benefit of laquinimod treatment of 0.6 mg/day on brain atrophy and disability progression after 1 year of treatment, also in patients without relapses during this period. A disproportionally large effect on disability compared to relapses was also observed. The results suggest that in addition to peripheral inflammatory modulating effects, laquinimod could also have neuroprotective effects, and a mode of affecting central nervous system (CNS) inflammatory processes beyond the classical MS dogma of active T-cell driven lesions. This is important in Huntington's disease where intrinsic CNS inflammatory phenotypes are observed to correlate with disease progression.

The study aims to detect potential beneficial effects in deteriorating clinical signs and symptoms of HD. Based on previous studies in patients with HD, the UHDRS-TMS has been shown to be one of the more sensitive clinical measures to detect decline in symptoms of HD, and hence TMS has been chosen as primary endpoint.

### **2.2. Study Objectives**

#### **2.2.1. Primary Study Objective**

The primary objective of this study is to assess the efficacy of laquinimod 0.5 and 1.0 mg qd in patients with HD after 12 months of treatment using the Unified Huntington's Disease Rating Scale (UHDRS) Total Motor Score (TMS).

Due to the decision from 10 January 2016 to discontinue treatment of the laquinimod 1.5 mg dose arm, and the low number of enrolled patients compared to the target at this time, data from

the laquinimod 1.5 mg treatment arm will be presented descriptively only, and will not be included in any inferential analyses for efficacy or safety.

### **2.2.2. Secondary Study Objectives:**

- To assess the effect of laquinimod on brain atrophy in patients with HD after 12 months of treatment using MRI measures of caudate volume.
- To assess the effect of laquinimod on the cognitive capacity in patients with HD after 12 months of treatment using the cognitive assessment battery (CAB) for patients with HD [comprised of: Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLT-R), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version)].
- To assess the effect of laquinimod on the clinical global impression in patients with HD after 12 months of treatment using the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-Plus)
- To assess the effect of laquinimod on the functional capacity in patients with HD after 12 months of treatment using the UHDRS-TFC scale

### **2.2.3. Exploratory Study Objectives:**

- To assess the effect of laquinimod on brain atrophy in patients with HD after 12 months of treatment using MRI measures of whole brain volume, white-matter volume and ventricular volume.
- To assess the effect of laquinimod on the functional capacity in patients with HD after 12 months of treatment using the UHDRS-functional assessment (FA) scale
- To assess the effect of laquinimod on motor function in patients with HD after 12 months of treatment using the objective instrument Q-Motor
- To assess the effect of laquinimod on physical performance in patients with HD after 12 months of treatment using the modified Physical Performance Test (mPPT).
- To assess the effect of laquinimod on the quality of life in patients with HD after 12 months of treatment using the Huntington's Disease Quality of Life (HD-QoL) and EQ-5D-5L instruments
- To assess the effect of laquinimod on work productivity in patients with HD after 12 months of treatment.
- To assess the effect of laquinimod on functional impairment due to cognitive decline in patients with HD after 12 months of treatment using the Clinical Dementia Rating - Sum of Boxes (CDR-SB)
- To assess the effect of laquinimod on depression and anxiety in patients with HD after 12 months of treatment using the Hospital Anxiety and Depression Scale (HADS)
- To assess the effect of laquinimod on behavioral signs and symptoms in patients with HD after 12 months of treatment using the Problem Behaviors Assessment-Short form (PBA-s)
- To evaluate the pharmacokinetics of laquinimod and its metabolites in patients with HD

- To investigate the relationship between exposure to laquinimod and its metabolites and outcome measures (eg, clinical effect and toxicity parameters).

**2.2.4. Safety and Tolerability Study Objectives:**

- To evaluate safety and tolerability of laquinimod in patients with HD during 12 months of treatment by evaluating adverse events (AEs), electrocardiography (ECG), and clinical laboratory parameters, vital signs, physical examinations, and premature discontinuations from the study.

**2.2.5. Ancillary Study Objectives:**

- To explore potential correlation between genetic polymorphisms in deoxyribonucleic acid (DNA) and pharmacokinetics, clinical response to laquinimod, and/or adverse drug reactions, if these occur
- To explore potential correlation between ribonucleic acid (RNA) expression profile in blood cells and clinical response to laquinimod
- To evaluate changes in cytokines and other soluble protein levels following treatment with laquinimod as potential biomarkers for laquinimod mechanism of action and/or response predictive factors
- To explore gene expression and/or protein profile in monocytes in response to laquinimod treatment
- To explore change in microglial activation state in response to treatment with laquinimod
- To assess the correlation between microglial activation state at baseline and the clinical characteristics of HD patients (age, gender, number of triplets, disease onset, disease duration, motor and behavioral scores).
- To explore changes in MRS metabolite levels in response to treatment with laquinimod that reflect neuronal integrity (NAA) and astrocytosis (myo-inositol) in the putamen and frontal white matter.

### 3. STUDY DESIGN

#### 3.1. General Design and Study Schema

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of laquinimod treatment at dosages of 0.5, 1.0, and 1.5 mg/day in adults with Huntington's Disease.

The study will consist of a screening period (2 weeks up to 5 weeks), followed by a 52-week double-blind treatment period and a follow-up visit (one month after end of treatment). Prior to 10 January 2016, a total of 400 patients were planned to be equally randomized in a 1:1:1:1 ratio (100 patients within each treatment arm) to receive laquinimod 0.5, 1.0, 1.5 mg/day, or matching placebo for 52 weeks. A total of 123 patients were randomized prior to 10 January 2016.

As of 10 January 2016, following the decision to discontinue treatment of the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day, 1.0 mg/day, or matching placebo for 52 weeks. Approximately 300 patients (100 patients within each study arm), plus the 30 patients who were already randomized to the laquinimod 1.5 mg treatment arm, are planned to be enrolled in the study.

After signing the informed consent, including consent to provide a blood sample for genetic analyses including CAG repeat length analysis, patients will be screened for a period of 2 weeks up to 5 weeks in order to determine whether they are eligible to participate in the study. Patients with a legal guardian should be consented according to local requirements.

The procedures and assessments performed during each of the study visits are detailed in Section 3.11.

During the visits, vital sign measurements, physical examinations and ECG should preferably be performed prior to the blood draw for clinical laboratory tests and pharmacokinetic sampling. Further, the efficacy assessments (TMS, HD-CAB, CIBIC-plus and TFC) should be done prior to the exploratory assessments.

Patients who complete all scheduled visits will have final procedures and assessments performed at the final visit (Visit 8, Month 12). Patients who withdraw from the study before completing the 52-week evaluation period will have Visit 8 procedures and assessments performed at their last visit.

An independent DSMB will oversee the study. The DSMB will review unblinded accumulating safety data on a regular basis to ensure the continuing safety of the study patients and study conduct issues.

The study schema is presented in [Figure 1](#) (prior to 10 January 2016) and in [Figure 2](#) (from 10 January 2016).

Figure 1: Overall Study Schema (prior to 10 January 2016)

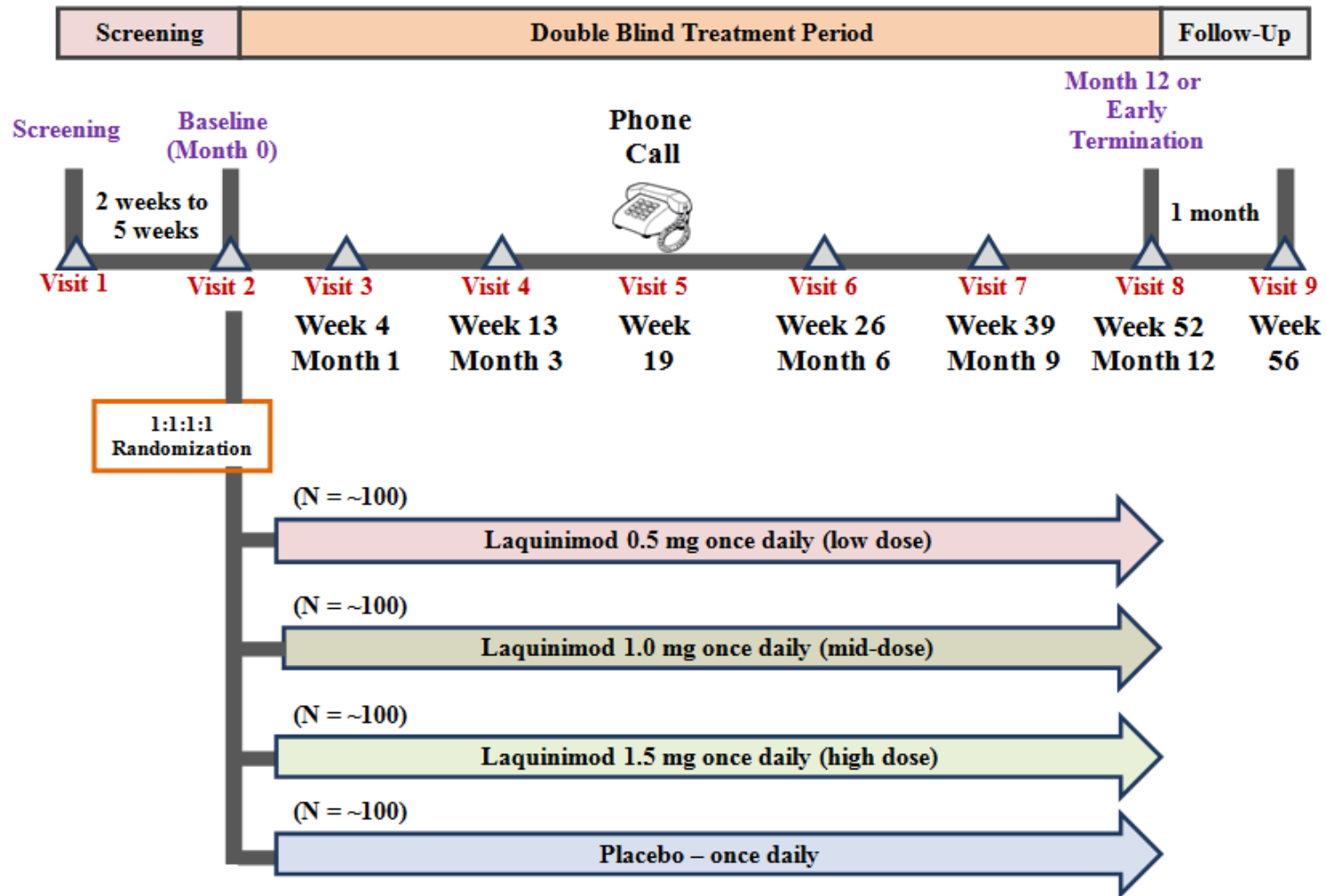
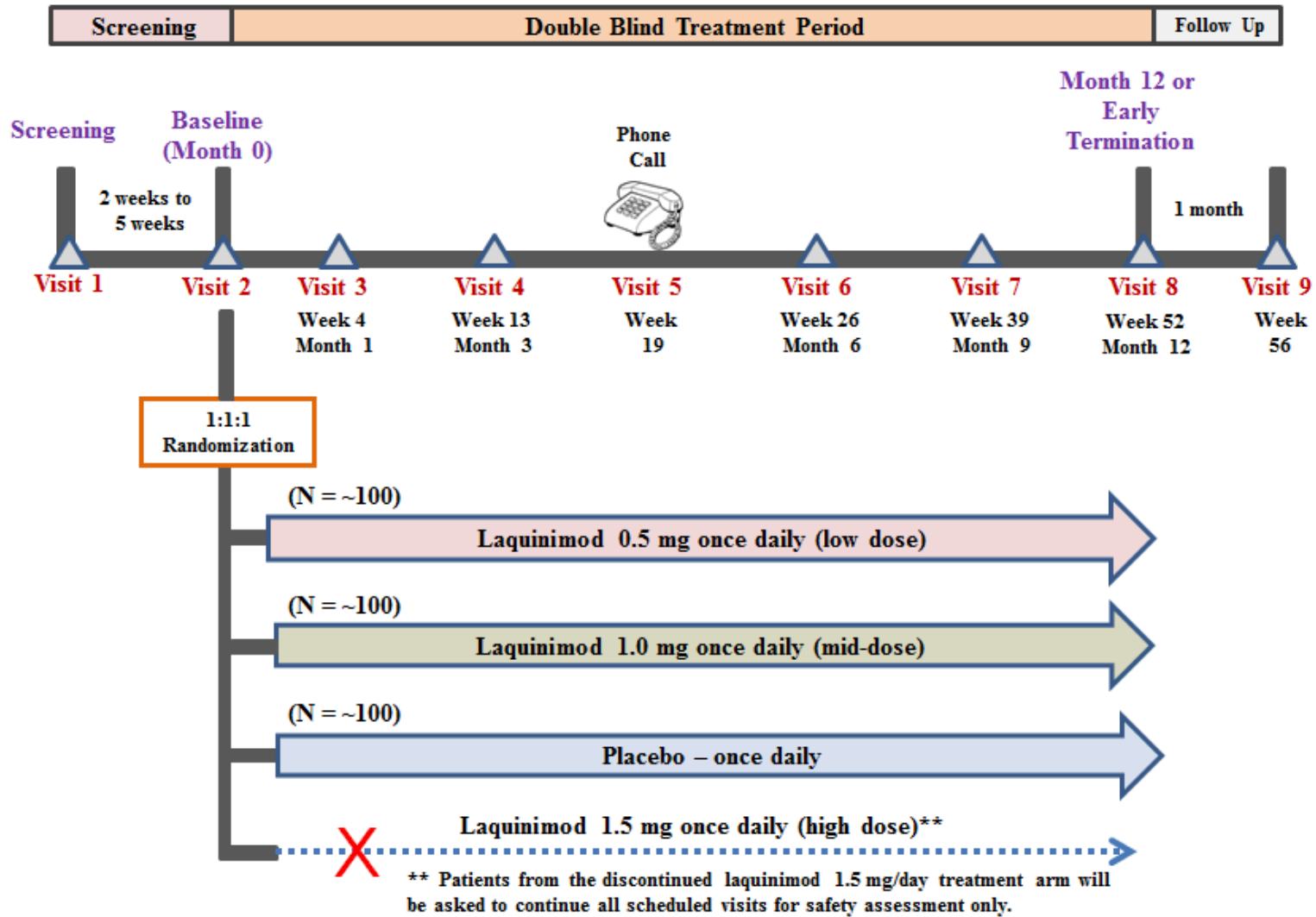


Figure 2: Overall Study Schema (from 10 January 2016)





### **3.2. Primary, Secondary and Exploratory Measures and Endpoints**

#### **3.2.1. Primary Efficacy Measure and Endpoints**

The primary efficacy variable and endpoint for this study is the change from baseline in the UHDRS-TMS (defined as the sum of the scores of all UHDRS-TMS subitems) at Month 12/ ET (evaluated at baseline and Months 1, 3, 6 and 12).

#### **3.2.2. Secondary Efficacy Measures and Endpoints**

The secondary efficacy variables and endpoints for this study are:

- Percent change from baseline in caudate volume at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in HD-CAB total score (sum of the standardized sub-components) at Month 12/ET (evaluated at baseline and Months 6 and 12)
- CIBIC-Plus global score at Month 12/ET (evaluated at Months 6 and 12) as compared to baseline (rated by an independent rater)
- Change from baseline in UHDRS- TFC at Month 12/ET (evaluated at baseline and Months 6 and 12)

#### **3.2.3. Exploratory Efficacy Measures and Endpoints**

The exploratory efficacy variables and endpoints for this study are:

- Change from baseline in brain atrophy as defined by the percentage change in volume in: whole brain volume and white-matter volume at Month 12/ET and absolute change in ventricular volume at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in UHDRS- FA at Month 12/ET (evaluated at baseline and Months 6 and 12)
- Change from baseline in Q-Motor assessments at Month 12/ET (evaluated at baseline and Months 1, 3, 6 and 12)
- Change from baseline in mPPT at Month 12/ET (evaluated at baseline and Months 6, and 12)
- Change from baseline in HD QoL and EQ-5D-5L at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in WLQ at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in HD-CAB sub-components at Month 12/ET (evaluated at baseline and Months 6 and 12):  
Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLTR), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version)
- Change from baseline in CDR-SB at Month 12/ET (evaluated at baseline and Month12)
- Change from baseline in HADS at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in PBA-s at Month 12/ET (evaluated at baseline and Month 12)

### **3.2.4. Safety Measures and Endpoints**

The safety of laquinimod will be assessed throughout the study by evaluating adverse events, clinical laboratory test results, vital signs measurements, electrocardiography (ECG), physical examination results, and suicidality (as assessed by changes from baseline in C-SSRS scores).

### **3.2.5. Tolerability Measures and Endpoints**

Tolerability variables and endpoints will include the following:

- Proportion of subjects (%) who prematurely discontinued from the study, reason of discontinuation and the time to ET
- Proportion of subjects (%) who prematurely discontinued from the study due to AEs and the time to ET

### **3.2.6. Pharmacokinetic Measures and Endpoints**

#### **3.2.6.1. Pharmacokinetics (PK) Ancillary Study**

PK samples of laquinimod and its metabolites will be collected from approximately 15 patients per each of the three continuing treatment groups (at selected sites at Month 1), for a total of approximately 45 patients. Additionally, PK samples were collected from 2 patients in the laquinimod 1.5 mg/day treatment group when the treatment was stopped; no further PK samples will be collected from the laquinimod 1.5 mg/day treatment group.

The time of the previous dose as well as deviations from the blood sampling times will be recorded in the appropriate eCRF. Patients performing the 24-hour PK profile will come to the clinic after an overnight fast (minimum of 8 hours) and will be given breakfast 4 hours after drug administration.

Samples will be collected at pre-dose, 15, 30 min and 1, 2, 3, 6 and 24 hours post dose.

Steady state pharmacokinetic parameters for laquinimod ( $AUC_{\tau}$ ,  $C_{\max}$  and  $C_{\min}$ ,  $t_{\max}$ ), will be calculated for each patient. Additional parameters for laquinimod and pharmacokinetic parameters for its metabolites may be calculated if data permit.

For patients participating in this ancillary study, the morning dose and the 24 hours dose administration (the day after) will take place at the clinic.

#### **3.2.6.2. Population PK (PPK) Study**

A single blood sample will be collected from all patients at Months 1, 3, 6 and 12 for evaluation of laquinimod and its metabolites.

Pharmacokinetics of laquinimod will be evaluated using a Population PK approach. The effect of covariates on the PK of laquinimod will be evaluated. Possible covariates will include demographic variables (e.g., age, gender, body weight and ethnicity), clinical variables (e.g. CAG repeat length), concomitant medications, blood and urine chemistry variables and markers of renal (creatinine clearance and serum creatinine) or hepatic function. Pharmacokinetic parameters for laquinimod metabolites may be calculated if data permit.

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

The PPK model may also include any unscheduled pharmacokinetic samples collected to assist with further investigations of cardiovascular events or other clinical event of interest for safety (see Section 8.1).

### **3.2.7. Pharmacodynamic Measures and Endpoints**

Biomarker assessment will include the following:

- Cytokines, Soluble protein (or any other soluble marker) levels will be determined at baseline, Months 6 and 12.
- Monocyte gene expression and/or protein profile will be explored at baseline and Month 12. This study will be performed only at selected sites in a subgroup of patients.
- PET scans and imaging analysis of microglial activation marker TSPO will be performed at baseline and Month 12. This study will be performed only in a subgroup of patients.
- MRI scans for MRS to explore the potential effect on metabolic changes in the putamen and frontal white matter will be done in a subgroup of patients at baseline and Month 12.

### **3.2.8. Pharmacogenomic Measures and Endpoints**

Pharmacogenomic (PGx) assessment will include CAG repeats analysis in the huntingtin gene and might include other DNA variations and RNA expression patterns potentially associated with clinical treatment responses to laquinimod (e.g. clinical effect, pharmacokinetics, tolerability, and safety features or disease susceptibility and severity features). The final list of genes that might be investigated will be selected in a later stage before the analysis so as to allow updating with new scientific information. Genomic analysis could also include a sequencing of the whole genome if required.

The CAG repeat length in the huntingtin gene will be established by a central laboratory for all patients, as part of the screening process to determine eligibility for the study. This will be done also for patients where a historical CAG repeat length result is available. If during this screening process a CAG repeat length result that differs from the patient's historical result is obtained, the central laboratory results should be used for determining eligibility. The exact CAG repeat length will not be available to the sites, only to the Sponsor. The central laboratory report will only note if the patient is within the eligibility criteria range (36-49 inclusive) or not. This will be explicitly explained and noted in the ICF of the patient. In either case, the investigator should review the CAG repeat results with the patient at the baseline visit, or at an unscheduled visit if a baseline visit will not take place.

### **3.3. Randomization and Blinding**

This is a randomized, double-blind, placebo-controlled study. Prior to 10 January 2016, eligible patients were randomly assigned to receive treatment with laquinimod at a dosage of 0.5, 1.0 or 1.5 mg qd or a matching placebo in a 1:1:1:1 ratio.

As of 10 January 2016, following a decision to discontinue treatment of the laquinimod 1.5 mg dose arm, future eligible patients will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day or 1.0 mg/day or matching placebo for 52 weeks. No change was performed to the original randomization list except that the patient numbers assigned to laquinimod 1.5 mg/day were removed from the list by the interactive response technology (IRT) vendor.

All patients who discontinued the 1.5 mg/day dose have been unblinded. No attempts will be made to re-randomize patients whose 1.5 mg treatment was stopped to a lower dose of laquinimod. The remaining ongoing patients retained their originally randomized treatment assignments.

Patients and investigators will remain blinded to treatment assignment during the study.

The randomization code will be generated by the Clinical Supply Chain (CSC) department following specifications from the Biostatistics Department.

In addition, the sponsor's clinical personnel involved in the study will be blinded to the study drug identity until the database is locked for analysis and the treatment assignment revealed. However, in case a prioritized sample analysis is needed, bioanalytical personnel may not be blinded. A statistician not assigned to the study will be responsible for reviewing the randomization code, and the final randomization code will be maintained by the CSC department.

Patients will be randomly assigned to treatment through a qualified randomization service provider (e.g., IRT). This system is used to ensure a balance across treatment groups.

### **3.4. Study Drugs and Dosage**

Patients will be randomized to receive laquinimod 0.5, 1.0, or 1.5 mg qd or matching placebo (prior to 10 January 2016), or randomly assigned to receive treatment with laquinimod at a dosage of 0.5 mg/day, 1.0 mg/day or placebo in a 1:1:1 ratio (from 10 January 2016). Every patient will take 3 capsules once daily, at the same time of the day, during the entire study period. Study drug will be administered as described in Section 3.4.1 and Section 3.4.2 below. The capsules will be taken orally and must be swallowed whole with a glass of water. The capsule should not be opened. Laquinimod can be taken with or without food.

#### **3.4.1. Investigational Product and Dosage**

Laquinimod will be provided as off-white, opaque, hard gelatin capsules. The capsules should be swallowed whole with water.

- Patients randomized to the laquinimod 1.5 mg qd treatment arm received 3 capsules of 0.5 mg laquinimod (Note: The treatment of this high dose arm was discontinued as of 10 January 2016).
- Patients randomized to the laquinimod 1.0 mg qd treatment arm will receive 2 capsules of 0.5 mg laquinimod and 1 capsule of matching placebo.

- Patients randomized to the laquinimod 0.5 mg qd treatment arm will receive 1 capsule of 0.5 mg laquinimod and 2 capsules of matching placebo.

A more detailed description of administration procedures is given in Section 5.1.

### **3.4.2. Other Study Drugs and Dosage - Placebo**

Matching placebo for laquinimod capsules will be provided as off-white opaque, hard gelatin capsules. Patients randomized to the placebo treatment arm will receive 3 capsules of matching placebo capsules.

A more detailed description of administration procedures is given in Section 5.1.

### **3.5. Duration of Patient Participation**

Subjects are expected to participate in this study for approximately 14 months, consisting of a screening period of 2 weeks up to 5 weeks, a double-blind treatment period of 12 months and a 1 month follow-up period.

### **3.6. Stopping Rules and Discontinuation Criteria**

Safety stopping rules are detailed in [Appendix A](#) (Guidance on Safety Monitoring).

These include:

- Elevated liver enzymes (as detailed in [Appendix A](#))
- Pregnancy
- Need for concomitant treatment with moderate and strong CYP3A4 inhibitors
- Patients that are diagnosed with a malignant solid or liquid tumor while participating in the study
- Acute coronary syndrome, myocardial infarction or any major cardiovascular event

Female subjects will be reminded to continue using 2 methods of acceptable contraception throughout treatment duration, and up to 30 days from the date from the last dose of the study drug, and about the need to stop treatment immediately if pregnancy is suspected. During the conduct of the study, serious adverse events will be reviewed (see Section 7.1.5) as they are reported from the investigational center to identify safety concerns. The study may be terminated by the sponsor at any time.

A patient may discontinue participation in the study at any time for any reason (e.g., lack of efficacy, consent withdrawn, and adverse event). The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (e.g., protocol violation or deviation as defined in Section 11.1.1, noncompliance, adverse event).

#### Liver Impairment

To avoid exposures to higher levels of laquinimod (see Section 1.3.2.1), a stopping rule related to liver impairment has been introduced. Patients who develop any chronic liver disease associated with hepatic function impairment while participating in the study should stop study medication.

#### Renal Impairment

To avoid exposures to higher levels of laquinimod (see Section 1.3.2.1), a stopping rule related to renal impairment has been introduced. Patients who develop chronic renal disease associated with moderate or severe functional impairment, defined as estimated creatinine clearance (CrCl)  $<60$  mL/min/1.73 m<sup>2</sup>, while participating in the study should stop study medication temporarily, and the assessment of estimated CrCl should be repeated. If the development of renal impairment is confirmed (estimated CrCl  $<60$  mL/min/1.73 m<sup>2</sup>), the patient should stop study medication permanently.

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

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

The reasons for temporary study drug discontinuation should be recorded in the appropriate section of the study drug dispensing and compliance log in the electronic Case Report Form (eCRF).

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

### **3.6.2. Early Termination (ET)**

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

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

Patients in the 1.5 mg/day (high dose) treatment arm, whose treatment with laquinimod was discontinued, were invited to attend an early termination visit (to return study medication and perform drug accountability). At this visit, only safety assessments were to be completed. These included vital signs, clinical laboratory tests, pregnancy test, adverse event inquiry, drug accountability, review of concomitant medication, and C-SSRS (see also Section 3.11.3.1.5). Patients were asked to continue scheduled follow up safety visits per the current schedule.

Women of child bearing potential should continue using 2 acceptable contraception methods up to 30 days after the last dose of study medication has been administered.

Moderate/strong CYP3A4 inhibitors are disallowed during the 30 days after the last laquinimod dose has been administered (see [Appendix B](#)).

Plasma levels of drugs that are CYP1A2 substrates may decrease when combined with laquinimod and within 30 days after the last laquinimod dose, rendering these drugs less effective (see [Appendix C](#)).

### **3.7. Study Drug Supply and Accountability**

#### **3.7.1. Study Drug Storage and Security**

Laquinimod and matching placebo capsules must be stored at room temperature (15-25°C), in a dry place, and in a securely locked, substantially constructed cabinet or enclosure. Only authorized personnel will have access to the study drug. The study site personnel at each site will be responsible for correct storage and handling of the study drug. Maintenance of a temperature log (manual or automated) is required and should be available for review by the monitor for the duration of the study. The temperature shall be recorded daily and the max/min thermometer reset after each reading. Complete instructions on receipt, storage, and handling of study drugs will be detailed in the Pharmacy Manual.

#### **3.7.2. Study Drug Accountability**

Each study drug shipment will include a packing slip, listing the contents of the shipment and any applicable forms.

The investigator is responsible for ensuring that deliveries of study drug and other study materials from the sponsor are correctly received and recorded, handled and stored safely and properly in accordance with the local regulations, and used in accordance with this protocol. Study drugs accountability records must be maintained at the site at all times.

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

The accountability of the returned study drugs should be performed and recorded by the sponsor's assigned monitor. The Subject Number, the date, batch code/batch number, pack number and quantity of study drugs returned by the subject will be checked for correctness and recorded on the appropriate accountability forms, to be provided by the sponsor.

The monitor will use the IRT to record the returns.

### **3.8. Maintenance of Randomization and Blinding**

The randomization code will be maintained by the CSC department. At the time of analysis, when treatment codes are revealed, the CSC department will provide the randomization code to the statistician assigned to this study.

Staff responsible for bioanalysis and pharmacokinetic data analysis will not have access to any clinical data and will provide concentration data to other staff members in a blinded manner (i.e., a dummy subject identifier will be linked to an individual subject's concentration data).

For information about personnel who may be aware of treatment assignments, see Section 3.3. These individuals will not be involved in conduct of any study procedures or assessment of any adverse events.

For a serious adverse event considered related and unexpected (ie, reasonable possibility; see Section 7.1.4) to the study drug, the sponsor's Global Patient Safety & Pharmacovigilance

Department may independently request that the treatment code be revealed (on a case-by-case basis). If this occurs, the investigator will remain blinded to treatment.

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

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

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

In blinded studies, for adverse events that are defined as: Suspected, Unexpected, Serious, Adverse Reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance may independently request that the treatment code be revealed (on a case-by-case basis) to comply with regulatory requirements. If this occurs, the investigator will remain blinded to treatment.

As of 10 January 2016, treatment with laquinimod was discontinued for all patients in the 1.5 mg dose group; all these discontinued patients have been unblinded. No attempts will be made to re-randomize patients whose 1.5 mg treatment was stopped to a lower dose of laquinimod.

However, the blinding was maintained for the patients in the remaining ongoing 3 treatment arms (0.5 mg/day, 1.0 mg/day, and placebo).

### **3.9. Source Data Recorded on the Case Report Form**

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

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

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

### **3.10. Time Schedule**

The study started in Q4 2014 (first patient randomized) and is expected to be completed in Q1 2018 (last patient last visit).




As of 10 January 2016, treatment with laquinimod was discontinued for all patients in the 1.5 mg/day dose arm.


Approximately 300 patients (100 patients within each study arm), plus the 30 patients who were already randomized to the laquinimod 1.5 mg dose arm, from ~51 investigational centers in North America, Europe and Russia are planned to be enrolled in the study.


### **3.11. Study Procedures**


Study procedures and assessments with their timing are summarized in [Table 3](#).

**Table 3: TV5600-CNS-20007 (LEGATO-HD) - Study Procedures and Assessments**

TV5600-CNS-20007 (LEGATO-HD)	Pre-treatment	Baseline (Dosing)	Double-blind Treatment Period						Follow-Up	Unscheduled Visit
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 - Termination Visit <sup>a</sup>	Visit 9	-
Time (Weeks)	Screening	Baseline	Week 4	Week 13	Week 19	Week 26	Week 39	Week 52	Week 56	-
Time (Months)		Month 0	Month 1	Month 3		Month 6	Month 9	Month 12 (or ET)		
Visit Window	2 weeks up to 5 weeks		±3 days	±7 days	±7 days	±7 days	±7 days	±7 days	±5 days	
Informed consent	X <sup>b</sup>									
Inclusion and exclusion criteria	X <sup>c</sup>	X <sup>c</sup>								
Medical and psychiatric history / demographics	X									
Cardiovascular risk factor assessment and management <sup>d e</sup>	X									
ISCED	X									
HD history	X									
Prior medication history	X									
Drug test and/or CDT test <sup>f</sup>	X									
Clinical laboratory tests <sup>g</sup>	X <sup>h</sup>	X	X	X		X	X	X	X	X <sup>i</sup>
Clinical hematology	X	X	X	X		X	X	X	X	
Anemia panel <sup>j</sup>		X	Anemia panel is performed if there is a confirmed hemoglobin decrease of >1 g/dL from baseline							
Lipid profile <sup>g</sup>		X						X		
Thyroid function (T3, T4, TSH)		X				X		X		
Blood collection for soluble biomarkers (cytokines)		X				X		X		X <sup>i</sup>
Blood collection for gene expression analysis		X				X		X		
Blood sample for genomic analysis (including CAG analysis)	X									
Blood sample for TSPO genotype	X									

TV5600-CNS-20007 (LEGATO-HD)	Pre-treatment	Baseline (Dosing)	Double-blind Treatment Period						Follow-Up	Unscheduled Visit
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 - Termination Visit <sup>a</sup>	Visit 9	-
Time (Weeks)	Screening	Baseline	Week 4	Week 13	Week 19	Week 26	Week 39	Week 52	Week 56	-
Time (Months)		Month 0	Month 1	Month 3		Month 6	Month 9	Month 12 (or ET)		
Visit Window	2 weeks up to 5 weeks		±3 days	±7 days	±7 days	±7 days	±7 days	±7 days	±5 days	
analysis <sup>k</sup>										
Blood sample for monocyte analysis <sup>k 1</sup>		X						X		
Urinalysis	X									
Physical examination, including weight	X <sup>m</sup>	X	X	X		X	X	X	X	
ECG <sup>n</sup>	X	X	X	X		X		X	X	
Vital signs measurements	X	X	X	X		X	X	X	X	X
Serum -hCG in women of childbearing potential	X <sup>o</sup>	X <sup>o</sup>	X	X		X	X	X	X	
Urine -hCG in women of child- bearing potential		X <sup>p</sup>	X	X		X	X	X <sup>p</sup>	X	
Ascertaining use of acceptable contraception		X	X	X	X	X	X	X	X	X
Home urine pregnancy test			Starting after Month1 (Visit 3), a urine -hCG test will be performed at home in women of child-bearing potential every 28 (±2) days.							
Site call to patient for result inquiry			A telephone call will be scheduled to be performed within 72 hours of the urine test date to inquire about the results.							
C-SSRS (baseline screening version)	X									
C-SSRS (since last visit version)		X	X	X		X	X	X	X	
Randomization		X								
MRI scan <sup>q</sup>	X <sup>n</sup>	X <sup>r</sup>						X <sup>s</sup>		
Estimated creatinine clearance calculation <sup>t</sup>	X	X	X	X		X	X	X	X	X <sup>i</sup>
MRS scan <sup>k</sup>		X						X		
PET scan <sup>k u v</sup>		X <sup>p</sup>						X <sup>p</sup>		

TV5600-CNS-20007 (LEGATO-HD)	Pre-treatment	Baseline (Dosing)	Double-blind Treatment Period						Follow-Up	Unscheduled Visit
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 - Termination Visit <sup>a</sup>	Visit 9	-
Time (Weeks)	Screening	Baseline	Week 4	Week 13	Week 19	Week 26	Week 39	Week 52	Week 56	-
Time (Months)		Month 0	Month 1	Month 3		Month 6	Month 9	Month 12 (or ET)		
Visit Window	2 weeks up to 5 weeks		±3 days	±7 days	±7 days	±7 days	±7 days	±7 days	±5 days	
UHDRS-TMS	X <sup>w</sup>	X	X	X		X		X		
UHDRS-TFC	X <sup>w</sup>	X				X		X		
UHDRS-FA		X				X		X		
mPPT		X				X		X		
PBA-s <sup>x</sup>		X						X		
CIBIS <sup>x</sup>		X								
CIBIC-plus <sup>x</sup>						X		X		
HD-QoL <sup>y</sup>		X						X		
EQ-5D-5L <sup>z</sup>		X						X		
WLQ <sup>z</sup>		X						X		
Q-Motor Assessments	X	X	X	X		X		X		
HD-CAB <sup>aa</sup>	X <sup>bb</sup>	X	X <sup>cc</sup>	X <sup>cc</sup>		X		X		
CDR-SB <sup>x</sup>		X						X		
HADS		X						X		
PK (drug and metabolites concentration) sampling			X <sup>y</sup>	X		X		X		X <sup>i</sup>
24-hour PK profiling <sup>dd</sup> for drug and metabolites			X							
Review study compliance		X	X	X	X	X	X	X		X
Study Drug Dispensing		X	X	X		X	X			
Study Drug Collection and Reconciliation			X	X		X	X	X		X

TV5600-CNS-20007 (LEGATO-HD)	Pre-treatment	Baseline (Dosing)	Double-blind Treatment Period						Follow-Up	Unscheduled Visit
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 - Termination Visit <sup>a</sup>	Visit 9	-
Time (Weeks)	Screening	Baseline	Week 4	Week 13	Week 19	Week 26	Week 39	Week 52	Week 56	-
Time (Months)		Month 0	Month 1	Month 3		Month 6	Month 9	Month 12 (or ET)		
Visit Window	2 weeks up to 5 weeks		±3 days	±7 days	±7 days	±7 days	±7 days	±7 days	±5 days	
Concomitant Medication Inquiry		Concomitant medication will be monitored throughout the treatment and follow-up periods.								
Adverse events inquiry		Adverse events will be monitored throughout the treatment and follow-up periods.								

- <sup>a</sup> For patients in the high dose group (1.5 mg/day) who were discontinued, only safety and no efficacy assessments had to be performed at the Early Termination visit. The patients will be asked to continue all scheduled visits for safety assessment only after study drug discontinuation.
- <sup>b</sup> Patients with a legal guardian should be consented according to local requirements.
- <sup>c</sup> Inclusion/exclusion criteria should be met at screening and reviewed at baseline (Visit 2) before the patient is randomized.
- <sup>d</sup> Including smoking history. In addition, an evaluation of cardiovascular risk factors should take place as soon as possible for patients already in the study, following approval of Global Amendment 04.
- <sup>e</sup> Assessment of changes in cardiovascular risk and appropriate cardiovascular risk management with appropriate medical follow-up, if clinically indicated, should be performed during the scheduled and unscheduled visits.
- <sup>f</sup> When applicable, patients will be screened for drug substances in urine and/or CDT level in blood at screening to confirm abstinence in former (more than 12 months from screening) alcohol and/or drug abusers.
- <sup>g</sup> For visits 2 through 9, Patients must have fasted no less than 8 hours prior to the blood draw.
- <sup>h</sup> When applicable per local requirements, patients will undergo an HIV test at screening.
- <sup>i</sup> Unscheduled urgent safety laboratory samples, pharmacokinetic blood samples, and/or samples for potential biomarker analysis may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.
- <sup>j</sup> Anemia panel includes B12, blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, IFN- $\gamma$ , TNF- $\alpha$ , and hepcidin. Assessed at baseline and also at 1 subsequent time point with B12 if hemoglobin decrease of >1 g/dL from the patient's hemoglobin level at baseline and the decrease is confirmed.
- <sup>k</sup> Only at selected sites in a subgroup of patients
- <sup>l</sup> Blood sample for monocyte collection and analysis has to be done in accordance with the laboratory manual. For UK patients, the sample can be drawn prior to the baseline or Month 12 visit, as it coincides with the PET scan visits
- <sup>m</sup> Height will be assessed during the physical exam at screening (Visit 1)
- <sup>n</sup> ECG will be performed in triplicate at baseline (approximately 10±5 minutes apart). All other visits will have a single ECG performed.
- <sup>o</sup> At the screening visit, only serum  $\beta$ -HCG test will be performed. For the baseline visit - urine pregnancy test (beta human chorionic gonadotropin [ $\beta$ -hCG]) result is required for women of child-bearing potential prior to randomization. The urine test should be conducted at the site to allow randomization. A serum  $\beta$ -HCG test should also be used to confirm the urine test; however, the randomization should be performed based on the results of the urine pregnancy test.

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- <sup>p</sup> An additional urine -HCG test will be performed at the PET facilities at Imperial College in London at the Baseline visit and at Visit 8 for women of child-bearing potential participating in the PET substudy. Its result will be available on site prior to any procedures involving ionizing radiation and will be considered accordingly.
- <sup>q</sup> If anxiolysis is required in order to perform the MRI scan, the scan should be performed at the end of the study visit day.
- <sup>r</sup> The baseline MRI can be performed at the screening visit, but no later than 7 days prior to baseline. If performed at the screening visit, as many screening assessments as possible should be conducted prior to the MRI scan in order to assess eligibility.
- <sup>s</sup> If a patient terminates within 3 months of the baseline visit, they will not undergo an Early Termination scan. If a patient terminates prior to Month 12, the Early termination scans should be performed as soon as possible, but not more than 7 days after discontinuation of study drug. Month 12 scans should be performed 7 days prior to the Termination Visit. The early termination MRI scan was not to be done for the patients in the discontinued 1.5 mg/day treatment arm .
- <sup>t</sup> Estimated creatinine clearance will be calculated at all in clinic study visits. Patients who develop chronic renal disease associated with moderate or severe functional impairment, defined as estimated creatinine clearance (CrCl) <60 mL/min/1.73 m<sup>2</sup>, while participating in the study should stop study medication temporarily and the creatinine clearance assessment should be repeated. If the renal impairment is confirmed (estimated CrCl <60 mL/min/1.73 m<sup>2</sup>), the patient should stop study medication permanently.
- <sup>u</sup> The PET scan can be done at any time prior to the date of the baseline visit, after eligibility of the patient has been confirmed. It can also be done 2 to 5 weeks prior to the Month 12 visit.
- <sup>v</sup> Patients taking benzodiazepines should be instructed to stop taking them for 3 days prior to having the PET scan.
- <sup>w</sup> UHDRS-TMS>5 and UHDRS-TFC 8 are required for study eligibility
- <sup>x</sup> Where possible, the same person should act as a patient's caregiver/informant throughout the study. If this is not possible, a patient should have no more than 2 caregivers throughout the study. All possible attempts should be made to assure that caregiver will attend the clinical visits in person together with the patient. If the caregiver/informant is not available to attend the clinic visit, the interview can be done over phone.
- <sup>y</sup> HD-QoL will be assessed by both caregiver/informant and patient. All possible attempts should be made to assure that caregiver/informant will attend the clinical visits in person together with the patient. If the caregiver/informant is not available to attend the clinic visit, the caregiver/informant form should be omitted.
- <sup>z</sup> The WLQ/EQ-5D-5L could be completed by the patients with caregiver/informant assistance if needed.
- <sup>aa</sup> Includes Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLTR), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version).
- <sup>bb</sup> The HD-CAB is performed at screening to reduce practice effects during the treatment phase.
- <sup>cc</sup> Reduced battery (only SDMT and Trail Making Test).
- <sup>dd</sup> Only at selected sites in a subgroup of patients (approximately 15 patients per each of the three continuing treatment groups, for a total of approximately 45 patients) at Month 1. Patients participating in the 24-hour PK profiling will not have the single PK sample drawn at Visit 3. Additionally, PK samples were collected from 2 patients in the laquinimod 1.5 mg/day treatment group when the treatment was stopped; no further PK samples will be collected from the laquinimod 1.5 mg/day treatment group.

Abbreviations: ET = early termination; CDT = carbohydrate deficient transferrin; ECG = electrocardiogram; C-SSRS = Columbia-Suicide Severity Rating Scale; UHDRS = Unified Huntington's Disease Rating Scale; CIBIS = Clinician's Interview-Based Impression of Severity; CIBIC-Plus = Clinician's Interview-Based Impression of Change plus Caregiver Input; HD-CAB = HD Cognitive Assessment Battery; HD-QoL = Huntington's disease Quality of Life; HIV = human immunodeficiency virus; CAG = cytosine-adenine-guanine; TMS = Total Motor Score; PBA-s = Problem Behaviors Assessment-Short form; SDMT = Symbol Digit Modalities Test. TFC = Total Functional Capacity; Q-Motor = Quantitative motor; CDR-SB = Clinical Dementia Rating – Sum of Boxes; HADS = Hospital Anxiety and Depression Scale

### 3.11.1. Procedures for Screening and Enrollment (Visit 1)

A signed and dated informed consent form will be obtained before screening procedures commence. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the protocol-specific evaluations. Patients will acknowledge and agree to the possible use of this information for the study by giving informed consent. Patients with a legal guardian should be consented according to local requirements.

After informed consent is obtained, patients who are screened will be assigned an 8-digit permanent identification number such that all patients from each investigational center are given consecutive identification numbers in successive order of inclusion. The first 2 digits of the screening number will be the number assigned to the country where the investigational center is located, the next 3 digits will be the designated investigator center number, and the last 3 digits will be assigned at the investigator center (e.g., if the number assigned to the country is 01, the 3<sup>rd</sup> patient screened at center 5 would be given the number of 01005003).

For patients for whom a unique HD-ID number is available, this identification number will be collected in the CRF.

The International Standard Classification of Education (ISCED) will also be administered at screening as part of a panel of demographic measures including date of birth and gender. The ISCED is a scale that ranges from 0 to 8 (pre-primary school to doctoral level) that is used to establish education level equivalence across different countries/educational systems. Education levels are determined by using informal questioning of the patient, and then scores on the 0-6 scale are assigned using country-specific tables that establish international education level equivalence ([UNESCO, 2012](#)).

A patient who is screened but not randomized, e.g., because entry criteria were not met or enrollment did not occur within the specified time, may be considered for screening again if, e.g., there is a change in the patient's medical background or a modification of study entry criteria.

Re-screening will be permitted on a case by case basis. A new informed consent form should be signed in any case of re-screening. A new Subject Number will be assigned to the subject.

The screening visit (Visit 1) will take place up to 5 weeks before the baseline visit. The following procedures will be performed at Visit 1:

- obtain written informed consent before any other study-related procedures are performed
- review inclusion/exclusion criteria
- review medical and psychiatric history/demographics
- evaluation and management of major modifiable cardiac risk factors (eg, diabetes, high blood pressure, hyperlipidemia, tobacco smoking) and referral to treatment and follow-up in suitable clinic if needed.
- ISCED
- HD history
- review prior medication history
- blood sample for genomic analysis including CAG analysis

- when applicable, patients will be screened for drug substances in urine and/or CDT level in blood to confirm abstinence in former (more than 12 months from screening) alcohol and/or drug abusers
- perform clinical laboratory tests
- when applicable per local requirements, patients will undergo an HIV test
- clinical hematology
- perform urinalysis
- perform vital signs measurements
- perform single electrocardiography (ECG)
- perform full physical examination (including weight and height)
- serum -HCG in women of childbearing potential
- blood sample for TSPO genotype analysis (**Only at selected sites in a subgroup of patients**)
- C-SSRS (baseline screening version)
- UHDRS-TMS (**required for study eligibility**)
- UHDRS-TFC (**required for study eligibility**)
- Estimated creatinine clearance calculation based on laboratory results (for inclusion in study).
- Q-Motor assessments
- HD-CAB
  - Includes Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLTR), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version)
  - The HD-CAB is performed at screening to reduce practice effects during the treatment phase.
- MRI scan
  - The baseline MRI can be performed at the screening visit, but no later than 7 days prior to baseline. If performed at the screening visit, as many screening assessments as possible should be conducted prior to the MRI scan in order to assess eligibility. If the screening period is extended by up to 30 days, the MRI scan does not have to be repeated.
- inform patients of study restrictions and compliance requirements

### **3.11.2. Procedures Before Study Drug Treatment and Randomization (Baseline [Visit 2])**

Patients who meet the inclusion/exclusion criteria at Visit 1 will continue to Visit 2, when baseline evaluations will be conducted.

The following procedures will be performed at Visit 2 in patients who continue to meet the inclusion/exclusion criteria:

- review inclusion/exclusion criteria
- perform clinical laboratory tests
- estimated creatinine clearance calculation
- clinical hematology



- anemia panel (blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, interleukin [IL]-1, IL-6, interferon [IFN]- , tumor necrosis factor [TNF]- , and hepcidin) and B12
- lipid profile
- thyroid function (T3, T4, TSH)
- blood sample for soluble biomarkers (cytokines)
- blood sample for gene expression analysis
- blood sample for monocyte analysis (**Only at selected sites in a subgroup of patients**)
  - Blood sample for monocyte collection and analysis has to be done in accordance with the laboratory manual;
  - For UK patients, the sample can be drawn prior to the baseline visit, as it coincides with the PET scan visits
- perform full physical examination (including weight)
- perform vital signs measurements
- ECG – in triplicate (approximately 10±5 minutes apart)
- urine -HCG in women of child-bearing potential
  - The urine test should be conducted at the site to allow randomization. A serum -HCG test should also be used to confirm the urine test; however, the randomization should be performed based on the results of the urine pregnancy test.
- serum -HCG in women of child-bearing potential
- additional urine -HCG in women of child-bearing potential at PET facilities (**Only in a subgroup of patients**)
- Ascertaining use of acceptable contraception
- C-SSRS (since last visit version)
- MRI scan
  - The baseline MRI can be performed at the screening visit, but no later than 7 days prior to baseline.
  - If anxiety is required in order to perform the MRI scan, the scan should be performed at the end of the study visit day.
- MRS scan (**Only at selected sites in a subgroup of patients**)
- PET scan (**Only in a subgroup of patients**)
  - The PET scan can be done at any time prior to the date of the baseline visit, after eligibility of the patient has been confirmed.
  - Patients taking benzodiazepines should be instructed to stop taking them for 3 days prior to having the PET scan.
- UHDRS-TMS
- UHDRS-TFC
- UHDRS-FA
- mPPT
- PBA-s
- CIBIS
- HD-QoL
- EQ-5D-5L

- WLQ
- Q-Motor assessments
- HD-CAB
  - Includes Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLTR), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version)
- CDR-SB
- HADS
- Review study compliance
- Review of concomitant medications
- Adverse event inquiry
- Randomization
- Study drug dispensing

In case an unscheduled visit is performed, all mandatory activities according to the protocol, for this visit, should be performed.

A patient who does not meet the inclusion/exclusion criteria may be considered for screening again if there is a change in the patient's medical background, a modification of study entry criteria, or other relevant change.

Patients who continue to meet the inclusion/exclusion criteria will be assigned a permanent unique randomization number and a treatment number (kit, bottle) using an IRT. These two newly assigned numbers will be entered into the CRF, and study drug will be dispensed.

### **3.11.3. Procedures During Study Drug Treatment**

#### **3.11.3.1. Double-Blind Treatment Period (Weeks 4 Through 52 [Visits 3 Through 8])**

##### **3.11.3.1.1. Months 1 and 3 (Visits 3 and 4)**

The following procedures/assessments will be performed at Months 1 and 3 (Visits 3 and 4):

- Review of concomitant medications
- Adverse events inquiry
- perform full physical examination (including weight)
- perform vital signs measurements
- perform single ECG
- perform clinical laboratory tests
- estimated creatinine clearance calculation
- clinical hematology
- serum -HCG in women of child-bearing potential
- urine -HCG in women of child-bearing potential
  - Starting after Month 1 (Visit 3), a urine -hCG test will be performed at home in women of child-bearing potential every 28 ( $\pm$ 2) days. A telephone call will be scheduled to be performed within 72 hours of the urine test date.
- Ascertaining use of acceptable contraception

- C-SSRS (since last visit version)
- UHDRS-TMS
- Q-Motor assessments
- Reduced cognitive battery (only SDMT and Trail Making Test)
- PK drug concentration sampling
- 24-hour PK profiling (**only at selected sites in a subgroup of patients**) – **at Visit 3 only**
  - Patients participating in the 24-hour PK profiling will not have the single PK sample drawn at Visit 3.
- Review study compliance
- Study drug collection and reconciliation
- Study drug dispensing

### **3.11.3.1.2. Week 19 (Visit 5) – Phone Call**

Patients will be contacted by telephone at Week 19 to evaluate tolerability to the study drug through assessment of adverse events and concomitant medication usage, and to review study compliance.

Use of acceptable contraception will be ascertained.

The home urine -hCG test will be performed in women of child-bearing potential, and a telephone call will be scheduled to be performed within 72 hours of the urine test date to inquire about the results.

### **3.11.3.1.3. Month 6 (Visit 6)**

The following procedures/assessments will be performed at Month 6 (Visit 6):

- Review of concomitant medications
- Adverse events inquiry
- perform full physical examination (including weight)
- perform vital signs measurements
- perform single ECG
- perform clinical laboratory tests
- estimated creatinine clearance calculation
- clinical hematology
- thyroid function (T3, T4, TSH)
- blood sample for soluble biomarkers (cytokines)
- blood sample for gene expression analysis
- serum -HCG in women of child-bearing potential
- urine -HCG in women of child-bearing potential
- Ascertaining use of acceptable contraception
- C-SSRS (since last visit version)
- UHDRS-TMS
- UHDRS-TFC
- UHDRS-FA

- mPPT
- CIBIC-plus
- Q-Motor assessments
- HD-CAB
  - Includes Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLTR), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version)
- PK drug concentration sampling
- Review study compliance
- Study drug collection and reconciliation
- Study drug dispensing

#### **3.11.3.1.4. Month 9 (Visit 7)**

The following procedures/assessments will be performed at Month 9 (Visit 7):

- Review of concomitant medications
- Adverse events inquiry
- perform full physical examination (including weight)
- perform vital signs measurements
- perform clinical laboratory tests
- estimated creatinine clearance calculation
- clinical hematology
- serum -HCG in women of child-bearing potential
- urine -HCG in women of child-bearing potential
- Ascertaining use of acceptable contraception
- C-SSRS (since last visit version)
- Review study compliance
- Study drug collection and reconciliation
- Study drug dispensing

#### **3.11.3.1.5. Month 12 (Visit 8) –or Early Termination**

The following procedures/assessments will be performed at Month 12 (Visit 8) or early termination:

- Review of concomitant medications
- Adverse events inquiry
- perform full physical examination (including weight)
- perform vital signs measurements
- perform single ECG
- perform clinical laboratory tests
- estimated creatinine clearance calculation
- clinical hematology
- lipid profile
- thyroid function (T3, T4, TSH)

- blood sample for soluble biomarkers (cytokines)
- blood sample for gene expression analysis
- blood sample for monocyte analysis (**Only at selected sites in a subgroup of patients**)
  - Blood sample for monocyte collection and analysis has to be done in accordance with the laboratory manual
  - For UK patients, the sample can be drawn prior to the Month 12 visit, as it coincides with the PET scan visits
- serum -HCG in women of child-bearing potential
- urine -HCG in women of child-bearing potential
- additional urine -HCG in women of child-bearing potential at PET facilities (**Only in a subgroup of patients**)
- Ascertaining use of acceptable contraception
- PK drug concentration sampling
- C-SSRS (since last visit version)
- MRI scan
  - If anxiolysis is required in order to perform the MRI scan, the scan should be performed at the end of the study visit day.
- MRS scan (**Only at selected sites in a subgroup of patients**)
- PET scan (**Only in a subgroup of patients**)
  - The PET scan can be done 2 to 5 weeks prior to the Month 12 visit.
  - Patients taking benzodiazepines should be instructed to stop taking them for 3 days prior to having the PET scan.
- UHDRS-TMS
- UHDRS-TFC
- UHDRS-FA
- mPPT
- PBA-s
- CIBIC-plus
- HD-QoL
- EQ-5D-5L
- WLQ
- Q-Motor assessments
- HD-CAB
  - Includes Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLRT-R), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version)
- CDR-SB
- HADS
- Review study compliance
- Study drug collection and reconciliation

Moderate/strong CYP3A4 inhibitors are disallowed during the 30 days after the last laquinimod dose has been administered (see [Appendix B](#)).

Plasma levels of drugs that are CYP1A2 substrates may decrease when combined with laquinimod and within 30 days after the last laquinimod dose, rendering these drugs less effective (see [Appendix C](#)).

Early termination refers to the study drug termination and not termination of the patient from the study. Patients in the 1.5 mg/day (high dose) treatment arm, whose treatment with laquinimod was discontinued, were invited to attend an early termination safety visit to return study medication and perform drug accountability. At this visit, only safety assessments (vital signs, clinical laboratory tests, pregnancy test, adverse event inquiry, drug accountability, review of concomitant medication, and C-SSRS) were to be conducted (see Section [3.6.2](#)), and none of the efficacy assessments. Patients were asked to continue all scheduled visits for safety assessment after study drug discontinuation.

Patients in the high dose group (1.5mg/day) who were requested to discontinue study drug before week 52, but who continue to attend scheduled study visits for safety assessment, are not considered to have completed the study.

### **3.11.4. Procedures After Study Drug Treatment**

#### **3.11.4.1. Follow-Up (Week 56, Visit 9)**

The following procedures/assessments will be performed at the follow up visit (Week 56, Visit 9):

- Review of concomitant medications
- Adverse events inquiry
- perform clinical laboratory tests
- estimated creatinine clearance calculation
- clinical hematology
- perform full physical examination (including weight)
- perform vital signs measurements
- perform single ECG
- serum -HCG in women of child-bearing potential
- urine -HCG in women of child-bearing potential
- Ascertaining use of acceptable contraception
- C-SSRS (since last visit version)

Patients who participate in the study in compliance with the protocol for the entire duration of the double-blind treatment will be considered to have completed the study.

For patients who complete the study or withdraw prematurely, final evaluations will be performed at the end-of-treatment visit or as soon as possible thereafter. Procedures for patients who withdraw prematurely from the study are described in Section [4.3](#).

If it is not possible to schedule the ET visit within 2 weeks after end of treatment, only the safety evaluations for that visit (vital signs, clinical laboratory tests, pregnancy test, adverse event

inquiry, drug accountability, review of concomitant medication, and C-SSRS, see Section 3.6.2) need to be performed.

Patients with ongoing adverse events or clinically significant abnormal laboratory test results (as interpreted by the investigator) will be monitored as described in Section 7.1.2 and Section 7.3, respectively.

### **3.11.5. Unscheduled Visits**

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 on the CRF as well as any other data obtained (e.g., adverse events, concomitant medications and treatments, and results from procedures or tests).

Mandatory Unscheduled Visit Procedures (except for subjects that perform the unscheduled visit for repeat MRI scan):

- Vital signs
- Evaluation of AEs
- Review of concomitant medications
- Review of study drug accountability
- Compliance
- Ascertaining use of acceptable contraception

Other procedures may be performed at the discretion of the investigator, and must be recorded in the source documentation.

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

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

## 4. SELECTION AND WITHDRAWAL OF PATIENTS

### 4.1. Patient Inclusion Criteria

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

- a. **[New criterion]** Documentation of prior positive genetic testing for HD, or a clinical diagnosis of symptomatic HD (Diagnostic Confidence Level 4).
- b. **[Revision 1]** Presence of 36-49 CAG repeats, inclusive, in the huntingtin gene based on centralized CAG testing during screening.
- c. Male or female between 21-55 years of age, inclusive, with an onset of HD at or after 18 years of age.
- d. **[Revision 1]** Women of child-bearing potential (women who are not post menopausal or who have not undergone surgical sterilization) must practice an acceptable method of birth control for 30 days before taking the study treatment, and 2 acceptable methods of birth control during all study duration and until 30 days after the last dose of treatment was administered. Acceptable methods of birth control in this study include: Intrauterine device, barrier method (condom or diaphragm with spermicide) and hormonal methods of birth control (e.g., oral contraceptive, contraceptive patch, long-acting injectable contraceptive).
- e. A sum of >5 points on the UHDRS-TMS at the screening visit
- f. UHDRS-TFC ≥ 8 at the screening visit.
- g. Able and willing to provide written informed consent prior to any study related procedure being performed at the screening visit. Patients with a legal guardian should be consented according to local requirements.
- h. Willing to provide a blood sample for genomic CAG analysis at the screening visit.
- i. Willing and able to take oral medication and able to comply with the study specific procedures.
- j. Ambulatory, being able to travel to the study centre, and judged by the investigator as likely to be able to continue to travel for the duration of the study
- k. Availability and willingness of a caregiver, informant, or family member to provide input at study visits assessing CIBIC-Plus, CDR-SB, PBA-s and HD-QoL. A caregiver is recommended to be someone who attends to the patient at least 2 to 3 times per week for at least 3 hours per occasion, and the suitability of the caregiver should be judged by the investigator.
- l. For patients taking allowed antidepressant medication, the dosing of medication must have been kept constant for at least 30 days before baseline and must be kept constant during the study.



## 4.2. Patient Exclusion Criteria

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

- a. Use of immunosuppressive agents, or cytotoxic agents, including cyclophosphamide and azathioprine within 12 months prior to screening
- b. Previous use of laquinimod
- c. Use of moderate/strong inhibitors of CYP3A4 within 2 weeks prior to randomization.
- d. Use of inducers of CYP3A4 within 2 weeks prior to randomization.
- e. Pregnant or breastfeeding.
- f. **[Revision 1]** Serum levels  $\geq 2 \times \text{ULN}$  of either ALT or AST at screening.
- g. **[Revision 1]** Serum direct bilirubin which is  $\geq 1.5 \times \text{ULN}$  at screening.
- h. **[Revision 2]** Estimated creatinine clearance  $< 60 \text{ mL/min}$  at screening, calculated using the Cockcroft Gault equation:  
$$(140 - \text{age}) \times \text{mass (kg)} \times [0.85 \text{ if female}] / 72 \times \text{serum creatinine (mg/dL)}$$
- i. **[Revision 1]** Subjects with a clinically significant or unstable medical or surgical condition that may put the patient at risk when participating in the study or may influence the results of the study or affect the patient's ability to take part in the study, as determined by medical history, physical examinations, ECG, or laboratory tests. Such conditions may include:
  1. A major cardiovascular event (e.g. myocardial infarction, acute coronary syndrome, de-compensated congestive heart failure, pulmonary embolism, coronary revascularization, angina) that occurred prior to randomization.
  2. Significant cardiovascular risk factors (such as, but not limited to, uncontrolled hypertension, uncontrolled diabetes), per investigator discretion.
  3. Any acute pulmonary disorder
  4. A CNS disorder other than HD that may jeopardize the subject's participation in the study, including such disorders that are demonstrated on the baseline MRI (based on local read).
  5. A gastrointestinal disorder that may affect the absorption of study medication.
  6. Acute or chronic renal disease including acute kidney injury (AKI).
  7. Any form of acute or chronic liver disease.
  8. Known human immunodeficiency virus positive status. Patients will undergo an HIV test at screening per local requirements, if applicable.
  9. Any malignancies, excluding basal cell carcinoma, in the 5 years prior to randomization.

- j. Any clinically significant, abnormal, screening laboratory result which in the opinion of the investigator, affects the patients' suitability for the study or puts the patient at risk if he/she enters the study
- k. Unsuitable for MRI (e.g., claustrophobia, metal implants)
- l. Alcohol and/or drug abuse within the 12 months prior to screening, as defined by Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition Text Revision (DSM-IV TR) criteria for substance abuse. For former alcohol and/or drug abusers, the abstinence should be confirmed by laboratory tests (drug testing and/or carbohydrate deficient transferrin (CDT) level in blood).
- m. Patients with active suicidal ideation during the past month as measured by a most severe suicide ideation score of 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or 5 (Active Suicidal Ideation with Specific Plan and Intent) on the baseline screening Columbia-Suicide Severity Rating Scale (C-SSRS) or subjects who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) if the attempt or acts were performed within 1 year of screening, or subjects who, in the opinion of the investigator, present a serious risk of suicide.
- n. Patients with known intracranial neoplasms, vascular malformations, or intracranial hemorrhage
- o. Known drug hypersensitivity that would preclude administration of laquinimod or placebo, such as hypersensitivity to mannitol, meglumine or sodium stearyl fumarate.
- p. Swallowing difficulties that would preclude administration of laquinimod or placebo capsules.
- q. [Revision 1] Treatment with any investigational product within 30 days of screening or patients planning to participate in another clinical study assessing any investigational product during the study. Patients in non-interventional and/or observational studies will not be excluded from participating in this study.
- r. Treatment with tetrabenazine within 30 days of the study baseline visit
- s. Treatment with antipsychotic medication within 30 days of the study baseline visit

### **4.3. Withdrawal Criteria and Procedures**

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient is free to withdraw from the study at any time. The investigator also has the right to withdraw a patient from the study in the event of intercurrent illness, adverse events, pregnancy (see Section 7.3.3), or other reasons concerning the health or well-being of the patient, or in the event of lack of cooperation. In addition, a patient may be withdrawn from the study as described in Sections 3.6, 3.8, 3.11.4, 5.4, and 7.1.7.

Specific safety reasons for withdrawing a patient from the study are described in detail in [Appendix A](#) and Section 3.6. These include:

- Elevated liver enzymes (as detailed in [Appendix A](#))
- Pregnancy

- Need for concomitant treatment with moderate and strong CYP3A4 inhibitors
- Patients that are diagnosed with a malignant solid or liquid tumor
- Acute coronary syndrome, myocardial infarction or any major cardiovascular event

Should a patient decide to withdraw after administration of study drug(s), or should the investigator decide to withdraw the patient, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient's withdrawal (including all Visit 8 procedures) should be made and an explanation given as to why the patient is withdrawing or being withdrawn from the study.

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

All evaluations should be performed according to the protocol on the last day the patient takes study drug, or as soon as possible thereafter. If it is not possible to schedule the ET visit within 2 weeks after end of treatment, only the safety evaluations for that visit need to be performed.

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

## 5. TREATMENT OF PATIENTS

### 5.1. Study Drugs Administered

Until 10 January 2016, at the baseline visit, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 3 laquinimod treatment groups or to the placebo treatment group. Three capsules will be administered orally once each day, at the same time of the day, as follows:

- Oral laquinimod 0.5 mg: 3 capsules, 1 containing 0.5 mg laquinimod and 2 capsules containing matching placebo, to be administered orally qd.
- Oral laquinimod 1.0 mg: 3 capsules, 2 containing 0.5 mg laquinimod and 1 capsule containing matching placebo, to be administered orally qd.
- Oral laquinimod 1.5 mg: 3 capsules containing 0.5 mg laquinimod (Note: The treatment of this high dose arm was discontinued as of 10 January 2016)
- Matching placebo: 3 capsules, containing 0.5 mg matching placebo, to be administered orally qd.

As of 10 January 2016, following the decision to discontinue treatment of the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day, 1.0 mg/day, or matching placebo for 52 weeks.

The capsules will be taken orally and must be swallowed whole with a glass of water. The capsule should not be opened. Laquinimod can be taken with or without food.

The time of the dosing will be recorded on the CRF.

Compliance to study drug administration will be monitored. See Section 5.4 for additional information.

Study drug will be packaged in bottles and provided for patients to take at home (see Section 3.4). Study drug exposure will be measured and compliance to study drug administration will be monitored.

### 5.2. Restrictions

There are no restrictions in this study.

However, regarding fasting prior to in-clinic visits that will require fasting blood draws:

For visits 2 through 9, patients must have fasted (no food or beverages) no less than 8 hours prior to each morning visit that will require fasting blood draws (i.e. a blood draw for the lipid profile, or for the safety laboratory panels which include clinical chemistries and hormone concentrations).

Patients will be permitted to have water up until 1 hour before blood draws.

For patients participating in the PK-profiling ancillary study, the fasting conditions will be held up to 4 hours after the dosing.

### 5.3. Prior and Concomitant Therapy or Medication

Any prior or concomitant therapy, medication, or procedure a patient has had within 3 months before study drug administration and up to the end of the study period, including follow-up, will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization (WHO) drug dictionary (WHO Drug).

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

#### 5.3.1. Disallowed Previous Medications/Therapies Prior to and During the Study

The following medications will not be allowed prior to and during this study:

- Use of tetrabenazine within 30 days prior to baseline and during the study;
- Use of antipsychotic medication within 30 days prior to baseline and during the study;
- Use of moderate/strong inhibitors of CYP3A4, such as erythromycin and ketoconazole (more examples listed in [Appendix B](#)), within 2 weeks prior to randomization, during the study and until 30 days after the last study dose has been administered. 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.
- Use of inducers of CYP3A4 within 2 weeks prior to randomization and during the study;
- Immunosuppressive or immunomodulating agents, or cytotoxic agents, including cyclophosphamide and azathioprine within 12 months prior to screening and during the study;
- Use of experimental or investigational drugs and/or participation in drug clinical studies within 30 days of screening and during the study.

For patients taking antidepressant medication, the dose has to be kept constant for at least 30 days prior to randomization and during the whole study period.

[Appendix B](#) provides a list of medications disallowed prior to and during the study.

Patients who for their safety and well-being, according to the treating physician, are in need of antipsychotic medication or changed dose of antidepressant medication during the study, will be allowed to continue in the study, and the change in concomitant medication will be recorded in the CRF.

### **5.3.2. Other Concomitant Medications/Therapies**

Studies have shown that laquinimod is a strong inducer of CYP1A2 and a weak inhibitor of CYP3A4. Therefore, co-administration of laquinimod may affect the systemic exposure of drugs metabolized by CYP450 1A2 or CYP3A4.

#### **5.3.2.1. CYP1A2**

Laquinimod 0.6 mg/day reduced the systemic exposure of caffeine (a compound mainly metabolized by CYP1A2) 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 7 \(Appendix C\)](#) presents a partial list of drugs that are mainly metabolized by CYP1A2, i.e. CYP1A2 plays a major role in their biotransformation. The systemic exposure of these drugs is expected to be significantly reduced by laquinimod co-administration. 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.

#### **5.3.2.2. CYP3A4**

Laquinimod 0.6 mg/day increases the systemic exposure of midazolam (a sensitive CYP3A4 substrate) 1.5-fold and for the 1.2 mg/day dose 1.7 fold. Therefore, plasma levels of drugs that are CYP3A4 substrates may increase when combined with laquinimod. Patients taking drugs that are metabolized by CYP3A4, specifically those with a Narrow Therapeutic Index ([Table 6, Appendix C](#)) should be advised that plasma levels of these drugs could increase when combined with laquinimod.

### **5.4. Procedures for Monitoring Patient Compliance**

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

### **5.5. Total Blood Volume**

The total amount of blood to be drawn throughout the entire study for serum chemistry, hematology, pharmacokinetic, biomarker and pharmacogenomic measurements is approximately 350 mL/patient.

Patients who will participate in the PK profiling ancillary study will have approximately 32 mL extra blood drawn throughout the study.

Patients who will participate in the monocyte ancillary study will have approximately 50 mL extra blood drawn throughout the entire study.

## **6. ASSESSMENT OF EFFICACY**

### **6.1. Primary Efficacy Variables**

The primary efficacy variable and endpoint for this study is the change from baseline in the UHDRS-TMS (defined as the sum of the scores of all UHDRS-TMS subitems) at Month 12/ ET (evaluated at baseline and Months 1, 3, 6 and 12).

The TMS component of UHDRS comprises 31 assessments of different motor signs, including eye movements, hand motor coordination, speech, involuntary movements, gait and posture. Each assessment is rated on a 5-point scale from 0 (normal) to 4 (maximally abnormal). All UHDRS-TMS raters have to be certified by the European Huntington's Disease Network (EHDN) UHDRS-TMS online certification ([Reilmann et al, 2009](#)).

### **6.2. Secondary Efficacy Variables**

#### **6.2.1. Percent Change from Baseline in Caudate Volume at Month 12/ET (Evaluated at Baseline and Month 12)**

Participants will undergo 3T MRI at baseline and Month 12 following unaccelerated volumetric T1-weighted acquisition protocols developed during the ADNI study ([www.adni-info.org](http://www.adni-info.org)). Change in caudate volume over the scanning interval will be calculated using the Boundary Shift Integral (BSI) technique ([Hobbs et al, 2009](#); [Freeborough and Fox, 1997](#); [Leung et al, 2010](#)). Change in whole brain and ventricular volume will also be calculated using this approach (see Section 6.3.1). The BSI is an intensity-driven technique within the MIDAS software ([Freeborough et al, 1997](#)) which measures change over time in the brain directly from within-subject registered (aligned) MR scan pairs. This technique has been optimised to provide robust measures of brain-volume change from multi-site data ([Leung et al, 2010](#)) and has been shown to be sensitive to HD-related pathology over a 12-month interval in the multi-site TRACK-HD study ([Tabrizi et al, 2011](#)). Details of how the BSI has been implemented for this study are described in the Imaging Review Charter.

White-matter volume change (see Section 6.3.1) will be estimated using a non-linear registration approach. Voxel-level volume change derived from within-subject non-linear registration will be summed over an automated baseline white-matter mask, to estimate within-subject volume change over the interval. This analysis is detailed in the Imaging Review Charter.

End-point quality control will be performed by trained analysts to ensure accuracy.

Longitudinal change in caudate, whole-brain and white-matter volume will be measured in mls and converted to a percentage of their baseline value for subsequent analysis. Longitudinal change in ventricular volume will be measured and analysed in absolute terms (ml).

MRI scans may be evaluated locally for any incidental pathology (ie, pathology unrelated to, or inconsistent with, the subject's known HD) according to locally determined procedures. If such pathology is found, the Treating Neurologist/Physician should be notified. The MRI reading center will evaluate the scans only for the purpose of performing quantitative measurements. In order not to compromise blinding of the study, the MRI Reading Center will not report quantitative MRI findings back to the clinical site.



Patients who develop unsuitability for MRI measures after baseline visit, will be allowed to continue in the study without performing the MRI assessment.

### **6.2.2. Change from Baseline in HD-CAB Total Score (Sum of the Standardized Sub-Components) at Month 12/ET (Evaluated at Baseline and Months 6 and 12)**

The following sections describe the tests that will be included in the HD-CAB.

The CAB assessments will be performed only in those sites that have access to the devices needed to perform the assessments and, where this is the case, only in those patients who are capable of performing the assessments.

To avoid variability due to different operating systems, hardware and computer accessories (i.e. mouse), sites will be provided with standardized equipment (tablets) to perform the computerized cognitive assessments.

#### **6.2.2.1. Symbol Digit Modalities Test (SDMT)**

The SDMT is a paper-and-pencil test of attention, psychomotor speed and working memory. Participants view a 'key' at the top of the page containing symbols paired with numbers. The remainder of the page displays rows of symbols, and the participant has 90 seconds to write in the corresponding number that matches each symbol.

#### **6.2.2.2. Emotion Recognition**

Recognition of facial expressions of emotions is examined using computerized images of faces depicting 6 basic emotions or a neutral expression. Participants are asked to indicate the emotion expressed in each photograph by selecting from the words fear, disgust, happy, sad, surprise, angry, and neutral (10 stimuli per emotion).

#### **6.2.2.3. Trail Making Test**

Visual attention and task switching are assessed using the Trail Making test, which consists of 25 circles on a standard sheet of paper. For Trails A, participants are required to connect, as quickly as possible, circles containing numbers in ascending numerical order. For Trails B, participants are to connect, as quickly as possible, circles containing numbers and letters, alternating between numbers and letters in ascending order (e.g., 1, A, 2, B, 3, C, etc.) (Bowie and Harvey, 2006) Trail A is administered first, followed by Trail B to ensure preparedness for Trail B; however, only the Trail B score is used as an outcome measure in the HD-CAB.

#### **6.2.2.4. Hopkins Verbal Learning Test, revised (HVLTR)**

The HVLTR is a paper-based instrument that offers a brief assessment of verbal learning and memory (recall). It is easy to administer and score and is well tolerated even by significantly impaired individuals.

Its use has been validated with brain-disordered populations (e.g., Alzheimer's disease, HD, amnesic disorders) as a measure of verbal learning and memory. There are six alternate forms available, but 3 of the 6 forms, which have relatively greater equivalence with each other (Forms 4, 5, and 6) will be used, in randomized order. Each form consists of a list of 12 nouns (targets) with 4 words drawn from each of 3 semantic categories. The semantic categories differ across

the 6 forms, but the forms are very similar in their psychometric properties. Only the three learning trials (Trials 1-3) and the delayed recall trial (Trial 4) will be administered as part of the HD-CAB. The primary scores that will be examined as part of the HD-CAB is the sum of Trials 1-4; however, the sum of Trials 1-3 and separately Trial 4 will also be examined in exploratory analyses. The HVLTR has high test-retest reliability, and its construct, concurrent, and discriminant validity have been well established.

#### **6.2.2.5. Paced Tapping at 3 Hz**

Psychomotor function is assessed in a computerized Paced Tapping test. Participants tap on left and right mouse buttons, alternating between thumbs, at 3.0 Hz. They first listen to a tone presented at the 3.0 Hz rate, and then begin tapping in time with the tone. After 11 taps with the tone, the repetition tone is discontinued, and participants attempt to continue tapping at the same rate until the end of the trial (31 taps later). Four trials are administered.

#### **6.2.2.6. One Touch Stockings of Cambridge (OTS)**

OTS is a computerized spatial planning task which gives a measure of frontal lobe function. OTS is a variant of the Stockings of Cambridge task, and places greater demands on working memory as the participant has to visualize the solution. As with Stockings of Cambridge, the participant is shown 2 displays containing 3 colored balls. The displays are presented in such a way that they can easily be perceived as stacks of colored balls held in stockings or socks suspended from a beam.

Along the bottom of the screen, there is a row of numbered boxes. The test administrator first demonstrates to the participant how to use the balls in the lower display to copy the pattern in the upper display, and completes 1 demonstration problem, where the solution requires 1 move. The participant must then complete 3 further problems, 1 each of 2 moves, 3 moves, and 4 moves.

Next, the participant is shown further problems, and must work out in their head how many moves the solutions to these problems require, then select the appropriate box at the bottom of the screen to indicate their response.

#### **6.2.3. CIBIC-Plus Global Score at Month 12/ET (Evaluated at Months 6 and 12) as Compared to Baseline (Rated by an Independent Rater)**

Global change in HD will be measured using the CIBIS scale at baseline and the CIBIC-Plus scale at subsequent time points. The CIBIC-Plus (version ADCS-CGIC) was developed, validated, and is commonly used in studies of anti-dementia drugs in Alzheimer's disease (Joffres et al, 2000).

An independent rater whose only role in the study is to conduct these global assessments will evaluate the patient's overall disease severity during the baseline visit (Visit 2) prior to the administration of study drug. This assessment, known as the CIBIS, rates the patient on a 7-point Likert scale from extremely severe HD to no symptoms of HD.

At each subsequent visit in which the evaluation is performed (Months 6 and 12; Visits 6 and 8), the CIBIC-Plus will be preferentially administered by the same independent rater, but without knowledge of other endpoint assessments or the AEs experienced by the patient during the study (so as not to confound the rating of CIBIC-Plus as an efficacy measure or to unblind the study).

The independent rater is not permitted to discuss the medical condition of the patient with the treating physician. Instead, the independent rater exclusively will consider observations of the patient's cognitive, functional, and behavioral performance obtained through interviewing the patient and the caregiver. The rater then compares those findings to the baseline assessment. The overall impression of change from baseline (CIBIC-Plus) is rated on a 7-point scale: 1 = marked improvement; 2 = moderate improvement; 3 = minimal improvement; 4 = no change; 5 = minimal worsening; 6 = moderate worsening; 7 = marked worsening; all assessments were relative to baseline. A higher score indicates a worsening of global function.

In HD, the inclusion of caregiver input is particularly critical for a global assessment as previous studies have demonstrated that patients have limited awareness and recognition of their deficits.

Where possible, the same person should act as a patient's caregiver/informant throughout the study. If this is not possible, a patient should have no more than 2 caregivers throughout the study. All possible attempts should be made to assure that caregiver will attend the clinical visits in person together with the patient. If the caregiver/informant is not available to attend the clinic visit, the interview can be done over phone.

#### **6.2.4. Change from Baseline in UHDRS- TFC at Month 12/ET (Evaluated at Baseline and Months 6 and 12)**

The Unified Huntington's Disease Rating Scale (UHDRS) motor section (see Section 6.1) and Total Functional Capacity will be used as measures of disease severity. The UHDRS is a research tool, which has been developed by the Huntington Study Group to provide a uniform measure of clinical performance and course of HD. The UHDRS has undergone extensive reliability and validity testing and has been used in many research studies as a primary outcome measure ([Huntington Study Group, 1996](#)).

The TFC scale of the UHDRS assesses 5 functional domains associated with disability (occupation, finances, domestic chores, activities of daily living, and care level) and is rated from 0-13 (maximum functionality).

### **6.3. Exploratory Variables**

#### **6.3.1. Change from Baseline in Brain Atrophy as Defined by the Percentage Change in Volume In: Whole Brain Volume and White-Matter Volume at Month 12/ET and Absolute Change in Ventricular Volume at Month 12/ET (Evaluated at Baseline and Month 12)**

For a description of the MRI procedure and analysis, see Section 6.2.1.

#### **6.3.2. Change from baseline in UHDRS- FA at Month 12/ET (evaluated at baseline and Months 6 and 12)**

The FA scale of the UHDRS assesses several functional domains associated with disability (occupation, finances, capability to drive a car, ability to take care of children, ability to make a phone call, etc.) and is rated from 0-25 (maximum functionality).

#### **6.3.3. Change from baseline in Q-Motor assessments at Month 12/ET (evaluated at baseline and Months 1, 3, 6 and 12)**

Motor deficits can be objectively assessed using different Q-Motor assessments ([Reilmann, 2012](#)). All Q-Motor assessments are based on the application of precalibrated and temperature controlled force transducers and 3-dimensional position sensors with very high sensitivity and test-retest reliability across sessions and sites in a multicenter clinical study. Q-Motor measures thus aim to reduce the limited sensitivity of categorical clinical rating scales, the intra- and inter-rater variability, and placebo effects observed in scales such as UHDRS-TMS. In addition, Q-Motor assessments allow for the objective monitoring of unintended motor side-effects in clinical studies.

Tasks detailed in the sections below have been selected for use in the current study. Data transfer will be performed using a secure web based platform, allowing continuous centralized data monitoring and quality control. Data analysis will be performed blinded and automated as described in the statistical analysis plan (SAP).

Q-Motor assessments will be performed only in those sites that have access to the devices needed to perform the assessments and, where this is the case, only in those patients who are capable of performing the assessments.

##### **6.3.3.1. Digitomotography (Speeded Index Finger Tapping)**

The patient will place their hand on a hand rest with their index finger positioned above a force-transducer. Recordings will start after practice runs. The patient will be instructed to finger tap as fast as possible between 2 auditory cues. The beginning of a tap is defined as a rise of the force by 0.05 N above maximal baseline level. The tap ends when it drops to 0.05 N before the maximal baseline level is reached again. The duration and variability of tap durations (TD), inter-onset intervals (IOI), inter peak intervals (IPI), and inter tap intervals (ITI) are the exploratory outcome measures for speeded tapping. In addition, variability of peak tapping forces (TF) will be calculated, and the tapping frequency (Freq), ie, the number of taps between the onsets of the first and the last tap divided by the time in between, will be determined. Five trials of 10 seconds duration are performed with each hand ([Bechtel et al, 2010](#)).

### **6.3.3.2. Dysdiadochomotography (Pronation/Supination Hand Tapping)**

This task assesses the regularity of hand taps performed when alternating between the palm and dorsal surface of the hand performing a repetitive pronation/supination movement. The force and duration of the hand taps are recorded similarly to the speeded tapping task. A tone cues the start and end of an assessment. Five trials of 10 seconds duration are performed with each hand.

### **6.3.3.3. Manumotography and Choreomotography (Grip Force and Chorea Analysis)**

This task assesses the coordination of isometric grip forces in the precision grip between the thumb and index finger (Reilmann et al, 2001, Reilmann et al, 2010). Grip forces are assessed during grip initiation, object transport, and in a static holding phase. Patients are instructed to grasp and lift a device equipped with a force transducer and 3-dimensional position sensor in the precision grip between thumb and index finger and hold it stable adjacent to a marker 10-cm high. Grip forces and 3-dimensional position and orientation of the object are recorded. Mean isometric grip forces and grip force variability in the static phase (expressed as coefficient of variation = standard deviation [SD]/mean  $\times$  100) (GFV-C) are calculated during a 15-second period prior to the second cueing tone.

Five trials of 20 seconds duration are performed with each hand. Chorea is assessed calculating a “position-index” and “orientation-index” (Reilmann et al, 2011). Start and end of assessment are signaled by a cueing tone.

### **6.3.3.4. Pedomotography (Speeded Foot Tapping)**

The patient will place a foot on the foot device such that the ball of the foot is positioned above a force-transducer. Recordings will start after practice runs. The patient will be instructed to tap with the foot as fast as possible between 2 auditory cues. The beginning of a tap is defined as a rise of the force by 0.05 N above maximal baseline level. The tap ends when it dropped to 0.05 N before the maximal baseline level is reached again. The duration and variability of TD, IOI, IPI, and ITI are the exploratory outcome measures for speeded foot tapping. In addition, variability of peak TF will be calculated, and the tapping Freq, ie, the number of taps between the onsets of the first and the last tap divided by the time in between, will be determined. Five trials of 10 seconds duration are performed with each foot.

### **6.3.4. Change from baseline in mPPT at Month 12/ET (evaluated at baseline and Months 6 and 12)**

The modified PPT quantifies the patient’s performance in physical tasks (Brown et al, 2000). It is a standardized 9-item test that measures the patient’s performance on functional tasks. Assistive devices are permitted for the tasks that require a standing position. Both the speed and accuracy at which the patients complete the items are taken into account during scoring. The maximum score of the test is 36, with higher scores indicating better performance.

### **6.3.5. Change from baseline in HD QoL and EQ-5D-5L at Month 12/ET (evaluated at baseline and Month 12)**

#### **6.3.5.1. HD-QoL**

The HD-QoL is a standardized instrument for measuring health-related quality of life ([Hocaoglu et al, 2012](#)). It is a validated disease-specific measure designed for HD, and can provide a summary score of overall health-related quality of life, as well as scores on several discrete scales. HD-QoL is for people who are living with HD; this includes people who are at risk for HD, people who have tested positive for the huntingtin gene but do not have symptoms, and also for people at early through to late stages of disease. HD-QoL can be used across the full spectrum of HD.

HD-QoL will be assessed by both caregiver/informant and patient. All possible attempts should be made to assure that caregiver/informant will attend the clinical visits in person together with the patient. If the caregiver/informant is not available to attend the clinic visit, the caregiver/informant form should be omitted.

#### **6.3.5.2. EQ-5D-5L**

The EQ-5D 3 level version (EQ-5D-3L) was introduced in 1990 ([EuroQoL Group, 1990](#)). It essentially consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In developing the 5L, the 5-dimensional structure of the original EQ-5D-3L was retained but the levels on each dimension were expanded to 5-levels based on qualitative and quantitative studies conducted by the EuroQoL Group. The labels for each of the dimensions are: no problems, slight problems, moderate problems, severe problems and unable to/extreme problems. The EQ-VAS is still an integral part of the EQ-5D-5L but has been adapted to make it more user friendly. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score.

The EQ-5D-5L could be completed by the patients with caregiver assistance if needed.

### **6.3.6. Change from baseline in WLQ at Month 12/ET (evaluated at baseline and Month 12)**

Huntington's Disease imposes a substantial burden on patients in the form of impaired ability to perform productive activity such as paid employment, domestic household activity, or schooling. The WLQ captures a multidimensional look at work productivity. It is designed to measure productivity among workers who are employed, but may be performing at less than full capacity. It measures the degree to which health problems interfere with specific aspects of job performance and the productivity impact of these work limitations. The eight-item version will be used to reduce respondent burden ([Lerner et al, 2001](#)).

The work productivity will be assessed in all patients, also those with milder disease.

However, if the patient is unemployed, this questionnaire will not be completed.

The WLQ could be completed by the patients with caregiver assistance if needed.

**6.3.7. Change from baseline in HD-CAB sub-components at Month 12/ET (evaluated at baseline and Months 6 and 12)**

For a description of the HD-CAB sub-components, see Section 6.2.2.

**6.3.8. Change from baseline in CDR-SB at Month 12/ET (evaluated at baseline and Month 12)**

The Clinical Dementia Rating – Sum of Boxes (CDR-SB) is a widely used scale that has demonstrated validity and reliability in the longitudinal assessment of patients with cognitive and functional deficits that do not rise to the level of a diagnosis of overt dementia<sup>3</sup>.

The utilization of CDR-SB scores for staging dementia severity offers several advantages over the global score because the optimal characteristics of both scores can be combined into a single score. First, CDR-SB scores are much simpler to calculate than the global score and they do not require an algorithm for computation, which will ultimately result in fewer calculation errors for those not using the online system. Second, CDR-SB scores can be treated as interval data in statistical analyses, whereas global CDR scores are ordinal by the nature of the algorithm approach to condensing the data. Finally, the most significant advantage to using CDR-SB scores for staging of dementia severity is the increased precision afforded for tracking changes across time (O'Bryant et al, 2008).

The CDR is obtained through semistructured interviews of patients and informants, and cognitive functioning is rated in 6 domains of functioning: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a 5-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment (personal care is scored on a 4-point scale without a 0.5 rating available). The global CDR score is computed via an algorithm (Morris, 1993). The CDR-SB score is obtained by summing each of the domain box scores, with scores ranging from 0 to 18.

Where possible, the same person should act as a patient's caregiver/informant throughout the study. If this is not possible, a patient should have no more than 2 caregivers throughout the study. All possible attempts should be made to assure that caregiver/informant will attend the clinical visits in person together with the patient. If the caregiver/informant is not available to attend the clinic visit, the interview can be done over phone.

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<sup>3</sup> Food and Drug Administration (FDA) Guidance for Industry: Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease. Center for Drug Evaluation and Research (CDER). February 2013.

### **6.3.9. Change from baseline in HADS at Month 12/ET (evaluated at baseline and Month 12)**

The HADS ([Zigmond and Snaith, 1983](#)) is a 14 item (each item scored 0-3), self-administered rating scale that consists of two subscales assessing the presence and severity of depression (0–21) and anxiety (0–21), with a global score of 0–42. It was designed to diminish the influence of somatic symptoms and consequently does not include items relating to the physical symptoms of depression and has a medium overall cognitive complexity. Completion time: 5–10 min. It has been validated in a study comprised of 50 patients with HD ([De Souza et al, 2001](#)).

### **6.3.10. Change from Baseline in Problem Behaviors Assessment-Short Form (PBA-s) at Month 12/ET (Evaluated at Baseline and Month 12)**

Because of the prominence of psychiatric symptoms in HD, it is recommended that the PBA-s form be used in all HD studies with any need for behavioral assessment as a comprehensive screen for the most common psychiatric symptoms in HD ([Craufurd et al, 2001](#); [Kingma et al, 2008](#)). The PBA-s also includes questions concerning suicidal behavior, a particular concern in HD. The PBA-s is based on the same set of core behavioral symptoms as the UHDRS Behavioral questions, which were used previously as the global psychiatric measure in most HD studies. The PBA-s has more detailed questions and more specific guidance on administration and scoring.

The PBA-s is a brief semi-structured interview with both the patient and the informant covering the most common behavioral and psychiatric manifestations of HD. The interview is not restricted to a single construct, but rather covers several broad symptom domains relevant to HD, comprising 11 items: low mood, suicidal ideation, anxiety, irritability, anger/aggressive behavior, loss of motivation, perseverative thinking or behavior, obsessive-compulsive behaviors, paranoid thinking, hallucinations, behavior suggestive of disorientation.

Each symptom is rated for severity on a 5-point scale according to detailed scoring criteria which roughly correspond to the following: 0 = “not at all”; 1 = trivial; 2 = mild; 3 = moderate (disrupting everyday activities) and 4 = severe or intolerable.

Each symptom is also scored for frequency on a 5-point scale as follows: 0 = symptom absent; 1 = less than once weekly; 2 = at least once a week; 3 = most days (up to and including some part of every day); and 4 = all day, every day. Severity and frequency scores are multiplied to produce an overall ‘PBA score’ for each symptom.

Where possible, the same person should act as a patient’s caregiver/informant throughout the study. If this is not possible, a patient should have no more than 2 caregivers throughout the study. All possible attempts should be made to assure that caregiver/informant will attend the clinical visits in person together with the patient. If the caregiver is not available to attend the clinic visit, the interview can be done over phone.

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

Methods and timing of assessing efficacy data are discussed in Section 3.11. Procedures for recording efficacy data are discussed in Section 13.1, and methods of analyses are discussed in Section 9.6.2.



## **7. ASSESSMENT OF SAFETY**

In this study, safety will be assessed by qualified study staff by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, physical examination findings (including body weight and height measurements), and suicidality (as assessed by changes from baseline in C-SSRS scores) and premature discontinuations from the study.

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

The DSMB will meet monthly until 40 patients from each study group (i.e. a total of 160 patients) will have been exposed to their respective full dose for at least 3 months. Conditional on the absence of significant emerging safety concerns, enrolment in all the study arms will be approved to continue by the DSMB. The DSMB will then continue to meet at least bi-monthly, or as decided by the DSMB, throughout the study. The DSMB can call a meeting at any time based on safety concerns, and decisions about discontinuing patients, should that happen, will be explained in a report to all sites and patients.

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

DSMB sessions can be open or closed. During open sessions, representatives of the sponsor and the Steering Committee may be present and information is provided and discussed in a blinded fashion. During closed sessions, the only participants are members of the DSMB and the designated unblinded statistician (if approved to be present).

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

### **7.1. Adverse Events**

#### **7.1.1. Definition of an Adverse Event**

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

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

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

are present before study entry and do not worsen during the study will not be considered adverse events.

New symptoms of HD or deterioration of previously existing symptoms should be recorded as an adverse event only if the presentation and/or outcome is more severe than would normally be expected from the normal course of the disease in a particular subject.

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

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

### **7.1.2. Recording and Reporting Adverse Events**

For adverse event recording, the study period is defined for each patient as that time period from signature of the informed consent form through the end of the follow-up period. For this study, the follow-up period is defined as 1 month following the last dose of study medication

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

At each contact with the patient, the investigator or designee must query the patient for adverse events by asking an open-ended question such as, "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and

symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the Serious Adverse Event Form.

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

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

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

### **7.1.3. Severity of an Adverse Event**

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

- Mild:** No limitation of usual activities
- Moderate:** Some limitation of usual activities
- Severe:** Inability to carry out usual activities

**7.1.4. Relationship of an Adverse Event to the Study Drug**

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

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

**7.1.5. Serious Adverse Events****7.1.5.1. Definition of a Serious Adverse Event**

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

- death
- a life-threatening adverse event (ie, the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event.

Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered serious adverse events.

- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

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

#### **7.1.5.2. Expectedness**

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

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

#### **7.1.5.3. Reporting a Serious Adverse Event**

##### **7.1.5.3.1. Investigator Responsibility**

To satisfy regulatory requirements, all serious adverse events (as described in Section 7.1.5.1) that occur during the study period (including the protocol-defined follow-up period), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator within 24 hours of becoming aware of it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor subjects for adverse events once the study has ended. Serious adverse events occurring to a patient after the defined study period should be reported to the sponsor only if the investigator becomes aware of them.

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

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

- study number TV5600-CNS-20007 (LEGATO-HD)

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

Additional information may include the following:

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

The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with local regulations.

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

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

For all countries, The sponsor's Global Patient Safety & Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO/CRO for local submission to the regulatory authorities and IEC/IRBs and investigators, according to regulations.

The blinding will be maintained for the people who are involved directly in the study. Therefore, in case of a suspected unexpected serious adverse reaction (SUSAR), only the LSO/CRO will receive the unblinded report for regulatory submission; the others will receive a blinded report.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is similar to that for reporting a serious adverse event (see Section 7.2).

#### **7.1.5.3.2. Sponsor Responsibility**

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

In addition to notifying the investigators and regulatory authorities (and IEC/IRB, if appropriate), other measures may be required, including the following:

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

#### **7.1.6. Protocol-Defined Adverse Events for Expedited Reporting**

Ischemic cardiac events (such as myocardial infarction, unstable angina, acute coronary syndrome, etc), cerebrovascular events (such as cerebral arterial occlusion, cerebral ischemia, etc), and deaths should be reported to the sponsor within 24 hours, including completion of the corresponding dedicated CRF.

#### **7.1.7. Withdrawal Due to an Adverse Event**

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

A complete final evaluation at the time of the patient's withdrawal (Visit 8 procedures) should be made. In addition, a blood sample will be obtained for the measurement of study drug concentrations. The patient will be monitored at the discretion of the investigator (e.g., until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The investigator must inform the clinical project physician/clinical leader (CPP/CL) as soon as possible of all patients who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient discontinues treatment for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event.

An exception to this requirement will be the occurrence of an adverse event which in the opinion of the investigator is not severe enough to warrant discontinuation but which requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be need to take a prohibited medication, not the adverse event.

#### **7.1.8. Medical Emergencies**

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

Equipment, supplies, and properly skilled medical personnel must be accessible for an adverse event requiring immediate treatment.

Any dose of study drug (whether laquinimod or placebo), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor. When the identification of the study drug must be known, the investigator must follow the procedures outlined in Section 3.8.

#### **7.1.9. Medication Error and Special Situations**

Any administration of study medication that is not in accordance with the study protocol should be reported on the CRF either as a violation, if it meets the violation criteria according to the protocol (Section 11.1.2), or as a deviation in the patients source documents, regardless of whether an adverse event occurs as a result. All instances of incorrect medication administration should be categorized as 'Non-Compliance to IMP'.

Types of Medication Errors and/or special situations:

1. Medication error - Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient or consumer.
2. Overdose - Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.
3. Misuse - Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
4. Abuse - Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
5. Off-label use - Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
6. Occupational exposure- Exposure to a medicinal product, as a result of one's professional or non-professional occupation.

#### **7.1.10. Protocol Deviations Because of an Adverse Event**

If a patient experiences an adverse event or medical emergency, departures from the protocol may be allowed on a case-by-case basis. After stabilization and/or treatment has been administered to ensure patient safety, the investigator or other physician in attendance must



contact the individual identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study. Any departures from the protocol because of adverse events must be noted on the CRF and in source documents, along with the reason for such departures.

## 7.2. Pregnancy

To further emphasize the importance of use of acceptable contraception and avoidance of pregnancy under laquinimod exposure, and to reduce as much as possible the exposure to laquinimod if a pregnancy occurs despite all recommended measures, all women of child-bearing potential (for example women who are not postmenopausal or have not undergone surgical sterilization) and not using acceptable methods of contraception, will be instructed about the teratogenicity and potential delayed risks for a child exposed in utero to laquinimod. These subjects will be counseled about the importance of using 2 acceptable methods of contraception throughout the entire study 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. Patients who are women of child-bearing potential must use 2 acceptable methods of contraception for 30 days prior to initiation of treatment, throughout treatment duration and until 30 days after the last dose of treatment.

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

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

Additionally, monthly pregnancy tests (urine dipstick and/or serum pregnancy -hCG test, as applicable per the relevant time point) will be performed. Early terminated subjects who are in the study for the purpose of follow-up will not be required to take the pregnancy tests if the last study drug dose was taken more than 30 days prior to the visit.

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

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 adverse event or serious adverse event, as appropriate.

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

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

### **7.3. Clinical Laboratory Tests**

All clinical laboratory test results outside of the reference range will be interpreted by the investigator as belonging to 1 of the following categories:

- abnormal but not a clinically significant worsening
- abnormal and a clinically significant worsening

A laboratory test result that has significantly worsened (according to medical judgment) from the baseline result will be recorded on the source documentation, transcribed onto the CRF as an adverse event, and monitored as described in Section 7.1.2. An adverse event includes a laboratory or diagnostic test abnormality (once confirmed by repeat testing) that results in the withdrawal of the patient from the study, the temporary or permanent cessation of treatment with study drug, or medical treatment or further diagnostic work-up.

Clinical laboratory tests (serum chemistry and hematology) will be performed at Visits 1-4 and 6-9. Urinalysis will be performed at screening. When applicable per local requirements, patients will undergo an HIV test at screening. Also when applicable, patients will be screened for drug substances in urine and/or CDT level in blood at screening to confirm abstinence in former alcohol and/or drug abusers.

Specific laboratory tests to be performed are listed below.

#### **7.3.1. Serum Chemistry**

The following serum chemistry tests will be performed at all scheduled visits:

- calcium
- phosphorus
- sodium
- potassium
- chloride
- bicarbonate and carbon dioxide
- glucose
- blood urea nitrogen (BUN)
- creatinine (Note: Estimated creatinine clearance will be calculated at all in-clinic study visits.)
- uric acid
- ALT
- AST
- lactic dehydrogenase (LDH)
- gamma-glutamyl transpeptidase (GGT)
- alkaline phosphatase

- creatine phosphokinase (CPK)
  - In case of CPK results >ULN, troponin and creatine kinase MB isoenzyme (CK-MB) will be tested by the central laboratory.
  - In case of CPK>10×ULN, an unscheduled visit to assess urine myoglobin will be required. The following blood tests will be repeated at the unscheduled visit: CPK, blood urea nitrogen, creatinine, electrolytes including potassium, calcium, phosphate.
- total protein
- albumin
- Fibrinogen
- CRP
- pancreatic amylase
  - Lipase will be tested in case of abnormal pancreatic amylase results
- total bilirubin
  - Only if total bilirubin is elevated, the following tests will be performed:
    - direct bilirubin
    - indirect bilirubin
- lipid profile [total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides] - **at baseline and Month 12 only**
- thyroid function (T3, T4, TSH) – **at baseline, Months 6 and 12 only**

### 7.3.2. Hematology

The following hematology tests will be performed:

- Hemoglobin
- hematocrit
- red blood cell (RBC) count
- mean corpuscular volume (MCV)
- red cell distribution width (RDW)
- Mean platelet volume (MPV)
- Reticulocytes (percentage and absolute count)
- platelet count
- white blood cell (WBC) count and differential count
  - polymorphonuclear leukocytes (neutrophils)
  - lymphocytes
  - eosinophils
  - monocytes
  - basophils

### 7.3.3. Anemia panel

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

- At baseline: B12, blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, interferon IFN- $\gamma$ , TNF- $\alpha$ , and hepcidin.
- In case of hemoglobin decrease of >1g/dL from the patient's hemoglobin level at baseline:
  - - Subject will be re-tested to ascertain true decrease
  - - If decrease confirmed, a thorough anemia work-up will be done including:
    - Directed medical history and physical examination
    - Anemia panel (Blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, IFN- $\gamma$ , TNF- $\alpha$ , and hepcidin) and B12
    - Additional investigations and follow-up per the investigator's discretion or Sponsor's request.

#### **7.3.4. Urgent Safety Laboratory Panel**

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

The following tests will be performed on these samples:

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

#### **7.3.5. Urinalysis**

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

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

#### **7.3.6. Human Chorionic Gonadotrophin Tests**

Human chorionic gonadotropin ( $\beta$ -hCG) serum test will be performed for all women of child-bearing potential (women who are not post menopausal or who have not undergone surgical sterilization) at screening (Visit 1) and at all subsequent study visits. Age-appropriate normal ranges for HCG should be used. If the reading for the serum pregnancy test is indeterminate, the test should be repeated after 3-4 days to see whether there is an increase in  $\beta$ -hCG or whether it is a stable elevation. If no increase is observed, the patient will not be considered to be pregnant. However, no study drug will be administered until this is resolved.

Urine  $\beta$ -hCG tests will be performed for all women of child-bearing potential at baseline (Visit 2), and at all subsequent visits, and if clinically indicated at any other time.

In addition, starting after Visit 3, a urine  $\beta$ -hCG test will be performed in women of child-bearing potential every 28 ( $\pm 2$ ) days, by the patient at home, and recorded in the patient's medical records. The patient will be contacted by telephone within 72 hours after the scheduled test is to be performed and asked specific questions regarding the test. In case of suspected pregnancy (positive urine  $\beta$ -hCG test result), absence 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 (within 10 days) with all remaining study drugs capsules.

Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.

#### **7.4. Vital Signs**

Vital signs will be measured at all in-clinic visits (Visits 1-4 and 6-9). Vital signs include the following:

- pulse
- blood pressure
- body temperature

Before pulse and blood pressure are measured, the patient must be in a supine position and resting for at least 5 minutes. The same position and arm should be used each time vital signs are measured for a given patient. For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as a clinically significant change (worsening) from a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

#### **7.5. Electrocardiography**

A single 12-lead ECG will be conducted at screening (Visit 1), and at the following in-clinic visits: Week 4, Week 13, Week 26, Week 52 and follow-up (Visits 3, 4, 6, 8 and 9). During the baseline visit (Visit 2) a 12-lead ECG will be conducted in triplicate (approximately  $10 \pm 5$  minutes apart). A qualified physician at a central diagnostic center will be responsible for interpreting the ECG. Any ECG finding that is judged by the site investigator as a clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

#### **7.6. Physical Examinations**

Physical examinations, including height (to be obtained at the screening visit only) and weight will be performed at all in-clinic visits (Visits 1-4 and 6-9). Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared with a

baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

## 7.7. Estimated Creatinine Clearance Calculation

Significant changes in laquinimod exposure, in particular in terms of unbound drug fraction, are predicted in patients with renal impairment (see Section 1.3.2.1). Consequently, estimated CrCl will be calculated at all visits to monitor chronic renal function in the study in order to identify patients with potentially impaired laquinimod clearance. Patients with a confirmed CrCl <60 mL/min/1.73 m<sup>2</sup> should stop study medication temporarily, and the CrCl assessment should be repeated. If the renal impairment is confirmed (estimated CrCl <60 mL/min/1.73 m<sup>2</sup>), the patient should stop study medication permanently (see Section 3.6).

Following recent findings connecting Gd-based contrast agents and nephrogenic systemic fibrosis, the estimated CrCl result should be available prior to the baseline MRI scan. Estimated CrCl calculation will be done in accordance with the central laboratory creatinine value measurement performed at the screening visit. The central laboratory will report calculated estimated CrCl; however, if the result is not available prior to the baseline MRI scan, estimated CrCl may be calculated using the Cockcroft-Gault equation (eg, available online CrCl calculator: <http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault>).

## 7.8. Cardiovascular Risk Assessment and Management

Evaluation of major modifiable cardiac risk factors (eg, body mass index [BMI], diabetes, high blood pressure, hyperlipidemia, tobacco smoking) will be performed at the time points indicated in Table 3. In addition, an evaluation of cardiovascular risk factors should take place as soon as possible for patients already in the study, following approval of Global Amendment 04.

Assessment of changes in cardiovascular risk and appropriate cardiovascular risk management with appropriate medical follow-up, if clinically indicated, should be performed during the scheduled and unscheduled visits.

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

## 7.9. Other Safety Measures and Variables

### 7.9.1. Concomitant Therapy or Medication

Concomitant therapy or medication usage will be monitored throughout the study. Details of prohibited medications are found in Section 5.3.

### 7.9.2. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be used to rate the patient's degree of suicidal ideation on a scale ranging from "no suicidal ideation" to "active suicidal ideation with specific plan and intent" (Posner et al, 2011). The baseline screening version of the C-SSRS will be completed at screening (Visit 1). On subsequent visits (Visits 2-4 and Visits 6-9) The C-SSRS since last visit version will be completed.

Patients with active suicidal ideation, as measured by a score of 4 or 5 on the C-SSRS at the screening visit, will not be eligible for the study.

A referral for psychiatric evaluation is required for any increase in the scale from baseline.

In any event of suspected active suicidality (e.g. active suicidal ideation or intent, significant suicidal behavior) or clinical findings suggesting that the patient is dangerous to himself or herself, the patient should be referred for **immediate** psychiatric evaluation.

### **7.9.3. 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.

For complete guidance on monitoring subjects with elevated pancreatic amylase levels, see [Appendix A](#) (Section 7).

## **7.10. Methods and Timing of Assessing, Recording, and Analyzing Safety Data**

Methods and timing of assessing safety data are discussed in Section [3.11](#). Procedures for recording safety data are discussed in Section [13.1](#) and methods of analyses are discussed in Section [9.8.2](#).

Furthermore, all adverse events will be reviewed on a periodic basis (e.g., scheduled safety reviews for laquinimod) as safety data becomes available (see Section [7](#)).

## **8. ASSESSMENT OF PHARMACOKINETICS/ PHARMACOGENOMICS/OTHER ANCILLARY STUDIES**

### **8.1. Pharmacokinetic Variables**

Samples will be analyzed for laquinimod and its metabolites using appropriate validated methods. Incurred sample reanalysis may be performed.

#### **8.1.1. Blood Sampling and Handling**

Whole blood samples (4 mL) will be collected via venipuncture in the morning for plasma concentration measurements of laquinimod and its metabolites as follows:

PPK samples will be collected at visits at Months 1, 3, 6 and 12 from all subjects.

PK samples of laquinimod and its metabolites will be collected from approximately 15 patients per each of the three continuing treatment groups (at selected sites at Month 1), for a total of approximately 45 patients, at the following timepoints – pre-dose, 15, 30 min and 1, 2, 3, 6 and 24 hours post dose. Additionally, PK samples were collected from 2 patients in the laquinimod 1.5 mg/day treatment group when the treatment was stopped; no further PK samples will be collected from the laquinimod 1.5 mg/day treatment group.

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 for safety. The samples should be collected as soon as possible in association with the event.

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

Samples will be collected into disodium ethylenediamine tetraacetate (Na<sub>2</sub>EDTA) Vacutainer tubes, inverted slowly 6 to 8 times to mix the contents, and placed on water/ice (~0-5°C). Blood samples will be centrifuged (2000g, ~10 minutes, 0°C-5°C) between 5 minutes and 1 hour after sampling. If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. Other measures should be taken as appropriate to prevent samples from any heating during centrifugation. Separated plasma will be placed on water/ice (~0-5°C) and transferred in 3 portions (1 aliquot of 300 uL for laquinimod analysis and 2 approximately equal portions of ~750 uL for metabolite analysis) into 3 opaque, labeled, polypropylene tubes (sets A, B, and C respectively). Tubes will be placed in an upright position into frozen storage at nominal -70°C (if -70°C storage is not possible at the site, store at -20°C) within 1 hour from the start of the centrifugation.

Sample labels should include the study number, patient randomization number, period, nominal collection time, set (A, B, or C), indication that they are pharmacokinetic samples, and an indication of storage conditions at the site (-70°C or -20°C).



### **8.1.2. Shipment of Samples**

Plasma samples for all patients will be shipped from the investigational center to the central coordinating laboratory, where they will be stored at nominal -70°C until shipped to Bioanalytical Laboratory of Teva Pharmaceutical Works Private Ltd. Co., Debrecen, Hungary for analysis. The bioanalytical laboratory will be notified before the shipment of the samples. Shipping information will be sent when the samples are shipped.

Set A and B samples will be transported, frozen with sufficient dry ice for 4 days, by next-day courier to the bioanalytical laboratory.

Set C samples will be sent to the same laboratory as that for sets A and B on subsequent days by next-day courier,.

Sample shipments should be sent no later in the week than Wednesday morning for next-day delivery. Samples are not to arrive on the weekend.

## **8.2. Pharmacodynamic Variables**

Biomarker assessment will include the following:

Cytokines, and other soluble proteins (or any other soluble marker) levels will be determined in plasma in order to better understand laquinimod mechanism of action and explore response predictive markers.

Monocytes, which were shown to play an important role in laquinimod mechanism of action in preclinical studies, will be isolated from patients' blood using cell separation method. Monocyte gene expression and/or protein profile will be explored. This experiment will help us understand the molecular mechanism of laquinimod in patients. This study will be performed only at selected sites in a subgroup of patients.

TSPO is highly expressed in activated microglia which have been found to contribute to neuroinflammation in many types of CNS disorders. Change in microglial activation state, will be investigated. PET scans and imaging analysis of microglial activation marker TSPO will be performed. This study will be performed only at selected sites in a subgroup of patients.

MRS will be performed in order to explore the potential effect on metabolic changes in the putamen and frontal white matter that are associated with the earliest stages of Huntington's Disease. This study will be performed only at selected sites in a subgroup of patients.

The above biological markers will also be used to aim to identify responders to laquinimod treatment, and explore response predictive markers, to potentially identify patients in which clinical benefits could be further investigated.

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

### **8.2.1. Sampling and Handling**

Blood samples for Biomarker assessment:

- 8.5 mL blood samples for plasma cytokine and protein analysis will be collected from all subjects at Baseline, Months 6 and 12.
- 50 mL whole blood samples for monocyte isolation will be collected at baseline and Month 12 only at selected sites in a subgroup of patients (aiming at 25 per treatment arm). The sample collection has to be done in accordance with the laboratory manual. For UK patients, the sample can be drawn prior to the baseline or Month 12 visit, as it coincides with the PET scan visits.

Biomarker samples will be stored for a period of up to 15 years and then destroyed.

### **8.2.2. Shipment and Analysis of Samples**

Plasma samples will be collected in BD P800 tubes (or equivalent) and will be transferred to -70°C within maximum 4 hours (if -70°C storage is not possible at the site, store at -20°C). Tubes will be sent to the central laboratory on dry ice.

Analysis will be performed if and when required. Since new biomarker techniques continue to be developed, the method and laboratory that will be recommended for cytokine and protein analysis will be determined at a later stage.

For monocyte isolation experiments - whole blood samples will be sent at ambient temperature as specified in the laboratory manual to the CRO.

### **8.2.3. Magnetic Resonance Spectroscopy (MRS)**

The principal motivation for including MRS as an endpoint in this study will be to assess the potential effect of Laquinimod on metabolic changes in the putamen and frontal white matter that are associated with the earliest stages of Huntington's Disease. The biochemical changes measured by MRS may be reversible and responsive to pharmacological intervention, making them a promising biomarker in HD.

Previous studies by the Vancouver site investigators have demonstrated that the neuronal marker metabolite NAA exhibited significantly decreased concentrations in the putamen between controls and pre-HD, and between pre-HD and early-HD, and that these changes were robust, consistent, and had a low degree of variability when followed longitudinally over 24 months. The concentration of Myo-inositol (MI), a glial cell marker in the putamen was substantially increased in early HD vs pre-HD and controls ([Sturrock et al, 2010](#)).

At selected sites, the MRS analysis will add two single voxel acquisitions to the MRI protocol in this study. The putamen and frontal white matter voxels will be collected using the same protocol that was used in the MRS study for the TRACK-HD study and will be described in detail in a separate imaging manual. The magnetic resonance (MR) spectra will be obtained using a single-voxel PRESS localization sequence with a Repetition time (TR) of 2000ms, an Echo time (TE) of 35ms and 1024 points will be acquired. Sites with 3.0T Philips MRI scanners will be provided with a standardized 'Exam Card' (a precise specification of MR pulse sequence parameters). Two MRS voxels will be acquired. The first voxel will be the previous in the left putamen with a voxel size of 35 mm x 10 mm x 15 mm (5250 mm<sup>3</sup>). The second voxel will be placed in frontal white matter and will have a voxel size of 15 mm x 15 mm x 10 mm (2250 mm<sup>3</sup>).

The MRS results will be analysed using LCModel, which is the most commonly used MRS data analysis package. Its advantages include the fact it is almost completely objective, it provides a

measure of confidence in the resulting concentrations and because it is used by so many groups worldwide, the analysed results are easier to compare with results from other MRS studies.

Metabolite concentrations will be normalized to the unsuppressed water spectrum. Where possible, results will be corrected for  $T_1$  and  $T_2$  (uncoupled spins) relaxation using published times from the literature on normal brain, although at TE 35ms and TR 2000ms, these corrections are small. LCModel estimates the reliability of a “concentration” measurement and returns a standard deviation (%SD) for each metabolite. Standard deviations less than 20% are considered reliable and therefore any metabolite with a %SD greater than 20% will be excluded from further analysis. From the MR spectra, at least five metabolites of interest will be examined: N-acetyl aspartate (NAA, a marker of neuronal integrity), Creatine (Cr, a marker of brain energy metabolism), total Choline (tCho, a marker for neuronal membrane turnover), Glutamate (Glu, a major CNS excitatory neurotransmitter) and Myo-inositol (MI, an astrocyte marker).

Mean metabolite concentrations will be compared between treatment groups.

#### 8.2.4. PET Scan

At selected sites, patients will be referred to the Imperial College in London, where PET Imaging will be performed at the Imanova Imaging Centre on the Hammersmith Hospital site. The PET imaging will be performed at baseline and after treatment with laquinimod over a 12-month period of time.

All patients participating in the PET arm of the study will be exposed to additional ionizing radiation due to the PET/CT scans. There are no alternative methods available to explore neuroinflammation in vivo. While any ionizing radiation exposure increases the risk of future malignancy, for the radiation exposure in this study such exposure is small and the increased risk is minimal. Patients who recently took part in clinical studies or underwent medical procedures involving ionizing radiation, such that participation in this study would lead to an exposure of >10mSv in the last 12 months, will be excluded from participation in this ancillary study. This will not affect the patient's participation in the main study.

The 18-kDa TSPO is expressed within microglia and macrophages and has been used as a target for PET ligands to study neurodegenerative disease processes that involve microglial activation, such as HD, Parkinson's disease (PD) and Alzheimer's disease (AD) (Politis et al, 2012). The PET radioligand  $^{11}\text{C}$ -PK11195 has been used most frequently for this purpose, but signal quantification is limited by poor specific signal-to-background ratio.

$^{11}\text{C}$ -PBR28 is a second generation radioligand with high affinity to TSPO, favourable in vivo kinetics, and greater signal-to-noise ratio than  $^{11}\text{C}$ -(R)-PK 11195 (Fujita et al, 2008; Imaizumi et al, 2008; Kreisl et al, 2010; Kreisl et al, 2013).

One limitation of  $^{11}\text{C}$ -PBR28, shared by all tested second generation TSPO radioligands (including  $^{11}\text{C}$ -DAA1106), is differential affinity for the target protein (Owen et al, 2011). This differential affinity is caused by the rs6971 polymorphism on the TSPO gene that causes a non-conservative amino acid substitution, resulting in three patterns of TSPO binding (Owen et al, 2012). Subjects without the polymorphism (HH) have high affinity binding for PBR28, homozygotes (LL) have low affinity binding, and heterozygotes (HL) express both high and low affinity TSPO (mixed-affinity binding). Low affinity subjects are easily identified by PET due to negligible  $^{11}\text{C}$ -PBR28 binding in vivo; however, PET cannot easily resolve the difference

between high and mixed-affinity subjects. Previous work demonstrated that correcting in vitro binding data for rs6971 genotype improves the ability of 3H-PBR28 to detect differences in TSPO density (Kreisl et al, 2013). This simple strategy of TSPO genotype correction to PET imaging will be used in the present study.

This will be the first trial to assess in vivo changes in TSPO following a treatment aimed to reduce microglia activation. As such it will be an exploratory, ancillary, study. Previous PET studies looking at baseline increases of microglia activation in HD patients compared to normal volunteers have found significant differences even in small groups of patients (11 HD vs 10 normal volunteers, striatal differences in TSPO binding  $p=0.001$ ).

Not all benzodiazepines have been tested for TSPO binding. Patients taking benzodiazepines should be instructed to stop taking them for 3 days prior to having the PET scan.

#### **8.2.4.1. Collection of Genotyping Samples**

Genomic DNA will be collected at the screening visit as described in Section 8.3.1 and used to genotype the rs6971 polymorphism within the TSPO gene on chromosome 22q13.2 (Owen et al, 2011; Kreisl et al, 2013).

Patients who have A/A genotype for rs6971 polymorphism on the TSPO gene, which has been shown to result in low affinity binding (LAB) of the  $^{11}\text{C}$ -PBR28 radioligand, will be excluded from the PET ancillary study. Patients with LAB for TSPO can participate in the main study even if they are excluded from the PET ancillary study. Patients with G/G and A/G rs6971 genotype have been shown to have high (HAB) and mixed (MAB) affinity binding, respectively, and will be included in the PET ancillary study.

#### **8.2.4.2. Scanning Procedures**

For women of child-bearing potential, a urine pregnancy test will be performed on the same day, and prior to, the PET scan at Imperial College in London. If the result of this test is positive, the PET procedure will not be performed and the patient will be monitored as outlined in Section 7.2.

Specific activity, chemical purity, and radiochemical purity of  $^{11}\text{C}$ -PBR28 will be determined by radio high performance liquid chromatography (HPLC) coupled with a gamma detector. Specific activity will be determined by counting an aliquot in a dose calibrator and determining the mass by HPLC against a calibration curve of the cold standard. Identity will be confirmed by co-injecting the standard.

Approximately 400 MBq of  $^{11}\text{C}$ -PBR28 as intravenous bolus will be injected, and an approximately 90 minutes emission PET-CT scan will be acquired on a Siemens HiRez 6 PET/CTI scanner (Siemens Healthcare, Erlanger, Germany). A low dose CT scan of the head will be performed immediately before each PET study for subsequent attenuation and scatter correction of PET signal. Imaging data will be reconstructed with filter backprojection (direct inversion Fourier transform) with a 128 matrix, a zoom of 2.6, a transaxial Gaussian filter of 5 mm, scatter correction and attenuation correction. All subjects will have a volumetric T1-weighted MR sequence for co-registration purpose with PET images.

Patients will be advised that they should not participate in further research studies involving ionizing radiation for a year following the last performed scan.

### **8.3. Pharmacogenomic Variables**

It is recognized that genomic variation within the population can be an important contributory factor to inter-individual differences in drug response. Pharmacogenomic (PGx) studies investigate the association between genetic sequence polymorphisms and/or gene expression signatures and clinical response to a certain therapeutic intervention. It may help explaining inter-individual variability and subsequently identify population subgroups that respond differently to the drug. Furthermore, regulatory guidance and white papers indicate that PGx analyses employing DNA collected from all study participants may support investigation of unexpected adverse events.

In order to allow any subsequent analyses, appropriate samples will be requested from all patients in the study. PGx assessment will include CAG repeats analysis in huntingtin gene and might also include other DNA variations and RNA expression patterns potentially associated with clinical treatment responses to laquinimod (e.g. clinical effect, pharmacokinetics, tolerability, and safety features or disease susceptibility and severity features). The final list of genes that might be investigated will be selected in a later stage before the analysis so as to allow updating with new scientific information. Genomic analysis could also include a sequencing of the whole genome if required.

PGx assessment will be performed if variability in response measurements is observed and attributable to genomic parameters. Samples might be used for investigations related to CNS disorders diseases and/or response to laquinimod or related investigational drugs.

#### **8.3.1. Methods and Timing of Pharmacogenomic Blood Sampling**

PGx assessment will be performed using blood samples.

- Blood samples for DNA extraction will be collected at screening (or if not possible, at the next possible visit) in **two** 5.0 mL K3 EDTA Vacutainer plastic tubes (or equivalent).
- Blood samples for gene expression analysis (RNA extraction) will be collected at baseline, Month 6 and Month 12 from all subjects in PAXgene RNA 10 mL tubes (or equivalent).

PGx samples will be stored for a period of up to 15 years from patient last visit in the main study and then destroyed.

#### **8.3.2. Shipment of Samples**

PGx samples will be stored at -70°C (if -70°C storage is not possible at the site, store at -20°C) and sent to the central laboratory on dry ice. Following DNA and RNA extractions, the samples will be stored at -70°C and labeled with a new code, so genomic data will not be recorded with subject number or initials. Data will be kept confidential and stored separately.

The PGx sample analyses will be performed if and when required. Since new PGx techniques continue to be developed, we cannot anticipate the method and laboratory that will be recommended for the DNA/RNA analysis.

## **9. STATISTICS**

### **9.1. Study Design and Randomization**

This is a double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of laquinimod (0.5 mg and 1.0 mg qd) treatment in patients with HD. Prior to 10 January 2016, eligible patients were randomly assigned to receive treatment with laquinimod at a dosage of 0.5 mg, 1.0 mg, or 1.5 mg/day or a matching placebo in a 1:1:1:1 ratio.

Randomization will be as described in Section 3.3.

As of 10 January 2016, following a decision to discontinue treatment of the laquinimod 1.5 mg dose arm, future eligible patients will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day or 1.0 mg/day or matching placebo for 52 weeks.

No change was performed to the original randomization list except that the patient numbers assigned to laquinimod 1.5 mg/day were removed from the list by the IRT vendor. Patients and investigators will remain blinded to treatment assignment during the study.

All patients who discontinued the 1.5 mg/day dose have been unblinded. No attempts will be made to re-randomize patients whose 1.5 mg treatment was stopped to a lower dose of laquinimod. The remaining ongoing patients retained their originally randomized treatment assignments.

### **9.2. Sample Size and Power Considerations**

The study aims to detect potential beneficial effects in deteriorating clinical signs and symptoms. Based on previous studies in patients with HD, the UHDRS-TMS has been shown to be one of the more sensitive clinical measures to detect decline in symptoms of HD. It is estimated that approximately 100 patients per arm will enable a power of 80% to detect a beneficial effect compared to placebo, of 2.5 points or more in the change from baseline in UHDRS-TMS of an active laquinimod arm, assuming SD of 6.2 and type I error of 5%.

As the intention is to investigate laquinimod as a treatment with the potential to slow disease progression and prohibit neuronal death in the CNS, the study should also be sized to be able to detect changes in brain atrophy rate after treatment with laquinimod. One of the most sensitive measures to detect brain atrophy over time in patients with HD is change in the caudate volume.

It is estimated that approximately 100 patients per arm will enable a power of 80% to detect a beneficial effect of 0.95 (30% of the estimated decline in placebo) or more in the percent change from baseline in caudate brain atrophy of an active laquinimod arm compared to placebo, assuming SD of 2.36 and type I error of 5%.

### **9.3. Analysis Sets/Populations**

Due to the decision from 10 January 2016 to discontinue treatment of the laquinimod 1.5 mg dose arm, and the low number of enrolled patients compared to the target at this time, data from the laquinimod 1.5 mg dose arm will be presented descriptively only and will not be included in any inferential analyses for efficacy or safety.

**9.3.1. Intent-to-Treat Population**

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

**9.3.2. Safety Population**

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

**9.3.3. Full Analysis Set (FAS)**

The full analysis set (FAS) will include all patients in the ITT population who receive at least 1 dose of study drug and have at least 1 post-baseline efficacy assessment.

**9.4. Data Handling Conventions**

For all variables, only the observed data from the patients will be used in the by visit summary.

For efficacy endpoints that are measured at baseline and at month 12 only, the Last Observation Carried Forward (LOCF) method will be applied for early terminated patient observation.

Detailed data imputation rule will be specified in the statistical analysis plan.

**9.5. Study Population**

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

The Safety population will be used for safety variables.

The FAS will be used for efficacy variables.

**9.5.1. Patient Disposition**

Data from patients screened, patients screened but not treated, patients in the safety population and FAS, patients who complete the study, and patients who withdraw from the study will be summarized using descriptive statistics. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

**9.5.2. Demographic and Baseline Characteristics**

Patient demographic and baseline characteristics will be examined to assess the comparability of the treatment groups and will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number, mean, SD, standard error, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

## **9.6. Efficacy Analyses**

### **9.6.1. Efficacy Variables**

#### **9.6.1.1. Primary Efficacy Variable and Endpoint**

The primary efficacy variable and endpoint for this study is the change from baseline in the UHDRS-TMS (defined as the sum of the scores of all UHDRS-TMS subitems) at Month 12/ ET (evaluated at baseline and Months 1, 3, 6 and 12)

#### **9.6.1.2. Secondary Efficacy Variables and Endpoints**

The secondary efficacy variables and endpoints for this study are:

- Percent change from baseline in caudate volume at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in HD-CAB total score (sum of the standardized sub-components) at Month 12/ET (evaluated at baseline and Months 6 and 12)
- CIBIC-Plus global score at Month 12/ET (evaluated at Months 6 and 12) as compared to baseline (rated by an independent investigator)
- Change from baseline in UHDRS- TFC at Month 12/ET (evaluated at baseline, Months 6 and 12)

#### **9.6.1.3. Exploratory Efficacy Variables and Endpoints**

- Change from baseline in brain atrophy as defined by the percentage change in volume in: whole brain volume and white-matter volume at Month 12/ET and absolute change in ventricular volume at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in UHDRS- FA at Month 12/ET (evaluated at baseline and Months 6 and 12)
- Change from baseline in Q-Motor assessments at Month 12/ET (evaluated at baseline and Months 1, 3, 6 and 12)
- Change from baseline in mPPT at Month 12/ET (evaluated at baseline and Months 6 and 12)
- Change from baseline in HD QoL and EQ-5D-5L at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in WLQ at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in HD-CAB sub-components at Month 12/ET (evaluated at baseline and Months 6 and 12):  
Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLTR), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version)
- Change from baseline in CDR-SB at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in HADS at Month 12/ET (evaluated at baseline and Month 12)
- Change from baseline in PBA-s at Month 12/ET (evaluated at baseline and Month 12)



#### **9.6.1.4. Pharmacodynamic Analyses**

- Change from baseline in microglial activation marker TSPO at Month 12/ET
- Change from baseline in brain MRS metabolite markers of neuronal integrity (NAA) and striatal astrocytosis (myo-inositol) at Month 12 in putamen and frontal white matter
- Change from baseline in soluble biomarkers at Months 6 and 12
- Change from baseline in monocyte gene expression and/or proteomic profile at Month 12.

#### **9.6.2. Planned Method of Analysis**

The full analysis set (see Section 9.3) will be used for all efficacy analyses. Summaries will be presented by treatment group.

##### **9.6.2.1. Primary Efficacy Endpoint Analysis**

The change from baseline in UHDRS-TMS, will be analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical week in trial by treatment interaction, center, and UHDRS-TMS at baseline. The unstructured covariance matrix for repeated observations within patients will be used. In case that the model will not converge, the Maximum-Likelihood (ML) estimation method will be used instead of the default Restricted ML (REML). If the model still does not converge then a simpler covariance structures with less parameters will be used, according to the following order: Heterogeneous Autoregressive(1) [ARH(1)], Heterogeneous Compound Symmetry (CSH), Autoregressive(1) [AR(1)], and Compound Symmetry (CS). The estimated mean changes from baseline at the Month 12/Early Termination visit will be compared between the active treatment arms and the placebo arm.

The Hochberg's Step-Up method for multiple comparisons between treatment arms will be used to control inflation in type I error rate.

##### **9.6.2.2. Secondary Efficacy Endpoints Analyses**

According to the hierarchical method to control inflation in type I error rate for multiple endpoints, any statistically significant dose that will be observed in the primary analysis will continue to be tested for the secondary endpoints at an alpha level of 5%, according to the secondary endpoints order.

The secondary efficacy endpoints: change from baseline in HD-CAB total score and change from baseline in UHDRS-TFC, will be analyzed in the same way as the primary efficacy endpoint except that the efficacy endpoint evaluation at baseline will be included in the model instead of baseline UHDRS-TMS.

The CIBIC-Plus will be analyzed in the same way as the primary efficacy endpoint except that the baseline CIBIS (Clinician's Interview-Based Impression of Severity) will be included in the model as the efficacy measure at baseline.

The percent change from baseline to Month 12/Early Termination in caudate volume will be analyzed using an Analysis Of Covariance (ANCOVA) model (SAS® MIXED procedure). The model will include the following fixed effects: treatment, center, and caudate volume at baseline.

The estimated means at the Month 12 visit will be compared between the active treatment arms and the placebo arm. Early terminated patient observation will have their Last Observation Carried Forward (LOCF).

### **9.6.2.3. Exploratory Efficacy Endpoints Analyses**

The exploratory efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint except that the efficacy endpoint evaluation at baseline will be included in the model instead of baseline UHDRS-TMS.

The change from baseline to Month 12/Early Termination of continuous efficacy endpoints that are measured at baseline and at month 12 only, will be analyzed using an ANCOVA model (SAS® MIXED procedure). The model will include the following fixed effects: treatment, center, and the efficacy measure at baseline. The estimated means at the Month 12 visit will be compared between the active treatment arms and the placebo arm. Early terminated patient observation will have their Last Observation Carried Forward (LOCF).

### **9.6.2.4. Sensitivity Analysis**

No sensitivity analyses are planned for this study.

### **9.6.2.5. Pooling of Small Centers**

Centers with low number of patients will be pooled according to geographical region.

Details will be provided in the Statistical Analyses Plan (SAP).

The pooled center variable will be used in all statistical models that include center as covariate.

## **9.7. Multiple Comparisons and Multiplicity**

The Hochberg's Step-Up method for multiple comparisons between treatment arms in combination with the hierarchical method between the primary efficacy endpoint and the secondary efficacy endpoints, will be used to maintain the experiment wise type I error of 5% level. First, the Hochberg method will be applied for the comparisons of the 2 active doses to placebo in the primary endpoint analysis. Then, using the hierarchical method, any statistically significant dose will continue to be tested for the secondary endpoints at an alpha level of 5% and according to the order of the secondary endpoints.

## **9.8. Safety Variables and Analysis**

### **9.8.1. Safety Variables**

Safety variables and endpoints will include the following:

- Adverse events reports throughout the study
- ECG findings throughout the study
- Clinical safety laboratory tests throughout the study
- Vital signs measurements throughout the study
- Physical examination findings throughout the study
- Changes from baseline suicidality (C-SSRS) scores throughout the study

Tolerability variables:

- Proportion of subjects (%) who prematurely discontinued from the study, reason of discontinuation and the time to ET
- Proportion of subjects (%) who prematurely discontinued from the study due to AEs and the time to ET

### **9.8.2. Safety Analysis**

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

Changes in laboratory and vital signs measurement data will be summarized descriptively. All values will be compared with prespecified boundaries to identify potentially clinically significant changes or values, and such values will be listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with study drug.

For continuous variables, descriptive statistics (n, mean, standard deviation, standard error, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will also be provided.

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

## **9.9. Pharmacokinetic and Pharmacodynamic Analysis**

### **9.9.1. Pharmacokinetics (PK) Ancillary Study**

PK samples of laquinimod and its metabolites will be collected from approximately 15 patients per each of the three continuing treatment groups (at selected sites at Month 1), for a total of approximately 45 patients. Additionally, PK samples were collected from 2 patients in the laquinimod 1.5 mg/day treatment group when the treatment was stopped; no further PK samples will be collected from the laquinimod 1.5 mg/day treatment group.

Samples will be collected at pre-dose, 15, 30 min and 1, 2, 3, 6 and 24 hours post dose.

Steady state pharmacokinetic parameters for laquinimod ( $AUC_{\tau}$ ,  $C_{\max}$  and  $C_{\min}$ ,  $t_{\max}$ ), will be calculated for each patient.

Additional parameters for laquinimod and pharmacokinetic parameters for its metabolites may be calculated if data permit.

The time of the previous dose as well as deviations from the blood sampling times will be recorded in the appropriate eCRF. Patients performing the 24 hours PK profile will come to the clinic after an overnight fast (minimum of 8 hours) and will be given breakfast 4 hours after drug administration.

The morning dose and the 24 hours dose administration (the day after) will take place at the clinic.

### **9.9.2. Population PK (PPK) Study**

A single blood sample will be collected from all patients at months 1, 3, 6 and 12 for evaluation of laquinimod and its metabolites.

Pharmacokinetics of laquinimod will be evaluated using a Population PK approach. The effect of covariates on the PK of laquinimod will be evaluated. Possible covariates will include demographic variables (e.g. age, gender, body weight and ethnicity), clinical variables (e.g. CAG repeat length), concomitant medications, blood and urine chemistry variables and markers of renal function (creatinine clearance and serum creatinine).

Pharmacokinetic parameters for laquinimod metabolites may be calculated if data permit.

The PPK model may also include any unscheduled pharmacokinetic samples collected to assist with further investigations of cardiovascular events or other clinical event of interest for safety (see Section 8.1).

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

### **9.10. Planned Interim Analysis**

No interim analysis is planned for this study.

### **9.11. Reporting Deviations from the Statistical Plan**

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

## **10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

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

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

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

## **11. QUALITY CONTROL AND QUALITY ASSURANCE**

### **11.1. Protocol Amendments and Protocol Deviations and Violations**

#### **11.1.1. Protocol Amendments**

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

#### **11.1.2. Protocol Deviations**

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

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

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

### **11.2. Information to Study Personnel**

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

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

### **11.3. Study Monitoring**

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

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

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

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

### **11.4. Clinical Product Complaints**

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

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

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the Product Complaint Form provided by Teva and emailing it to [clinical.productcomplaints@tevapharm.com](mailto:clinical.productcomplaints@tevapharm.com) within 48 hours of becoming aware of the issue.

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

#### **11.4.1. Product Complaint Information Needed from the Investigational Center**

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

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

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

#### **11.4.2. Handling the Study Drug at the Investigational Center**

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

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

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



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

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

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

#### **11.4.4. Documenting a Product Complaint**

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

### **11.5. Audit and Inspection**

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

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

## **12. ETHICS**

### **12.1. Informed Consent**

The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the IEC/IRB. Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, according to the IEC/IRB requirements. The patient's willingness to participate in the study will be documented in writing in a consent form, which will be signed and personally dated by the patient. Patients with a legal guardian should be consented according to local requirements.

Patients participating in ancillary studies will provide written informed consent specific to that study.

The investigator will keep the original consent forms, and copies will be given to the patients. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

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

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

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

### **12.3. Confidentiality Regarding Study Patients**

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

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

### **12.4. Declaration of the End of the Clinical Study**

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

## **12.5. Registration of the Clinical Study**

This clinical study will be registered on clinical trials registry websites according to local regulations and in compliance with Teva standard procedures.

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

### **13.1. Data Collection**

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

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

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

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

### **13.2. Data Quality Assurance**

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

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

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

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

### **13.3. Archiving of Case Report Forms and Source Documents**

#### **13.3.1. Investigator Responsibilities**

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

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

#### **13.3.2. Sponsor Responsibilities**

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

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

#### **14. FINANCING AND INSURANCE**

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

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

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

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

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

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

## **15. REPORTING AND PUBLICATION OF RESULTS**

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

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

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

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

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

## 16. SUMMARY OF CHANGES FOR PROTOCOL AMENDMENTS

### 16.1. GLOBAL PROTOCOL AMENDMENT 04 DATED 16 FEBRUARY 2016

The primary reason for this global amendment was to discontinue treatment for patients receiving 1.5 mg laquinimod as a proactive safety measure, and to implement additional safety measures to help ensure the safety of patients (both ongoing patients and those still to be enrolled) receiving 0.5 mg/day or 1.0 mg/day laquinimod or placebo. To avoid increased exposure to laquinimod, stopping rules have been introduced for renal impairment and hepatic impairment, with additional assessments of estimated creatinine clearance introduced for increased monitoring of renal function.

[Table 3](#) (Study Procedures and Assessments) has been revised to reflect changes described below. An additional study schema ([Figure 2](#)) has been included to reflect the amended study design.

The statistical analysis sections were updated accordingly, and the risks and benefits sections of the protocol have also been updated to reflect the new findings observed in the MS trials.

Additional clarifications related to study conduct were implemented in this amendment. These include (not all inclusive) clarifications regarding determination of eligibility of patients with exclusionary variance from historical CAG repeat results, testing of both troponin and CK-MB in case of creatine phosphokinase levels above the upper limit of the normal range to provide additional cardiovascular assessment, and adjustment of blood volume collected to allow for unscheduled visits.

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

A comparison table showing substantive changes from Amendment 03 to Amendment 04 is provided below. Previous text is presented in the column titled "Original text with changes shown", and the revised or new text is presented in the column titled "New wording". Revised or new text is shown in ***bold italics*** and deletions are shown in strikethrough. A few formatting and editing changes have also been made but are not detailed below.

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

The administrative letters #6 (dated 22 October 2015) and #7 (dated 05 November 2015) have also been added to the summary of changes section. The content of the administrative letters has been implemented in protocol Amendment 03 as applicable.



Original text with changes shown	New wording	Reason/Justification for change
<b>TITLE PAGE</b>		
<b>Sponsor’s Medical Expert</b> <del>Spyridon Papapetropoulos,</del> <i>Karl H.S. Kim</i> , MD, PhD Global Head, Neurodegeneration, Clinical Development <i>Project Physician</i> Teva Branded Pharmaceutical Products R&D, Inc. Tel: +1-610-727- <del>6044</del> 3357	<b>Sponsor’s Medical Expert</b> Karl H.S. Kim, MD, PhD Clinical Project Physician Teva Branded Pharmaceutical Products R&D, Inc. Tel: +1-610-727-3357	Change of personnel
<b>CLINICAL STUDY PERSONNEL CONTACT INFORMATION</b>		
<del>Dawn Baramki, Project Manager</del> <del>28459 Hidden Lake Drive</del> <del>Bonita Springs, FL 34134</del> <del>USA</del> <del>Tel: +1 (239) 992-8382</del> <i>Montserrat Sanz Gomez</i> <i>Project Manager, Clinical Research Service</i> <i>External Tel: +44 162 849 6339</i> <i>Mobile: +44 782 438 2575</i> <i>e-mail: Montserrat.SanzGomez@iconplc.com</i>	Montserrat Sanz Gomez Project Manager, Clinical Research Service External Tel: +44 162 849 6339 Mobile: +44 782 438 2575 e-mail: Montserrat.SanzGomez@iconplc.com	Change of personnel
<b>LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS</b>		
<i>AKI – Acute kidney injury</i>	AKI – Acute kidney injury	New abbreviation.
<i>CrCl – Creatinine Clearance</i>	CrCl – Creatinine Clearance	New abbreviation.
<i>qd – once daily</i>	qd – oncedaily	New abbreviation.
<i>BMI – body mass index</i>	BMI – body mass index	New abbreviation
<i>DMC– Data Monitoring Committee</i>	DMC– Data Monitoring Committee	New abbreviation
<i>MoA- <del>Mode</del> Mechanism of Action</i>	MoA- Mechanism of Action	Correction of terminology.
<b>1 BACKGROUND INFORMATION</b>		
<b>Section 1.1</b>		
Laquinimod is developed by Teva Pharmaceutical Industries, Ltd. for Multiple Sclerosis (MS), <del>Crohn’s Disease (CD), and Systemic Lupus Erythematosus (SLE) and HD</del> . The precise mechanism of action of laquinimod in MS is still under investigation. Available data support that laquinimod, is an immunomodulator that acts both on the peripheral immune system and within the central nervous system (CNS) on resident immunocompetent cells. The data collected to date suggests that laquinimod (i) reduces the levels of proinflammatory cytokines such as TNF- $\alpha$ ; (ii) reduces inflammation within the CNS; (iii) down regulates genes involved in inflammation and antigen presentation; and (iv) modulates T cell responses via a direct effect on antigen presenting cells, and skews	Laquinimod is developed by Teva Pharmaceutical Industries, Ltd. for Multiple Sclerosis (MS) and HD. The mechanism of action (MoA) of laquinimod includes modulation of the peripheral inflammation and central nervous system (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 inflammation, CNS inflammation, tissue damage, and neurodegeneration in CNS diseases that involve microglia and astrocytic activation, like MS and HD. Recently	The CD and SLE indications are no longer pursued.  Introduction revised for consistency with the IB.

Original text with changes shown	New wording	Reason/Justification for change
<p>monocytes to a regulatory phenotype. The presumed mechanism by which laquinimod exerts this effect is down regulation of both astrocytic and microglial pro-inflammatory response mediated by interference with the NF-<math>\kappa</math>B pathway, investigated in experimental autoimmune encephalomyelitis (EAE) and the Cuprizone models of demyelination (Wegner et al, 2010<sup>45</sup>; Bruck et al, 2012<sup>46</sup>; Aharoni et al, 2012<sup>47</sup>). <i>The mechanism of action (MoA) of laquinimod includes modulation of the peripheral inflammation and central nervous system (CNS)-resident inflammatory response resulting in down regulation of myelin and axonal damage. These effects are compatible with interference of NF-<math>\kappa</math>B activation and may represent a novel protective mechanism which down regulates peripheral inflammation, CNS inflammation, tissue damage, and neurodegeneration in CNS diseases that involve microglia and astrocytic activation, like MS and HD. Recently performed studies show that the aryl hydrocarbon receptor (AhR) pathway is involved in the efficacy of laquinimod in the experimental autoimmune encephalomyelitis (EAE) model. Further investigations are ongoing, assessing the role of AhR in the MoA of laquinimod.</i></p> <p>Further, laquinimod was shown to cause a <i>weak</i> decrease of CYP3A4 activity and is a strong inducer of CYP1A enzymes. CYP1A induction is a biomarker of activation of the AhR transcription factor; activation of this pathway by laquinimod has been demonstrated.</p> <p><del>Studies investigating laquinimod's mode of action have suggested that treatment with laquinimod interferes with the NF-<math>\kappa</math>B pathway results in immunomodulation, including modulation of the cytokine balance and reduction of inflammation. Laquinimod is not a general immunosuppressor, nor immunotoxic, but treatment with laquinimod results in a shift in the cytokine balance towards reduced pro-inflammatory cytokine production, induction of regulatory monocytes, reduced astrogliosis, and reduced infiltration to inflammatory target tissues, as demonstrated in animal models of MS and CD.</del></p> <p>...</p>	<p>performed studies show that the aryl hydrocarbon receptor (AhR) pathway is involved in the efficacy of laquinimod in the experimental autoimmune encephalomyelitis (EAE) model. Further investigations are ongoing, assessing the role of AhR in the MoA of laquinimod.</p> <p>Further, laquinimod was shown to cause a weak decrease of CYP3A4 activity and is a strong inducer of CYP1A enzymes. CYP1A induction is a biomarker of activation of the AhR transcription factor; activation of this pathway by laquinimod has been demonstrated.</p> <p>...</p>	
<p><b>Section 1.3.1.</b></p>		
<p>Laquinimod was shown to cause a <i>weak</i> decrease of CYP3A4 activity and is a strong inducer of CYP1A enzymes.</p>	<p>Laquinimod was shown to cause a weak decrease of CYP3A4 activity and is a strong inducer of CYP1A enzymes.</p>	<p>Clarification</p>
<p>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</p>	<p>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</p>	<p>Reflecting that 1.5 mg is no longer an intended clinical dose</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>safety margins in the range of 32 to 257-fold above the <i>originally</i> intended clinical dose of 1.5 mg/day based on maximal plasma concentrations.</p>	<p>gastrointestinal systems providing safety margins in the range of 32 to 257-fold above the originally intended clinical dose of 1.5 mg/day based on maximal plasma concentrations.</p>	<p>(changed several other times in this section)</p>
<p>In addition, an increase in the incidence of oral cavity tumors was noted in mid and high dose females (2/60 in each group). The oral effects may relate to the AhR activation properties of laquinimod since similar lesions were seen <i>following lifelong exposure of rats to</i> with other AhR activators. <i>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<sup>1</sup>) 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<sup>2</sup>). 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., including industrial chemicals (such as 2,3,7,8-tetrachlorodibenzo p dioxin [TCDD] and dioxin like compounds [DLCs]) and the dietary ingredient indole 3 carbinol (I3C) found in cruciferous vegetables. However, the incidence of oral cavity tumors in rats treated with laquinimod was lower than that seen with TCDD and DLCs, and was more similar to the incidence seen with I3C. Importantly, the oral cavity tumors seen with TCDD in rats did not translate into increased incidence of oral tumors in exposed humans, indicating a species difference in this response between rats and humans. It should be noted that several lines of evidence suggest that the oral lesions seen in rats are mediated by direct contact of the rat oral mucosa with high concentrations of laquinimod in the dosing solution during the gavage procedure. An effect on the oral mucosa in rats is not considered relevant to humans, who take laquinimod as a capsule that dissolves in the stomach. Based on sponsor's calculations, in the human stomach, the local concentration of laquinimod is expected to be low, and the type of epithelium exposed is not considered sensitive to the effects of laquinimod, with safety margins greater than 13 (dogs), 20 (rats) and 1000 (mice) for exposure in the stomach.</i></p>	<p>In addition, an increase in the incidence of oral cavity tumors was noted in mid and high dose females (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<sup>1</sup>) 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<sup>2</sup>). 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>Section updated in accordance with Investigator's Brochure</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>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.</p>	<p>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.</p>	<p>Reference to report in newly-added text in the non-clinical section.</p>
<p>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.</p>	<p>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.</p>	<p>Reference to report in newly-added text in the non-clinical section.</p>
<p><b>Section 1.3.2.1</b></p>		
<p>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 (<b><i>2.5- and 3.1-fold increase in laquinimod systemic exposure, respectively;</i></b>) and strong CYP3A4 inducers and moderate hepatic impairment. Studies have shown that laquinimod is a strong inducer of CYP1A2 and a weak inhibitor of CYP3A4. Therefore, co-administration of laquinimod may affect the systemic exposure of drugs metabolized by CYP450 1A2 or CYP3A4. ... <b><i>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 with 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</i></b></p>	<p>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 and moderate hepatic impairment. Studies have shown that laquinimod is a strong inducer of CYP1A2 and a weak inhibitor of CYP3A4. Therefore, co-administration of laquinimod may affect the systemic exposure of drugs metabolized by CYP450 1A2 or CYP3A4. ... 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 with 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</p>	<p>Added text on hepatic and renal impairment as background for new stopping rules.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><i>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.</i></p>	<p>(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><b>Section 1.4.1.</b></p>		
<p><i>Note: The table has been updated in line with the updated Reference Safety Information; myocardial infarction and cerebrovascular accident are now included.</i></p> <p>Table 1: Tabulated List of Adverse Reactions <del>in the Pooled ALLEGRO and BRAVO Studies</del></p> <p><i>Cardiac disorders Uncommon: Myocardial infarction</i></p> <p><i>Nervous system disorders Very Common: Headache Rare: Cerebrovascular accident</i></p>	<p>Note: The table has been updated in line with the updated Reference Safety Information; myocardial infarction and cerebrovascular accident are now included.</p> <p>Table 1: Tabulated List of Adverse Reactions</p> <p>Cardiac disorders Uncommon: Myocardial infarction</p> <p>Nervous system disorders Very Common: Headache Rare: Cerebrovascular accident</p>	<p>Updated in line with changes to the IB</p>
<p><b>Section 1.4.1.2.7</b></p>		
<p><i>Cardiovascular Events (in the high-dose treatment arms of the ongoing MS studies) In December 2015, the Data Monitoring Committee (DMC) for the Teva-sponsored MS studies LAQ-MS-305 (CONCERTO) and TV5600-CNS-20006 (ARPEGGIO) found an imbalance in serious cardiovascular events in the high-dose treatment arms of these studies (1.2 mg in CONCERTO, 1.5 mg in ARPEGGIO). Six cases of myocardial infarction occurred in the CONCERTO 1.2 mg treatment arm, compared with no events in the 0.6 mg or placebo treatment arms, along with a cerebral infarction in a 31-year-old man in the 1.2 mg treatment arm. In the ARPEGGIO study, 1 myocardial infarction event was identified in the laquinimod 1.5 mg</i></p>	<p>Cardiovascular Events (in the high-dose treatment arms of the ongoing MS studies) In December 2015, the Data Monitoring Committee (DMC) for the Teva-sponsored MS studies LAQ-MS-305 (CONCERTO) and TV5600-CNS-20006 (ARPEGGIO) found an imbalance in serious cardiovascular events in the high-dose treatment arms of these studies (1.2 mg in CONCERTO, 1.5 mg in ARPEGGIO). Six cases of myocardial infarction occurred in the CONCERTO 1.2 mg treatment arm, compared with no events in the 0.6 mg or placebo treatment arms, along with a cerebral infarction in a</p>	<p>New text added to reflect cardiovascular findings in the high dose treatment arms of the ongoing CONCERTO and ARPEGGIO MS studies.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><i>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.</i></p> <p><i>Due to these events, the DMC recommended stopping the high-dose treatment arms (1.2 mg/day and 1.5 mg/day) in the laquinimod MS trials. The DMC did not identify any overt cardiovascular risk in the 0.6 mg treatment arm, but felt that long-term monitoring for emergence of any signal was necessary. The DMC also recommended that study subjects continuing on laquinimod 0.6 mg be reconsented with information about the cardiovascular risk seen at higher doses.</i></p> <p><i>On 07 January 2016, the LEGATO-HD Data Safety Monitoring Board (DSMB) was called by Teva to review and discuss the recommendations of the DMC for the CONCERTO and ARPEGGIO MS trials and their implications on LEGATO-HD. The DSMB confirmed that no cardiovascular events had been observed to date for any dose of the LEGATO-HD trial and concurred with the Sponsor’s recommendation that the high-dose (ie, 1.5 mg) arm in this trial be discontinued as a proactive safety measure. The DSMB approved the continuation of the 0.5 mg/day and 1.0 mg/day arms with enhanced monitoring and safety precautions. Teva notified LEGATO-HD investigators on 10 January 2016 to immediately contact patients randomized to the high dose of 1.5 mg laquinimod and instruct them to discontinue study medication as a proactive measure to protect the safety of patients (endorsed by DSMB as noted above).</i></p> <p><i>Currently, the mechanism of the cardiovascular events remains unknown. Although no specific time-to-event patterns have been identified in the MS studies, 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 patients exhibited signs of myocardial tissue injury, the cardiac work-up in these cases revealed heterogeneous etiologies. Of note, the patients all had some established cardiovascular risk factors, including patients with probable myocarditis or with probable familial hypercholesterolemia. Further investigations into potential predictors and the potential causality are ongoing.</i></p>	<p>31-year-old man in the 1.2 mg treatment arm. In the ARPEGGIO study, 1 myocardial infarction event was identified in the laquinimod 1.5 mg treatment arm. The decisions were largely based on data from 15 November 2015 when total exposure in CONCERTO was 3070 patient-years in 2199 individuals, and total exposure in ARPEGGIO was 35 patient-years in 191 individuals.</p> <p>Due to these events, the DMC recommended stopping the high-dose treatment arms (1.2 mg/day and 1.5 mg/day) in the laquinimod MS trials. The DMC did not identify any overt cardiovascular risk in the 0.6 mg treatment arm, but felt that long-term monitoring for emergence of any signal was necessary. The DMC also recommended that study subjects continuing on laquinimod 0.6 mg be reconsented with information about the cardiovascular risk seen at higher doses.</p> <p>On 07 January 2016, the LEGATO-HD Data Safety Monitoring Board (DSMB) was called by Teva to review and discuss the recommendations of the DMC for the CONCERTO and ARPEGGIO MS trials and their implications on LEGATO-HD. The DSMB confirmed that no cardiovascular events had been observed to date for any dose of the LEGATO-HD trial and concurred with the Sponsor’s recommendation that the high-dose (ie, 1.5 mg) arm in this trial be discontinued as a proactive safety measure. The DSMB approved the continuation of the 0.5 mg/day and 1.0 mg/day arms with enhanced monitoring and safety precautions.</p> <p>Teva notified LEGATO-HD investigators on 10 January 2016 to immediately contact patients randomized to the high dose of 1.5 mg laquinimod and instruct them to discontinue study medication as a proactive measure to protect the safety of patients (endorsed by DSMB as noted above).</p> <p>Currently the mechanism of the cardiovascular events remains unknown. Although no specific time-to-event patterns have been identified in the MS studies, cardiovascular risk factors and demographics may play a role. Different pre-existing risk factors were noted, including</p>	

Original text with changes shown	New wording	Reason/Justification for change
	hypertension, high cholesterol, and/or smoking history. While all patients exhibited signs of myocardial tissue injury, the cardiac work-up in these cases revealed heterogeneous etiologies. Of note, the patients all had some established cardiovascular risk factors, including patients with probable myocarditis or with probable familial hypercholesterolemia. Further investigations into potential predictors and the potential causality are ongoing.	
<b>Section 1.4.1.3.1</b>		
Studies in rats have shown reproductive toxicity including teratogenicity (urogenital malformations) at doses similar to the clinical dose of 0.5 mg/day in humans. Delay in puberty and reduced fertility were noted in rat offspring exposed to laquinimod in utero at doses slightly higher than the <i>originally intended</i> clinical dose of 1.5 mg/day in humans (see Section 1.3.1). The relevance to humans of these findings is not known, but cannot be excluded.	Studies in rats have shown reproductive toxicity including teratogenicity (urogenital malformations) at doses similar to the clinical dose of 0.5 mg/day in humans. Delay in puberty and reduced fertility were noted in rat offspring exposed to laquinimod in utero at doses slightly higher than the originally intended clinical dose of 1.5 mg/day in humans (see Section 1.3.1). The relevance to humans of these findings is not known, but cannot be excluded.	Reflecting that 1.5 mg is no longer an intended clinical dose.
<b>1.4.1.3.2 Cancer</b> An increase in the incidence of uterine and oral cancers was observed in rats (see Section 1.3.1). It is the sponsor’s position that these findings are likely related to <del>the administration procedure or to</del> species-specific mechanisms. While a connection to humans cannot be entirely excluded, these mechanisms are likely not relevant to humans. Currently available clinical data does not suggest that laquinimod at a dose of 0.6 mg/day is associated with an increased risk of cancer.	<b>1.4.1.3.2 Cancer</b> An increase in the incidence of uterine and oral cancers was observed in rats (see 1.3.1). It is the sponsor’s position that these findings are likely related to species-specific mechanisms. While a connection to humans cannot be entirely excluded, these mechanisms are likely not relevant to humans. Currently available clinical data does not suggest that laquinimod at a dose of 0.6 mg/day is associated with an increased risk of cancer.	Administration procedure no longer considered a factor.
<b>Section 1.4.1.3.3</b>		
<b>14.1.3.3 Cardiotoxicity and Systemic Inflammation</b> In clinical studies performed with laquinimod’s predecessor, roquinimex, pericarditis/pleuritis and ischemic heart disorders were identified as important safety concerns. <del>Roquinimex demonstrated clinical efficacy in MS in Phase II studies. However, serious toxicities (including myocardial infarction, pericarditis and pleuritis) occurring</del> <i>that occurred</i> during Phase <del>III-3</del> trials led to <del>early termination</del> <i>discontinuation</i> of these trials. <i>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.</i> The mechanism by which roquinimex caused these events was not identified, but they were	<b>1.4.1.3.3 Cardiotoxicity and Systemic Inflammation</b> In clinical studies performed with laquinimod’s predecessor, 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	Updated following recent findings in the multiple sclerosis studies.

Original text with changes shown	New wording	Reason/Justification for change
<p>considered to be possible manifestations of a systemic inflammatory response, an assessment which was also supported by roquinimex nonclinical findings. A thorough analysis was done on the laquinimod safety data (which is mostly reflective of the 0.6 mg/day dose) to evaluate these <i>similar potential</i> safety issues. <b>Based on 2347 patients exposed to laquinimod 0.6 mg for over 10,000 MS patient-years, as well as the patients exposed to 0.6 mg in the CONCERTO and ARPEGGIO studies, This analysis analyses</b> showed that these safety issues do not constitute a signal of concern for laquinimod <i>in doses up to 0.6 mg/day. However, at doses of 1.2 and 1.5 mg, laquinimod manifested a potential clinical signal of myocardial infarction in the MS trials.</i></p>	<p>manifestations of a systemic inflammatory response, an assessment which was also supported by roquinimex nonclinical findings. A thorough analysis was done on the laquinimod safety data (which is mostly reflective of the 0.6 mg/day dose) to evaluate similar potential safety issues. Based on 2347 patients exposed to laquinimod 0.6 mg for over 10,000 MS 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 signal for laquinimod in doses up to 0.6 mg/day. However, at doses of 1.2 and 1.5 mg, laquinimod manifested a potential clinical signal of myocardial infarction in the MS trials.</p>	
<p><b>Section 1.4.1.6</b></p>		
<p><b><i>An imbalance in serious cardiovascular events in the high-dose treatment arms (1.2 mg/day and 1.5 mg/day) in the Teva-sponsored CONCERTO and ARPEGGIO studies in MS was identified (6 cases of myocardial infarction in the CONCERTO 1.2 mg treatment arm, compared with no events in the 0.6 mg or placebo treatment arms, along with a cerebral infarction in a 31-year-old man on the 1.2 mg treatment arm. In the ARPEGGIO study, 1 myocardial infarction event was identified in the laquinimod 1.5 mg treatment arm. Due to these events, the DMC recommended stopping higher-dose laquinimod treatment arms (1.2 and 1.5 mg) in the laquinimod MS trials (see Section 1.4.1.2.7). No cardiovascular events have been observed to date for any dose in the LEGATO-HD trial.</i></b></p> <p><b><i>On 07 January 2016, the LEGATO-HD DSMB met and approved the Sponsor's proposal to discontinue the 1.5 mg arm of the study as a proactive safety measure, and approved the continuation of the 0.5 mg/day and 1.0 mg/day arms with enhanced monitoring and safety precautions. Teva notified LEGATO-HD investigators on 10 January 2016 to immediately contact patients randomized to the high dose of 1.5 mg laquinimod and instruct them to discontinue study medication as a proactive measure to protect the safety of patients currently participating in the LEGATO-HD study. This action was endorsed by DSMB as noted above. Patients in the 1.5 mg/day (high dose) treatment arm, whose treatment with laquinimod was discontinued, were asked to continue all scheduled visits for safety assessment after study drug discontinuation. Appropriate risk mitigation procedures have been implemented via this</i></b></p>	<p>An imbalance in serious cardiovascular events in the high-dose treatment arms (1.2mg/day and 1.5mg/day) in the Teva-sponsored CONCERTO and ARPEGGIO studies in MS was identified (6 cases of myocardial infarction in the CONCERTO 1.2 mg treatment arm, compared with no events in the 0.6 mg or placebo treatment arms, along with a cerebral infarction in a 31-year-old man on the 1.2 mg treatment arm. In the ARPEGGIO study, 1 myocardial infarction event was identified in the laquinimod 1.5 mg treatment arm. Due to these events, the DMC recommended stopping higher-dose laquinimod treatment arms (1.2 and 1.5 mg) in the laquinimod MS trials (see Section 1.4.1.2.7). No cardiovascular events have been observed to date for any dose in the LEGATO-HD trial.</p> <p>On 07 January 2016, the LEGATO-HD DSMB met and approved the Sponsor's proposal to discontinue the 1.5 mg arm of the study as a proactive safety measure, and approved the continuation of the 0.5 mg/day and 1.0 mg/day arms with enhanced monitoring and safety precautions.</p> <p>Teva notified LEGATO-HD investigators on 10 January 2016 to immediately contact patients randomized to the high dose of 1.5 mg laquinimod and instruct them to discontinue study medication as a proactive measure to protect the safety of patients currently participating in the LEGATO-HD study. This action was endorsed by DSMB as noted above. Patients</p>	<p>Updated overall risk/benefit assessment following recent findings in the multiple sclerosis studies.</p>



Original text with changes shown	New wording	Reason/Justification for change
<p><i>protocol amendment to restrict excess drug exposure due to impairment of liver or kidney function, as well as to assure evaluation and management of cardiovascular risk factors.</i>  <b>LEGATO-HD is the first "proof of concept" study in the HD patient population, which represents a disease with a fatal outcome and a severe unmet medical need (no current available medications). Based on data accumulated to date, the LEGATO-HD study aims for disease modification beyond symptomatic treatment.</b>  <b>Thus, the LEGATO study in the HD patient population represents different benefit/risk considerations.</b>                      Based on the above described risks and means for their mitigation, it is judged that potential benefit from administration of laquinimod to patients with HD outweighs the risks <b>based on currently available information</b>, supporting investigation of its role in <del>this</del> the <b>Huntington's disease</b> patient population.                      For an overall risk benefit assessment of laquinimod treatment in human patients, additional information may be found in the current Investigator's Brochure.</p>	<p>in the 1.5 mg/day (high dose) treatment arm, whose treatment with laquinimod was discontinued, were asked to continue all scheduled visits for safety assessment after study drug discontinuation.                      Appropriate risk mitigation procedures have been implemented via this protocol amendment to restrict excess drug exposure due to impairment of liver or kidney function, as well as to assure evaluation and management of cardiovascular risk factors.                      LEGATO-HD is the first "proof of concept" study in the HD patient population, which represents a disease with a fatal outcome and a severe unmet medical need (no current available medications). Based on data accumulated to date, the LEGATO-HD study aims for disease modification beyond symptomatic treatment.                      Thus, the LEGATO study in the HD patient population represents different benefit/risk considerations.                      Based on the above described risks and means for their mitigation, it is judged that potential benefit from administration of laquinimod to patients with HD outweighs the risks based on currently available information, supporting investigation of its role in the Huntington's disease patient population.                      For an overall risk benefit assessment of laquinimod treatment in human patients, additional information may be found in the current Investigator's Brochure.</p>	
<b>Section 1.5</b>		
<p>The safety and efficacy of laquinimod given 0.5, 1.0, 1.5, or 2.0 mg/day have been investigated in 180 patients with CD for 8 weeks (study CD-LAQ-201). Significant effect on the primary endpoint (Crohn's Disease Activity Index) was seen after treatment with laquinimod 0.5 mg/day; laquinimod 1 mg had a lower magnitude effect that was also less robust than the effect of laquinimod 0.5 mg. Laquinimod 1.5 mg and 2.0 mg did not have an overall clinical effect compared to the pooled placebo. However, when evaluating reduction in calprotectin levels, an objective marker of disease activity, similar efficacy was observed across the laquinimod doses. Laquinimod showed an overall favorable safety and tolerability profile in this study. <b>Laquinimod is no longer being developed as a treatment for</b></p>	<p>The safety and efficacy of laquinimod given 0.5, 1.0, 1.5, or 2.0 mg/day have been investigated in 180 patients with CD for 8 weeks (study CD-LAQ-201). Significant effect on the primary endpoint (Crohn's Disease Activity Index) was seen after treatment with laquinimod 0.5 mg/day; laquinimod 1 mg had a lower magnitude effect that was also less robust than the effect of laquinimod 0.5 mg. Laquinimod 1.5 mg and 2.0 mg did not have an overall clinical effect compared to the pooled placebo. However, when evaluating reduction in calprotectin levels, an objective marker of disease activity, similar efficacy was observed across the laquinimod doses.</p>	<p>These indications are no longer pursued.</p>

Original text with changes shown	New wording	Reason/Justification for change
<i>CD.</i>	Laquinimod showed an overall favorable safety and tolerability profile in this study. Laquinimod is no longer being developed as a treatment for CD.	
The safety and efficacy of laquinimod given 0.5 or 1.0 mg/day have also been investigated in two studies in SLE patients [with lupus nephritis (LN-LAQ-201) and with lupus arthritis (LA-LAQ-202)] for 24 and 12 weeks, respectively. In LN-LAQ-201, 46 patients were enrolled: 15 received placebo, 16 received laquinimod 0.5 mg and 15 received laquinimod 1 mg. In LA-LAQ-202, 82 patients were enrolled: 26 were randomized to receive placebo, and 28 patients were randomized to each of the laquinimod arms (0.5 mg, and 1 mg). Overall laquinimod was safe and well tolerated in these studies. No clinically meaningful effect of laquinimod treatment could be seen in patients with LA. Beneficial effect of laquinimod was seen in patients with LN with both doses investigated, with the 0.5 mg dose showing a greater improvement in several efficacy variables. <i>Laquinimod is no longer being developed as a treatment for SLE.</i>	The safety and efficacy of laquinimod given 0.5 or 1.0 mg/day have also been investigated in two studies in SLE patients [with lupus nephritis (LN-LAQ-201) and with lupus arthritis (LA-LAQ-202)] for 24 and 12 weeks, respectively. In LN-LAQ-201, 46 patients were enrolled: 15 received placebo, 16 received laquinimod 0.5 mg and 15 received laquinimod 1 mg. In LA-LAQ-202, 82 patients were enrolled: 26 were randomized to receive placebo, and 28 patients were randomized to each of the laquinimod arms (0.5 mg, and 1 mg). Overall laquinimod was safe and well tolerated in these studies. No clinically meaningful effect of laquinimod treatment could be seen in patients with LA. Beneficial effect of laquinimod was seen in patients with LN with both doses investigated, with the 0.5 mg dose showing a greater improvement in several efficacy variables. Laquinimod is no longer being developed as a treatment for SLE.	These indications are no longer pursued.
<i>Note: 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). In CONCERTO there were 6 such cases in the 1.2 mg arm but none in the 0.6 mg or placebo arms, along with a myocardial infarction in the ARPEGGIO 1.5 mg dose group and a cerebral infarction in a 31-year-old patient in the 1.2 mg arm of CONCERTO. Due to these events and the DMC recommendation to stop all high-dose laquinimod treatment arms (1.2 mg/day and 1.5 mg/day) in the MS trials; accordingly, the high-dose arms were discontinued in both trials as of 01 January 2016. On 07 January 2016, the LEGATO-HD DSMB was called urgently by Teva to review and discuss new information regarding the occurrence of an imbalance in cardiovascular events from the high-dose laquinimod arms in the multiple sclerosis trials CONCERTO and ARPEGGIO (1.2 mg in CONCERTO, 1.5 mg in ARPEGGIO). The most recent study data for LEGATO-HD were also reviewed in open</i>	Note: 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). In CONCERTO there were 6 such cases in the 1.2 mg arm but none in the 0.6 mg or placebo arms, along with a myocardial infarction in the ARPEGGIO 1.5 mg dose group and a cerebral infarction in a 31-year-old patient in the 1.2 mg arm of CONCERTO. Due to these events and the DMC recommendation to stop all high-dose laquinimod treatment arms (1.2mg/day and 1.5mg/day) in the MS trials; accordingly, the high-dose arms were discontinued in both trials as of 01 January 2016 On 07 January 2016 the LEGATO-HD DSMB was called urgently by Teva to review and discuss new information regarding the occurrence of an imbalance in cardiovascular events from the high-dose laquinimod arms in the multiple	New text added following recent findings in the multiple sclerosis studies.

Original text with changes shown	New wording	Reason/Justification for change
<p><i>and closed sessions. No cardiovascular signal was detected from the LEGATO-HD study as of 10 January 2016. The DSMB agreed with the plan to discontinue the 1.5 mg arm of LEGATO-HD as a proactive safety measure and approved the continuation of the 0.5 mg/day and 1.0 mg/day arms with enhanced monitoring and safety precautions. Therefore, these treatment arms will be continued with updated informed consent and an amended protocol while the sponsor closely monitors cardiovascular events in all laquinimod studies for emergence of any potential cardiovascular signal.</i></p> <p>A more detailed description of study drug administration is presented in Section 5.1.</p>	<p>sclerosis trials CONCERTO and ARPEGGIO (1.2 mg in CONCERTO, 1.5 mg in ARPEGGIO). The most recent study data for LEGATO-HD were also reviewed in open and closed sessions. No cardiovascular signal was detected from the LEGATO-HD study as of 10 January 2016. The DSMB agreed with the plan to discontinue the 1.5 mg arm of LEGATO-HD as a proactive safety measure and approved the continuation of the 0.5 mg/day and 1.0 mg/day arms with enhanced monitoring and safety precautions. Therefore, these treatment arms will be continued with updated informed consent and an amended protocol while the sponsor closely monitors cardiovascular events in all laquinimod studies for emergence of any potential cardiovascular signal. A more detailed description of study drug administration is presented in Section 5.1.</p>	
<p><b>2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES</b></p>		
<p><b>Section 2.1</b></p>		
<p>The purpose of this Phase II clinical study is to investigate the efficacy and safety of multiple doses of laquinimod (0.5, 1.0 and 1.5 mg/day) as a potential treatment for patients with Huntington's disease (HD). As no drug is currently available to treat HD disease progression, the study will be placebo controlled. <i>Prior to 10 January 2016, a total of 400 patients were planned to be equally randomized in a 1:1:1:1 ratio (100 patients within each treatment arm) to receive laquinimod 0.5, 1.0, 1.5 mg/day, or matching placebo for 52 weeks.</i> <i>As of 10 January 2016, following the decision to discontinue treatment of the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day, 1.0 mg/day, or matching placebo for 52 weeks. Approximately 300 patients (100 patients within each study arm), plus the 30 patients who were already randomized to the laquinimod 1.5 mg treatment arm, are planned to be enrolled in the study.</i> ...</p>	<p>The purpose of this Phase II clinical study is to investigate the efficacy and safety of multiple doses of laquinimod (0.5, 1.0 and 1.5 mg/day) as a potential treatment for patients with Huntington's disease (HD). As no drug is currently available to treat HD disease progression, the study will be placebo controlled. Prior to 10 January 2016, a total of 400 patients were planned to be equally randomized in a 1:1:1:1 ratio (100 patients within each treatment arm) to receive laquinimod 0.5, 1.0, 1.5 mg/day, or matching placebo for 52 weeks. As of 10 January 2016, following the decision to discontinue treatment of the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day, 1.0 mg/day, or matching placebo for 52 weeks. Approximately 300 patients (100 patients within each study arm), plus the 30 patients who were already randomized to the laquinimod 1.5 mg treatment arm, are planned to be enrolled in the study. ...</p>	<p>Clarification of the study randomization following the discontinuation of the laquinimod 1.5 mg/day treatment arm.</p>
<p><b>Section 2.2.1 (Other section affected by this change: 9.3)</b></p>		

Original text with changes shown	New wording	Reason/Justification for change
<p>The primary objective of this study is to assess the efficacy of laquinimod 0.5, <del>and 1.0, and 1.5 mg qd on</del> in patients with HD after 12 months of treatment using the Unified Huntington’s Disease Rating Scale (UHDRS) Total Motor Score (TMS).</p> <p><i>Due to the decision from 10 January 2016 to discontinue treatment of the laquinimod 1.5 mg dose arm, and the low number of enrolled patients compared to the target at this time, data from the laquinimod 1.5 mg treatment arm will be presented descriptively only, and will not be included in any inferential analyses for efficacy or safety.</i></p>	<p>The primary objective of this study is to assess the efficacy of laquinimod 0.5, and 1.0 mg qd in patients with HD after 12 months of treatment using the Unified Huntington’s Disease Rating Scale (UHDRS) Total Motor Score (TMS).</p> <p>Due to the decision from 10 January 2016 to discontinue treatment of the laquinimod 1.5 mg dose arm, and the low number of enrolled patients compared to the target at this time, data from the laquinimod 1.5 mg treatment arm will be presented descriptively only, and will not be included in any inferential analyses for efficacy or safety.</p>	<p>Clarification following the discontinuation of the laquinimod 1.5 mg/day treatment arm.</p>
<p><b>Section 2.2.3</b></p>		
<p>...</p> <ul style="list-style-type: none"> <li>To evaluate the pharmacokinetics of laquinimod <i>and its metabolites</i> in patients with HD</li> <li>To investigate the relationship between exposure to laquinimod <i>and its metabolites</i> and outcome measures (e.g., clinical effect and toxicity parameters).</li> </ul>	<p>...</p> <ul style="list-style-type: none"> <li>To evaluate the pharmacokinetics of laquinimod and its metabolites in patients with HD</li> <li>To investigate the relationship between exposure to laquinimod and its metabolites and outcome measures (e.g., clinical effect and toxicity parameters).</li> </ul>	<p>Assessment of laquinimod metabolites was added to the overall exploratory PK assessment for better characterization of laquinimod disposition.</p>
<p><b>3 STUDY DESIGN</b></p>		
<p><b>Section 3.1</b></p>		
<p>This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of laquinimod treatment at dosages of 0.5, 1.0, and 1.5 mg/day in adults with Huntington’s Disease.</p> <p>The study will consist of a screening period (2 weeks up to 5 weeks), followed by a 52-week double-blind treatment period and a follow-up visit (one month after end of treatment). <i>Prior to 10 January 2016, A a</i> total of 400 patients <del>are</del> <i>were</i> planned to be equally randomized in a 1:1:1:1 ratio (100 patients within each treatment arm) to receive laquinimod 0.5, 1.0, 1.5 mg/day, or matching placebo for 52 weeks. <i>A total of 123 patients were randomized prior to 10 January 2016.</i></p> <p><i>As of 10 January 2016, following the decision to discontinue treatment of the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day, 1.0 mg/day, or matching placebo for 52 weeks. Approximately 300</i></p>	<p>This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of laquinimod treatment at dosages of 0.5, 1.0, and 1.5 mg/day in adults with Huntington’s Disease.</p> <p>The study will consist of a screening period (2 weeks up to 5 weeks), followed by a 52-week double-blind treatment period and a follow-up visit (one month after end of treatment). Prior to 10 January 2016, a total of 400 patients were planned to be equally randomized in a 1:1:1:1 ratio (100 patients within each treatment arm) to receive laquinimod 0.5, 1.0, 1.5 mg/day, or matching placebo for 52 weeks. A total of 123 patients were randomized prior to 10 January 2016.</p> <p>As of 10 January 2016, following the decision to discontinue treatment of the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a</p>	<p>Clarification of the study randomization following the discontinuation of the laquinimod 1.5 mg/day treatment arm.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><i>patients (100 patients within each study arm), plus the 30 patients who were already randomized to the laquinimod 1.5 mg treatment arm, are planned to be enrolled in the study.</i></p> <p>...</p>	<p>1:1:1 ratio to receive laquinimod 0.5 mg/day, 1.0 mg/day, or matching placebo for 52 weeks. Approximately 300 patients (100 patients within each study arm), plus the 30 patients who were already randomized to the laquinimod 1.5 mg treatment arm, are planned to be enrolled in the study.</p> <p>...</p>	
<p>The study schema is presented in Figure 1 (<i>prior to 10 January 2016</i>), and in Figure 2 (<i>from 10 January 2016</i>).</p>	<p>The study schema is presented in Figure 1 (prior to 10 January 2016), and in Figure 2 (from 10 January 2016).</p>	<p>Clarification regarding the study schemas.</p>
<p><i>(Newly added Figure 2)</i></p>	<p>(Newly added Figure 2)</p>	<p>Reflects the removal of the 1.5 mg/day treatment group.</p>
<p><b>Section 3.2.6.1. (Other sections affected by this change: 8.1.1; 9.9.1)</b></p>		
<p><del>Blood samples for PK evaluation of laquinimod and its metabolites will be collected at selected sites at Month 1 from a total of 60 patients (15 patients per treatment group).</del> <i>PK samples of laquinimod and its metabolites will be collected from approximately 15 patients per each of the three continuing treatment groups (at selected sites at Month 1), for a total of approximately 45 patients. Additionally, PK samples were collected from 2 patients in the laquinimod 1.5 mg/day treatment group when the treatment was stopped; no further PK samples will be collected from the laquinimod 1.5 mg/day treatment group.</i></p> <p>...</p> <p>Steady state pharmacokinetic parameters <i>for laquinimod</i> (AUC<sub>tau</sub>, C<sub>max</sub> and C<sub>min</sub>, t<sub>max</sub>), will be calculated for each patient. <i>Additional parameters for laquinimod and pharmacokinetic parameters for its metabolites may be calculated if data permit.</i></p> <p>For patients participating in this ancillary study, the morning dose and the 24 hours dose administration (the day after) will take place at the clinic.</p> <p>...</p>	<p>PK samples of laquinimod and its metabolites will be collected from approximately 15 patients per each of the three continuing treatment groups (at selected sites at Month 1), for a total of approximately 45 patients. Additionally, PK samples were collected from 2 patients in the laquinimod 1.5 mg/day treatment group when the treatment was stopped; no further PK samples will be collected from the laquinimod 1.5 mg/day treatment group.</p> <p>...</p> <p>Steady state pharmacokinetic parameters for laquinimod (AUC<sub>tau</sub>, C<sub>max</sub> and C<sub>min</sub>, t<sub>max</sub>), will be calculated for each patient. Additional parameters for laquinimod and pharmacokinetic parameters for its metabolites may be calculated if data permit.</p> <p>...</p>	<p>Revision following discontinuation of 1.5 mg treatment arm. Assessment of laquinimod metabolites was added to the overall exploratory PK assessment for better characterization of laquinimod disposition.</p>
<p><b>Section 3.2.6.2 (Other sections affected by this change: 8.1; 9.9.2)</b></p>		
<p>A single blood sample will be collected from all patients at Months 1, 3, 6 and 12 <i>for evaluation of laquinimod and its metabolites.</i> <i>Pharmacokinetic parameters for laquinimod metabolites may be calculated if data permit.</i></p> <p>...</p> <p>The date and time of the blood sample, as well as the date and time of the last study drug dose prior to the sample will be recorded on the eCRF.</p>	<p>A single blood sample will be collected from all patients at Months 1, 3, 6 and 12 for evaluation of laquinimod and its metabolites.</p> <p>...</p> <p>Pharmacokinetic parameters for laquinimod metabolites may be calculated if data permit.</p> <p>The date and time of the blood sample, as well as the date and</p>	<p>PPK analysis can include the newly added unscheduled PK samples.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><i>The PPK model may also include any unscheduled pharmacokinetic samples collected to assist with further investigations of cardiovascular events or other clinical event of interest (see Section 8.1).</i></p>	<p>time of the last study drug dose prior to the sample will be recorded on the eCRF. The PPK model may also include any unscheduled pharmacokinetic samples collected to assist with further investigations of cardiovascular events or other clinical event of interest (see Section 8.1).</p>	
<p><b>Section 3.3</b></p>		
<p>This is a randomized, double-blind, placebo-controlled study. <i>Prior to 10 January 2016, eligible patients will be were</i> randomly assigned to receive treatment with laquinimod at a dosage of 0.5, 1.0, or 1.5 mg qd or a matching placebo in a 1:1:1 ratio. <i>As of 10 January 2016, following the decision to discontinue treatment of the laquinimod 1.5 mg dose arm, future eligible patients will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day or 1.0 mg/day or matching placebo for 52 weeks.</i> <i>No change was performed to the original randomization list except that the patient numbers assigned to laquinimod 1.5 mg/day were removed from the list by the interactive response technology (IRT) vendor.</i> <i>All patients that discontinued the 1.5 mg/day dose have been unblinded.</i> <i>No attempts will be made to re-randomize patients whose 1.5 mg treatment was stopped to a lower dose of laquinimod. The remaining ongoing patients retained their originally randomized treatment assignments.</i> Patients and investigators will remain blinded to treatment assignment during the study. ...</p>	<p>This is a randomized, double-blind, placebo-controlled study. Prior to 10 January 2016, eligible patients were randomly assigned to receive treatment with laquinimod at a dosage of 0.5, 1.0, or 1.5 mg qd or a matching placebo in a 1:1:1 ratio. As of 10 January 2016, following the decision to discontinue treatment of the laquinimod 1.5 mg dose arm, future eligible patients will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day or 1.0 mg/day or matching placebo for 52 weeks. No change was performed to the original randomization list except that the patient numbers assigned to laquinimod 1.5 mg/day were removed from the list by the interactive response technology (IRT) vendor. All patients that discontinued the 1.5 mg/day dose have been unblinded. No attempts will be made to re-randomize patients whose 1.5 mg treatment was stopped to a lower dose of laquinimod. The remaining ongoing patients retained their originally randomized treatment assignments. Patients and investigators will remain blinded to treatment assignment during the study. ...</p>	<p>1.5 mg/day treatment arm has been discontinued and patients in that arm unblinded.</p>
<p><b>Section 3.4</b></p>		
<p>Patients will be randomized to receive laquinimod 0.5, 1.0, or 1.5 mg qd or matching placebo (<i>prior to 10 January 2016</i>), or randomly assigned to receive treatment with laquinimod at a dosage of 0.5 mg/day, 1.0 mg/day or placebo in a 1:1:1 ratio (<i>from 10 January 2016</i>). Every patient will take 3 capsules once daily, at the same time of the day, during the entire study period. Study drug will be administered as described in Section 3.4.1 and Section 3.4.2. below. The capsules will be taken orally and must be swallowed whole with a glass of water. The capsule should not be opened. Laquinimod can be taken with or without food.</p>	<p>Patients will be randomized to receive laquinimod 0.5, 1.0, or 1.5 mg qd or matching placebo (<i>prior to 10 January 2016</i>), or randomly assigned to receive treatment with laquinimod at a dosage of 0.5 mg/day, 1.0 mg/day or placebo in a 1:1:1 ratio (<i>from 10 January 2016</i>). Every patient will take 3 capsules once daily, at the same time of the day, during the entire study period. Study drug will be administered as described in Section 3.4.1 and Section 3.4.2. below. The capsules will be taken orally and must be swallowed whole with a glass of</p>	<p>1.5 mg/day treatment arm has been discontinued.</p>

Original text with changes shown	New wording	Reason/Justification for change
	water. The capsule should not be opened. Laquinimod can be taken with or without food.	
<b>Section 3.4.1</b>		
<p>Laquinimod will be provided as off-white, opaque, hard gelatin capsules. The capsules should be swallowed whole with water.</p> <ul style="list-style-type: none"> <li>Patients randomized to the laquinimod 1.5 mg qd treatment arm <del>will</del> received 3 capsules of 0.5 mg laquinimod (<i>Note: The treatment of this high dose arm was discontinued as of 10 January 2016</i>).</li> </ul> <p>...</p>	<p>Laquinimod will be provided as off-white, opaque, hard gelatin capsules. The capsules should be swallowed whole with water.</p> <ul style="list-style-type: none"> <li>Patients randomized to the laquinimod 1.5 mg qd treatment arm received 3 capsules of 0.5 mg laquinimod (<i>Note: The treatment of this high dose arm was discontinued as of 10 January 2016</i>).</li> </ul> <p>...</p>	<p>Updated following the discontinuation of the 1.5 mg/day treatment arm.</p>
<b>Section 3.6 (Other sections affected by change: 4.3; APPENDIX A)</b>		
<p>Safety stopping rules are detailed in Appendix A (Guidance on Safety Monitoring). These include:</p> <ul style="list-style-type: none"> <li>Elevated liver enzymes (as detailed in Appendix A)</li> <li>Pregnancy</li> <li>Need for concomitant treatment with moderate and strong CYP3A4 inhibitors</li> <li>Patients that are diagnosed with <del>invasive cancer</del> <i>a malignant solid or liquid tumor</i> while participating in the study</li> <li><i>Acute coronary syndrome, myocardial infarction or any major cardiovascular event</i></li> </ul>	<p>Safety stopping rules are detailed in Appendix A (Guidance on Safety Monitoring). These include:</p> <ul style="list-style-type: none"> <li>Elevated liver enzymes (as detailed in Appendix A)</li> <li>Pregnancy</li> <li>Need for concomitant treatment with moderate and strong CYP3A4 inhibitors</li> <li>Patients that are diagnosed with a malignant solid or liquid tumor while participating in the study</li> <li>Acute coronary syndrome, myocardial infarction or any major cardiovascular event</li> </ul>	<p>Correction of terminology.</p> <p>Newly added cardiovascular stopping rule.</p>
<b>Section 3.6 (Other sections affected by change: APPENDIX A)</b>		
<p>...</p> <p><b>Liver Impairment</b> <i>To avoid exposures to higher levels of laquinimod (see Section 1.3.2.1), a stopping rule related to liver impairment has been introduced. Patients who develop any chronic liver disease associated with hepatic function impairment while participating in the study should stop study medication.</i></p> <p><b>Renal Impairment</b> <i>To avoid exposures to higher levels of laquinimod (see Section 1.3.2.1), a stopping rule related to renal impairment has been introduced. Patients who develop chronic renal disease associated with moderate or severe functional impairment, defined as estimated creatinine clearance (CrCl) &lt;60 mL/min/1.73 m<sup>2</sup>, while participating in the study should stop study</i></p>	<p>...</p> <p>Liver Impairment To avoid exposures to higher levels of laquinimod (see Section 1.3.2.1), a stopping rule related to liver impairment has been introduced. Patients who develop any chronic liver disease associated with hepatic function impairment while participating in the study should stop study medication.</p> <p>Renal Impairment To avoid exposures to higher levels of laquinimod (see Section 1.3.2.1), a stopping rule related to renal impairment has been introduced. Patients who develop chronic renal disease associated with moderate or severe functional</p>	<p>New stopping rules implemented to avoid increased exposure to laquinimod in cases of organ impairment.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><i>medication temporarily and the assessment of estimated CrCl should be repeated. If the development of renal impairment is confirmed (estimated CrCl &lt;60 mL/min/1.73 m<sup>2</sup>), the patient should stop study medication permanently.</i></p>	<p>impairment, defined as estimated creatinine clearance (CrCl) &lt;60 mL/min/1.73 m<sup>2</sup>, while participating in the study should stop study medication temporarily and the assessment of estimated CrCl should be repeated. If the development of renal impairment is confirmed (estimated CrCl &lt;60 mL/min/1.73 m<sup>2</sup>), the patient should stop study medication permanently.</p>	
<p><b>Section 3.6.2 (Other sections affected by change: 3.11.3.1.5)</b></p>		
<p><b>3.6.2 Early Termination (ET)</b>  <i>An ET visit should be completed for all patients who prematurely terminate treatment or who become pregnant (see Section 3.11.4 for details of procedures).                      Early termination refers to the study drug termination and not termination of the patient from the study. Patients will be asked to continue all scheduled visits and safety assessments after study drug discontinuation (with the exception of drug dispensing and accountability, pregnancy testing, and pharmacokinetic sampling).                      Patients in the 1.5 mg/day (high dose) treatment arm, whose treatment with laquinimod was discontinued, were invited to attend an early termination visit (to return study medication and perform drug accountability). At this visit, only safety assessments were to be completed. These included vital signs; clinical laboratory tests; pregnancy test; adverse event inquiry; drug accountability; review of concomitant medication, and C-SSRS (see also Section 3.11.3.1.5) . Subjects were asked to continue scheduled follow up safety visits per the current schedule.                      Women of child bearing potential should continue using 2 acceptable contraception methods up to 30 days after the last dose of study medication has been administered.                      Moderate/strong CYP3A4 inhibitors are disallowed during the 30 days after the last laquinimod dose has been administered (see Appendix B).                      Plasma levels of drugs that are CYP1A2 substrates may decrease when combined with laquinimod and within 30 days after the last laquinimod dose, rendering these drugs less effective (see Appendix C).</i></p>	<p><b>3.6.2 Early Termination (ET)</b>                      An ET visit should be completed for all patients who prematurely terminate treatment or who become pregnant (see Section 3.11.4 for details of procedures).                      Early termination refers to the study drug termination and not termination of the patient from the study. Patients will be asked to continue all scheduled visits and safety assessments after study drug discontinuation (with the exception of drug dispensing and accountability, pregnancy testing, and pharmacokinetic sampling).                      Patients in the 1.5 mg/day (high dose) treatment arm, whose treatment with laquinimod was discontinued, were invited to attend an early termination visit (to return study medication and perform drug accountability). At this visit, only safety assessments were to be completed. These included vital signs; clinical laboratory tests; pregnancy test; adverse event inquiry; drug accountability; review of concomitant medication, and C-SSRS (see also Section 3.11.3.1.5) .                      Subjects were asked to continue scheduled follow up safety visits per the current schedule.                      Women of child bearing potential should continue using 2 acceptable contraception methods up to 30 days after the last dose of study medication has been administered.                      Moderate/strong CYP3A4 inhibitors are disallowed during the 30 days after the last laquinimod dose has been administered (see Appendix B).                      Plasma levels of drugs that are CYP1A2 substrates may decrease when combined with laquinimod and within 30 days after the last laquinimod dose, rendering these drugs less effective (see Appendix C).</p>	<p>New section added for clarification regarding the early termination visit.</p>



Original text with changes shown	New wording	Reason/Justification for change
<b>Section 3.8</b>		
<p>...</p> <p><i>As of 10 January 2016, treatment with laquinimod was discontinued for all patients in the 1.5 mg dose group; all these discontinued patients have been unblinded. No attempts will be made to re-randomize patients whose 1.5 mg treatment was stopped to a lower dose of laquinimod.</i></p> <p><i>However, the blinding was maintained for the patients in the remaining ongoing 3 treatment arms (0.5 mg/day, 1.0 mg/day, and placebo).</i></p>	<p>...</p> <p>As of 10 January 2016, treatment with laquinimod was discontinued for all patients in the 1.5 mg dose group; all these discontinued patients have been unblinded. No attempts will be made to re-randomize patients whose 1.5 mg treatment was stopped to a lower dose of laquinimod.</p> <p>However, the blinding was maintained for the patients in the remaining ongoing 3 treatment arms (0.5 mg/day, 1.0 mg/day, and placebo).</p>	<p>Clarification regarding maintenance of the blinding for the remaining treatment arms.</p>
<b>Section 3.10</b>		
<p>The study <del>is expected to start</del> <i>started</i> in <del>Q3 2014</del> <i>Q4 2014</i> (first patient randomized) and is expected to be completed in <del>Q4 2016</del> <i>Q1 2018</i> (last patient last visit).</p> <p><i>As of 10 January 2016, treatment with laquinimod was discontinued for all patients in the 1.5 mg/day dose arm.</i></p> <p>Approximately <del>400</del> <i>300</i> patients (<i>100 patients within each study arm</i>), plus the <i>30 patients that were already randomized to the laquinimod 1.5 mg dose arm</i> from ~51 investigational centers in North America, Europe and Russia are planned to be enrolled in the study.</p>	<p>The study started in Q4 2014 (first patient randomized) and is expected to be completed in Q1 2018 (last patient last visit).</p> <p>As of 10 January 2016, treatment with laquinimod was discontinued for all patients in the 1.5 mg/daydose arm.</p> <p>Approximately 300 patients (100 patients within each study arm), plus the 30 patients that were already randomized to the laquinimod 1.5 mg dose arm, from ~51 investigational centers in North America, Europe and Russia are planned to be enrolled in the study.</p>	<p>Revised to reflect actual start date and planned completion.</p> <p>Number of patients updated following the discontinuation of the 1.5 mg/day treatment arm.</p>
<b>Section 3.11 – Table 3</b>		
<i>Estimated</i> creatinine clearance calculation	Estimated creatinine clearance calculation	Name of procedure clarified.
PK (drug and metabolites concentration) sampling	PK (drug and metabolites concentration) sampling	Name of procedure clarified.
24-hour PK profiling for drug and metabolites	24-hour PK profiling for drug and metabolites	Name of procedure clarified.
Footnote a. For patients in the high dose group (1.5 mg/day) who were discontinued, only safety and no efficacy assessments had to be performed at the Early Termination visit. The patients will be asked to continue all scheduled visits for safety assessment only after study drug discontinuation.	Footnote a. For patients in the high dose group (1.5 mg/day) who were discontinued, only safety and no efficacy assessments had to be performed at the Early Termination visit. The patients will be asked to continue all scheduled visits for safety assessment only after study drug discontinuation.	Newly added footnote for clarification regarding the discontinued 1.5 mg/day dose arm.
<i>Footnote d. Including smoking history. In addition, an evaluation of</i>	Footnote d. Including smoking history. In addition, an	Newly added footnote

Original text with changes shown	New wording	Reason/Justification for change
<i>cardiovascular risk factors should take place as soon as possible for patients already in the study, following approval of Global Amendment 04.</i>	evaluation of cardiovascular risk factors should take place as soon as possible for patients already in the study, following approval of Global Amendment 04.	for cardiovascular risk factor assessment and management.
<i>Footnote e. Assessment of changes in cardiovascular risk and appropriate cardiovascular risk management with appropriate medical follow-up, if clinically indicated, should be performed during the scheduled and unscheduled visits.</i>	Footnote e. Assessment of changes in cardiovascular risk and appropriate cardiovascular risk management with appropriate medical follow-up, if clinically indicated, should be performed during the scheduled and unscheduled visits.	Newly added footnote for cardiovascular risk factor assessment and management.
<i>Footnote i: <b>Unscheduled urgent safety laboratory samples, pharmacokinetic blood samples, and/or samples for potential biomarker analysis may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.</b></i>	Footnote i: <b>Unscheduled urgent safety laboratory samples, pharmacokinetic blood samples, and/or samples for potential biomarker analysis may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.</b>	Newly added footnote for clarification regarding urgent samples that may be collected during the study.
Footnote r. If a patient terminates within 3 months of the baseline visit, they will not undergo an Early Termination scan. If a patient terminates prior to Month 12, the Early termination scans should be performed as soon as possible, but not more than 7 days after discontinuation of study drug. Month 12 scans should be performed 7 days prior to the Termination Visit. <b>The early termination MRI scan was not to be done for the patients in the discontinued 1.5 mg/day treatment arm .</b>	Footnote r. If a patient terminates within 3 months of the baseline visit, they will not undergo an Early Termination scan. If a patient terminates prior to Month 12, the Early termination scans should be performed as soon as possible, but not more than 7 days after discontinuation of study drug. Month 12 scans should be performed 7 days prior to the Termination Visit. The early termination MRI scan was not to be done for the patients in the discontinued 1.5 mg/day treatment arm .	Clarification.
Footnote t. <del>Estimated</del> Creatinine clearance will be calculated based on laboratory results at screening (for inclusion in study) at every in-clinic study visit. <b>Patients who develop chronic renal disease associated with moderate or severe functional impairment, defined as estimated creatinine clearance (CrCl) &lt;60 mL/min/1.73 m<sup>2</sup>, while participating in the study should stop study medication temporarily and the creatinine clearance assessment should be repeated. If the renal impairment is confirmed (estimated CrCl &lt;60 mL/min/1.73 m<sup>2</sup>), the patient should stop study medication permanently.</b>	Footnote t. Estimated creatinine clearance will be calculated at every in-clinic visit. Patients who develop chronic renal disease associated with moderate or severe functional impairment, defined as estimated creatinine clearance (CrCl) <60 mL/min/1.73 m <sup>2</sup> , while participating in the study should stop study medication temporarily and the creatinine clearance assessment should be repeated. If the renal impairment is confirmed (estimated CrCl <60 mL/min/1.73 m <sup>2</sup> ), the patient should stop study medication permanently.	Extra monitoring added in case of decrease in renal function.
Footnote dd. Only at selected sites in a subgroup of patients, <del>N=60 (15 from each treatment arm)</del> , (approximately 15 patients per each of the three continuing treatment groups, for a total of approximately 45 patients) at Month 1. Patients participating in the 24-hour PK profiling will not have the single PK sample drawn at Visit 3. <b>Additionally, PK samples were collected from 2 patients in the laquinimod 1.5 mg/day treatment group when the</b>	Footnote dd. Only at selected sites in a subgroup of patients (approximately 15 patients per each of the three continuing treatment groups, for a total of approximately 45 patients) at Month 1. Patients participating in the 24-hour PK profiling will not have the single PK sample drawn at Visit 3. Additionally, PK samples were collected from 2 patients in	Revised following the discontinuation of the 1.5 mg/day treatment arm.

Original text with changes shown	New wording	Reason/Justification for change
<p><i>treatment was stopped; no further PK samples will be collected from the laquinimod 1.5 mg/day treatment group.</i></p>	<p>the laquinimod 1.5 mg/day treatment group when the treatment was stopped; no further PK samples will be collected from the laquinimod 1.5 mg/day treatment group.</p>	
<p><b>Section 3.11.1</b></p>		
<p>...</p> <p>The screening visit (Visit 1) will take place up to 5 weeks before the baseline visit. The following procedures will be performed at Visit 1:</p> <ul style="list-style-type: none"> <li>• obtain written informed consent before any other study-related procedures are performed</li> <li>• review inclusion/exclusion criteria</li> <li>• review medical and psychiatric history/demographics</li> <li>• <b><i>evaluation and management of major modifiable cardiac risk factors (eg, diabetes, high blood pressure, hyperlipidemia, tobacco smoking) and referral to treatment and follow-up in suitable clinic if needed.</i></b></li> <li>• ...</li> <li>• <b><i>Estimated c<sub>cr</sub> creatinine clearance calculation based on laboratory results (for inclusion in study).</i></b></li> <li>• ...</li> <li>• MRI scan             <ul style="list-style-type: none"> <li>○ The baseline MRI can be performed at the screening visit, but no later than 7 days prior to baseline. If performed at the screening visit, as many screening assessments as possible should be conducted prior to the MRI scan in order to assess eligibility. <b><i>If the screening period is extended by up to 30 days, the MRI scan does not have to be repeated.</i></b></li> </ul> </li> <li>• inform patients of study restrictions and compliance requirements</li> </ul>	<p>...</p> <p>The screening visit (Visit 1) will take place up to 5 weeks before the baseline visit. The following procedures will be performed at Visit 1:</p> <ul style="list-style-type: none"> <li>• obtain written informed consent before any other study-related procedures are performed</li> <li>• review inclusion/exclusion criteria</li> <li>• review medical and psychiatric history/demographics</li> <li>• evaluation and management of major modifiable cardiac risk factors (eg, diabetes, high blood pressure, hyperlipidemia, tobacco smoking) and referral to treatment and follow-up in suitable clinic if needed.</li> <li>• ...</li> <li>• Estimated creatinine clearance calculation based on laboratory results (for inclusion in study).</li> <li>• MRI scan             <ul style="list-style-type: none"> <li>○ The baseline MRI can be performed at the screening visit, but no later than 7 days prior to baseline. If performed at the screening visit, as many screening assessments as possible should be conducted prior to the MRI scan in order to assess eligibility. <b><i>If the screening period is extended by up to 30 days, the MRI scan does not have to be repeated.</i></b></li> </ul> </li> <li>• inform patients of study restrictions and compliance requirements</li> </ul>	<p>As an enhanced monitoring and safety precaution, data on patient's smoking habits will now be collected and evaluation of cardiac risk factors will be performed.</p> <p>Clarification regarding other procedures and assessments.</p>
<p><b>Section 3.11.2 (Other sections affected by this change: 3.11.3.1.1; 3.11.3.1.3-5; 3.11.4.1)</b></p>		
<p>Patients who meet the inclusion/exclusion criteria at Visit 1 will continue to Visit 2, when baseline evaluations will be conducted. The following procedures will be performed at Visit 2 in patients who continue to meet the inclusion/exclusion criteria:</p> <ul style="list-style-type: none"> <li>• review inclusion/exclusion criteria</li> </ul>	<p>Patients who meet the inclusion/exclusion criteria at Visit 1 will continue to Visit 2, when baseline evaluations will be conducted. The following procedures will be performed at Visit 2 in patients who continue to meet the inclusion/exclusion criteria:</p>	<p>Extra creatinine clearance monitoring added in case of decrease in renal function.</p>

Original text with changes shown	New wording	Reason/Justification for change
<ul style="list-style-type: none"> <li>• perform clinical laboratory tests</li> <li>• <i>estimated creatinine clearance calculation</i></li> <li>• clinical hematology</li> </ul> <p>...</p>	<ul style="list-style-type: none"> <li>• review inclusion/exclusion criteria</li> <li>• perform clinical laboratory tests</li> <li>• estimated creatinine clearance calculation</li> <li>• clinical hematology</li> </ul> <p>...</p>	
<b>Section 3.11.3.1.5</b>		
<p>...</p> <p><i>Early termination refers to the study drug termination and not termination of the patient from the study. Patients in the 1.5 mg/day (high dose) treatment arm, whose treatment with laquinimod was discontinued, were invited to attend an early termination safety visit to return study medication and perform drug accountability. At this visit, only safety assessments (vital signs, clinical laboratory tests, pregnancy test, adverse event inquiry, drug accountability, review of concomitant medication, and C-SSRS) were to be conducted (see Section 3.6.2), and none of the efficacy assessments. Patients were asked to continue all scheduled visits for safety assessment after study drug discontinuation.</i></p> <p><i>Patients in the high dose group (1.5mg/day) who were requested to discontinue study drug before week 52 but continue to attend scheduled study visits for safety assessment are not considered to have completed the study .</i></p>	<p>Early termination refers to the study drug termination and not termination of the patient from the study. Patients in the 1.5 mg/day (high dose) treatment arm, whose treatment with laquinimod was discontinued, were invited to attend an early termination safety visit to return study medication and perform drug accountability. At this visit, only safety assessments (vital signs, clinical laboratory tests, pregnancy test, adverse event inquiry, drug accountability, review of concomitant medication, and C-SSRS) were to be conducted (see Section 3.6.2), and none of the efficacy assessments. Patients were asked to continue all scheduled visits for safety assessment after study drug discontinuation.</p> <p>Patients in the high dose group (1.5mg/day) who were requested to discontinue study drug before week 52 but continue to attend scheduled study visits for safety assessment are not considered to have completed the study .</p>	<p>Clarification regarding end-of-treatment assessments of discontinued patients.</p>
<b>Section 3.11.4.1 (Other sections affected by this change: 4.3)</b>		
<p>...</p> <p>For patients who complete the study or withdraw prematurely, final evaluations will be performed at the end-of treatment visit or as soon as possible thereafter. Procedures for patients who withdraw prematurely from the study are described in Section 4.3.</p> <p><i>If it is not possible to schedule the ET visit within 2 weeks after end of treatment, only the safety evaluations for that visit (vital signs; clinical laboratory tests; pregnancy test; adverse event inquiry; drug accountability; review of concomitant medication, and C-SSRS; see Section 3.6.2) need to be performed.</i></p>	<p>...</p> <p>For patients who complete the study or withdraw prematurely, final evaluations will be performed at the end-of treatment visit or as soon as possible thereafter. Procedures for patients who withdraw prematurely from the study are described in Section 4.3 If it is not possible to schedule the ET visit within 2 weeks after end of treatment, only the safety evaluations for that visit (vital signs; clinical laboratory tests; pregnancy test; adverse event inquiry; drug accountability; review of concomitant medication, and C-SSRS; see Section 3.6.2) need to be performed.</p>	<p>Clarification.</p>
<b>Section 3.11.5</b>		
<p>...</p> <p>Other procedures may be performed at the discretion of the investigator, <i>and</i></p>	<p>Other procedures may be performed at the discretion of the investigator, and must be recorded in the source</p>	<p>Clarification. Additional</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><i>must be recorded in the source documentation. According to the judgment of the investigator or medical monitor, the following unscheduled procedures may be performed:</i></p> <ul style="list-style-type: none"> <li>• <i>urgent safety laboratory test panel (see Section 7.3.4)</i></li> <li>• <i>estimated creatinine clearance calculation</i></li> <li>• <i>collection of unscheduled pharmacokinetic blood sample</i></li> <li>• <i>collection of sample for potential biomarker analysis</i></li> </ul>	<p>documentation. According to the judgment of the investigator or medical monitor, the following unscheduled procedures may be performed:</p> <ul style="list-style-type: none"> <li>• urgent safety laboratory test panel (see Section 7.3.4)</li> <li>• estimated creatinine clearance calculation</li> <li>• collection of unscheduled pharmacokinetic blood sample</li> <li>• collection of sample for potential biomarker analysis</li> </ul>	<p>assessments for monitoring of cardiac risk.</p>
<p><b>4 SELECTION AND WITHDRAWAL OF PATIENTS</b></p>		
<p><b>Section 4.2</b></p>		
<p>f. [Revision 1] Serum levels <math>\geq 2</math>xULN of either ALT or AST at screening.</p>	<p>f. [Revision 1] Serum levels <math>\geq 2</math>xULN of either ALT or AST at screening.</p>	<p>More stringent exclusion criterion for hepatic parameters.</p>
<p>g. [Revision 1] Serum direct bilirubin which is <math>\geq 1.5</math>xULN at screening.</p>	<p>g. [Revision 1] Serum direct bilirubin which is <math>\geq 1.5</math>xULN at screening.</p>	<p>More stringent exclusion criterion for hepatic parameters</p>
<p>h. [Revision 2] Estimated creatinine clearance <math>&lt;60</math> mL/min at screening, calculated using the Cockcroft Gault equation: (140 - age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/dL)</p>	<p>h. [Revision 2] Estimated creatinine clearance <math>&lt;60</math> mL/min at screening, calculated using the Cockcroft Gault equation: (140 - age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/dL)</p>	<p>Correction of terminology.</p>
<p>i. [Revision 1] Subjects with a clinically significant or unstable medical or surgical condition that may put the patient at risk when participating in the study or may influence the results of the study or affect the patient's ability to take part in the study, as determined by medical history, physical examinations, ECG, or laboratory tests. Such conditions may include:</p> <ol style="list-style-type: none"> <li>1. A major cardiovascular event (e.g. myocardial infarction, acute coronary syndrome, de-compensated congestive heart failure, pulmonary embolism, coronary revascularization, <i>angina</i>) that occurred <del>during the past 6 months</del> prior to randomization.</li> <li>2. Significant cardiovascular risk factors (such as, but not limited to, uncontrolled hypertension, uncontrolled diabetes), per investigator discretion.</li> <li>3. Any acute pulmonary disorder</li> <li>4. A CNS disorder other than HD that may jeopardize the subject's participation in the study, including such disorders that are demonstrated on the baseline MRI (based on local read).</li> <li>5. A gastrointestinal disorder that may affect the absorption of study</li> </ol>	<p>i. [Revision 1] Subjects with a clinically significant or unstable medical or surgical condition that may put the patient at risk when participating in the study or may influence the results of the study or affect the patient's ability to take part in the study, as determined by medical history, physical examinations, ECG, or laboratory tests. Such conditions may include:</p> <ol style="list-style-type: none"> <li>1. A major cardiovascular event (e.g. myocardial infarction, acute coronary syndrome, de-compensated congestive heart failure, pulmonary embolism, coronary revascularization, angina) that occurred prior to randomization.</li> <li>2. Significant cardiovascular risk factors (such as, but not limited to, uncontrolled hypertension, uncontrolled diabetes), per investigator discretion.</li> <li>3. Any acute pulmonary disorder</li> <li>4. A CNS disorder other than HD that may jeopardize the subject's participation in the study, including such disorders</li> </ol>	<p>More stringent criterion for exclusion of patients with significant cardiac events or conditions in their medical history.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>medication.</p> <p><del>5 6. Acute or chronic renal disease including acute kidney injury (AKI).</del></p> <p><del>6 7. Cirrhotic patients with moderate or severe hepatic impairment Any form of acute or chronic liver disease.</del></p> <p>7 8. Known human immunodeficiency virus positive status. Patients will undergo an HIV test at screening per local requirements, if applicable.</p> <p>8 9. Any malignancies, excluding basal cell carcinoma, in the 5 years prior to randomization.</p>	<p>that are demonstrated on the baseline MRI (based on local read).</p> <p>5. A gastrointestinal disorder that may affect the absorption of study medication.</p> <p>6. Acute or chronic renal disease including acute kidney injury (AKI).</p> <p>7. Any form of acute or chronic liver disease.</p> <p>8. Known human immunodeficiency virus positive status. Patients will undergo an HIV test at screening per local requirements, if applicable.</p> <p>9. Any malignancies, excluding basal cell carcinoma, in the 5 years prior to randomization.</p>	
<b>Section 4.3</b>		
<p><i>For patients in the 1.5 mg arm who were withdrawn from study treatment, the reason will be recorded as 'sponsor requested patient to be withdrawn'.</i></p>	<p>For patients in the 1.5 mg arm who were withdrawn from study treatment, the reason will be recorded as 'sponsor requested patient to be withdrawn'.</p>	<p>Clarification due to discontinuation of 1.5 mg arm</p>
<b>5 TREATMENT OF PATIENTS</b>		
<b>Section 5.1</b>		
<p><del>Until 10 January 2016, at the baseline visit, patients will be were</del> randomly assigned in a 1:1:1:1 ratio to 1 of 3 laquinimod treatment groups or to the placebo treatment group. Three capsules will be administered orally once each day, at the same time of the day, as follows:</p> <ul style="list-style-type: none"> <li>• Oral laquinimod 0.5 mg: 3 capsules, 1 containing 0.5 mg laquinimod and 2 capsules containing matching placebo, to be administered orally qd.</li> <li>• Oral laquinimod 1.0 mg: 3 capsules, 2 containing 0.5 mg laquinimod and 1 capsule containing matching placebo, to be administered orally qd.</li> <li>• Oral laquinimod 1.5 mg: 3 capsules containing 0.5 mg laquinimod (<i>Note: The treatment of this high dose arm was discontinued as of 10 January 2016</i>)</li> <li>• Matching placebo: 3 capsules, containing 0.5 mg matching placebo, to be administered orally qd.</li> </ul> <p><i>As of 10 January 2016, following the decision to discontinue treatment of the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day, 1.0 mg/day, or matching placebo for 52 weeks.</i></p> <p>...</p>	<p>Until 10 January 2016, at the baseline visit, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 3 laquinimod treatment groups or to the placebo treatment group. Three capsules will be administered orally once each day, at the same time of the day, as follows:</p> <ul style="list-style-type: none"> <li>• Oral laquinimod 0.5 mg: 3 capsules, 1 containing 0.5 mg laquinimod and 2 capsules containing matching placebo, to be administered orally qd.</li> <li>• Oral laquinimod 1.0 mg: 3 capsules, 2 containing 0.5 mg laquinimod and 1 capsule containing matching placebo, to be administered orally qd.</li> <li>• Oral laquinimod 1.5 mg: 3 capsules containing 0.5 mg laquinimod (<i>Note: The treatment of this high dose arm was discontinued as of 10 January 2016</i>)</li> <li>• Matching placebo: 3 capsules, containing 0.5 mg matching placebo, to be administered orally qd.</li> </ul> <p>As of 10 January 2016, following the decision to discontinue treatment of the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day, 1.0 mg/day, or</p>	<p>Revision following discontinuation of 1.5 mg treatment arm.</p>

Original text with changes shown	New wording	Reason/Justification for change
	matching placebo for 52 weeks. ...	
<b>Section 5.3.1</b>		
<p>The following medications will <u>not be allowed</u> prior to and during this study:</p> <ul style="list-style-type: none"> <li>• Use of tetrabenazine within 30 days prior to baseline and during the study;</li> <li>• Use of antipsychotic medication within 30 days prior to baseline and during the study;</li> <li>• Use of moderate/strong inhibitors of CYP3A4, <i>such as erythromycin and ketoconazole (more examples listed in Appendix B)</i>, within 2 weeks prior to randomization, during the study and until 30 days after the last study dose has been administered. <i>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.</i></li> </ul> <p>...</p>	<p>The following medications will <u>not be allowed</u> prior to and during this study:</p> <ul style="list-style-type: none"> <li>• Use of tetrabenazine within 30 days prior to baseline and during the study;</li> <li>• Use of antipsychotic medication within 30 days prior to baseline and during the study;</li> <li>• Use of moderate/strong inhibitors of CYP3A4, such as erythromycin and ketoconazole (more examples listed in Appendix B), within 2 weeks prior to randomization, during the study and until 30 days after the last study dose has been administered. 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.</li> </ul> <p>...</p>	<p>Clarification.</p> <p>Rationale for disallowed medication added</p>
<b>Section 5.5</b>		
<p>The total amount of blood to be drawn throughout the entire study for serum chemistry, hematology, pharmacokinetic, biomarker and pharmacogenomic measurements is approximately <del>300</del> 350 mL/patient.</p>	<p>The total amount of blood to be drawn throughout the entire study for serum chemistry, hematology, pharmacokinetic, biomarker and pharmacogenomic measurements is approximately 350 mL/patient.</p>	<p>Adjustment to allow for unscheduled visits.</p>
<b>7 ASSESSMENT OF SAFETY</b>		
<b>Section 7.1.6</b>		
<p><del>No protocol defined adverse events for expedited reporting were identified for this study.</del></p> <p><i>Ischemic cardiac events (such as myocardial infarction, unstable angina, acute coronary syndrome etc), cerebrovascular events (such as cerebral arterial occlusion, cerebral ischemia, etc) and deaths should be reported to the sponsor within 24 hours, including completion of the corresponding dedicated CRF.</i></p>	<p>Ischemic cardiac events (such as myocardial infarction, unstable angina, acute coronary syndrome etc), cerebrovascular events (such as cerebral arterial occlusion, cerebral ischemia, etc) and deaths should be reported to the sponsor within 24 hours, including completion of the corresponding dedicated CRF.</p>	<p>Due to cardiovascular findings at higher dose levels, adverse events for expedited reporting have been identified.</p>
<b>Section 7.3.1 (Other sections affected by this change: APPENDIX A)</b>		

Original text with changes shown	New wording	Reason/Justification for change
<p>The following serum chemistry tests will be performed at all scheduled visits:</p> <ul style="list-style-type: none"> <li>• calcium</li> <li>• phosphorus</li> <li>• ...</li> <li>• creatinine (<i>Note: Estimated creatinine clearance will be calculated at all in-clinic study visits</i>)</li> <li>• ...</li> <li>• creatine phosphokinase (CPK) <ul style="list-style-type: none"> <li>-In case of CPK results &gt;ULN, troponin <del>or</del> <i>and</i> creatine kinase MB isoenzyme (CK-MB) will be tested by the central laboratory.</li> <li>-In case of CPK&gt;10×ULN, an unscheduled visit to assess urine myoglobin will be required. The following blood tests will be repeated at the unscheduled visit: CPK, blood urea nitrogen, creatinine, electrolytes including potassium, calcium, phosphate.</li> </ul> </li> </ul> <p>...</p>	<p>The following serum chemistry tests will be performed at all scheduled visits:</p> <ul style="list-style-type: none"> <li>• calcium</li> <li>• phosphorus</li> <li>• ...</li> <li>• creatinine (Note: Estimated creatinine clearance will be calculated at all in-clinic study visits)</li> <li>• ...</li> <li>• creatine phosphokinase (CPK) <ul style="list-style-type: none"> <li>-In case of CPK results &gt;ULN, troponin and creatine kinase MB isoenzyme (CK-MB) will be tested by the central laboratory.</li> <li>-In case of CPK&gt;10×ULN, an unscheduled visit to assess urine myoglobin will be required. The following blood tests will be repeated at the unscheduled visit: CPK, blood urea nitrogen, creatinine, electrolytes including potassium, calcium, phosphate.</li> </ul> </li> </ul> <p>...</p>	<p>Clarification regarding estimated creatinine clearance calculation.</p> <p>In case of CPK &gt;ULN, both troponin and CK-MB will be tested to give additional cardiovascular assessment.</p>
<p><b>Section 7.3.4 (Other sections affected by this change: Table 3; 3.11.5)</b></p>		
<p><b>7.3.4 Urgent Safety Laboratory Panel</b> <i>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.</i></p> <p><i>The following tests will be performed on these samples:</i></p> <ul style="list-style-type: none"> <li>• serum chemistry panel (see Section 7.3.1)</li> <li>• CBC panel (see Section 7.3.2)</li> <li>• CK-MB</li> <li>• troponin</li> </ul>	<p><b>7.3.4 Urgent Safety Laboratory Panel</b> 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.</p> <p>The following tests will be performed on these samples:</p> <ul style="list-style-type: none"> <li>• serum chemistry panel (see Section 7.3.1)</li> <li>• CBC panel (see Section 7.3.2)</li> <li>• CK-MB</li> <li>• troponin</li> </ul>	<p>Unscheduled laboratory test samples may be collected to allow further investigation of events of interest. Numbering of subsequent headings has changes.</p>
<p><b>Section 7.7 (Other sections affected by change: 3.11)</b></p>		
<p><b>7.7 Estimated Creatinine Clearance Calculation</b> <i>Significant changes in laquinimod exposure, in particular in terms of unbound drug fraction, are predicted in patients with renal impairment (see Section 1.3.2.1). Consequently, estimated CrCl will be calculated at all</i></p>	<p>7.7 Estimated Creatinine Clearance Calculation Significant changes in laquinimod exposure, in particular in terms of unbound drug fraction, are predicted in patients with renal impairment (see Section 1.3.2.1). Consequently,</p>	<p>New section - Extra creatinine clearance monitoring added in case of</p>



Original text with changes shown	New wording	Reason/Justification for change
<p><i>visits to monitor chronic renal function in the study in order to identify patients with potentially impaired laquinimod clearance. Patients with a confirmed CrCl &lt;60 mL/min/1.73 m<sup>2</sup> should stop study medication temporarily and the CrCl assessment should be repeated. If the renal impairment is confirmed (estimated CrCl &lt;60 mL/min/1.73 m<sup>2</sup>), the patient should stop study medication permanently (see Section 3.6). Following recent findings connecting Gd-based contrast agents and nephrogenic systemic fibrosis, the estimated CrCl result should be available prior to the baseline MRI scan. Estimated CrCl calculation will be done in accordance with the central laboratory creatinine value measurement performed at the screening visit. The central laboratory will report calculated CrCl; however, if the result is not available prior to the baseline MRI scan, estimated CrCl may be calculated using the Cockcroft-Gault equation (eg available online CrCl calculator): <a href="http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault">http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault</a></i></p>	<p>estimated CrCl will be calculated at all visits to monitor chronic renal function in the study in order to identify patients with potentially impaired laquinimod clearance. Patients with a confirmed CrCl &lt;60 mL/min/1.73 m<sup>2</sup> should stop study medication temporarily and the CrCl assessment should be repeated. If the renal impairment is confirmed (estimated CrCl &lt;60 mL/min/1.73 m<sup>2</sup>), the patient should stop study medication permanently (see Section 3.6). Following recent findings connecting Gd-based contrast agents and nephrogenic systemic fibrosis, the estimated CrCl result should be available prior to the baseline MRI scan. Estimated CrCl calculation will be done in accordance with the central laboratory creatinine value measurement performed at the screening visit. The central laboratory will report calculated CrCl; however, if the result is not available prior to the baseline MRI scan, estimated CrCl may be calculated using the Cockcroft-Gault equation (eg available online CrCl calculator): <a href="http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault">http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault</a></p>	<p>decrease in renal function.</p>
<p><b>Section 7.8 (Other sections affected by change: 3.11. Study Procedures)</b></p>		
<p><i>Evaluation and management of major modifiable cardiac risk factors (eg, body mass index [BMI], diabetes, high blood pressure, hyperlipidemia, tobacco smoking) will be performed at the time points indicated in Table 3. In addition, an evaluation of cardiovascular risk factors should take place as soon as possible for patients already in the study, following approval of Global Amendment 04. Assessment of changes in cardiovascular risk and appropriate cardiovascular risk management with appropriate medical follow-up, if clinically indicated, should be performed during the scheduled and unscheduled visits. Cardiovascular risk management should be conducted according to evidence-based, local standard-of-care procedures. Patients will undergo referral to a suitable clinic if needed.</i></p>	<p>Evaluation and management of major modifiable cardiac risk factors (eg, body mass index [BMI], diabetes, high blood pressure, hyperlipidemia, tobacco smoking) will be performed at the time points indicated in Table 3. In addition, an evaluation of cardiovascular risk factors should take place as soon as possible for patients already in the study, following approval of Global Amendment 04. Assessment of changes in cardiovascular risk and appropriate cardiovascular risk management with appropriate medical follow-up, if clinically indicated, should be performed during the scheduled and unscheduled visits. Cardiovascular risk management should be conducted according to evidence-based, local standard-of-care procedures. Patients will undergo referral to a suitable clinic if needed.</p>	<p>Additional assessments for monitoring of cardiac risk</p>
<p><b>8 ASSESSMENT OF PHARMACOKINETICS/PHARMACOGENOMICS/OTHER ANCILLARY STUDIES</b></p>		
<p><b>Section 8.1.</b></p>		

Original text with changes shown	New wording	Reason/Justification for change
<p>Samples will be analyzed for laquinimod <i>and its metabolites</i> using <del>an</del> appropriate validated methods. Incurred sample reanalysis may be performed.</p>	<p>Samples will be analyzed for laquinimod and its metabolites using appropriate validated methods. Incurred sample reanalysis may be performed.</p>	<p>Clarification.</p>
<p><b>Section 8.1.1</b></p>		
<p>Whole blood samples (4 mL) will be collected via venipuncture in the morning for plasma concentration measurements of laquinimod <i>and its metabolites</i> as follows:                      PPK samples <i>will be collected</i> at visits at Months 1, 3, 6 and 12 from all subjects.  <del>PK samples at Month 1 from a total of 60 patients (15 patients per dose group) at the following timepoints – pre-dose, 15, 30 min and 1, 2, 3, 6 and 24 hours post-dose. PK samples of laquinimod and its metabolites will be collected from approximately 15 patients per each of the three continuing treatment groups (at selected sites at Month 1), for a total of approximately 45 patients, at the following timepoints – pre-dose, 15, 30 min and 1, 2, 3, 6 and 24 hours post dose. Additionally, PK samples were collected from 2 patients in the laquinimod 1.5 mg/day treatment group when the treatment was stopped; no further PK samples will be collected from the laquinimod 1.5 mg/day treatment group.</del>  <i>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 for safety. The samples should be collected as soon as possible in association with the event.</i>                      The dates and times of study drug administration and the date and time of each pharmacokinetic sample will be recorded on the source documentation and transcribed onto the CRF.                      ...                      Other measures should be taken as appropriate to prevent samples from <i>any</i> heating <del>significantly</del> during centrifugation. Separated plasma <del>will be will be placed on water/ice (~0-5°C) and transferred in 3 portions (1 aliquot of 300uL for laquinimod analysis, and 2 approximately equal portions of ~750 uL for metabolites analysis) into 3 opaque, labeled, polypropylene tubes (sets A , B and C respectively).</del> <i>transferred in approximately equal portions into 2 opaque, labeled, polypropylene tubes (sets A and B) and Tubes will be placed in an upright position into frozen storage at nominal -70°C (if -70°C storage is not possible at the site, store at -20°C) (at nominal -20°C) within 21 hours from the start of the centrifugation.</i></p>	<p>Whole blood samples (4 mL) will be collected via venipuncture in the morning for plasma concentration measurements of laquinimod and its metabolites as follows:                      PPK samples will be collected at visits at Months 1, 3, 6 and 12 from all subjects.                      PK samples of laquinimod and its metabolites will be collected from approximately 15 patients per each of the three continuing treatment groups (at selected sites at Month 1), for a total of approximately 45 patients, at the following timepoints – pre-dose, 15, 30 min and 1, 2, 3, 6 and 24 hours post dose. Additionally, PK samples were collected from 2 patients in the laquinimod 1.5 mg/day treatment group when the treatment was stopped; no further PK samples will be collected from the laquinimod 1.5 mg/day treatment group.                      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 for safety. The samples should be collected as soon as possible in association with the event.                      The dates and times of study drug administration and the date and time of each pharmacokinetic sample will be recorded on the source documentation and transcribed onto the CRF.                      ...                      Other measures should be taken as appropriate to prevent samples from any heating during centrifugation. Separated plasma will be will be placed on water/ice (~0-5°C) and transferred in 3 portions (1 aliquot of 300uL for laquinimod analysis, and 2 approximately equal portions of ~750 uL for metabolites analysis) into 3 opaque, labeled, polypropylene tubes (sets A , B and C respectively). Tubes will be placed in an upright position into frozen storage at nominal -70°C (if -70°C storage is not possible at the site, store at -20°C) within 1 hour from the start of the centrifugation.</p>	<p>Revision following discontinuation of 1.5 mg treatment arm.</p> <p>Details regarding metabolites PK sampling and handling added.</p> <p>Unscheduled samples may be collected to allow further investigation of events of interest.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>Sample labels should include the study number, patient randomization number, period, nominal collection time, set (A, <del>or</del> B, or C), and indication that they are pharmacokinetic samples, <b>and an indication of storage conditions at the site (-70°C or -20°C).</b></p>	<p>Sample labels should include the study number, patient randomization number, period, nominal collection time, set (A, B, or C), indication that they are pharmacokinetic samples, and an indication of storage conditions at the site (-70°C or -20°C).</p>	
<p><b>Section 8.1.2</b></p>		
<p>... Set A <b>and B</b> samples will be transported, frozen with sufficient dry ice for 4 days, by next-day courier to the bioanalytical laboratory.</p> <p>Set <del>BC</del> samples will <del>either</del> be sent to the same laboratory as that for sets A <b>and B</b> on a subsequent days by next-day courier, <del>or be retained at the central laboratory until the study is completed and the clinical study report has been issued (unless shipment to another facility is requested by the sponsor).</del> <del>Instructions as to the disposition of the B samples will be provided by the sponsor.</del></p> <p>Sample shipments should be sent no later in the week than Wednesday morning for next-day delivery. Samples are not to arrive on the weekend.</p>	<p>... Set A and B samples will be transported, frozen with sufficient dry ice for 4 days, by next-day courier to the bioanalytical laboratory.</p> <p>Set C samples will be sent to the same laboratory as that for sets A and B on subsequent days by next-day courier.</p> <p>Sample shipments should be sent no later in the week than Wednesday morning for next-day delivery. Samples are not to arrive on the weekend.</p>	<p>Details regarding metabolites PK sample shipment added.</p>
<p><b>Section 8.2</b></p>		
<p>... <b>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.</b></p>	<p>... 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.</p>	<p>New text - Unscheduled samples may be collected to allow further investigation of events of interest.</p>
<p><b>9 STATISTICS</b></p>		
<p><b>Section 9.1</b></p>		
<p>This is a double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of laquinimod (0.5 mg <b>and</b> 1.0 mg, <del>or</del> <del>1.5 mg qd</del>) treatment in patients with HD. Randomization will be as described in Section 3.3.</p> <p><b>Prior to 10 January 2016, eligible Ppatients will be</b> randomly assigned to receive treatment with laquinimod at a dosage of 0.5 mg, 1.0 mg, or 1.5 mg/day or a matching placebo in a 1:1:1:1 ratio. <del>Randomization will be as described in Section 3.3.</del></p> <p><b>As of 10 January 2016, following a decision to discontinue treatment of</b></p>	<p>This is a double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of laquinimod (0.5 mg and 1.0 mg qd) treatment in patients with HD. Randomization will be as described in Section 3.3.</p> <p>Prior to 10 January 2016, eligible patients were randomly assigned to receive treatment with laquinimod at a dosage of 0.5 mg, 1.0 mg, or 1.5 mg/day or a matching placebo in a 1:1:1:1 ratio. As of 10 January 2016, following a decision to discontinue treatment of the laquinimod 1.5 mg dose arm,</p>	<p>Revised following the discontinuation of the 1.5 mg/day treatment arm.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><i>the laquinimod 1.5 mg dose arm, future eligible patients will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day or 1.0 mg/day or matching placebo for 52 weeks.</i></p> <p><i>No change was performed to the original randomization list except that the patient numbers assigned to laquinimod 1.5 mg/day were removed from the list by the IRT vendor. Patients and investigators will remain blinded to treatment assignment during the study.</i></p> <p><i>All patients that discontinued the 1.5 mg/day dose have been unblinded. No attempts will be made to re-randomize patients whose 1.5 mg treatment was stopped to a lower dose of laquinimod. The remaining ongoing patients retained their originally randomized treatment.</i></p>	<p>future eligible patients will be randomized in a 1:1:1 ratio to receive laquinimod 0.5 mg/day or 1.0 mg/day or matching placebo for 52 weeks.</p> <p>No change was performed to the original randomization list except that the patient numbers assigned to laquinimod 1.5 mg/day were removed from the list by the IRT vendor.</p> <p>Patients and investigators will remain blinded to treatment assignment during the study.</p> <p>All patients that discontinued the 1.5 mg/day dose have been unblinded. No attempts will be made to re-randomize patients whose 1.5 mg treatment was stopped to a lower dose of laquinimod. The remaining ongoing patients retained their originally randomized treatment.</p>	
<b>Section 9.3</b>		
<p><i>Due to the decision from 10 January 2016 to discontinue treatment of the laquinimod 1.5 mg treatment arm, and the low number of enrolled patients compared to the target at this time, data from the laquinimod 1.5 mg treatment arm will be presented descriptively only, and will not be included in any inferential analyses for efficacy or safety.</i></p>	<p>Due to the decision from 10 January 2016 to discontinue treatment of the laquinimod 1.5 mg treatment arm, and the low number of enrolled patients compared to the target at this time, data from the laquinimod 1.5 mg treatment arm will be presented descriptively only, and will not be included in any inferential analyses for efficacy or safety.</p>	<p>Newly-added text for clarification following the discontinuation of the 1.5 mg/day treatment arm.</p>
<b>Section 9.7</b>		
<p>First, the Hochberg method will be applied for the comparisons of the 3 2 active doses to placebo in the primary endpoint analysis.</p>	<p>First, the Hochberg method will be applied for the comparisons of the 2 active doses to placebo in the primary endpoint analysis.</p>	<p>Revised following the discontinuation of the 1.5 mg/day treatment arm.</p>
<b>Section 9.9.1</b>		
<p><del>Blood samples for PK evaluation of laquinimod will be collected at selected sites at month 1 from 60 patients in total (15 patients per treatment group).</del></p> <p><i>PK samples of laquinimod and its metabolites will be collected from approximately 15 patients per each of the three continuing treatment groups (at selected sites at Month 1), for a total of approximately 45 patients. Additionally, PK samples were collected from 2 patients in the laquinimod 1.5 mg/day treatment group when the treatment was stopped; no further PK samples will be collected from the laquinimod 1.5 mg/day treatment group.</i></p> <p>Samples will be collected at pre-dose, 15, 30 min and 1, 2, 3, 6 and 24 hours post dose.</p> <p>Steady state pharmacokinetic parameters <i>for laquinimod</i> (<math>AUC_{tau}</math>, <math>C_{max}</math> and</p>	<p>PK samples of laquinimod and its metabolites will be collected from approximately 15 patients per each of the three continuing treatment groups (at selected sites at Month 1), for a total of approximately 45 patients. Additionally, PK samples were collected from 2 patients in the laquinimod 1.5 mg/day treatment group when the treatment was stopped; no further PK samples will be collected from the laquinimod 1.5 mg/day treatment group.</p> <p>Samples will be collected at pre-dose, 15, 30 min and 1, 2, 3, 6 and 24 hours post dose.</p> <p>Steady state pharmacokinetic parameters for laquinimod (<math>AUC_{tau}</math>, <math>C_{max}</math> and <math>C_{min}</math>, <math>t_{max}</math>), will be calculated for each</p>	<p>Assessment of laquinimod metabolites was added to the overall exploratory PK assessment for better characterization of laquinimod disposition.</p> <p>Revised following the discontinuation of the 1.5 mg/day treatment</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><math>C_{min}</math>, <math>t_{max}</math>), will be calculated for each patient. <i>Additional parameters for laquinimod and pharmacokinetic parameters for metabolites may be calculated if data permit.</i> ...</p>	<p>patient. Additional parameters for laquinimod and pharmacokinetic parameters for metabolites may be calculated if data permit. ...</p>	<p>arm.</p>
<p><b>Section 9.9.2</b></p>		
<p>A single blood sample will be collected from all patients at months 1, 3, 6 and 12 <i>for evaluation of laquinimod and its metabolites.</i> ... <i>Pharmacokinetic parameters for laquinimod metabolites may be calculated if data permit.</i>  <i>The PPK model may also include any unscheduled pharmacokinetic samples collected to assist with further investigations of cardiovascular events or other clinical event of interest for safety (see Section 8.1).</i> ...</p>	<p>A single blood sample will be collected from all patients at months 1, 3, 6 and 12 for evaluation of laquinimod and its metabolites. ... Pharmacokinetic parameters for laquinimod metabolites may be calculated if data permit.  The PPK model may also include any unscheduled pharmacokinetic samples collected to assist with further investigations of cardiovascular events or other clinical event of interest for safety (see Section 8.1). ...</p>	<p>Assessment of laquinimod metabolites was added to the overall exploratory PK assessment for better characterization of laquinimod disposition. Clarification regarding the PPK model.</p>
<p><b>APPENDIX A – GUIDANCE ON SAFETY MONITORING</b></p>		
<p><b>6. Cancer</b> Patients who are diagnosed with <del>invasive cancer</del> <i>a malignant solid or liquid tumor</i> while participating in the study should be discontinued from the study.</p>	<p><b>6. Cancer</b> Patients who are diagnosed with a malignant solid or liquid tumor while participating in the study should be discontinued from the study.</p>	<p>Correction of terminology.</p>
<p><b>7. Guidance on monitoring subjects with elevated pancreatic amylase levels</b> ... <i>Necessary medical procedures including repeat labs will be performed based on clinical needs determined by the treating physician's judgement.</i></p>	<p><b>7. Guidance on monitoring subjects with elevated pancreatic amylase levels</b> ... Necessary medical procedures including repeat labs will be performed based on clinical needs determined by the treating physician's judgement.</p>	<p>Clarification</p>
<p><b>8. Guidance on monitoring subjects with hemoglobin decrease</b> ... <i>Necessary medical procedures including repeat labs will be performed based on clinical needs determined by the treating physician's judgement.</i></p>	<p><b>8. Guidance on monitoring subjects with hemoglobin Decrease</b> ... Necessary medical procedures including repeat labs will be performed based on clinical needs determined by the treating physician's judgement.</p>	<p>Clarification</p>
<p><b>10. Acute Coronary Syndrome, Myocardial Infarction or Any Major Cardiovascular Event</b> <i>Patients who experience acute coronary syndrome, myocardial infarction or any major cardiovascular event will permanently discontinue treatment</i></p>	<p>10. Acute Coronary Syndrome, Myocardial Infarction or Any Major Cardiovascular Event Patients who experience acute coronary syndrome, myocardial infarction or any major cardiovascular event will</p>	<p>New stopping rule implemented for patients who experience</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><i>with study medication. Patients will be asked to continue all scheduled visits for safety assessment.</i></p>	<p>permanently discontinue treatment with study medication. Patients will be asked to continue all scheduled visits for safety assessment.</p>	<p>cardiovascular events.</p>
<p><b>11. Liver Impairment</b> <i>Patients who develop liver disease associated with liver functional impairment while participating in the study should stop study medication.</i></p>	<p>11. Liver Impairment Patients who develop liver disease associated with liver functional impairment while participating in the study should stop study medication.</p>	<p>New stopping rule implemented to avoid increased exposure to laquinimod in cases of organ impairment</p>
<p><b>12. Renal Impairment</b> <i>Patients who develop chronic renal disease associated with moderate-severe functional impairment, defined as estimated creatinine clearance (CrCl) &lt;60 mL/min/1.73 m<sup>2</sup>, while participating in the study should stop study medication temporarily until normalization of renal function or confirmation of renal impairment diagnosis. In case moderate-severe renal impairment is diagnosed, the patient will permanently discontinue treatment with study medication.</i></p>	<p>12. Renal Impairment Patients who develop chronic renal disease associated with moderate-severe functional impairment, defined as estimated creatinine clearance (CrCl) &lt;60 mL/min/1.73 m<sup>2</sup>, while participating in the study should stop study medication temporarily until normalization of renal function or confirmation of renal impairment diagnosis. In case moderate-severe renal impairment is diagnosed, the patient will permanently discontinue treatment with study medication.</p>	<p>New stopping rule implemented to avoid increased exposure to laquinimod in cases of organ impairment</p>
<b>APPENDIX B – LIST OF DISALLOWED MEDICATIONS PRIOR TO AND DURING STUDY</b>		
<p>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.</p> <p><i>Moderate and strong CYP3A4 inhibitors are prohibited because concomitant administration is predicted to increase laquinimod exposure and may increase the likelihood of adverse events.</i></p>	<p>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.</p> <p>Moderate and strong CYP3A4 inhibitors are prohibited because concomitant administration is predicted to increase laquinimod exposure and may increase the likelihood of adverse events.</p>	<p>New text for clarification.</p>
<b>REFERENCES</b>		
<p><del>Wegner C, Stadelmann C, Pfortner R, Raymond E, Feigelson S, Alon R et al. Laquinimod interferes with migratory capacity of T cells and reduces IL-17 levels, inflammatory demyelination and acute axonal damage in mice with experimental autoimmune encephalomyelitis. J Neuroimmunol. 2010;227(1-2):133-43</del></p> <p>Brück W, Pfortner R, Pham T, Zhang J, Hayardeny L, Piryatinsky V et al. Reduced astrocytic NF-<math>\kappa</math>B activation by laquinimod protects from cuprizone induced demyelination. Acta Neuropathol. 2012 Sep;124(3):411-</p>	<p>(Deleted from list)</p>	<p>These reference are no longer relevant following the revision of the text in Section 1.1.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>24</p> <p>Aharoni R, Saada R, Eilam R, Hayardeny L, Sela M, Arnon R. Oral treatment with laquinimod augments regulatory T cells and brain derived neurotrophic factor expression and reduces injury in the CNS of mice with experimental autoimmune encephalomyelitis. J Neuroimmunol. 2012;251(1-2):14-24.</p>		

## 16.2. ADMINISTRATIVE LETTER 07 DATED 05 NOVEMBER 2015



05 November 2015

Re: TV5600-CNS-20007 (LEGATO-HD)

Administrative change to the Protocol dated 16 February 2015

The purpose of this administrative letter #7 is to allow baseline MRS scans to be performed at the screening visit. Per protocol, the MRS scan (only at selected sites in a subgroup of patients) will be captured directly following the acquisition of the Baseline MRI scan.

For patients participating in the ancillary studies:

- MRI scans for MRS to explore the potential effect on metabolic changes in the putamen and frontal white matter will be done in a subgroup of patients at baseline and Month 12.

Per amendment #3 (dated 24SEP2015), the time window for the baseline MRI has been changed to ensure quality baseline MRI scan prior to treatment initiation.

The language will read: "The baseline MRI can be performed at the screening visit, but no later than 7 days prior to baseline. If performed at the screening visit, as many screening assessments as possible should be conducted prior to the MRI scan in order to assess eligibility."

This language will be updated in the current protocol amendment.

If you have any questions, please contact your CRA or the Teva Clinical Program Manager, Sarah Boe (sarah.boe@tevapharm.com).

Sincerely,

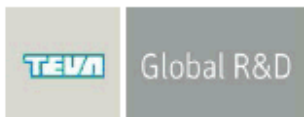
A handwritten signature in grey ink, appearing to read "Spyridon Papapetropoulos".

Spyridon Papapetropoulos, MD, PhD  
Global Head, Neurodegeneration, Clinical Development  
Global Research and Development  
Teva Pharmaceuticals

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### 16.3. ADMINISTRATIVE LETTER 06 DATED 22 OCTOBER 2015



22 October 2015

Re: TV5600-CNS-20007 (LEGATO-HD)

Administrative change to the Protocol dated 16 February 2015

The purpose of this administrative letter is to allow baseline MRI scans to be performed at the screening visit.

The protocol currently states: "The baseline MRI may be performed as soon as possible after confirmation of eligibility but not less than 7 days prior to baseline."

The language will read: "The baseline MRI can be performed at the screening visit, but no later than 7 days prior to baseline. If performed at the screening visit, as many screening assessments as possible should be conducted prior to the MRI scan in order to assess eligibility."

This language will be updated in the current protocol amendment.

If you have any questions, please contact your CRA or the Teva Clinical Program Manager, Sarah Boe (sarah.boe@tevapharm.com).

Sincerely,

A handwritten signature in black ink, appearing to be "Spyridon Papapetropoulos", written over a horizontal line.

Spyridon Papapetropoulos, MD, PhD  
Global Head, Neurodegeneration, Clinical Development  
Global Research and Development  
Teva Pharmaceuticals

**16.4. SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03  
DATED 24 SEPTEMBER 2015**

The primary reason for this amendment is to update study eligibility requirements (i.e. shorter washout period from previous investigational product) and clarify various aspects of study conduct (i.e. option of MRI scan at screening was introduced and frequency of several scales was reduced to lessen patient burden, etc.).

The revisions listed below have been made to the protocol, as appropriate, and are considered substantial by the sponsor's Authorized Representative.

A comparison table showing substantive changes from Amendment 02 to Amendment 03 is provided below. Previous text is presented in the column titled "Original text with changes shown," and the revised or new text is presented in the column titled "new wording". Revised or new text is shown in ***bold italics*** and deletions are shown in strikethrough. Few formatting changes have also been made but are not detailed below.

Changes to the synopsis are not detailed in the table but have been made according to the corresponding changes in the body of the protocol.

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

The administrative letters issued since the release of Amendment 02 have been added to the summary of changes section. Also, although already mentioned in the amendment history page, the administrative letters preceding Amendment 02 have also been added for revision history tracking purposes, in line with current Teva standards.

Original text with changes shown	New wording	Reason/Justification for change
<b>TITLE PAGE</b>		
Clinical Study Protocol <i>with Amendment 02 03</i>	Clinical Study Protocol with Amendment 03	Revised to reflect amendment.
<p><b>Sponsor’s Safety Officer</b>  <del>Dana Gorsetman</del> <b>Orit Neudorfer</b>, MD                      Global Patient Safety &amp; PhV                      Teva Pharmaceutical Industries, Ltd.                      Tel: +972-3-9267531 <b>9148028</b></p>	<p><b>Sponsor’s Safety Officer</b>                      Orit Neudorfer, MD                      Global Patient Safety &amp; PhV                      Teva Pharmaceutical Industries, Ltd.                      Tel: +972-3- 9148028</p>	Updated to reflect the identity and contact details of the new safety physician.
<b>1 BACKGROUND INFORMATION</b>		
<b>Section 1.1 (Other sections affected by this change: 1.3.1)</b>		
Further, laquinimod was shown to cause a decrease of CYP3A4 activity and is a <del>potent</del> strong inducer of CYP1A enzymes.	Further, laquinimod was shown to cause a decrease of CYP3A4 activity and is a strong inducer of CYP1A enzymes.	Language updated for consistency with other laquinimod protocols and Investigator’s Brochure.
<b>Section 1.2</b>		
The capsules are packed in either high-density polyethylene (HDPE) bottles equipped with child-resistant caps <del>or aluminium/aluminium blister cards</del> and should be stored at room temperature (+15°C to +25°C), <del>with excursions permitted to +15°C to +30°C.</del>	The capsules are packed in either high-density polyethylene (HDPE) bottles equipped with child-resistant caps and should be stored at room temperature (+15°C to +25°C).	Clarification regarding the primary packaging configuration and storage.
<b>Section 1.4.1.3.1.</b>		
<p>To prevent such exposure, female patients who are of child-bearing potential (<i>for example women who are not postmenopausal or surgically sterilized</i>) <b>must practice an acceptable method of birth control</b> (see Section 7.2) <del>are required to use effective contraception</del> for 30 days before initiation of treatment, and 2 <b>acceptable</b> methods of <del>effective (acceptable) contraception</del> birth control throughout treatment and for 30 days after cessation of treatment. Use of <del>effective</del> <b>acceptable</b> contraception will be ascertained at every study visit.</p> <p>...</p> <p>All female patients should be counseled by the investigator about the potential risks of exposure to laquinimod during pregnancy and the need to use <del>effective</del> <b>acceptable</b> contraception and avoid pregnancy</p>	<p>To prevent such exposure, female patients who are of child-bearing potential (for example women who are not postmenopausal or surgically sterilized) must practice an acceptable method of birth control (see Section 7.2) for 30 days before initiation of treatment, and 2 acceptable methods of birth control throughout treatment and for 30 days after cessation of treatment. Use of acceptable contraception will be ascertained at every study visit.</p> <p>...</p> <p>All female patients should be counseled by the investigator about the potential risks of exposure to laquinimod during pregnancy and the need to use acceptable contraception and avoid pregnancy throughout treatment with laquinimod and</p>	Language updated for consistency with other laquinimod protocols.

Original text with changes shown	New wording	Reason/Justification for change
throughout treatment with laquinimod and for 30 days after cessation of treatment.	for 30 days after cessation of treatment.	
<b>3 STUDY DESIGN</b>		
<b>Section 3.2.3 (Other sections affected by this change: 9.6.1.3)</b>		
<p>...</p> <ul style="list-style-type: none"> <li>• Change from baseline in CDR-SB at Month 12/ET (evaluated at baseline and Months <del>6 and</del> 12)</li> <li>• Change from baseline in HADS at Month 12/ET (evaluated at baseline and Months <del>1, 3, 6, and</del> 12)</li> <li>• Change from baseline in PBA-s at Month 12/ET (evaluated at baseline and Months <del>1, 3, 6, and</del> 12)</li> </ul>	<p>...</p> <ul style="list-style-type: none"> <li>• Change from baseline in CDR-SB at Month 12/ET (evaluated at baseline and Month 12)</li> <li>• Change from baseline in HADS at Month 12/ET (evaluated at baseline and Month 12)</li> <li>• Change from baseline in PBA-s at Month 12/ET (evaluated at baseline and Month 12)</li> </ul>	To reduce patient burden, the CDR-SB, HADS and PBA-s scales will only be assessed at baseline and at Month 12/ET.
<b>Section 3.6</b>		
Female subjects will be reminded to continue using <del>an acceptable method of contraception</del> <b>2 methods of acceptable contraception throughout treatment duration, and</b> up to 30 days from the date from the last dose of the study drug, <b>and about the need to stop treatment immediately if pregnancy is suspected.</b>	Female subjects will be reminded to continue using 2 methods of acceptable contraception throughout treatment duration, and up to 30 days from the date from the last dose of the study drug, and about the need to stop treatment immediately if pregnancy is suspected.	Language updated for consistency with other laquinimod protocols.
<b>Section 3.7.1</b>		
Laquinimod and matching placebo capsules must be stored at room temperature (15-25°C), in a dry place, and in a securely locked, substantially constructed cabinet or enclosure. Only authorized personnel will have access to the study drug. The study site personnel at each site will be responsible for correct storage and handling of the study drug. <b>Maintenance of a temperature log (manual or automated) is required and should be available for review by the monitor for the duration of the study. The temperature shall be recorded daily and the max/min thermometer reset after each reading. Complete instructions on receipt, storage, and handling of study drugs will be detailed in the Pharmacy Manual.</b>	Laquinimod and matching placebo capsules must be stored at room temperature (15-25°C), in a dry place, and in a securely locked, substantially constructed cabinet or enclosure. Only authorized personnel will have access to the study drug. The study site personnel at each site will be responsible for correct storage and handling of the study drug. Maintenance of a temperature log (manual or automated) is required and should be available for review by the monitor for the duration of the study. The temperature shall be recorded daily and the max/min thermometer reset after each reading. Complete instructions on receipt, storage, and handling of study drugs will be detailed in the Pharmacy Manual.	Clarification.
<b>Section 3.7.2</b>		
During the study, all <b>used and</b> unused study drugs and the corresponding accountability forms must be returned by the monitor to the sponsor or sponsor’s designee on an on-going basis for	During the study, all used and unused study drugs and the corresponding accountability forms must be returned by the monitor to the sponsor or sponsor’s designee on an on-going	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
reconciliation and destruction, <i>with account given for any discrepancies</i> . A photocopy of these records must be kept at the study sites.	basis for reconciliation and destruction, with account given for any discrepancies . A photocopy of these records must be kept at the study sites.	
<b>Section 3.10</b>		
Approximately 400 patients from ~ <del>35</del> <b>51</b> investigational centers in North America <del>and</del> , Europe <i>and Russia</i> are planned to be enrolled in the study.	Approximately 400 patients from ~51 investigational centers in North America, Europe and Russia are planned to be enrolled in the study.	Updated number of and location of centers.
<b>Section 3.11 – Table 3</b>		
No "X" in MRI scan row at the screening visit.	"X" added to the MRI scan row at screening, and reference to footnote m.	The option to perform the MRI scan at screening has been introduced to reduce patient burden.
(Not applicable)	A row for the anemia panel has been added to the table.	Newly added procedure for consistency with other laquinimod protocols.
Row name "Ascertaining use of <del>effective</del> <i>acceptable</i> contraception"	Row name changed to "Ascertaining use of acceptable contraception"	Language updated for consistency with other laquinimod protocols.
PBA-s was assessed at baseline and at Months 1, 3, 6 and 12 CDR-SB was assessed at baseline and at Months 6 and 12 HADS was assessed at baseline and at Months 1, 3, 6 and 12	PBA-s is assessed at baseline and at Month 12. CDR-SB is assessed at baseline and at Month 12. HADS is assessed at baseline and at Month 12.	To reduce patient burden, these scales will only be assessed at baseline and at Month 12/ET.
(Not applicable)	Footnote f: Anemia panel includes B12, blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, IFN- , TNF- , and hepcidin. Assessed at baseline and also at 1 subsequent time point with B12 if hemoglobin decrease of >1 g/dL from the patient's hemoglobin level at baseline and the decrease is confirmed.	Newly added footnote for clarification regarding the anemia panel.
Footnote <del>i</del> <b>j</b> : ECG will be performed in triplicate at baseline ( <i>approximately 10±5 minutes apart</i> ). All other visits will have a single ECG performed.	Footnote j: ECG will be performed in triplicate at baseline (approximately 10±5 minutes apart). All other visits will have a single ECG performed.	Clarification regarding ECG measurements.
Footnote <del>j</del> <b>k</b> : At the screening visit, only serum -HCG test will be	Footnote k: At the screening visit, only serum -HCG test	Clarification that both

Original text with changes shown	New wording	Reason/Justification for change
<p>performed. For the baseline visit - <del>Serum</del> <b>urine</b> pregnancy test (beta human chorionic gonadotropin [ -hCG]) result is required for women of child-bearing potential <del>within the 7 days</del> prior to randomization. <del>Whenever possible, this should be sent to the central laboratory for analysis. The sample may be sent to a local laboratory if timing does not permit sending to the central laboratory.</del> <b>The urine test may be conducted at the site to allow randomization. A serum -HCG test should also be used to confirm the urine test; however, the randomization should be performed based on the results of the urine pregnancy test.</b></p>	<p>will be performed. For the baseline visit - urine pregnancy test (beta human chorionic gonadotropin [ -hCG]) result is required for women of child-bearing potential prior to randomization. The urine test may be conducted at the site to allow randomization. A serum -HCG test should also be used to confirm the urine test; however, the randomization should be performed based on the results of the urine pregnancy test.</p>	<p>urine and pregnancy tests will be performed at baseline, and the randomization will be based on the results of urine pregnancy test.</p>
<p>Footnote <del>m n</del>: The baseline MRI <del>may be performed as soon as possible after confirmation of eligibility but not less than 7 days prior to baseline</del> <b>can be performed at the screening visit, but no later than 7 days prior to baseline. If performed at the screening visit, as many screening assessments as possible should be conducted prior to the MRI scan.</b></p>	<p>Footnote <del>m n</del>: The baseline MRI can be performed at the screening visit, but no later than 7 days prior to baseline. If performed at the screening visit, as many screening assessments as possible should be conducted prior to the MRI scan in order to assess eligibility.</p>	<p>The time window for the baseline MRI has been changed to reduce patient burden but ensure quality baseline MRI scan prior to randomization.</p>
<p><b>Section 3.11.1</b></p>		
<ul style="list-style-type: none"> <li>• ...</li> <li>• perform full physical examination (including weight and height)</li> <li>• serum -HCG in women of child-bearing potential <del>within the 7 days prior to initiation of treatment</del></li> <li>• HD-CAB             <ul style="list-style-type: none"> <li>○ Includes Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLTR), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version)</li> <li>○ The HD-CAB is performed at screening to reduce practice effects during the treatment phase.</li> </ul> </li> <li>• <b>MRI scan</b> <ul style="list-style-type: none"> <li>○ <b>The baseline MRI can be performed at the</b></li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• ...</li> <li>• perform full physical examination (including weight and height)</li> <li>• serum -HCG in women of child-bearing potential</li> <li>• HD-CAB             <ul style="list-style-type: none"> <li>○ Includes Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLTR), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version)</li> <li>○ The HD-CAB is performed at screening to reduce practice effects during the treatment phase.</li> </ul> </li> <li>• MRI scan</li> </ul>	<p>The option to perform the MRI scan at screening has been introduced to reduce patient burden.</p> <p>Clarification regarding time frame of the serum -HCG test.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><i>screening visit, but no later than 7 days prior to baseline. If performed at the screening visit, as many screening assessments as possible should be conducted prior to the MRI scan in order to assess eligibility.</i></p> <ul style="list-style-type: none"> <li>inform patients of study restrictions and compliance requirements</li> </ul>	<ul style="list-style-type: none"> <li>The baseline MRI can be performed at the screening visit, but no later than 7 days prior to baseline. If performed at the screening visit, as many screening assessments as possible should be conducted prior to the MRI scan in order to assess eligibility.</li> <li>inform patients of study restrictions and compliance requirements</li> </ul>	
<b>Section 3.11.2</b>		
<ul style="list-style-type: none"> <li>review inclusion/exclusion criteria</li> <li>perform clinical laboratory tests</li> <li><b>clinical hematology</b></li> <li>anemia panel (blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, interleukin [IL]-1, IL-6, interferon [IFN]- , tumor necrosis factor [TNF]- , and hepcidin) and B12</li> </ul> <p>...</p> <ul style="list-style-type: none"> <li>perform vital signs measurements</li> <li>ECG – in triplicate (<i>approximately 10±5 minutes apart</i>)</li> <li>urine -HCG in women of child-bearing potential             <ul style="list-style-type: none"> <li><i>The urine test should be conducted at the site to allow randomization. A serum -HCG test should also be used to confirm the urine test; however, the randomization should be performed based on the results of the urine pregnancy test.</i></li> </ul> </li> <li>serum -HCG in women of child-bearing potential</li> <li><del>Serum pregnancy test ( -HCG) is performed by the central lab within 7 days prior to the baseline visit and result obtained prior to randomization—no need for additional test in Baseline visit. The sample should be sent to the lab at least 48 hours prior to the baseline visit to ensure results are available.</del></li> <li><del>Serum pregnancy test ( -HCG) is performed by a local lab within 7 days prior to the baseline visit, or at the day of the baseline visit, and result obtained prior to randomization at</del></li> </ul>	<ul style="list-style-type: none"> <li>review inclusion/exclusion criteria</li> <li>perform clinical laboratory tests</li> <li>clinical hematology</li> <li>anemia panel (blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, interleukin [IL]-1, IL-6, interferon [IFN]- , tumor necrosis factor [TNF]- , and hepcidin) and B12</li> </ul> <p>...</p> <ul style="list-style-type: none"> <li>perform vital signs measurements</li> <li>ECG – in triplicate (approximately 10±5 minutes apart)</li> <li>urine -HCG in women of child-bearing potential             <ul style="list-style-type: none"> <li>The urine test should be conducted at the site to allow randomization. A serum -HCG test should also be used to confirm the urine test; however, the randomization should be performed based on the results of the urine pregnancy test.</li> </ul> </li> <li>serum -HCG in women of child-bearing potential</li> <li>additional urine -HCG in women of child-bearing potential at PET facilities (<b>Only in a subgroup of patients</b>)</li> <li>Ascertaining use of acceptable contraception</li> <li>C-SSRS (since last visit version)</li> <li>MRI scan             <ul style="list-style-type: none"> <li>The baseline MRI can be performed at</li> </ul> </li> </ul>	<p>Anemia panel added at baseline for consistency with other laquinimod protocols.</p> <p>Clarification regarding ECG measurement.</p> <p>The time window for the baseline MRI has been changed to reduce patient burden but ensure quality baseline MRI scan prior to randomization.</p> <p>Placement of urine pregnancy test in list modified.</p> <p>Clarification that both urine and pregnancy tests will be performed at baseline, and the randomization will be based on the results of urine pregnancy test.</p> <p>Statement on performance of</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><del>the baseline visit day. If the local lab sample is collected on the baseline visit day, a sample does not need to be sent to the central laboratory as well.</del>  Results must be obtained prior to randomizing the patient, documented in an official lab report and filed with patient's source documents. In case an unscheduled visit is performed, all mandatory activities according to the protocol, for this visit, should be performed.</p> <ul style="list-style-type: none"> <li><del>• urine -HCG in women of child bearing potential</del></li> <li>• additional urine -HCG in women of child-bearing potential at PET facilities (<b>Only in a subgroup of patients</b>)</li> <li>• Ascertaining use of <del>effective</del> <b>acceptable</b> contraception</li> <li>• C-SSRS (since last visit version)</li> <li>• MRI scan <ul style="list-style-type: none"> <li>○ The baseline MRI <del>can be performed as soon as possible after confirmation of eligibility but not less than 7 days prior to baseline.</del> <b>can be performed at the screening visit, but no later than 7 days prior to baseline.</b></li> <li>○ If anxiolysis is required in order to perform the MRI scan, the scan should be performed at the end of the study visit day.</li> </ul> </li> </ul> <p>...</p> <ul style="list-style-type: none"> <li>• Randomization</li> <li>• Study drug dispensing</li> </ul> <p><b><i>In case an unscheduled visit is performed, all mandatory activities according to the protocol, for this visit, should be performed.</i></b></p> <p>A patient who does not meet the inclusion/exclusion criteria may be considered for screening again if there is a change in the patient's medical background, a modification of study entry criteria, or other relevant change.</p> <p>...</p>	<p>the screening visit, but no later than 7 days prior to baseline.</p> <ul style="list-style-type: none"> <li>○ If anxiolysis is required in order to perform the MRI scan, the scan should be performed at the end of the study visit day.</li> </ul> <p>...</p> <ul style="list-style-type: none"> <li>• Randomization</li> <li>• Study drug dispensing</li> </ul> <p>In case an unscheduled visit is performed, all mandatory activities according to the protocol, for this visit, should be performed.</p> <p>A patient who does not meet the inclusion/exclusion criteria may be considered for screening again if there is a change in the patient's medical background, a modification of study entry criteria, or other relevant change.</p> <p>...</p>	<p>procedures in case of unscheduled visit moved below.</p>
<b>Section 3.11.3.1.1</b>		
<p>..</p> <ul style="list-style-type: none"> <li>• Ascertaining use of <del>effective</del> acceptable contraception</li> <li>• C-SSRS (since last visit version)</li> </ul>	<p>..</p> <ul style="list-style-type: none"> <li>• Ascertaining use of acceptable contraception</li> <li>• C-SSRS (since last visit version)</li> </ul>	<p>Language updated for consistency with other laquinimod protocols.</p>



Original text with changes shown	New wording	Reason/Justification for change
<ul style="list-style-type: none"> <li>• UHDRS-TMS</li> <li>• <del>PBA-s</del></li> <li>• Q-Motor assessments</li> <li>• <del>HADS</del></li> <li>• Reduced cognitive battery (only SDMT and Trail Making Test)</li> </ul> <p>...</p>	<ul style="list-style-type: none"> <li>• UHDRS-TMS</li> <li>• Q-Motor assessments</li> <li>• Reduced cognitive battery (only SDMT and Trail Making Test)</li> </ul> <p>...</p>	<p>To reduce patient burden, the PBA-s and the HADS will only be assessed at baseline and at Month 12/ET.</p>
<b>Section 3.11.3.1.2</b>		
Use of <del>effective</del> acceptable contraception will be ascertained.	Use of acceptable contraception will be ascertained.	Language updated for consistency with other laquinimod protocols.
<b>Section 3.11.3.1.3</b>		
<p>...</p> <ul style="list-style-type: none"> <li>• Ascertaining use of <del>effective</del> <b>acceptable</b> contraception</li> <li>• C-SSRS (since last visit version)</li> <li>• UHDRS-TMS</li> <li>• UHDRS-TFC</li> <li>• UHDRS-FA</li> <li>• mPPT</li> <li>• <del>PBA-s</del></li> <li>• CIBIC-plus</li> <li>• Q-Motor assessments</li> <li>• HD-CAB</li> <li>• Includes Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLTR), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version)</li> <li>• <del>CDR-SB</del></li> <li>• <del>HADS</del></li> <li>• PK drug concentration sampling</li> </ul> <p>...</p>	<p>...</p> <ul style="list-style-type: none"> <li>• Ascertaining use of acceptable contraception</li> <li>• C-SSRS (since last visit version)</li> <li>• UHDRS-TMS</li> <li>• UHDRS-TFC</li> <li>• UHDRS-FA</li> <li>• mPPT</li> <li>• CIBIC-plus</li> <li>• Q-Motor assessments</li> <li>• HD-CAB</li> <li>○ Includes Symbol Digit Modalities Test (SDMT), Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised (HVLTR), Paced Tapping at 3 Hz, One Touch Stockings of Cambridge (OTS, abbreviated 10 trial version)</li> <li>• PK drug concentration sampling</li> </ul> <p>...</p>	<p>Language updated for consistency with other laquinimod protocols.</p> <p>To reduce patient burden, the PBA-s, the CDR-SB and the HADS will only be assessed at baseline and at Month 12/ET.</p>
<b>Section 3.11.3.1.4 (Other sections affected by this change: 3.11.3.1.5; 3.11.4.1; 3.11.5)</b>		
<p>...</p> <ul style="list-style-type: none"> <li>• Ascertaining use of <del>effective</del> <b>acceptable</b> contraception</li> </ul> <p>...</p>	<p>...</p> <ul style="list-style-type: none"> <li>• Ascertaining use of acceptable contraception</li> </ul> <p>...</p>	Language updated for consistency with other laquinimod protocols.

Original text with changes shown	New wording	Reason/Justification for change
<b>4 SELECTION AND WITHDRAWAL OF PATIENTS</b>		
<b>Section 4.1 (Other sections affected by this change: 7.2; 7.3.5; Appendix A, Section 5)</b>		
<p>d. <b>[Revision 1]</b> Women of child-bearing potential (women who are not post menopausal or who have <i>not</i> undergone surgical sterilization) must practice an acceptable method of birth control for 30 days before taking the study treatment, and 2 acceptable methods of birth control during all study duration and until 30 days after the last dose of treatment was administered. Acceptable methods of birth control in this study include: Intrauterine device, barrier method (condom or diaphragm with spermicide) and hormonal methods of birth control (e.g., oral contraceptive, contraceptive patch, long-acting injectable contraceptive).</p>	<p>d. [Revision 1] Women of child-bearing potential (women who are not post menopausal or who have not undergone surgical sterilization) must practice an acceptable method of birth control for 30 days before taking the study treatment, and 2 acceptable methods of birth control during all study duration and until 30 days after the last dose of treatment was administered. Acceptable methods of birth control in this study include: Intrauterine device, barrier method (condom or diaphragm with spermicide) and hormonal methods of birth control (e.g., oral contraceptive, contraceptive patch, long-acting injectable contraceptive).</p>	<p>Corrected per Administrative Letter 05 Issued 29 April 2015.</p>
<b>Section 4.2</b>		
<p>q. <b>[Revision 1]</b> Treatment with any investigational product within <del>12 weeks</del> <b>30 days</b> of screening or patients planning to participate in another clinical study assessing any investigational product during the study. <b><i>Patients in non-interventional and/or observational studies will not be excluded from participating in this study.</i></b></p>	<p>q. <b>[Revision 1]</b> Treatment with any investigational product within 30 days of screening or patients planning to participate in another clinical study assessing any investigational product during the study. Patients in non-interventional and/or observational studies will not be excluded from participating in this study.</p>	<p>Washout time from previous investigational product shortened.  Correction of the criterion to match the wording in the synopsis.</p>
<b>5 TREATMENT OF PATIENTS</b>		
<b>Section 5.2</b>		
<p><del>Patients will begin to fast (no food or beverages) at approximately 22:00 hours on the evening prior to each morning visit that will require fasting blood draws.</del> For visits 2 through 9, patients must have fasted (<b><i>no food or beverages</i></b>) no less than 8 hours prior to <b><i>each morning visit that will require fasting blood draws</i></b> (i.e. a blood draw for the lipid profile, or for the safety laboratory panels which include clinical chemistries and hormone concentrations).</p>	<p>For visits 2 through 9, patients must have fasted (no food or beverages) no less than 8 hours prior to each morning visit that will require fasting blood draws (i.e. a blood draw for the lipid profile, or for the safety laboratory panels which include clinical chemistries and hormone concentrations).</p>	<p>Clarification regarding the required fasting prior to blood draws.</p>
<b>Section 5.3.1.</b>		
<p>The following medications will <u>not be allowed</u> <b><i>prior to and</i></b> during this study:</p>	<p>The following medications will <u>not be allowed</u> prior to and during this study:</p>	<p>Clarification regarding time window for</p>

Original text with changes shown	New wording	Reason/Justification for change
<ul style="list-style-type: none"> <li>• Use of tetrabenazine within 30 days prior to baseline <i>and during the study</i>;</li> <li>• Use of antipsychotic medication within 30 days prior to baseline <i>and during the study</i>;</li> <li>• Use of moderate/strong inhibitors of CYP3A4 within 2 weeks prior to randomization, <i>during the study and until 30 days after the last study dose has been administered.</i></li> <li>• Use of inducers of CYP3A4 within 2 weeks prior to randomization <i>and during the study</i>;</li> <li>• Immunosuppressive or immunomodulating agents, or cytotoxic agents, including cyclophosphamide and azathioprine within 12 months prior to screening <i>and during the study</i>;</li> <li>• Use of experimental or investigational drugs and/or participation in drug clinical studies within <del>12 weeks</del> <i>30 days</i> of screening</li> </ul>	<ul style="list-style-type: none"> <li>• Use of tetrabenazine within 30 days prior to baseline and during the study;</li> <li>• Use of antipsychotic medication within 30 days prior to baseline and during the study;</li> <li>• Use of moderate/strong inhibitors of CYP3A4 within 2 weeks prior to randomization, during the study and until 30 days after the last study dose has been administered.</li> <li>• Use of inducers of CYP3A4 within 2 weeks prior to randomization and during the study;</li> <li>• Immunosuppressive or immunomodulating agents, or cytotoxic agents, including cyclophosphamide and azathioprine within 12 months prior to screening and during the study;</li> <li>• Use of experimental or investigational drugs and/or participation in drug clinical studies within 30 days of screening</li> </ul>	<p>disallowed medications. Washout time from previous investigational product shortened.</p>
<b>6 ASSESSMENT OF EFFICACY</b>		
<b>Section 6.3.8</b>		
<p><b>6.3.8. Change from baseline in CDR-SB at Month 12/ET (evaluated at baseline and Months <del>6 and</del> 12)</b></p>	<p><b>6.3.8. Change from baseline in CDR-SB at Month 12/ET (evaluated at baseline and Month 12)</b></p>	<p>To reduce patient burden, the CDR-SB will only be assessed at baseline and at Month 12/ET.</p>
<b>Section 6.3.9</b>		
<p><b>6.3.9 Change from baseline in HADS at Month 12/ET (evaluated at baseline and Months <del>1, 3, 6 and</del> 12)</b></p>	<p><b>6.3.9 Change from baseline in HADS at Month 12/ET (evaluated at baseline and Month 12)</b></p>	<p>To reduce patient burden, the HADS will only be assessed at baseline and at Month 12/ET.</p>
<b>Section 6.3.10</b>		
<p><b>6.3.10 Change from Baseline in Problem Behaviors Assessment-Short Form (PBA-s) at Month 12/ET (Evaluated at Baseline and Months <del>1, 3, 6, and</del> 12)</b></p>	<p><b>6.3.10 Change from Baseline in Problem Behaviors Assessment-Short Form (PBA-s) at Month 12/ET (Evaluated at Baseline and Month 12)</b></p>	<p>To reduce patient burden, the PBA-s will only be assessed at baseline and at Month 12/ET.</p>

Original text with changes shown	New wording	Reason/Justification for change
<b>7 ASSESSMENT OF SAFETY</b>		
<b>Section 7.1.5.3.1</b>		
<p>The following information should be provided to record the event accurately and completely:</p> <p>...</p> <ul style="list-style-type: none"> <li>• <del>patient initials</del></li> <li>• onset date and <i>detailed</i> description of adverse event</li> </ul> <p>...</p> <p>Additional information may include the following:</p> <p>...</p> <ul style="list-style-type: none"> <li>• <i>explanation of assessment of relatedness</i></li> </ul> <p>...</p> <p><del>The sponsor or its designee must ensure that the IEC/IRB is also informed of the event, in accordance with local regulations. The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with local regulations.</del></p> <p><i>For all countries</i>, the sponsor’s Global Patient Safety &amp; Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO/CRO for local submission to the regulatory authorities and IEC/IRBs and investigators, according to regulations.</p>	<p>The following information should be provided to record the event accurately and completely:</p> <p>...</p> <ul style="list-style-type: none"> <li>• onset date and detailed description of adverse event</li> </ul> <p>...</p> <p>Additional information may include the following:</p> <p>...</p> <ul style="list-style-type: none"> <li>• explanation of assessment of relatedness</li> </ul> <p>...</p> <p>The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with local regulations.</p> <p>For all countries, the sponsor’s Global Patient Safety &amp; Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO/CRO for local submission to the regulatory authorities and IEC/IRBs and investigators, according to regulations.</p>	<p>Text has been updated in line with current Teva standards</p>
<b>Section 7.1.9</b>		
<p>(Not applicable)</p>	<p><b>7.1.9 Medication Error and Special Situations</b></p> <p>Any administration of study medication that is not in accordance with the study protocol should be reported on the CRF either as a violation, if it meets the violation criteria according to the protocol (Section 11.1.2), or as a deviation in the patients source documents, regardless of whether an adverse event occurs as a result. All instances of incorrect medication administration should be categorized as 'Non-Compliance to IMP'.</p> <p>Types of Medication Errors and/or special situations:</p> <p>1. Medication error - Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient or consumer.</p>	<p>New text added for clarification regarding medication errors and special situations.</p>

Original text with changes shown	New wording	Reason/Justification for change
	<p>2. Overdose - Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.</p> <p>3. Misuse - Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.</p> <p>4. Abuse - Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.</p> <p>5. Off-label use - Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.</p> <p>6. Occupational exposure- Exposure to a medicinal product, as a result of one’s professional or non-professional occupation.</p>	
<b>Section 7.2 (Other sections affected by this change: Appendix A, Section 5</b>		
<p>To further emphasize the importance of use of <del>effective</del><b>acceptable</b> contraception and avoidance of pregnancy under laquinimod exposure, and to reduce as much as possible the exposure to laquinimod if a pregnancy occurs despite all recommended measures, all women of childbearing potential (for example women who are not postmenopausal or have <b>not</b> undergone surgical sterilization) and not using <del>effective</del><b>acceptable methods of</b> contraception, will be instructed about the teratogenicity and potential delayed risks for a child exposed in utero to laquinimod. These subjects will be counseled about the importance of using <del>effective</del><b>2 acceptable methods of</b> contraception throughout the entire study 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. Patients who are women of childbearing potential must use <del>2 effective</del><b>acceptable</b> methods of contraception for 30 days prior to initiation of treatment, throughout treatment duration and until 30 days after the last dose of treatment.</p>	<p>To further emphasize the importance of use of effective contraception and avoidance of pregnancy under laquinimod exposure, and to reduce as much as possible the exposure to laquinimod if a pregnancy occurs despite all recommended measures, all women of childbearing potential (for example women who are not postmenopausal or have not undergone surgical sterilization) and not using acceptable methods of contraception, will be instructed about the teratogenicity and potential delayed risks for a child exposed in utero to laquinimod. These subjects will be counseled about the importance of using 2 acceptable methods of contraception throughout the entire study 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. Patients who are women of childbearing potential must use 2 acceptable methods of contraception for 30 days prior to initiation of treatment, throughout treatment duration and until 30 days after the last dose of treatment.</p>	<p>Correction per Administrative Letter 05 Issued 29 April 2015.</p> <p>Language updated for consistency with other laquinimod protocols.</p>

Original text with changes shown	New wording	Reason/Justification for change
<b>Section 7.3.1</b>		
<p>...</p> <ul style="list-style-type: none"> <li>• creatine phosphokinase (CPK)</li> <li><del>○ Troponin or CPK-MB and will be tested in case of abnormal CPK results</del></li> <li><i>in case of CPK results &gt;ULN, troponin or creatine kinase MB isoenzyme (CK-MB) will be tested by the central laboratory.</i></li> <li>○ In case of CPK &gt; 10 ULN <del>Urine Myoglobin will be tested</del> <i>an unscheduled visit to assess urine myoglobin will be required. The following blood tests will be repeated at the unscheduled visit: CPK, blood urea nitrogen, creatinine, electrolytes including potassium, calcium, phosphate.</i></li> <li>• total protein</li> </ul> <p>...</p>	<p>...</p> <ul style="list-style-type: none"> <li>• creatine phosphokinase (CPK)</li> <li>○ in case of CPK results &gt;ULN, troponin or creatine kinase MB isoenzyme (CK-MB) will be tested by the central laboratory.</li> <li>○ in case of CPK &gt;10×ULN, an unscheduled visit to assess urine myoglobin will be required. The following blood tests will be repeated at the unscheduled visit: CPK, blood urea nitrogen, creatinine, electrolytes including potassium, calcium, phosphate.</li> <li>• total protein</li> </ul> <p>...</p>	<p>Clarification regarding monitoring in case of increased CPK for consistency with other laquinimod protocols.</p>
<b>Section 7.3.2</b>		
<p>The following hematology tests will be performed:</p> <ul style="list-style-type: none"> <li>• Hemoglobin</li> <li><del>• In case of hemoglobin decrease of &gt;1g/dL from the subject's hemoglobin level at baseline:</del></li> <li><del>–Subject will be re-tested to ascertain true decrease</del></li> <li><del>–If true decrease, a thorough anemia work up will be done including:</del> <ul style="list-style-type: none"> <li><del>○ Directed medical history and physical examination</del></li> <li><del>○ Blood smear, serum iron, ferritin, total iron binding capacity, folic acid, B12, haptoglobin, and serum sample for cytokines</del></li> <li><del>○ Additional investigations and follow up per the investigator's discretion or Sponsor's request.</del></li> </ul> </li> <li>• hematocrit</li> </ul> <p>...</p>	<p>The following hematology tests will be performed:</p> <ul style="list-style-type: none"> <li>• Hemoglobin</li> <li>• hematocrit</li> </ul> <p>...</p>	<p>Following the addition of the anemia panel to baseline, this section has been deleted from here, moved to a separate subsection (7.3.3) and clarified.</p>
<b>Section 7.3.3</b>		
<p>(Previous wording from Section 7.3.2) <i>The anemia panel is assessed at baseline (with B12) and also at 1</i></p>	<p><b>7.3.3. Anemia Panel</b> The anemia panel is assessed at baseline(with B12) and also</p>	<p>Following the addition of the anemia panel to</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><i>subsequent time point if hemoglobin decrease of &gt;1 g/dL from the patient's hemoglobin level at baseline and the decrease is confirmed.</i></p> <p>• <i>At baseline: B12, blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, interferon IFN- , TNF- , and hepcidin.</i></p> <p>In case of hemoglobin decrease of &gt;1g/dL from the subject's hemoglobin level at baseline</p> <ul style="list-style-type: none"> <li>- Subject will be re-tested to ascertain true decrease</li> <li>- If <del>true decrease</del> <i>decrease confirmed</i>, a thorough anemia work-up will be done including: <ul style="list-style-type: none"> <li>○ Directed medical history and physical examination</li> <li>○ <i>Anemia panel</i> (Blood smear, serum iron, ferritin, total iron binding capacity, folic acid, <del>B12</del>, haptoglobin, <del>and serum sample for cytokines</del> IL-1, IL-6, IFN- , TNF- , and hepcidin)-<i>and B12</i></li> <li>○ Additional investigations and follow-up per the investigator's discretion or Sponsor's request</li> </ul> </li> </ul>	<p>at 1 subsequent time point if hemoglobin decrease of &gt;1 g/dL from the patient's hemoglobin level at baseline and the decrease is confirmed.</p> <ul style="list-style-type: none"> <li>• At baseline: B12, blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, interferon IFN- , TNF- , and hepcidin.</li> <li>• In case of hemoglobin decrease of &gt;1 g/dL from the patient's hemoglobin level at baseline: <ul style="list-style-type: none"> <li>– patient will be re-tested to ascertain true decrease</li> <li>– if decrease confirmed, a thorough anemia work-up will be done including: <ul style="list-style-type: none"> <li>○ Directed medical history and physical examination</li> <li>○ anemia panel (blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, IFN- , TNF- , and hepcidin) and B12</li> <li>○ additional investigations and follow-up per the investigator's discretion or sponsor's request</li> </ul> </li> </ul> </li> </ul>	<p>baseline, newly created section with explanation and guidance regarding the anemia panel.</p> <p>Some text moved from Section 7.3.2 and clarified for consistency with other laquinimod protocols.</p>
<b>Section 7.3.5</b>		
<p>(Previous wording from Section 7.3.4)</p> <p>Human chorionic gonadotropin ( -hCG) serum test will be performed for all women of childbearing potential (women who are not post menopausal or who have not undergone surgical sterilization) at screening (Visit 1) and at all subsequent study visits. <del>An indeterminate reading for the serum pregnancy test should be checked twice (urine test) and the patient referred to a gynecologist if required;</del> <i>Age-appropriate normal ranges for HCG should be used. If the reading for the serum pregnancy test is indeterminate, the test should be repeated after 3-4 days to see whether there is an increase in -hCG or whether it is a stable elevation. If no increase is observed, the patient will not be considered to be pregnant. However,</i> no study drug will be administered until this is resolved.</p> <p>Urine -hCG tests will be performed for all women of childbearing potential at baseline (Visit 2), and at all subsequent visits, and if clinically indicated at any other time.</p>	<p><b>7.3.5. Human Chorionic Gonadotrophin Tests</b></p> <p>Human chorionic gonadotropin ( -hCG) serum test will be performed for all women of childbearing potential (women who are not post menopausal or who have not undergone surgical sterilization) at screening (Visit 1) and at all subsequent study visits. Age-appropriate normal ranges for HCG should be used. If the reading for the serum pregnancy test is indeterminate, the test should be repeated after 3-4 days to see whether there is an increase in -hCG or whether it is a stable elevation. If no increase is observed, the patient will not be considered to be pregnant. However, no study drug will be administered until this is resolved.</p> <p>Urine -hCG tests will be performed for all women of childbearing potential at baseline (Visit 2), and at all subsequent visits, and if clinically indicated at any other time.</p>	<p>Correction per Administrative Letter 05 Issued 29 April 2015.</p> <p>Clarification regarding procedure in case of indeterminate serum - hCG test.</p> <p>A serum -hCG test is performed at screening only; urine pregnancy tests at all other visits.</p>

Original text with changes shown	New wording	Reason/Justification for change
<b>Section 7.5</b>		
<p>A single 12-lead ECG will be conducted at screening (Visit 1), and at the following in-clinic visits: Week 4, Week 13, Week 26, Week 52 and follow-up (Visits 3, 4, 6, 8 and 9). During the baseline visit (Visit 2) <i>a</i> 12-lead ECG will be conducted in triplicate (<i>approximately 10±5 minutes apart</i>)</p> <p>....</p>	<p>A single 12-lead ECG will be conducted at screening (Visit 1), and at the following in-clinic visits: Week 4, Week 13, Week 26, Week 52 and follow-up (Visits 3, 4, 6, 8 and 9). During the baseline visit (Visit 2) a 12-lead ECG will be conducted in triplicate (approximately 10±5 minutes apart).</p> <p>...</p>	<p>Clarification regarding ECG measurements.</p>
<b>APPENDIXA</b>		
<p><b>Section 1.1.1.</b></p> <p>...</p> <p>ALT, AST, GGT, ALP, total and direct bilirubin, CBC and differential (to assess for eosinophilia) and INR should be monitored on days 5 (±2), 8 (±2), 14 (±2 3), and 28 (±2 3). On at least 1 of these days, the test should be performed centrally. (INR should be sent to a local laboratory only.)</p> <p>...</p>	<p><b>Section 1.1.1.</b></p> <p>...</p> <p>ALT, AST, GGT, ALP, total and direct bilirubin, CBC and differential (to assess for eosinophilia) and INR should be monitored on days 5 (±2), 8 (±2), 14 (±3), and 28 (±3). On at least 1 of these days, the test should be performed centrally. (INR should be sent to a local laboratory only.)</p> <p>...</p>	<p>Time window increased to ±3 days for the Day 14 and Day 28 monitoring of liver enzyme elevation.</p>
<p><b>5. Management of Pregnancy and Pregnancy Testing During the Study</b></p> <p><i>Exposure to laquinimod during pregnancy should be avoided.</i></p> <p>...</p> <p><i>The patients' understanding of the importance of preventive pregnancy measures and their ability to follow the required instructions will be ascertained by the investigator and recorded in source documents at every visit. Any female patient who becomes pregnant during the study will discontinue her participation in the study and will not perform the activities described for scheduled follow-up visits.</i></p> <p>To further emphasize the importance of use of <del>effective</del> <b>acceptable</b> contraception and avoidance of pregnancy under laquinimod exposure, and to reduce as much as possible the exposure to laquinimod if a pregnancy occurs despite all recommended measures, the following measures will be taken:</p> <p>1. Female subjects of child-bearing potential (women who are not post menopausal or who have <i>not</i> undergone surgical sterilization) will be reminded at each study visit about:</p> <p>a. The importance of using <del>effective</del> <b>acceptable</b> contraception.</p>	<p><b>5. Management of Pregnancy and Pregnancy Testing During the Study</b></p> <p>Exposure to laquinimod during pregnancy should be avoided.</p> <p>...</p> <p>The patients' understanding of the importance of preventive pregnancy measures and their ability to follow the required instructions will be ascertained by the investigator and recorded in source documents at every visit. Any female patient who becomes pregnant during the study will discontinue her participation in the study and will not perform the activities described for scheduled follow-up visits.</p> <p>To further emphasize the importance of use of acceptable contraception and avoidance of pregnancy under laquinimod exposure, and to reduce as much as possible the exposure to laquinimod if a pregnancy occurs despite all recommended measures, the following measures will be taken:</p> <p>1. Female subjects of child-bearing potential (women who are not post menopausal or who have not undergone surgical sterilization) will be reminded at each study visit about:</p> <p>a. The importance of using acceptable contraception.</p>	<p>Language updated for consistency with other laquinimod protocols.</p>



Original text with changes shown	New wording	Reason/Justification for change
<p>b. The importance of immediately stopping the study drug and informing the site in any case of suspected pregnancy (following a positive urine test, absence of menstruation or any other reason suggesting pregnancy).</p> <p>2. At each scheduled visit, female subjects of childbearing potential (women who are not post menopausal or who have <i>not</i> undergone surgical sterilization) will undergo a urine -hCG test. In addition, a serum pregnancy -hCG test will be performed at each visit.</p> <p>...</p>	<p>b. The importance of immediately stopping the study drug and informing the site in any case of suspected pregnancy (following a positive urine test, absence of menstruation or any other reason suggesting pregnancy).</p> <p>2. At each scheduled visit, female subjects of childbearing potential (women who are not post menopausal or who have not undergone surgical sterilization) will undergo a urine -hCG test. In addition, a serum pregnancy -hCG test will be performed at each visit.</p> <p>...</p>	
(Not applicable)	<p><b>8. Guidance on monitoring subjects with hemoglobin decrease</b></p> <p>The anemia panel is assessed at baseline and also at 1 subsequent time point (with B12) if hemoglobin decrease of &gt;1 g/dL from the patient’s hemoglobin level at baseline and the decrease is confirmed.</p> <ul style="list-style-type: none"> <li>• At baseline: B12, blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, interferon IFN- , TNF- , and hepcidin.</li> <li>• In case of hemoglobin decrease of &gt;1 g/dL from the patient’s hemoglobin level at baseline: <ul style="list-style-type: none"> <li>– patient will be re-tested to confirm decrease</li> <li>– if decrease confirmed, a thorough anemia work-up will be done including: <ul style="list-style-type: none"> <li>• directed medical history and physical examination</li> <li>• anemia panel (blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, IFN- , TNF- , and hepcidin) and B12</li> <li>• additional investigations and follow-up per the investigator’s discretion or sponsor’s request</li> </ul> </li> </ul> </li> </ul>	<p>Newly added section to appendix to clarify monitoring of subjects with hemoglobin decrease.</p>
(Not applicable)	<p><b>9. Guidance on monitoring subjects with CPK increase</b></p> <ul style="list-style-type: none"> <li>• In case of CPK results &gt;ULN, troponin or creatine kinase MB isoenzyme (CK-MB) will be tested by the central laboratory.</li> <li>• In case of CPK &gt;10×ULN, an unscheduled visit to assess urine myoglobin will be required. The</li> </ul>	<p>Newly added section to appendix to clarify monitoring of subjects with CPK increase.</p>

Original text with changes shown	New wording	Reason/Justification for change
	<p>following blood tests will be repeated at the unscheduled visit: CPK, blood urea nitrogen, creatinine, electrolytes including potassium, calcium, phosphate.</p>	
<b>APPENDIX B</b>		
<p><b><i>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.</i></b></p> <p>Table 4: A Partial List of Moderate/Strong CYP3A4 Inhibitors. <del>These Drugs May Increase the Level of Laquinimod and Therefore Are Disallowed 2 Weeks Prior to Study, During Study and 30 Days After Last Study Dose.</del> (additional CYP3A4 inhibitor added to the medication class antivirals [elvitegravir])</p> <p>Notes:</p> <ul style="list-style-type: none"> <li>• 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, <del>we do not predict that</del> such interactions are expected with laquinimod.</li> <li>• <del>Moderate/strong CYP3A4 inhibitors are disallowed during 30 days after the last dose has been administered</del></li> </ul>	<p>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.</p> <p>Table 4: A Partial List of Moderate/Strong CYP3A4 Inhibitors Disallowed 2 Weeks Prior to Study, During Study and 30 Days After Last Study Dose. (see Appendix B for revised table)</p> <p>Note:</p> <ul style="list-style-type: none"> <li>• Interactions between drugs and grapefruit juice are documented for drugs with low bioavailability due to pre-systemic gut-wall metabolism. Based on the suggested high oral bioavailability of laquinimod in humans, such interactions are not expected with laquinimod.</li> </ul>	<p>Language updated for consistency with other laquinimod protocols and Investigator’s Brochure. 2<sup>nd</sup> note bullet deleted due to redundancy.</p>
<p><b><i>CYP3A4 inducers are disallowed within 2 weeks of baseline and during the treatment period.</i></b></p> <p>Table 5: A Partial List of CYP3A4 Inducers. <del>These Drugs May Decrease the Level of Laquinimod and Are Therefore Disallowed 2 Weeks Prior to Study and During Study</del></p> <p>(additional CYP3A4 inducers added to the following medication classes: anticonvulsants [<i>Oxcarbazepine</i>] and antipsychotics [<i>Thioridazine</i>], and psychostimulants [<i>armodafinil</i>]. The following medication class was deleted: Alzheimer's Treatments [Semagacestat])</p>	<p>CYP3A4 inducers are disallowed within 2 weeks of baseline and during the treatment period.</p> <p>Table 5: A Partial List of CYP3A4 Inducers. (see Appendix C for revised table)</p>	<p>Language updated for consistency with other laquinimod protocols and Investigator’s Brochure</p>

Original text with changes shown	New wording	Reason/Justification for change																										
<b>APPENDIX C - LIST OF OTHER CONCOMITANT MEDICATION/THERAPIES</b>																												
<p>Table 6: <del>Partial List of Drugs with a Narrow Therapeutic Index That Are Metabolized by CYP3A4 (Plasma Levels of These Drugs Could Increase when Combined with Laquinimod)</del> <i>A Partial List of Cytochrome P450 3A4 Substrates with a Narrow Therapeutic Index</i></p> <table border="1" data-bbox="191 461 657 594"> <thead> <tr> <th>Medication class</th> <th>Drug name</th> </tr> </thead> <tbody> <tr> <td>Opioids</td> <td>Fentanyl, Alfentanil</td> </tr> <tr> <td>Migraine treatment</td> <td>Ergotamine, Diergotamine</td> </tr> <tr> <td>Antiarrhythmic</td> <td>Quinidine</td> </tr> </tbody> </table> <table border="1" data-bbox="191 602 493 927"> <tbody> <tr><td><i>alfentanil</i></td></tr> <tr><td><i>cyclosporine</i></td></tr> <tr><td><i>diergotamine</i></td></tr> <tr><td><i>ergotamine</i></td></tr> <tr><td><i>fentanyl</i></td></tr> <tr><td><i>pimozide</i></td></tr> <tr><td><i>quinidine</i></td></tr> <tr><td><i>sirolimus</i></td></tr> <tr><td><i>tacrolimus</i></td></tr> </tbody> </table>	Medication class	Drug name	Opioids	Fentanyl, Alfentanil	Migraine treatment	Ergotamine, Diergotamine	Antiarrhythmic	Quinidine	<i>alfentanil</i>	<i>cyclosporine</i>	<i>diergotamine</i>	<i>ergotamine</i>	<i>fentanyl</i>	<i>pimozide</i>	<i>quinidine</i>	<i>sirolimus</i>	<i>tacrolimus</i>	<p>Table 6: A Partial List of Cytochrome P450 3A4 Substrates with a Narrow Therapeutic Index</p> <table border="1" data-bbox="961 367 1281 708"> <tbody> <tr><td><b>alfentanil</b></td></tr> <tr><td><b>cyclosporine</b></td></tr> <tr><td><b>diergotamine</b></td></tr> <tr><td><b>ergotamine</b></td></tr> <tr><td><b>fentanyl</b></td></tr> <tr><td><b>pimozide</b></td></tr> <tr><td><b>quinidine</b></td></tr> <tr><td><b>sirolimus</b></td></tr> <tr><td><b>tacrolimus</b></td></tr> </tbody> </table>	<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>	<p>List updated for consistency with other laquinimod protocols and Investigator's Brochure</p>
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<p>Table 7: A Partial List of Drugs That Are Mainly Metabolized by CYP1A2. <del>Drugs with a Narrow Therapeutic Index Appear in Bolded Text.</del> <i>For additional information on concomitant use of laquinimod with CYP1A2 and CYP3A4 substrates, please refer to the IB.</i></p>	<p>Table 7: A Partial List of Drugs That Are Mainly Metabolized by CYP1A2.</p>	<p>Deleted text is now table footnote and the referral to the IB has been added for consistency with other laquinimod protocols</p>																										

## 16.5. ADMINISTRATIVE LETTER 05 DATED 29 APRIL 2015



29 April 2015

Re: TV5600-CNS-20007 (LEGATO-HD)

Administrative Change to the Protocol dated 16 February 2015

The purpose of this administrative letter is to clarify the definition of women of child-bearing potential (WOCBP).

The protocol currently states, "Women of child-bearing potential (women who are not post-menopausal or who have undergone surgical sterilization)."

The language should read, "Women of child-bearing potential (women who are not post-menopausal or who have *not* undergone surgical sterilization)."

This language will be updated in the next protocol amendment.

If you have any questions, please contact your CRA or the Teva Clinical Program Manager, Melissa Grozinski-Wolff (melissa.grozinski-wolff@tevapharm.com).

Sincerely,

A handwritten signature in dark ink, appearing to read "Spyridon Papapetropoulos", with a horizontal line extending to the right.

Spyridon Papapetropoulos, MD, PhD  
Global Head, Neurodegeneration, Clinical Development  
Global Research and Development  
Teva Pharmaceuticals

**16.6. ADMINISTRATIVE LETTER 04 DATED 21 APRIL 2015**



21 April 2015

Re: TV5600-CNS-20007 (LEGATO-HD)

Administrative Change to the Protocol dated 16 February 2015

The purpose of this administrative letter is to clarify the change to the baseline MRI screening window.

Under Amendment 01, the baseline MRI window was  $\pm 5$  days. Per Amendment 02, the baseline MRI may be performed as soon as possible after confirmation of eligibility (eg, receipt of lab and ECG results, etc) but not less than 7 days prior to baseline. This change will take effect immediately and will ensure that potential patients have completed a successful baseline MRI prior to randomization and dosing.

This change does not impact study patients.

If you have any questions, please contact your CRA or the Teva Clinical Program Manager, Melissa Grozinski-Wolff (melissa.grozinski-wolff@tevapharm.com).

Sincerely,

A handwritten signature in dark ink, appearing to read "Spyridon Papapetropoulos", with a horizontal line extending to the right.

Spyridon Papapetropoulos, MD, PhD  
Global Head, Neurodegeneration, Clinical Development  
Global Research and Development  
Teva Pharmaceuticals

**16.7. ADMINISTRATIVE LETTER 03 DATED 18 FEBRUARY 2015**



18 February 2015

Re: TV5600-CNS-20007 (LEGATO-HD)

Administrative Changes to the Protocol dated 16 February 2015

The purpose of this administrative letter is to clarify the change to the screening visit urinalysis.

Under Amendment 01, the urinalysis was conducted via dipstick at the study site. Per Amendment 02, the urinalysis will be conducted by the central laboratory. This change will take effect immediately.

This change does not impact study patients.

Study sites that currently have lab kits onsite will automatically be provided with the new supplies. Sites that have yet to be supplied will receive the correct materials in their initial shipment.

If you have any questions, please contact your CRA.

Sincerely,

A handwritten signature in black ink, appearing to read "Spyridon Papapetropoulos".

Spyridon Papapetropoulos, MD, PhD  
Global Head, Neurodegeneration, Clinical Development  
Global Research and Development  
Teva Pharmaceuticals

**16.8. SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02  
DATED 16 FEBRUARY 2015**

The revisions listed below have been made to the protocol, as appropriate, and are considered substantial by the sponsor's Authorized Representative.

The primary reason for this amendment is to update study eligibility requirements and clarify various aspects of study conduct. An inclusion criterion requiring documentation of prior positive genetic testing for HD, or a clinical diagnosis of symptomatic HD (Diagnostic Confidence Level 4), was introduced. Also, the range of the CAG repeat length required for study eligibility was expanded (lower cut-off of 36 instead of 40).

During the IND process of Laquinimod for Huntington's disease trial, the FDA commented that given that laquinimod 0.6 mg/day leads to a 5- fold reduction in the systemic concentration of caffeine, a cytochrome P450 (CYP) 1A2 probe substrate, an even larger effect on CYP1A2 may be observed when the higher doses of 1.0 mg and 1.5 mg planned in the Huntington's Disease trial are administered. The FDA recommended that in view of this potential increased effect of laquinimod on the pharmacokinetics of CYP1A2 substrates, use of drugs metabolized by CYP1A2 should be avoided during the trial. Based on this recommendation, Teva has decided to modify all laquinimod protocols in which higher doses of laquinimod than 0.6 mg/day are administered and updated the guidance regarding the co-administration of laquinimod and drugs that are mainly metabolized by CYP1A2.

In addition, following the LAQ-MS-305 (CONCERTO) Data Monitoring Committee (DMC) recommendation, this amendment includes a requirement to perform abdominal computed tomography (CT) as soon as possible when pancreatitis is suspected. Evaluation of pancreatitis is important in order to enable adequate or better medical treatment/care. The complete guidance for monitoring subjects with elevated pancreatic amylase levels were added to Appendix A.

Typographical errors have been corrected throughout the protocol.

Previous changes to the protocol include the Global Amendment 01 following VHP assessment and the local UK amendments for the PET sub-study.

Substantive changes from the Local UK Amendment 01 to the Global Amendment 02 are provided below.

New text is shown in ***bold italics***; deleted text is marked by strikethrough.

Previous approved wording	Amended or new wording	Reason/justification for change
<b>COVER PAGE, INVESTIGATOR AGREEMENT, COORDINATING INVESTIGATOR AGREEMENT</b>		
Clinical Study Protocol with Amendment 01 and Local Amendment for Ethics Committee Submission in the United Kingdom 01	Clinical Study Protocol with Amendment 01 <del>and Local Amendment for Ethics Committee Submission in the United Kingdom 01</del>	Updated to reflect amendment.
<p align="center"><b>Authorized Representative (Signatory)</b> Jonathan Isaacsohn, MD Chief Medical Officer Global Research and Development Teva Pharmaceutical Industries, Ltd.</p>	<p align="center"><b>Authorized Representative (Signatory)</b> <del>Jonathan Isaacsohn, MD Chief Medical Officer Global Research and Development Teva Pharmaceutical Industries, Ltd.</del>  <b>Spyridon (Spyros) Papapetropoulos, MD, PhD</b> <i>Global Head, Neurodegeneration, Clinical Development Teva Branded Pharmaceutical Products R&amp;D, Inc.</i></p>	Updated to reflect the identity of the new Sponsor Authorized Representative and Signatory.
<p><b>Sponsor's Global Clinical Leader</b> Anna Wickenberg, PhD Global Clinical Leader Teva Pharmaceutical Industries, Ltd. Tel: +46-72-721-9122</p>	<p><del><b>Sponsor's Global Clinical Leader</b> Anna Wickenberg, PhD Global Clinical Leader Teva Pharmaceutical Industries, Ltd. Tel: +46-72-721-9122</del>  <b>Sponsor's Medical Expert</b> <b>Spyridon (Spyros) Papapetropoulos, MD, PhD</b> <i>Global Head, Neurodegeneration, Clinical Development Teva Branded Pharmaceutical Products R&amp;D, Inc. Tel: +1-610-727-6044</i></p>	Updated to reflect the identity and contact details of the new study medical expert.
<p>Maya Margalit, MD Global Patient Safety &amp; PhV Teva Pharmaceutical Industries, Ltd. Tel: +972-3-9267155</p>	<p><del>Maya Margalit</del> <b>Dana Gorsetman, MD</b> Global Patient Safety &amp; PhV Teva Pharmaceutical Industries, Ltd. Tel: +972-3-9267155531</p>	Updated to reflect the identity and contact details of the new safety physician.
<p>Global Coordinating Investigator: Ralf Reilmann, MD, PhD Title: Founding Director and CEO, George Huntington Institute; Chair - EHDN Huntington Center, University of Munster; Chair - Laboratory of Biomarkers and Neurodegeneration, University of Munster</p>	<p>Global Coordinating Investigator: Ralf Reilmann, MD, PhD Title: Founding Director and CEO, George Huntington Institute; <del>Chair - EHDN Huntington Center</del> <b>Dept. of Radiology, University of Münster; Department of Neurodegenerative Diseases and Hertie-Institute for Clinical Brain Research, University of Tübingen, Germany</b> <del>Chair - Laboratory of Biomarkers and Neurodegeneration, University of Munster</del></p>	Modified title of the coordinating investigator.



Previous approved wording	Amended or new wording	Reason/justification for change
<b>CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS</b>		
<p><b>Central Clinical Laboratory</b> Quest Diagnostics Unit B1 Parkway West, Cranford Lane Heston, Middlesex, TW5 9QA UK</p> <p><b>Electronic Data Capture</b> Pending: Information will be included in the Trial Master File.</p> <p><b>Central Institutional Review Board</b> Pending: Information will be included in the Trial Master File.</p> <p><b>Central Electrocardiogram Evaluation</b> Pending: Information will be included in the Trial Master File.</p>	<p><b>Central Clinical Laboratory</b> <del>Quest Diagnostics</del> <del>Unit B1 Parkway West, Cranford Lane</del> <del>Heston, Middlesex, TW5 9QA</del> <del>UK</del> <i>Quest Diagnostics Clinical Laboratories, Inc.</i> <i>27027 Tourney Road</i> <i>Suite 2E Valencia, CA 91355</i> <i>USA</i></p> <p><i>Quest Diagnostics Limited Unit B1</i> <i>Parkway West Industrial Estate Cranford Lane – Heston</i> <i>Middlesex TW5 9QA</i> <i>UK</i></p> <p><i>Quest Diagnostics Nichols Institute</i> <i>33608 Ortega Highway</i> <i>San Juan Capistrano, CA 92675-2042</i> <i>USA</i></p> <p><del><b>Electronic Data Capture</b></del> <del>Pending: Information will be included in the Trial Master File.</del></p> <p><del><b>Central Institutional Review Board</b></del> <del>Pending: Information will be included in the Trial Master File.</del></p> <p><del><b>Central Electrocardiogram Evaluation</b></del> <del>Pending: Information will be included in the Trial Master File.</del> <i>Biomedical Systems Corporation</i> <i>77 Projgress Parkway</i> <i>St. Louis, MO 63053</i> <i>USA</i></p> <p><b>Web and Phone Integrated Interactive Response Technology</b> <i>PAREXEL International</i> <i>Lady Bay House</i> <i>Meadow Grove</i> <i>Nottingham</i></p>	<p>Section updated to include the various vendors of this study.</p>

Previous approved wording	Amended or new wording	Reason/justification for change
	<p><i>NG2 3HF</i> <i>UK</i></p> <p><i>Computer-Based Rating System</i></p> <p><i>QuantiMedis GmbH</i> <i>Marientalstrasse 43</i> <i>48149 Münster</i> <i>Germany</i></p> <p><i>Stout Neuropsych Pty Ltd</i> <i>44 Stewart Street</i> <i>Ormond VIC 3204</i> <i>Australia</i></p> <p><i>Bioanalytical Laboratory</i> <i>Teva Pharm. Works Private Ltd. Co (TPW)</i> <i>Pallagi St 13</i> <i>4042 Debrecen</i> <i>Hungary</i></p> <p><i>Collaborator</i> <i>Huntington Study Group</i> <i>2604 Elmwood Avenue, Suite 335</i> <i>Rochester, NY 14618</i> <i>USA</i></p> <p><i>European Huntington's Disease Network</i> <i>University of Ulm</i> <i>Oberer Eselsberg 45/1</i> <i>D-89081 Ulm</i> <i>Germany</i></p> <p><i>Central MRI Vendor</i> <i>IXICO Technologies Limited</i> <i>4<sup>th</sup> Floor, Griffin Court</i> <i>15 Long Lane</i> <i>London</i> <i>EC1A 9PN</i></p>	

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	<p><i>United Kingdom</i></p> <p><i>Scale Management Bracket</i> <i>575 E. Swedesford Road, Suite 200</i> <i>Wayne, PA 19087</i> <i>USA</i></p> <p><i>MRS Analysis</i> <i>University of British Columbia MRI Research Centre</i> <i>Room M10 Purdy Pavilion</i> <i>2221 Wesbrook Mall</i> <i>Vancouver</i> <i>British Columbia</i> <i>V6T 2B5</i> <i>CANADA</i></p> <p><i>PET Substudy</i> <i>Imperial College London</i> <i>Hammersmith Hospital, Neurology Imaging Unit</i> <i>Du Cane Road</i> <i>London</i> <i>W12 0NN</i> <i>United Kingdom</i></p>	
<b>CLINICAL STUDY PERSONNEL CONTACT INFORMATION</b>		
<p><b><u>Global/EU :</u></b> Marianne Giuffra, Medical Director ICON Robert-Bosch-Str.26 63225 Langen Hessen Germany Tel: +49 (6103) 904 1760</p> <p><b><u>US:</u></b> Margaret Zalewski, Director, Medical Affairs ICON 2100 Pennbrook Parkway North Wales, PA 19454 USA</p>	<p><b><u>Global/EU:</u></b> <del>Marianne Giuffra, Medical Director</del> <del>ICON</del> <del>Robert Bosch Str.26</del> <del>63225 Langen Hessen</del> <del>Germany</del> <del>Tel: +49 (6103) 904 1760</del> <b>Marianne Giuffra, MD</b> <b>(Located in Germany)</b> <b>Office Phone (between 9-5pm CET): +49 6103 904 1760</b> <b>e-mail: marianne.giuffra@iconplc.com</b></p> <p><b><u>US:</u></b> <del>Margaret Zalewski, Director, Medical Affairs</del></p>	<p>Updated contact information for medical monitors and CRO call center.</p>

Previous approved wording	Amended or new wording	Reason/justification for change
<p>Tel: +1 (215) 616-4969</p>	<p><b>ICON</b> 2100 Pennbrook Parkway North Wales, PA 19454 USA Tel: +1 (215) 616-4969 <b>Margaret Zalewski, MD</b> <i>(Located in the East Coast of US)</i> <b>Office Phone (between 9-5 EST): +1 215 616 4969</b> <b>e-mail: Margaret.Zalewski@iconplc.com</b></p> <p><i>In a study-related medical emergency situation, when assigned Medical Monitors for a study cannot be reached, an on-call Physician can be reached 24 hours per day, 7 days per week via an ICON Call-Center: Telephone: +1 919 674 5468 [Toll (not free of charge) telephone number allowing a global reach from both landlines and mobile phones]</i></p> <p><i>On the following internet page (<a href="https://icophone.iconplc.com">https://icophone.iconplc.com</a>), a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the toll (not free of charge) number as indicated above. Toll-free numbers are unfortunately not available from mobile phones.</i></p>	
<b>SYNOPSIS</b>		
<p>Randomization will be performed by interactive response technology (IRT) using dynamic randomization to balance the treatment groups within centers. Subjects will be equally assigned to the 4 treatment groups of the study (3 active treatment groups and placebo, allocation ratio of 1:1:1:1).</p> <p>In case that the safety committee will not approve continuation of one or more doses of laquinimod, the dynamic randomization algorithm will be adjusted to apply an equal allocation ratio to all approved remaining treatment groups.</p>	<p><del>Randomization will be performed by interactive response technology (IRT) using dynamic randomization to balance the treatment groups within centers. Subjects will be equally assigned to the 4 treatment groups of the study (3 active treatment groups and placebo, allocation ratio of 1:1:1:1).</del></p> <p><del>In case that the safety committee will not approve continuation of one or more doses of laquinimod, the dynamic randomization algorithm will be adjusted to apply an equal allocation ratio to all approved remaining treatment groups.</del></p> <p><b>Patients will be randomly assigned to receive treatment with laquinimod at a dosage of 0.5, 1.0, or 1.5 mg qd or a matching placebo in a 1:1:1:1 ratio.</b></p>	<p>Clarification and correction of text to reflect the method of blinding and randomization as described in protocol.</p>

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	<p><i>Patients and investigators will remain blinded to treatment assignment during the study.</i></p> <p><i>The randomization code will be generated by the Clinical Supply Chain (CSC) department following specifications from the Biostatistics Department.</i></p> <p><i>In addition, the sponsor’s clinical personnel involved in the study will be blinded to the study drug identity until the database is locked for analysis and the treatment assignment revealed.</i></p>	
<ul style="list-style-type: none"> <li>○ Urinalysis at the screening visit (dipstick).</li> </ul>	<ul style="list-style-type: none"> <li>○ Urinalysis at the screening visit (dipstick).</li> </ul>	Sample analysis will be performed at the central lab.
<b>1 BACKGROUND INFORMATION</b>		
<b>Section 1.1 (Other sections affected by this change: 1.3.1)</b>		
<p>Further, laquinimod was shown to cause a marked decrease of CYP3A4 activity and is a potent 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.</p>	<p>Further, laquinimod was shown to cause a <del>marked</del> decrease of CYP3A4 activity and is a potent 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.</p>	<p>Laquinimod 0.6 mg/day and 1.2 mg/day increased the systemic exposure of midazolam (a sensitive CYP3A4 substrate) by 1.5 and 1.7 fold, respectively; therefore laquinimod is considered a weak CYP3A4 inhibitor.</p>
<b>Section 1.3.1</b>		
<p>Finally, a small increase in the incidence of oral cavity squamous cell carcinomas was noted in mid and high dose female rats (2/60 in each group). It is the sponsor’s position that this finding is likely a result of direct contact of the rat oral mucosa with high concentrations of laquinimod in the dosing solution.</p> <p>Although the mechanism leading to the local effect is unknown, the possibility that the local effect may relate to the AhR activation by laquinimod cannot be excluded. Oral cavity tumors have been observed in rat carcinogenicity studies for some AhR agonists, but the incidence rate of these tumors was higher than the incidence rate observed for laquinimod. Regardless of the mechanism underlying</p>	<p><del>Finally, a small increase in the incidence of oral cavity squamous cell carcinomas was noted in mid and high dose female rats (2/60 in each group). It is the sponsor’s position that this finding is likely a result of direct contact of the rat oral mucosa with high concentrations of laquinimod in the dosing solution.</del></p> <p><del>Although the mechanism leading to the local effect is unknown, the possibility that the local effect may relate to the AhR activation by laquinimod cannot be excluded. Oral cavity tumors have been observed in rat carcinogenicity studies for some AhR agonists, but the incidence rate of these tumors was higher than the incidence rate observed for laquinimod. Regardless of the mechanism underlying this local effect, whether non-specific cytotoxicity or local AhR activation, a local effect on the rat oral mucosa is not considered</del></p>	<p>Clarification regarding oral cavity tumors in non-clinical section.</p>

Previous approved wording	Amended or new wording	Reason/justification for change
<p>this local effect, whether non-specific cytotoxicity or local AhR activation, a local effect on the rat oral mucosa 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 large safety margins.</p>	<p><del>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 large safety margins.</del></p> <p><i>In addition, an increase in the incidence of oral cavity tumors was noted in mid and high dose females (2/60 in each group). The oral effects may relate to the AhR activation properties of laquinimod since similar lesions were seen with other AhR activators, including industrial chemicals (such as 2,3,7,8-tetrachlorodibenzo-p-dioxin [TCDD] and dioxin-like compounds [DLCs]) and the dietary ingredient indole-3-carbinol (I3C) found in cruciferous vegetables. However, the incidence of oral cavity tumors in rats treated with laquinimod was lower than that seen with TCDD and DLCs, and was more similar to the incidence seen with I3C. Importantly, the oral cavity tumors seen with TCDD in rats did not translate into increased incidence of oral tumors in exposed humans, indicating a species difference in this response between rats and humans. It should be noted that several lines of evidence suggest that the oral lesions seen in rats are mediated by direct contact of the rat oral mucosa with high concentrations of laquinimod in the dosing solution during the gavage procedure. An effect on the oral mucosa in rats is not considered relevant to humans, who take laquinimod as a capsule that dissolves in the stomach. Based on sponsor’s calculations, in the human stomach, the local concentration of laquinimod is expected to be low, and the type of epithelium exposed is not considered sensitive to the effects of laquinimod, with safety margins greater than 13 (dogs), 20 (rats) and 1000 (mice) for exposure in the stomach.</i></p>	
<b>Section 1.3.2.1</b>		
<p>Laquinimod is considered to have high oral bioavailability with linear, time independent and predictable PK that is characterized by high plasma protein binding (&gt;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</p>	<p>Laquinimod is considered to have high oral bioavailability with linear, time independent and predictable PK that is characterized by high plasma protein binding (&gt;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</p>	<p>New text regarding concomitant use of CYP1A2 substrates with laquinimod.</p> <p>This change was made In response to the FDA request to avoid the use of CYP1A2 substrates in th study</p>

Previous approved wording	Amended or new wording	Reason/justification for change
<p>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 (<math>T_{max}</math>) to approximately 5 hours and reduction of the maximum plasma concentration (<math>C_{max}</math>) by 30%. Food however did not significantly affect the overall extent of absorption AUC.</p> <p>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, strong CYP3A4 inducers and moderate hepatic impairment. Laquinimod 0.6 and 1.2 mg dose is a weak inhibitor of CYP3A4 and a strong inducer of CYP1A2.</p> <p>For additional information, please refer to the IB.</p>	<p>in reduction of the absorption rate reflected by prolongation of the time to maximal plasma drug concentration (<math>T_{max}</math>) to approximately 5 hours and reduction of the maximum plasma concentration (<math>C_{max}</math>) by 30%. Food however did not significantly affect the overall extent of absorption AUC.</p> <p>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, strong CYP3A4 inducers and moderate hepatic impairment. <del>Laquinimod 0.6 and 1.2 mg dose is a weak inhibitor of CYP3A4 and a strong inducer of CYP1A2.</del> <b><i>Studies have shown that laquinimod is a strong inducer of CYP1A2 and a weak inhibitor of CYP3A4. Therefore, co-administration of laquinimod may affect the systemic exposure of drugs metabolized by CYP450 1A2 or CYP3A4.</i></b></p> <p><del>For additional information, please refer to the IB.</del></p> <p><b><i>Plasma levels of drugs that are CYP1A2 substrates may decrease when combined with laquinimod and within 30 days after the last laquinimod dose, rendering these drugs less effective.</i></b></p> <p><b><i>In general, it is recommended to avoid the use of CYP1A2 substrates in clinical trials of laquinimod. Therapeutic alternatives may be considered in context.</i></b></p> <p><b><i>For additional information on concomitant use of laquinimod with CYP1A2 substrates, please refer to Section 5.3.2.</i></b></p>	
<b>Section 1.7</b>		
<p>Thus, the target patient population will be adult patients, with a CAG repeat length between 40 and 49, and the basic eligibility criteria will select a patient population with symptoms of HD, as assessed by a Unified Huntington’s Disease Rating Scale Total Motor Score (UHDRS-TMS) &gt;5, but with a largely retained functional capacity, as assessed with a HDRS-Total Functional Capacity</p>	<p>Thus, the target patient population will be adult patients, with a CAG repeat length between <del>40</del> 36 and 49, and the basic eligibility criteria will select a patient population with symptoms of HD, as assessed by a Unified Huntington’s Disease Rating Scale Total Motor Score (UHDRS-TMS) &gt;5, but with a largely retained functional capacity, as assessed with a HDRS-Total Functional Capacity (UHDRS-TFC) score ≥ 8. This will recruit a symptomatic</p>	<p>Updated to reflect CAG repeat length required for study eligibility.</p>

Previous approved wording	Amended or new wording	Reason/justification for change
(UHDRS-TFC) score 8. This will recruit a symptomatic early HD patient population.	early HD patient population.	
<b>3 STUDY DESIGN</b>		
<b>Section 3.1 (Other sections affected by this change: 3.11.1; Table 3)</b>		
After signing the informed consent, including consent to provide a blood sample for genetic analyses including CAG repeat length analysis, patients will be screened for a period of 2 weeks up to 5 weeks in order to determine whether they are eligible to participate in the study.	After signing the informed consent, including consent to provide a blood sample for genetic analyses including CAG repeat length analysis, patients will be screened for a period of 2 weeks up to 5 weeks in order to determine whether they are eligible to participate in the study. <i>Patients with a legal guardian should be consented according to local requirements.</i>	Text added for clarification.
<b>Section 3.2.8</b>		
The patient will be given the opportunity to decide whether the exact CAG repeat result will be disclosed to them or not. If not, the result will be reported only as within or outside of the eligibility range (40-49 inclusive).	<del>The patient will be given the opportunity to decide whether the exact CAG repeat result will be disclosed to them or not. If not, the result will be reported only as within or outside of the eligibility range (40-49 inclusive).</del> <i>The exact CAG repeat length will not be available to the sites, only to the Sponsor. The central laboratory report will only note if the patient is within the eligibility criteria range (36-49 inclusive) or not.</i>	To correctly reflect the reporting from the central laboratory, and per the administrative letter dated 14 November 2014, and updated to reflect CAG repeat length required for eligibility.
<b>Section 3.6</b>		
<i>(Not applicable)</i>	<p><b>3.6.1 Temporary Discontinuation of Study Drug Treatment</b></p> <p><i>Temporary discontinuation is defined as missing of more than 3 consecutive doses of the study drug. Skipping 14 or more consecutive doses of study drug will be considered a major protocol violation.</i></p> <p><i>The reasons for temporary study drug discontinuation should be recorded in the appropriate section of the study drug dispensing and compliance log in the electronic Case Report Form (eCRF).</i></p> <p><i>The subject will report any temporary discontinuation to the investigator and will be instructed by the investigator regarding continuation of treatment.</i></p>	Addition of new sections regarding temporary discontinuation of study drug.
<b>Section 3.10</b>		
The study is expected to start in Q3 2014 (first patient randomized) and be completed in Q3 2016 (last patient last	The study is expected to start in Q3 2014 (first patient randomized) and be completed in <del>Q3</del> <b>Q4</b> 2016 (last patient last visit).	Updated planned study end date and number of



Previous approved wording	Amended or new wording	Reason/justification for change
visit). Approximately 400 patients from ~30 investigational centers in North America and Europe are planned to be enrolled in the study.	Approximately 400 patients from ~ <del>30</del> 35 investigational centers in North America and Europe are planned to be enrolled in the study.	investigational centers.
<b>Section 3.11 – Table 3 (Other sections affected by this change: 5.2)</b>		
c. Patients must have fasted no less than 8 hours prior to the blood draw.	c. <i>For visits 2 through 9, P</i> patients must have fasted no less than 8 hours prior to the blood draw.	Clarification that fasting is not needed for the laboratory tests taken at the screening visit.
<b>Section 3.11 – Table 3 (Other sections affected by this change 3.11.2; 3.11.3.1.5; 8.2.1)</b>		
f. Blood sample for monocyte collection and analysis has to be done in the morning, at 12:00 (noon) at the latest.	f. Blood sample for monocyte collection and analysis has to be done <del>in the morning, at 12:00 (noon) at the latest</del> <i>in accordance with the laboratory manual. For UK patients, the sample can be drawn prior to the baseline or Month 12 visit, as it coincides with the PET scan visits.</i>	Reference to a specific time point for monocyte blood collection has been removed.  Clarification added regarding monocyte testing for UK patients.
<b>Section 3.11 – Table 3 (Other sections affected by this change: 7.4)</b>		
g. During the visits, vital sign measurements, physical examinations and ECG should be performed prior to the blood draw for clinical laboratory tests and pharmacokinetic sampling.	<del>g. During the visits, vital sign measurements, physical examinations and ECG should be performed prior to the blood draw for clinical laboratory tests and pharmacokinetic sampling.</del>	The prescribed order of laboratory tests, ECGs and vital signs has been deleted to simplify conduct of study procedures.
<b>Section 3.11 – Table 3 (Other sections affected by this change: 3.11; 7.4)</b>		
j. Including postural BP changes.	<del>j. Including postural BP changes.</del>	Footnote deleted; All references to "postural blood pressure changes" have been removed. Only supine measurements will be captured.
<b>Section 3.11 – Table 3 (Other sections affected by this change: 3.11.2)</b>		
j. At the screening visit, only serum -HCG test will be performed. For the baseline visit - Serum pregnancy test (beta human chorionic gonadotropin [ -hCG]) result is required for women of child-bearing potential within the 7 days prior to initiation of treatment.	j. At the screening visit, only serum -HCG test will be performed. For the baseline visit - Serum pregnancy test (beta human chorionic gonadotropin [ -hCG]) result is required for women of child-bearing potential within the 7 days prior to <del>initiation of treatment</del> <i>randomization. Whenever possible, this should be sent to the central laboratory for analysis. The sample may be sent to a local</i>	Clarification regarding procedure for the -HCG testing prior to randomization and acceptability of local laboratory.

Previous approved wording	Amended or new wording	Reason/justification for change
	<i>laboratory if timing does not permit sending to the central laboratory.</i>	
<b>Section 3.11 – Table 3</b>		
k. An additional urine -HCG test will be performed at the PET facilities at Imperial College in London at the Baseline visit and at Visit 8. This is a requirement for women of child-bearing potential participating in the PET substudy. Its result will be available on site prior to any procedures involving ionizing radiation and will be considered accordingly.	k. An additional urine -HCG test will be performed at the PET facilities at Imperial College in London at the Baseline visit and at Visit 8. <del>This is a requirement</del> for women of child-bearing potential participating in the PET substudy. Its result will be available on site prior to any procedures involving ionizing radiation and will be considered accordingly.	Clarification of footnote regarding the additional - HCG test prior to the PET scan.
<b>Section 3.11 – Table 3 (Other sections affected by this change: 3.11.2; 3.11.3.1.5)</b>		
(Not applicable)	l. If anxiolysis is required in order to perform the MRI scan, the scan should be performed at the end of the study visit day.	Clarification regarding timing of MRI scan in case of anxiolysis.
<b>Section 3.11 – Table 3</b>		
m. The MRI can be done +/- 5 days from the clinical visit – once the eligibility of the patient has been established at screening.	m. <del>The MRI can be done +/- 5 days from the clinical visit – once the eligibility of the patient has been established at screening.</del> <i>The baseline MRI may be performed as soon as possible after confirmation of eligibility but not less than 7 days prior to baseline.</i>	The time window for the baseline MRI has been changed to ensure quality baseline MRI scan prior to treatment initiation.
<b>Section 3.11 – Table 3</b>		
The PET scan can be done at any time within 14 days prior to the date of the baseline visit, after eligibility of the patient has been confirmed. It can also be done 14 days prior to the Month 12 visit.	The PET scan can be done at any time <del>within 14 days</del> prior to the date of the baseline visit, after eligibility of the patient has been confirmed. It can also be done <del>14 days</del> <i>2 to 5 weeks</i> prior to the Month 12 visit.	Revised time window for the PET scan prior to the baseline visit.
<b>Section 3.11 – Table 3 (Other sections affected by this change: 3.11.2; 3.11.3.1.5; 8.2.4)</b>		
(Not applicable)	Patients taking benzodiazepines should be instructed to stop taking them for 3 days prior to having the PET scan.	New text to disallow benzodiazepines 3 days prior to the PET scan, as benzodiazepines could interfere with TSPO binding.
<b>Section 3.11 – Table 3</b>		
(Not applicable)	<i>If a patient terminates within 3 months of the baseline visit, they will not undergo an Early Termination scan. If a patient terminates prior to Month 12, the Early termination scans should be performed as soon as possible, but not more than 7 days after</i>	Newly added footnote regarding the timing of the Month 12/Early Termination MRI scan.

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	<i>discontinuation of study drug. Month 12 scans should be performed 7 days prior to the Termination Visit.</i>	
<b>Section 3.11 – Table 3 (Other sections affected by this change: 3.11.3.1.1)</b>		
w. Only at selected sites in a subgroup of patients, N=60 (15 from each treatment arm), at Month 1.	w. Only at selected sites in a subgroup of patients, N=60 (15 from each treatment arm), at Month 1. <i>Patients participating in the 24-hour PK profiling will not have the single PK sample drawn at Visit 3.</i>	Clarification that patients participating in 24hr PK will not need the single PK sample drawn.
<b>Section 3.11.2</b>		
<p>...</p> <ul style="list-style-type: none"> <li>● blood sample for monocyte analysis (<b>Only at selected sites in a subgroup of patients</b>) <ul style="list-style-type: none"> <li>○ Blood sample for monocyte collection and analysis has to be done in the morning, at 12:00 (noon) at the latest</li> </ul> </li> <li>● perform full physical examination (including weight)</li> <li>● perform vital signs measurements (including postural BP changes)</li> <li>● ECG – in triplicate</li> <li>● serum -HCG in women of childbearing potential</li> <li>● urine -HCG in women of childbearing potential</li> <li>● Ascertaining use of effective contraception</li> <li>● C-SSRS (since last visit version)</li> <li>● MRI scan</li> <li>● MRS scan (<b>Only at selected sites in a subgroup of patients</b>)</li> </ul> <p>...</p>	<p>...</p> <ul style="list-style-type: none"> <li>● blood sample for monocyte analysis (<b>Only at selected sites in a subgroup of patients</b>) <ul style="list-style-type: none"> <li>○ Blood sample for monocyte collection and analysis has to be done <del>in the morning, at 12:00 (noon)</del> <i>at the latest in accordance with the laboratory manual.</i></li> <li>○ <i>For UK patients, the sample can be drawn prior to the baseline visit, as it coincides with the PET scan visit.</i></li> </ul> </li> <li>● perform full physical examination (including weight)</li> <li>● perform vital signs measurements <del>(including postural BP changes)</del></li> <li>● ECG – in triplicate</li> <li>● serum -HCG in women of childbearing potential <i>Women of child-bearing potential must have a serum -hCG within 7 days prior to the initiation of treatment. Whenever possible, this sample should be sent to the central laboratory for analysis. The sample may be sent to a local laboratory if timing does not permit sending to the central laboratory. The scenarios are as follows:</i> <ul style="list-style-type: none"> <li>○ <i>Serum pregnancy test ( -HCG) is performed by the central lab within 7 days prior to the baseline visit and result obtained prior to randomization – no need for additional test in Baseline visit. The sample should be sent to the lab at least 48 hours prior to the baseline visit to ensure results are</i></li> </ul> </li> </ul>	<p>Clarifications regarding various baseline assessments and procedures.</p> <p>Reference to specific time points for monocyte analysis was omitted; clarification regarding analysis for patients participating in the PET study.</p> <p>All references to postural blood pressure changes were removed. Only supine measurements will be captured.</p> <p>Clarification regarding procedure for the -HCG testing prior to randomization and acceptability of local laboratory.</p> <p>The time window for the baseline MRI has been changed to ensure quality baseline MRI scan prior to treatment initiation.</p>

Previous approved wording	Amended or new wording	Reason/justification for change
	<p><i>available.</i></p> <ul style="list-style-type: none"> <li>○ <i>Serum pregnancy test ( -HCG) is performed by a local lab within 7 days prior to the baseline visit, or at the day of the baseline visit, and result obtained prior to randomization at the baseline visit day. If the local lab sample is collected on the baseline visit day, a sample does not need to be sent to the central laboratory as well.</i></li> </ul> <p><i>Results must be obtained prior to randomizing the patient, documented in an official lab report and filed with patient's source documents. In case an unscheduled visit is performed, all mandatory activities according to the protocol, for this visit, should be performed.</i></p> <ul style="list-style-type: none"> <li>● urine -HCG in women of childbearing potential</li> <li>● additional urine -HCG in women of childbearing potential at PET facilities (<b>Only in a subgroup of patients</b>)</li> <li>● Ascertaining use of effective contraception</li> <li>● C-SSRS (since last visit version)</li> <li>● MRI scan</li> <li>●             <ul style="list-style-type: none"> <li>○ <i>The baseline MRI can be performed as soon as possible after confirmation of eligibility but not less than 7 days prior to baseline.</i></li> </ul> </li> <li>● MRS scan (<b>Only at selected sites in a subgroup of patients</b>)</li> <li>● PET scan (<b>Only at selected sites in a subgroup of patients</b>)             <ul style="list-style-type: none"> <li>○ <i>The PET scan can be done at any time prior to the date of the baseline visit, after eligibility of the patient has been confirmed.</i></li> <li>○ <i>Patients taking benzodiazepines should be instructed to stop taking them for 3 days prior to having the PET scan.</i></li> </ul> </li> <li>● UHDRS-TMS</li> </ul>	<p>Clarifications regarding performance of the PET scan.</p>

Previous approved wording	Amended or new wording	Reason/justification for change
...	...	
<b>Section 3.11.3.1.5</b>		
<p>...</p> <ul style="list-style-type: none"> <li>● blood sample for gene expression analysis</li> <li>● blood sample for monocyte analysis (<b>Only at selected sites in a subgroup of patients</b>) <ul style="list-style-type: none"> <li>○ Blood sample for monocyte collection and analysis has to be done in the morning, at 12:00 (noon) at the latest</li> </ul> </li> <li>● serum -HCG in women of childbearing potential</li> <li>● urine -HCG in women of childbearing potential</li> <li>● additional urine -HCG in women of childbearing potential at PET facilities (<b>Only in a subgroup of patients</b>)</li> <li>● Ascertaining use of effective contraception</li> <li>● PK drug concentration sampling</li> <li>● C-SSRS (since last visit version)</li> <li>● MRI scan</li> <li>● MRS scan (<b>Only at selected sites in a subgroup of patients</b>)</li> <li>● PET scan (<b>Only at selected sites in a subgroup of patients</b>)</li> <li>● UHDRS-TMS</li> </ul> <p>...</p>	<p>...</p> <ul style="list-style-type: none"> <li>● blood sample for gene expression analysis</li> <li>● blood sample for monocyte analysis (<b>Only at selected sites in a subgroup of patients</b>) <ul style="list-style-type: none"> <li>○ Blood sample for monocyte collection and analysis has to be done <del>in the morning, at 12:00 (noon) at the latest</del> <b>in accordance with the laboratory manual</b></li> <li>○ <b><i>For UK patients, the sample can be drawn prior to the Month 12 visit, as it coincides with the PET scan visit</i></b></li> </ul> </li> <li>● serum -HCG in women of childbearing potential</li> <li>● urine -HCG in women of childbearing potential</li> <li>● additional urine -HCG in women of childbearing potential at PET facilities (<b>Only in a subgroup of patients</b>)</li> <li>● Ascertaining use of effective contraception</li> <li>● PK drug concentration sampling</li> <li>● C-SSRS (since last visit version)</li> <li>● MRI scan <ul style="list-style-type: none"> <li>○ <b><i>If anxiolysis is required in order to perform the MRI scan, the scan should be performed at the end of the study visit day.</i></b></li> </ul> </li> <li>● MRS scan (<b>Only at selected sites in a subgroup of patients</b>)</li> <li>● PET scan (<b>Only at selected sites in a subgroup of patients</b>) <ul style="list-style-type: none"> <li>○ <b><i>The PET scan can be done 2 to 5 weeks prior to the Month 12 visit.</i></b></li> <li>○ <b><i>Patients taking benzodiazepines should be instructed to stop taking them for 3 days prior to having the PET scan.</i></b></li> </ul> </li> <li>● UHDRS-TMS</li> </ul>	<p>Clarifications regarding various baseline assessments and procedures.</p> <p>Reference to specific time points for monocyte analysis was omitted; clarification regarding analysis for patients participating in the PET study.</p> <p>All references to postural blood pressure changes were removed. Only supine measurements will be captured.</p> <p>Clarifications regarding performance of the PET scan.</p> <p>Newly added text regarding CYP1A2 substrates and CYP3A4 inhibitors following the last dose of study drug.</p>

Previous approved wording	Amended or new wording	Reason/justification for change
	<p>...</p> <p><i>Moderate/strong CYP3A4 inhibitors are disallowed during the 30 days after the last laquinimod dose has been administered (see Appendix B).</i></p> <p><i>Plasma levels of drugs that are CYP1A2 substrates may decrease when combined with laquinimod and within 30 days after the last laquinimod dose, rendering these drugs less effective (see Appendix C).</i></p>	
<b>4 SELECTION AND WITHDRAWAL OF PATIENTS</b>		
<b>Section 4.1</b>		
(Not applicable)	<p><i>l. [New criterion] Documentation of prior positive genetic testing for HD, or a clinical diagnosis of symptomatic HD (Diagnostic Confidence Level 4).</i></p>	<p>New inclusion criterion introduced.</p> <p>As a result, the lettering of the subsequent criteria have changed.</p>
<p>a. Presence of 40-49 CAG repeats, inclusive, in the huntingtin gene based on centralized CAG testing during screening.</p>	<p><b>ab. [Revision 1]</b> Presence of <del>40</del><b>36</b>-49 CAG repeats, inclusive, in the huntingtin gene based on centralized CAG testing during screening.</p>	<p>Modified number of CAG repeats in the huntingtin gene required for eligibility to only disallow patients with more than 49 CAG repeats.</p>
<b>Section 4.2</b>		
<p>h. Creatinine clearance &lt;60 mL/min at screening, calculated using the Cockcroft Gault equation: (140 - age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/dL) x 88.4</p>	<p>h. <b>[Revision 1]</b> Creatinine clearance &lt;60 mL/min at screening, calculated using the Cockcroft Gault equation: (140 - age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/dL) <del>x 88.4</del></p>	<p>Correction of the Cockcroft Gault equation.</p>
<b>5 TREATMENT OF PATIENTS</b>		
<b>Section 5.2</b>		
<p>Patients must have fasted no less than 8 hours prior to a blood draw for the lipid profile, or for the safety laboratory panels which include clinical chemistries and hormone concentrations.</p>	<p><b>For visits 2 through 9,</b> <del>P</del>patients must have fasted no less than 8 hours prior to a blood draw for the lipid profile, or for the safety laboratory panels which include clinical chemistries and hormone concentrations.</p>	<p>Clarification that screening laboratory tests do not need to be done fasting.</p>
<b>Section 5.3.1</b>		
<p>...</p> <ul style="list-style-type: none"> <li>• Use of inducers of CYP3A4 within 2 weeks</li> </ul>	<p>...</p> <ul style="list-style-type: none"> <li>• Use of inducers of CYP3A4 within 2 weeks prior to</li> </ul>	<p>Clarification regarding disallowed previous</p>

Previous approved wording	Amended or new wording	Reason/justification for change
<p>prior to randomization</p> <ul style="list-style-type: none"> <li>Immunosuppressive agents, or cytotoxic agents, including cyclophosphamide and azathioprine within 12 months prior to screening</li> </ul> <p>...</p>	<p>randomization</p> <ul style="list-style-type: none"> <li>Immunosuppressive <i>or immunomodulating</i> agents, or cytotoxic agents, including cyclophosphamide and azathioprine within 12 months prior to screening</li> </ul> <p>...</p>	<p>medications prior to the study.</p>
<p><b>Section 5.3.2</b></p>		
<p><b>5.3.2 Allowed Medications/Therapies During Study</b> Clinical studies have shown laquinimod 0.6 mg/day to be a potent inducer of CYP1A2. Subjects taking drugs that are metabolized by CYP1A2 (examples listed in Appendix C) should be advised that plasma levels of these drugs may need dose adjustment and more frequent clinical monitoring when treatment with laquinimod is initiated or stopped.</p> <p>Drug-Drug interaction studies have been performed with the laquinimod doses of 0.6 mg/day and 1.2 mg/day dose. 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 C) should be advised that plasma levels of these drugs could increase when combined with laquinimod.</p>	<p><b>5.3.2 Allowed Medications/Therapies During Study Other Concomitant Medications</b> <del>Clinical studies have shown laquinimod 0.6 mg/day to be a potent inducer of CYP1A2. Subjects taking drugs that are metabolized by CYP1A2 (examples listed in Appendix C) should be advised that plasma levels of these drugs may need dose adjustment and more frequent clinical monitoring when treatment with laquinimod is initiated or stopped.</del></p> <p><del>Drug-Drug interaction studies have been performed with the laquinimod doses of 0.6 mg/day and 1.2 mg/day dose. 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 C) should be advised that plasma levels of these drugs could increase when combined with laquinimod.</del></p> <p><i>Studies have shown that laquinimod is a strong inducer of CYP1A2 and a weak inhibitor of CYP3A4. Therefore, co-administration of laquinimod may affect the systemic exposure of drugs metabolized by CYP450 1A2 or CYP3A4.</i></p> <p><b>5.3.2.1 CYP1A2</b> <i>Laquinimod 0.6 mg/day reduces the systemic exposure of caffeine (a compound mainly metabolized by CYP1A2) 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.</i></p>	<p>Revised subsection regarding laquinimod possible effect on CYP1A2 and CYP3A4 substrates and partial lists of such drugs.</p> <p>This change was made In response to the FDA request to avoid the use of CYP1A2 substrates in th study.</p>

Previous approved wording	Amended or new wording	Reason/justification for change
	<p><i>Table 7, appendix C presents a partial list of drugs that are mainly metabolized by CYP1A2, i.e. CYP1A2 plays a major role in their biotransformation. The systemic exposure of these drugs is expected to be significantly reduced by laquinimod co-administration. Drugs that are mainly metabolized by CYP1A2 and have a narrow therapeutic index are of special concern and appear in bolded text.</i></p> <p><i>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.</i></p> <p><b>5.3.2.2. CYP3A4</b>  <i>Laquinimod 0.6 mg/day increases the systemic exposure of midazolam (a sensitive CYP3A4 substrate) 1.5-fold and for the 1.2 mg/day dose 1.7 fold. Therefore, plasma levels of drugs that are CYP3A4 substrates may increase when combined with laquinimod. Patients taking drugs that are metabolized by CYP3A4, specifically those with a Narrow Therapeutic Index (Appendix C) should be advised that plasma levels of these drugs could increase when combined with laquinimod.</i></p>	
<b>6 ASSESSMENT OF EFFICACY</b>		
<b>Section 6.2.1 (Other sections affected by this change: 17)</b>		
<p>Participants will undergo MRI at baseline and Month 12. Change in whole-brain, caudate and ventricular volume over the scanning interval will be calculated using the Boundary Shift Integral (BSI) technique (Freeborough and Fox, 1997, Leung et al, 2010). This is an intensity-driven technique within the MIDAS software (Freeborough et al, 1997) which measures change over time in the brain directly from within-subject registered (aligned) MR scan pairs. This technique has been optimised to provide robust measures of brain-volume change from multi-site data (Freeborough and Fox, 1997) and has been shown to be sensitive to HD-related pathology over a 12-month interval in the multi-site TRACK-HD study (Tabrizi et al, 2011). Imaging methods will follow those described within the</p>	<p>Participants will undergo <b>3T</b> MRI at baseline and Month 12 <b>following unaccelerated volumetric T1-weighted acquisition protocols developed during the ADNI study (<a href="http://www.adni-info.org">www.adni-info.org</a>).</b> Change in <del>whole brain, caudate and ventricular</del> volume over the scanning interval will be calculated using the Boundary Shift Integral (BSI) technique (<b>Hobbs et al, 2009</b>, Freeborough and Fox, 1997 Leung et al, 2010). <b>Change in whole brain and ventricular volume will also be calculated using this approach (see section 6.3.1).</b> <del>This</del> <b>The BSI</b> is an intensity-driven technique within the MIDAS software (Freeborough et al, 1997) which measures change over time in the brain directly from within-subject registered (aligned) MR scan pairs. This technique has been optimised to provide robust measures of brain-volume change from multi-site data (<del>Freeborough and Fox, 1997</del><b>Leung et al, 2010</b>) and has been</p>	<p>Updated text to reflect use of ADNI parameters instead of the TRACK-HD parameters.</p>



Previous approved wording	Amended or new wording	Reason/justification for change
<p>TRACK-HD study (Tabrizi et al, 2011, Tabrizi et al, 2012) and will be described in detail in a separate imaging manual. In brief, all images will undergo intensity normalisation using the N3 software (Sled et al, 1998, Boyes et al, 2008). The brain will be delineated at baseline and follow-up using MIDAS software (Freeborough et al, 1997). Within-subject scan pairs will be registered with 12 degrees-of-freedom and change in whole-brain volume estimated using the Brain BSI (BBSI). Change in caudate volume will be estimated using the caudate BSI (CBSI) (Hobbs et al, 2009) which involves delineation of the baseline caudates and an additional local rigid registration of the baseline and follow-up scans to achieve more accurate alignment of the caudates, prior to application of the BSI algorithm. The ventricles will be delineated at baseline and follow-up, after which the Ventricular BSI (VBSI) will be applied to estimate change in ventricular volume (Freeborough and Fox, 1997). White-matter volume change will be computed using methods described within the TRACK-HD study (Tabrizi et al, 2011 Tabrizi et al, 2012) and will be described in detail in a separate imaging manual. In brief, voxel-level volume change will be estimated using a fluid registration approach, which generates voxel-compression maps for each participant. These maps will be convolved with the native-space baseline white-matter segmentation generated using unified segmentation within SPM8 (<a href="http://www.fil.ion.ucl.ac.uk/spm">www.fil.ion.ucl.ac.uk/spm</a>), to provide an estimate of white-matter volume change. All segmentations and registrations will be visually checked by trained analysts to ensure accuracy. Longitudinal change in caudate, whole-brain and white-matter volume will be expressed as a percentage of their baseline value. Longitudinal change in ventricular volume will be expressed in absolute terms (ml). MRI scans may be evaluated locally for any incidental pathology (ie, pathology unrelated to, or inconsistent with, the subject's known HD) according to locally determined</p>	<p>shown to be sensitive to HD-related pathology over a 12-month interval in the multi-site TRACK-HD study (Tabrizi et al, 2011). <b><i>Details of how the BSI has been implemented for this study are described in the Imaging Review Charter.</i></b> <del>Imaging methods will follow those described within the TRACK-HD study (Tabrizi et al, 2011, Tabrizi et al, 2012) and will be described in detail in a separate imaging manual. In brief, all images will undergo intensity normalisation using the N3 software (Sled et al, 1998, Boyes et al, 2008). The brain will be delineated at baseline and follow up using MIDAS software (Freeborough et al, 1997). Within subject scan pairs will be registered with 12 degrees of freedom and change in whole brain volume estimated using the Brain BSI (BBSI). Change in caudate volume will be estimated using the caudate BSI (CBSI) (Hobbs et al, 2009) which involves delineation of the baseline caudates and an additional local rigid registration of the baseline and follow up scans to achieve more accurate alignment of the caudates, prior to application of the BSI algorithm. The ventricles will be delineated at baseline and follow up, after which the Ventricular BSI (VBSI) will be applied to estimate change in ventricular volume (Freeborough and Fox, 1997). White-matter volume change (see Section 6.3.1) will be computed estimated using a non-linear registration approach methods described within the TRACK-HD study (Tabrizi et al, 2011, Tabrizi et al, 2012) and will be described in detail in a separate imaging manual. In brief, voxel-level volume change will be estimated using a fluid registration approach, which generates voxel-compression maps for each participant. These maps will be convolved with the native space baseline white matter segmentation generated using unified segmentation within SPM8 (<a href="http://www.fil.ion.ucl.ac.uk/spm">www.fil.ion.ucl.ac.uk/spm</a>), to provide an estimate of white matter volume change</del> <b><i>derived from within-subject non-linear registration will be summed over an automated baseline white-matter mask, to estimate within-subject volume change over the interval. This analysis is detailed in the Imaging Review Charter.</i></b> <del>All segmentations and registrations will be visually checked by trained analysts to ensure accuracy.</del> <b><i>End-point quality control will be performed by trained analysts to ensure accuracy.</i></b> Longitudinal change in caudate, whole-brain and white-matter</p>	

Previous approved wording	Amended or new wording	Reason/justification for change
<p>procedures. If such pathology is found, the Treating Neurologist/ Physician should be notified. The MRI reading center will evaluate the scans only for the purpose of performing quantitative measurements. In order not to compromise blinding of the study, the MRI Reading Center will not report MRI findings back to clinical site. Patients who develop unsuitability for MRI measures after baseline visit, will be allowed to continue in the study without performing the MRI assessment.</p>	<p>volume will be <del>expressed as</del> <b><i>measured in mls and converted to a</i></b> percentage of their baseline value <b><i>for subsequent analysis.</i></b> Longitudinal change in ventricular volume will be <del>expressed</del> <b><i>measured and analysed</i></b> in absolute terms (ml). MRI scans may be evaluated locally for any incidental pathology (ie, pathology unrelated to, or inconsistent with, the subject’s known HD) according to locally determined procedures. If such pathology is found, the Treating Neurologist/ Physician should be notified. The MRI reading center will evaluate the scans only for the purpose of performing quantitative measurements. In order not to compromise blinding of the study, the MRI Reading Center will not report <b><i>quantitative</i></b> MRI findings back to <b><i>the</i></b> clinical site. Patients who develop unsuitability for MRI measures after baseline visit, will be allowed to continue in the study without performing the MRI assessment.</p>	
<p><b>7 ASSESSMENT OF SAFETY</b></p>		
<p><b>Section 7.1.5.3.1</b></p>		
<p>Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease. On the basis of this assessment, a decision will be made concerning the need for further medical intervention. ... The blinding will be maintained for the people who are involved directly in the study. Therefore, in case of a suspected unexpected serious adverse reaction (SUSAR), only the LSO/CRO will receive the unblinded report for regulatory submission.</p>	<p>Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease. <del>On the basis of this assessment, a decision will be made concerning the need for further medical intervention.</del> ... The blinding will be maintained for the people who are involved directly in the study. Therefore, in case of a suspected unexpected serious adverse reaction (SUSAR), only the LSO/CRO will receive the unblinded report for regulatory submission; <b><i>the others will receive a blinded report.</i></b></p>	<p>Language updated by PhV.</p>
<p><b>Section 7.1.5.3.2</b></p>		
<p>If a serious unexpected adverse event is believed to be related to the study drug or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of laquinimod and the appropriate regulatory authorities. In addition to notifying the investigators and regulatory authorities, other measures may be required, including the following:</p>	<p>If a serious unexpected adverse event is believed to be related to the study drug or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of laquinimod and the appropriate regulatory authorities (<b><i>and IEC/IRB, if appropriate.</i></b>) In addition to notifying the investigators and regulatory authorities (<b><i>and IEC/IRB, if appropriate.</i></b>), other measures may be required, including the following:</p>	<p>Language updated by PhV.</p>

Previous approved wording	Amended or new wording	Reason/justification for change
<ul style="list-style-type: none"> <li>● altering existing research by modifying the protocol</li> <li>● discontinuing or suspending the study</li> <li>● altering the process of informed consent by modifying the existing consent form and informing current study participants of new findings</li> <li>● modifying listings of expected toxicities to include adverse events newly identified as related to laquinimod</li> </ul>	<ul style="list-style-type: none"> <li>● altering existing research by modifying the protocol</li> <li>● discontinuing or suspending the study</li> <li>● altering the process of informed consent by modifying the existing consent form and informing current study participants of new findings</li> <li>● modifying listings of expected toxicities to include adverse events newly identified as related to laquinimod</li> </ul>	
<b>Section 7.4 (Other changes affected by this section: 3.11)</b>		
<p>Vital signs will be measured at all in-clinic visits (Visits 1-4 and 6-9). Vital signs include the following:</p> <ul style="list-style-type: none"> <li>● pulse</li> <li>● blood pressure (including postural BP changes)</li> <li>● body temperature</li> </ul> <p>Before pulse and blood pressure are measured, the patient must be in a supine position and resting for at least 5 minutes. The same position and arm should be used each time vital signs are measured for a given patient. For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as a clinically significant change (worsening) from a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2</p> <p>During the visits, vital sign measurements, physical examinations (see Section 7.6) and ECG (see Section 7.5) should be performed prior to the blood draw for clinical laboratory tests and pharmacokinetic sampling.</p>	<p>Vital signs will be measured at all in-clinic visits (Visits 1-4 and 6-9). Vital signs include the following:</p> <ul style="list-style-type: none"> <li>● pulse</li> <li>● blood pressure (<del>including postural BP changes</del>)</li> <li>● body temperature</li> </ul> <p>Before pulse and blood pressure are measured, the patient must be in a supine position and resting for at least 5 minutes. The same position and arm should be used each time vital signs are measured for a given patient. For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as a clinically significant change (worsening) from a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.</p> <p><del>During the visits, vital sign measurements, physical examinations (see Section 7.6) and ECG (see Section 7.5) should be performed prior to the blood draw for clinical laboratory tests and pharmacokinetic sampling.</del></p>	<p>All references to postural blood pressure changes were removed. Only supine measurements will be captured.</p> <p>The prescribed order of laboratory tests, ECGs and vital signs has been deleted to simplify conduct of study procedures.</p>
<b>Section 7.7.3</b>		
(Not applicable)	<b>7.7.3 Abdominal Computed Tomography Scan</b> <i>In case of pancreatitis or suspected pancreatitis, an abdominal computed tomography (CT) scan should be performed as soon as</i>	New section added per LAQ-MS-305 DMC request.

Previous approved wording	Amended or new wording	Reason/justification for change
	<p><i>possible in order to clarify the diagnosis and enable assessment of severity of this condition.</i></p> <p><i>For complete guidance on monitoring subjects with elevated pancreatic amylase levels, see Appendix A, Section 5.</i></p>	
<b>8 ASSESSMENT OF PHARMACOKINETICS/PHARMA COGENOMICS/OTHER ANCILLARY STUDIES</b>		
<b>Section 8.2.1 (Other sections affected by this change: Table 2; 3.11.2; 3.11.3.1.5 )</b>		
<p>...</p> <ul style="list-style-type: none"> <li>50 mL whole blood samples for monocyte isolation will be collected at baseline and Month 12 only at selected sites in a subgroup of patients. The sample collection has to be done in the morning, at 12:00 at the latest.</li> </ul> <p>...</p>	<p>...</p> <ul style="list-style-type: none"> <li>50 mL whole blood samples for monocyte isolation will be collected at baseline and Month 12 only at selected sites in a subgroup of patients (<i>aiming at 25 per treatment arm</i>). The sample collection has to be done in <del>the morning, at 12:00 at the latest.</del> <i>accordance with the laboratory manual.</i> <b><i>For UK patients, the sample can be drawn prior to the baseline or Month 12 visit, as it coincides with the PET scan visits.</i></b></li> </ul> <p>...</p>	<p>Reference to specific time points for monocyte analysis was omitted; updated number of patients for substudy; clarification regarding analysis for patients participating in the PET study.</p>
<b>Section 8.2.4 (Other sections affected by this change: Table 2; 3.11.2; 3.11.3.1.5 )</b>		
(Not applicable)	<p>Not all benzodiazepines have been tested for TSPO binding. Patients taking benzodiazepines should be instructed to stop taking them for 3 days prior to having the PET scan.</p>	<p>New text to disallow benzodiazepines 3 days prior to the PET scan.</p>
<b>11 QUALITY CONTROL AND QUALITY ASSURANCE</b>		
<b>Section 11.4</b>		
(Not applicable)	<p><b><i>11.4 Clinical Product Complaints</i></b>  <i>A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies and/or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to the following:</i></p> <ul style="list-style-type: none"> <li><i>suspected contamination</i></li> <li><i>questionable stability (eg, color change, flaking, crumbling, etc.)</i></li> <li><i>defective components</i></li> <li><i>missing or extra units (eg, primary container is received at the site with more or less than the designated number of units inside)</i></li> <li><i>incorrect packaging or incorrect or missing</i></li> </ul>	<p>New subsection added per regulatory authority request and change in Sponsor template.</p>

Previous approved wording	Amended or new wording	Reason/justification for change
	<p><i>labeling/labels</i></p> <ul style="list-style-type: none"> <li>● <i>unexpected or unanticipated taste or odor or both</i></li> <li>● <i>device not working correctly or appears defective in some manner</i></li> </ul> <p><i>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 <a href="mailto:clinical.productcomplaints@tevapharm.com">clinical.productcomplaints@tevapharm.com</a> within 48 hours of becoming aware of the issue.</i></p> <p><i>For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving a drug product, all relevant samples (eg, the remainder of the patient's drug supply) should be sent back to the sponsor for investigative testing whenever possible.</i></p> <p><b>11.4.1. Product Complaint Information Needed from the Investigational Center</b></p> <p><i>In the event that the Product Complaint Form cannot be completed, the investigator will obtain the following information, as available:</i></p> <ul style="list-style-type: none"> <li>● <i>investigational center number and principal investigator name</i></li> <li>● <i>name, phone number, and address of the source of the complaint</i></li> <li>● <i>clinical protocol number</i></li> <li>● <i>patient identifier (patient study number) and corresponding visit numbers, if applicable</i></li> <li>● <i>product name and strength for open-label studies</i></li> <li>● <i>patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies</i></li> <li>● <i>product available for return Yes/No</i></li> <li>● <i>product was taken or used according to protocol Yes/No</i></li> <li>● <i>description or nature of complaint</i></li> <li>● <i>associated serious adverse event Yes/No</i></li> </ul>	

Previous approved wording	Amended or new wording	Reason/justification for change
	<ul style="list-style-type: none"> <li>• <i>clinical supplies unblinded (for blinded studies) Yes/No</i></li> <li>• <i>date and name of person receiving the complaint</i></li> </ul> <p><i>Note: Reporting a complaint must not be delayed because not all the required information can be immediately obtained. Known information must be immediately reported. The sponsor will collaborate with the investigator to obtain any outstanding information.</i></p> <p><b>11.4.2 Handling the Study Drug at the Investigational Center</b> <i>The investigator is responsible for retaining the product in question in a location separate from the investigator’s clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the study drug. If it is determined that the investigational center must return all of the study drug, the sponsor will provide the information needed to handle the return. The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.</i></p> <p><b>11.4.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint</b> <i>If there is an adverse event or serious adverse event, the protocol should be followed.</i></p> <p><b>11.4.4. Documenting a Product Complaint</b> <i>The investigator will record a description of the product complaint in the source documentation as well as any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.</i></p>	

Previous approved wording	Amended or new wording	Reason/justification for change
<b>APPENDIX A</b>		
<p><b>2. Use of Moderate/Strong CYP3A4 Inhibitors</b> 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 B. ...</p>	<p><b>2. Use of Moderate/Strong CYP3A4 Inhibitors</b> 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 B. <b>3. Use of CYP3A4 Substrates with Narrow Therapeutic Index</b> <i>Plasma levels of drugs that are CYP3A4 substrates may increase when combined with laquinimod. Patients taking drugs that are metabolized by CYP3A4, specifically those with a Narrow Therapeutic Index (Table 6 in Appendix C) should be advised that plasma levels of these drugs could increase when combined with laquinimod.</i> <b>4. Use of CYP1A2 Substrates</b> <i>Plasma levels of drugs that are CYP1A2 substrates may decrease when combined with laquinimod and within 30 days after the last laquinimod dose, rendering these drugs less effective. In general, it is recommended to avoid the use of CYP1A2 substrates in clinical trials of laquinimod. Therapeutic alternatives may be considered in context. For additional information on concomitant use of laquinimod with CYP1A2 substrates, please refer to Section 5.3.2.</i> ...</p>	<p>Addition of text regarding use of CYP3A4 substrates with a narrow therapeutic index and CYP1A2 substrates in combination with laquinimod.</p> <p>This change was made In response to the FDA request to avoid the use of CYP1A2 substrates in th study.</p> <p>As a result, the numbering of the subsequent subsections has changed.</p>
(Not applicable)	<p><b>5. Guidance on monitoring subjects with elevated pancreatic amylase levels</b> <i>Amylase and pancreatic amylase will be measured at each study visit.</i></p> <p><i>In any case of abnormal pancreatic amylase results to a level exceeding of 1×ULN the subject will be invited to an unscheduled visit to test lipase levels. Lipase will be tested on all follow up visits until normalization of pancreatic amylase levels.</i></p> <p><i>In case of suspected pancreatitis, the subject should undergo a thorough clinical evaluation including an abdominal computed tomography (CT) scan as soon as possible in order to clarify the diagnosis and enable assessment of severity of this condition.</i></p>	<p>Addition of guidance on monitoring patients with elevated pancreatic amylase levels following CONCERTO DMC request.</p>

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<b>APPENDIX B (Other sections affected by this change: Section 5.3.1.1; Appendix A)</b>																																																												
<p><b>A partial list of moderate/strong CYP3A4 inhibitors:</b></p> <table border="1" data-bbox="191 354 825 740"> <thead> <tr> <th>Medication class</th> <th>Drug name</th> </tr> </thead> <tbody> <tr> <td><b>Protease inhibitors</b></td> <td>Indinavir, saquinavir, lopinavir, nelfinavir, amprenavir, atazanavir, darunavir, ritonavir</td> </tr> <tr> <td><b>Antivirals:</b></td> <td>Boceprevir, telaprevir</td> </tr> <tr> <td><b>Antifungals:</b></td> <td>Ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole</td> </tr> <tr> <td><b>Antibiotics</b></td> <td>Troleandomycin, clarithromycin, telithromycin, ciprofloxacin, erythromycin</td> </tr> <tr> <td><b>Antidepressant</b></td> <td>Nefazodone</td> </tr> <tr> <td><b>Calcium channel blocker</b></td> <td>Diltazem, verapamil, mibefradil</td> </tr> <tr> <td><b>Antiemetics</b></td> <td>Aprepitant, casopitant, netupitant</td> </tr> <tr> <td><b>Diuretics</b></td> <td>Conivaptan</td> </tr> <tr> <td><b>Antineoplastic agents</b></td> <td>Imatinib</td> </tr> </tbody> </table> <p>...</p> <p><b>A partial list of CYP3A4 inducers:</b></p> <ul style="list-style-type: none"> <li>• Carbamazepine</li> <li>• Phenobarbital</li> <li>• Phenytoin</li> <li>• Rifabutin</li> <li>• Rifampin</li> <li>• St. John's Wort</li> </ul>	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>	Diltazem, verapamil, mibefradil	<b>Antiemetics</b>	Aprepitant, casopitant, netupitant	<b>Diuretics</b>	Conivaptan	<b>Antineoplastic agents</b>	Imatinib	<p><b>Table 4: A partial list of moderate/strong CYP3A4 inhibitors; These drugs may increase the level of laquinimod and therefore are disallowed 2 weeks prior to study, during study and 30 days after last study dose:</b></p> <table border="1" data-bbox="856 448 1587 837"> <thead> <tr> <th>Medication class</th> <th>Drug name</th> </tr> </thead> <tbody> <tr> <td><b>Protease inhibitors</b></td> <td>Indinavir, saquinavir, lopinavir, nelfinavir, amprenavir, atazanavir, darunavir, ritonavir</td> </tr> <tr> <td><b>Antivirals:</b></td> <td>Boceprevir, telaprevir, <i>danoprevir, ledipasvir</i></td> </tr> <tr> <td><b>Antifungals:</b></td> <td>Ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole</td> </tr> <tr> <td><b>Antibiotics</b></td> <td>Troleandomycin, clarithromycin, telithromycin, ciprofloxacin, erythromycin</td> </tr> <tr> <td><b>Antidepressant</b></td> <td>Nefazodone</td> </tr> <tr> <td><b>Calcium channel blocker</b></td> <td><del>Diltazem</del><i>Diltiazem</i>, verapamil, mibefradil</td> </tr> <tr> <td><b>Antiemetics</b></td> <td>Aprepitant, casopitant, netupitant</td> </tr> <tr> <td><b>Diuretics</b></td> <td>Conivaptan</td> </tr> <tr> <td><b>Antineoplastic agents</b></td> <td>Imatinib</td> </tr> <tr> <td><b>Antiarrhythmics</b></td> <td>dronedarone</td> </tr> </tbody> </table> <p>...</p> <p><b>A partial list of CYP3A4 inducers:</b></p> <ul style="list-style-type: none"> <li>• Carbamazepine</li> <li>• Phenobarbital</li> <li>• Phenytoin</li> <li>• Rifabutin</li> <li>• Rifampin</li> <li>• St. John's Wort</li> </ul> <p><b>Table 5: A partial list of CYP3A4 inducers. 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<p><b>APPENDIX C: LIST OF ALLOWED MEDICATION/THERAPIES DURING STUDY</b> A partial list of CYP3A4 substrates with a narrow therapeutic index:</p> <ul style="list-style-type: none"> <li>● Alfentanil</li> <li>● Cyclosporine</li> <li>● Diergotamine</li> <li>● Ergotamine</li> <li>● Fentanyl</li> <li>● Pimozide</li> <li>● Quinidine</li> <li>● Sirolimus</li> <li>● Tacrolimus</li> </ul> <p><b>A partial list of drugs known to be metabolized by CYP1A2:</b></p> <ul style="list-style-type: none"> <li>● Clozapine</li> <li>● Duloxetine</li> <li>● Theophylline</li> <li>● Tizanidine</li> <li>● Alosetron</li> <li>● Ramelteon</li> <li>● Tacrine</li> </ul>	<p><b>APPENDIX C: LIST OF ALLOWED MEDICATION/THERAPIES DURING STUDY OTHER CONCOMITANT MEDICATIONS/THERAPIES</b> <del>A partial list of CYP3A4 substrates with a narrow therapeutic index:</del></p> <ul style="list-style-type: none"> <li><del>● Alfentanil</del></li> <li><del>● Cyclosporine</del></li> <li><del>● Diergotamine</del></li> <li><del>● Ergotamine</del></li> <li><del>● Fentanyl</del></li> <li><del>● Pimozide</del></li> <li><del>● Quinidine</del></li> <li><del>● Sirolimus</del></li> <li><del>● Tacrolimus</del></li> </ul> <p><i>Table 6: A partial list of drugs with a narrow therapeutic index that are metabolized by CYP3A4 (plasma levels of these drugs could increase when combined with laquinimod):</i> <i>Note: The medications list is considered partial. All medication that fall under prohibited medication classes should be excluded. Please contact the sponsor if you have questions about prohibited medication.</i></p> <table border="1"> <thead> <tr> <th><i>Medication class</i></th> <th><i>Drug name</i></th> </tr> </thead> <tbody> <tr> <td><i>Opioids</i></td> <td><i>Fentanyl, alfentanil</i></td> </tr> <tr> <td><i>Migraine treatment</i></td> <td><i>Ergotamine, diergotamine</i></td> </tr> <tr> <td><i>Antiarrhythmic</i></td> <td><i>Quinidine</i></td> </tr> </tbody> </table> <p><del><b>A partial list of drugs known to be metabolized by CYP1A2:</b></del></p> <ul style="list-style-type: none"> <li><del>● Clozapine</del></li> <li><del>● Duloxetine</del></li> </ul>	<i>Medication class</i>	<i>Drug name</i>	<i>Opioids</i>	<i>Fentanyl, alfentanil</i>	<i>Migraine treatment</i>	<i>Ergotamine, diergotamine</i>	<i>Antiarrhythmic</i>	<i>Quinidine</i>	<p>The lists of disallowed and allowed medications mentioned in Appendix B and Appendix C are now arranged according to medication classes, and are presented in a tabular format to facilitate usage.</p> <p>Several additional medications were added to the groups.</p> <p>A list of CYP1A2 substrates is included.</p>
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	<ul style="list-style-type: none"> <li>● <del>Theophylline</del></li> <li>● <del>Tizanidine</del></li> <li>● <del>Alosetron</del></li> <li>● <del>Ramelteon</del></li> <li>● <del>Tacrine</del></li> </ul> <p><i>Table 7: A partial list of drugs that are mainly metabolized by CYP1A2. Drugs with a narrow therapeutic index appear in bolded text.</i></p> <p><i>Note: The medications list is considered partial. All medication that fall under prohibited medication classes should be excluded. Please contact the sponsor if you have questions about prohibited medication.</i></p> <table border="1" data-bbox="850 662 1583 1388"> <thead> <tr> <th data-bbox="850 662 1104 716">Medication class</th> <th data-bbox="1104 662 1583 716">Drug name</th> </tr> </thead> <tbody> <tr> <td data-bbox="850 716 1104 829"><b>Antidepressant</b></td> <td data-bbox="1104 716 1583 829">Agomelatine, Duloxetine, Mirtazapine, Nortriptyline, Fluvoxamine</td> </tr> <tr> <td data-bbox="850 829 1104 935"><b>Antipsychotics</b></td> <td data-bbox="1104 829 1583 935">Chlorpromazine, <b>Clozapine</b>, Olanzapine, Thiothixene, Trifluoperazine</td> </tr> <tr> <td data-bbox="850 935 1104 1000"><b>Migraine Treatments</b></td> <td data-bbox="1104 935 1583 1000">Frovatriptan, Zolmitriptan</td> </tr> <tr> <td data-bbox="850 1000 1104 1105"><b>Anesthetics</b></td> <td data-bbox="1104 1000 1583 1105">Lidocaine (systemic use)</td> </tr> <tr> <td data-bbox="850 1105 1104 1170"><b>Antineoplastic agents</b></td> <td data-bbox="1104 1105 1583 1170">Erlotinib</td> </tr> <tr> <td data-bbox="850 1170 1104 1227"><b>Muscle relaxants</b></td> <td data-bbox="1104 1170 1583 1227">Cyclobenzaprine, <b>Tizanidine</b></td> </tr> <tr> <td data-bbox="850 1227 1104 1284"><b>Sleep disorders</b></td> <td data-bbox="1104 1227 1583 1284">Melatonin, Ramelteon</td> </tr> <tr> <td data-bbox="850 1284 1104 1341"><b>Respiratory Agents</b></td> <td data-bbox="1104 1284 1583 1341"><b>Aminophylline, theophylline</b></td> </tr> <tr> <td data-bbox="850 1341 1104 1388"><b>Benzodiazepines</b></td> <td data-bbox="1104 1341 1583 1388">Chlordiazepoxide</td> </tr> </tbody> </table>	Medication class	Drug name	<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	
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<b>Benzodiazepines</b>	Chlordiazepoxide																					

Previous approved wording	Amended or new wording		Reason/justification for change
	<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 (IBS treatment), Riluzole (ALS treatment), <b>methadone</b>	
<b>APPENDIX D</b>			
(Not applicable)	<p><i>Appendix D. Magnetic Resonance Imaging</i>  <i>The patients will undergo MRI scans at Baseline and Month 12 or Early Termination. The scans will be obtained according to a standard protocol that will be provided by the Imaging CRO (iCRO). The scans will be sent to the iCRO for approval and processing.</i></p> <p><i>MRI scan will be performed using the following schedule:</i></p> <ul style="list-style-type: none"> <li>• <i>Month 0/Baseline: as soon as possible after eligibility has been confirmed but not less than 7 days prior to baseline.</i></li> <li>• <i>Month 12: up to 7 days prior to the Month 12 visit.</i></li> <li>• <i>Early Termination: as soon as possible, but not more than 7 days after discontinuation of study drug.</i></li> </ul> <p><i>Note that the first MRI scan will be performed at least 7 days prior to the baseline visit to enable image approval and to set the reference for comparison to subsequent MRIs.</i></p> <p><i>If a patient terminates within 3 months of the baseline visit, they will not undergo an Early Termination scan.</i></p> <p><i>MRI facilities will undergo a qualification procedure, which will include the acquisition of a healthy volunteer dummy run to ensure that the implementation of the standard sequences on their system produces appropriate images for measuring the endpoints specified in the protocol. The healthy volunteer must sign an ethics committee-approved informed consent. The scans will be reviewed by the MRI facility and a report will be given to the healthy volunteer. Qualification of sites will be formally indicated by an</i></p>		Addition of appendix detailing MRI procedures.

Previous approved wording	Amended or new wording	Reason/justification for change
	<p><i>approval certification. Sites must be qualified prior to the first patient inclusion.</i></p> <p><i>Detailed instructions are provided in the Site Operations Guide. Confidential patient information such as patient full name must be omitted from the scan header, the compact disc labels, and any accompanying documentation. MRI scans will be transferred to the iCRO in electronic format, or when not possible, by courier. The procedure for sending electronic data and accompanying documentations is specified in the Site Operations Guide. The iCRO will perform quality control checks of all images received. If both scans from one visit fail QC, the scan will need to be repeated. If the baseline scan fails QC, rescanning of the patient should be performed as soon as possible, prior to randomization. In cases of a failed QC at all other visits, the window for rescanning will be no longer than 2 weeks. Images should be reviewed, by the site, at the time of acquisition so that any sequences affected by obvious artifacts can be repeated immediately.</i></p> <p><i>MRI scans are to be evaluated locally for any incidental pathology (ie, pathology unrelated to, or inconsistent with, the patient’s known HD) according to locally determined procedures. If such pathology is found, the Treating Neurologist should be notified. The iCRO will evaluate the scans for the purposes of performing quantitative analyses. In order not to compromise the blinding of the study, the iCRO will not report results from the quantitative analyses back to the clinical site.</i></p>	
<b>17 REFERENCES</b>		
<p>Crotti A, Benner C, Kerman BE, Gosselin D, Lagier-Tourenne C, Zuccato C, et al. Mutant Huntingtin promotes autonomous microglia activation via myeloid lineage-determining factors. Nat Neurosci. 2014 Mar 2. [Epub ahead of print]</p>	<p>Crotti A, Benner C, Kerman BE, Gosselin D, Lagier-Tourenne C, Zuccato C, et al. Mutant Huntingtin promotes autonomous microglia activation via myeloid lineage-determining factors. Nat Neurosci. 2014 Mar 2. [Epub ahead of print] <b>17(4):513-21.</b></p>	<p>Corrected from "Epub ahead of print" to actual journal reference.</p>
<p>Tabrizi SJ, Reilmann R, Roos RA et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. Lancet Neurol 2012;11:42-53.</p>	<p>Reference deleted from protocol.</p>	<p>This reference is no longer relevant following the revision of the text in Section 6.2.1.</p>
<p>Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity</p>	<p>Reference deleted from protocol.</p>	<p>This reference is no longer relevant following the</p>

<b>Previous approved wording</b>	<b>Amended or new wording</b>	<b>Reason/justification for change</b>
in MRI data. IEEE Trans Med Imaging 1998;17:87-97.		revision of the text in Section 6.2.1.
Boyes RG, Gunter JL, Frost C, Janke AL, Yeatman T, Hill DLG et al. Intensity non-uniformity correction using N3 on 3T scanners with multichannel phased array receiver coils. NeuroImage 2008; 39:1752-62.	Reference deleted from protocol.	This reference is no longer relevant following the revision of the text in Section 6.2.1.

**16.9. SUMMARY OF CHANGES FOR LOCAL PROTOCOL  
AMENDMENT 02 FOR ETHICS COMMITTEE SUBMISSION IN  
THE UNITED KINGDOM DATED 25 JANUARY 2015**

The revisions listed below have been made to the protocol, and synopsis as appropriate, and are considered non-substantial by the sponsor's Authorized Representative.

The primary reason for this amendment is to comply with the UK Ethics Committee's request to

- (i) exclude from the study patients who lack the capacity to provide their own consent, and
- (ii), for women of child bearing potential, to perform a home pregnancy test prior to traveling to London for the PET scan.

Substantive changes from the EC UK Local Amendment 01 to the EC UK Local Amendment 02 are provided below.


New text is shown in *bold italics*; deleted text is marked by strikethrough.

Previous approved wording	Amended or new wording	Reason/justification for change
<b>COVER PAGE</b>		
Clinical Study Protocol with Amendment 01 and Local Amendment for Ethics Committee Submission in the United Kingdom 01	Clinical Study Protocol with Amendment 01 and Local Amendment for Ethics Committee Submission in the United Kingdom <del>01</del> 02	Updated to reflect amendment.
Sponsor's Global Clinical Leader Anna Wickenberg, PhD Global Clinical Leader Teva Pharmaceutical Industries, Ltd. Tel: +46-72-721-9122	<del>Sponsor's Global Clinical Leader Anna Wickenberg, PhD Global Clinical Leader Teva Pharmaceutical Industries, Ltd. Tel: +46-72-721-9122</del> Sponsor's Medical Expert Spyridon (Spyros) Papapetropoulos, MD, PhD Global Head, Neurodegeneration, Clinical Development Teva Branded Pharmaceutical Products R&D, Inc. Tel: +1-610-727-6044	Identity and contact details of the new medical expert.
Maya Margalit, MD Global Patient Safety & PhV Teva Pharmaceutical Industries, Ltd. Tel: +972-3-9267155	Maya Margalit Dana Gorsetman, MD Global Patient Safety & PhV Teva Pharmaceutical Industries, Ltd. Tel: +972-3-9267155531	Identity and contact details of the new safety physician.
<b>COORDINATING INVESTIGATOR AGREEMENT</b>		
Global Coordinating Investigator: Ralf Reilmann, MD, PhD  Title: Founding Director and CEO, George Huntington Institute; Chair - EHDN Huntington Center, University of Munster; Chair - Laboratory of Biomarkers and Neurodegeneration, University of Munster	Global Coordinating Investigator: Ralf Reilmann, MD, PhD Title: Founding Director and CEO, George Huntington Institute; George Huntington Institute, Münster; <del>Chair – EHDN Huntington Center Dept. of Radiology, University of Münster; Department of Neurodegenerative Diseases and Hertie-Institute for Clinical Brain Research, University of Tübingen, Germany Chair – Laboratory of Biomarkers and Neurodegeneration, University of Münster</del>	Modified title of coordinating investigator.
<b>Section 3.11 – Table 3</b>		
1. An additional urine $\beta$ -HCG test will be performed at the PET facilities at Imperial College in London at the Baseline visit and at Visit 8. This is a requirement for women of child-bearing potential participating in the PET substudy. Its result will be available on site prior to any procedures involving ionizing radiation and will be considered accordingly.	1. <i>For women of child bearing potential, a urine pregnancy test should be performed at home prior to traveling to the Imperial College in London (no later than 2 days prior to travel) for the Baseline visit and Visit 8.</i> An additional urine $\beta$ -HCG test will be performed at the PET facilities at Imperial College London <del>at the Baseline visit and at Visit 8</del> on the same day and prior to the scan. This is a requirement for women of child-bearing potential	Clarification that women of child bearing potential should perform a home urine pregnancy test prior to traveling to London for the PET scan during the baseline and Month 12 visits,

Previous approved wording	Amended or new wording	Reason/justification for change
	participating in the PET substudy. Its result will be available on site prior to any procedures involving ionizing radiation and will be considered accordingly.	
<b>Section 4.1</b>		
f. Able and willing to provide written informed consent prior to any study related procedure being performed at the screening visit. Patients with a legal guardian should be consented according to local requirements.	f. <i>[Revision 1]</i> Able and willing to provide written informed consent prior to any study related procedure being performed at the screening visit. Patients with a legal guardian should be consented according to local requirements. <i>For the UK only: Only patients with the capacity to give their informed consent should be enrolled.</i>	Clarification added that in the UK, patients lacking capacity to provide their own informed consent will not be enrolled.
<b>Section 8.2.4.2</b>		
For women of child bearing potential, a urine pregnancy test will be performed on the same day, and prior to, the PET scan at Imperial College in London. If the result of this test is positive, the PET procedure will not be performed and the patient will be monitored as outlined in Section 7.2.	For women of child bearing potential, a urine pregnancy test <del>will be performed on the same day, and prior to, the PET scan at Imperial College in London</del> <i>should be performed at home prior to traveling to the Imperial College London (no later than 2 days prior to travel)</i> . If the result of this test is positive, <del>the PET procedure will not be performed and the patient will be monitored as outlined in Section 7.2.</del> <i>the patient should immediately contact both their main study site as well as the Imperial College team to cancel the PET scan visit. The main study site should follow the procedures outlined in Section 7.2 of the protocol.</i> <i>If the test is negative, the patient will have another urine pregnancy test performed on the same day, and prior to, the PET scan at Imperial College London. If the result of this test is positive, the PET procedure will not be performed and the patient will be monitored as outlined in Section 7.2.</i>	Clarification that women of child bearing potential should perform a home urine pregnancy test prior to traveling to London for the PET scan, and subsequent instructions following receipt of result.



## 16.10. ADMINISTRATIVE LETTER 02 DATED 14 NOVEMBER 2014



14 November 2014

Re: TV5600-CNS-20007 (LEGATO-HD)

Administrative Changes to the Protocol dated 10 September 2014

The purpose of this administrative letter is to notify sites of the following clarifications to the protocol:

1. Protocol Section 3.2.8- Pharmacogenomic Measures and Endpoints

Section 3.2.8 of the protocol notes that the patient will be given the opportunity to decide whether the exact CAG repeat result will be disclosed to them or not.

The exact CAG repeat will not be available to the sites. The central laboratory report will only note if the patient is within the eligibility criteria range or not.

2. Protocol Table 3- footnote "k".

Women of child-bearing potential must have a serum  $\beta$ hCG within 7 days prior to the initiation of treatment. Whenever possible, this sample should be sent to the central laboratory for analysis. The sample may be sent to a local laboratory if timing does not permit sending to the central laboratory. The scenarios are as follows:

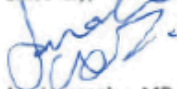
- Serum pregnancy test ( $\beta$ -HCG) is performed by the **central Lab** within 7 days prior to the baseline visit and result obtained prior to randomization – no need for additional test in Baseline visit. In this case, test will be considered an **unscheduled visit**. Please have the sample sent to the lab **at least 48 hours** prior to the baseline visit to ensure results are available.
- Serum pregnancy test ( $\beta$ -HCG) is performed by a **local lab** within 7 days prior to the baseline visit, or at the day of the baseline visit, and result obtained prior to randomization at the baseline visit day. If the local lab sample is collected on the baseline visit day, a sample does **not** need to be sent to the central laboratory as well.

Results must be obtained prior to randomizing the patient, documented in an official lab report and filed with patient's source documents. In case an unscheduled visit is performed, all mandatory activities according to the protocol, for this visit, should be performed.

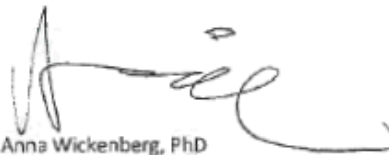
This administrative letter will be an addendum to the TV5600-CNS-20007 protocol, and is not considered a substantial amendment.

If you have any questions, please contact your CRA.

Sincerely,



Jon Isaacsohn, MD  
Chief Medical Officer  
Global Research and Development  
Teva Pharmaceuticals



Anna Wickenberg, PhD  
Clinical Lead  
Global Research and Development  
Teva Pharmaceuticals

**16.11. SUMMARY OF CHANGES FOR LOCAL PROTOCOL  
AMENDMENT 01 FOR ETHICS COMMITTEE SUBMISSION IN  
THE UNITED KINGDOM**

Dated: 30 September 2014

The revisions listed below have been made to the protocol, as appropriate, and are considered non-substantial by the sponsor's Authorized Representative.

The primary reason for this amendment is to introduce exclusion criteria specific to patients randomized to participate in the PET ancillary study investigating the microglial activation marker TSPO, as well as pregnancy testing for women of child bearing potential on the same day, prior to the scan.

Substantive changes from the Amendment 01 to the Local Amendment are provided below.

New text is shown in *bold italics*; deleted text is marked by strikethrough.

All changes will be implemented in the next global protocol amendment.

Previous approved wording	Amended or new wording	Reason/justification for change
<b>COVER PAGE, INVESTIGATOR AGREEMENT, COORDINATING INVESTIGATOR AGREEMENT</b>		
Clinical Study Protocol <i>with Amendment 01</i>	Clinical Study Protocol with Amendment 01 <i>and Local Amendment for Ethics Committee Submission in the United Kingdom 01</i>	Updated to reflect amendment.
<b>LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS</b>		
(Not applicable)	HAB - High affinity binding	Newly-added abbreviation.
(Not applicable)	LAB – low affinity binding	Newly-added abbreviation.
(Not applicable)	MAB – mixed affinity binding	Newly-added abbreviation.
<b>SYNOPSIS</b>		
Other ancillary studies: <ul style="list-style-type: none"> <li>Microglial activation state will be investigated at selected sites and patients (N=aiming at 20 per treatment arm). Positron emission tomography (PET) scans and imaging analysis of microglial activation marker translocator protein (TSPO) will be performed at baseline and Month 12.</li> </ul>	Other ancillary studies: <ul style="list-style-type: none"> <li>Microglial activation state will be investigated at selected sites and patients (N=aiming at <del>20</del> 10 per treatment arm). Positron emission tomography (PET) scans and imaging analysis of microglial activation marker translocator protein (TSPO) will be performed at baseline and Month 12.</li> </ul>	Updated number of patients to be recruited for this ancillary study.
<b>2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES</b>		
<b>Section 2.2.5</b>		
(Not applicable)	... <ul style="list-style-type: none"> <li>To assess the correlation between microglial activation state at baseline and the clinical characteristics of HD patients (age, gender, number of triplets, disease onset, disease duration, motor and behavioural scores).</li> </ul>	New ancillary objective added.
<b>3 STUDY DESIGN</b>		
<b>Section 3.11 – Table 2</b>		
(Not applicable)	<i>1. An additional urine -HCG test will be performed at the PET facilities at Imperial College in London at the Baseline visit and at Visit 8. This is a requirement for women of child-bearing potential participating in the PET substudy. Its result will be available on site prior to any procedures involving ionizing radiation and will be considered accordingly.</i>	New footnote describing pregnancy testing in women of child bearing potential randomized to the PET ancillary study at baseline and Month 12.  Consequently, the numbering of the subsequent footnotes has

Previous approved wording	Amended or new wording	Reason/justification for change
(Not applicable)	<i>New row added titled "Blood sample for TSPO genotype analysis"; the procedure will be performed at screening.</i>	Procedure added to correspond with Section 8.2.4.1.
<b>Section 3.11.1 (Other sections affected by this change: Table 2)</b>		
... <ul style="list-style-type: none"> <li>serum -HCG in women of childbearing potential within the 7 days prior to initiation of treatment</li> <li>C-SSRS (baseline screening version)</li> </ul> ...	... <ul style="list-style-type: none"> <li>serum -HCG in women of childbearing potential within the 7 days prior to initiation of treatment</li> <li><i>blood sample for TSPO genotype analysis (Only at selected sites in a subgroup of patients)</i></li> <li>C-SSRS (baseline screening version)</li> </ul> ...	Procedure added to correspond with Section 8.2.4.1.
<b>Section 3.11.2 (Other sections affected by this change: Table 2; 3.11.3.1.5; 8.2.4.2)</b>		
... <ul style="list-style-type: none"> <li>serum -HCG in women of childbearing potential</li> <li>urine -HCG in women of childbearing potential</li> <li>Ascertaining use of effective contraception</li> </ul> ...	... <ul style="list-style-type: none"> <li>serum -HCG in women of childbearing potential</li> <li>urine -HCG in women of childbearing potential</li> <li><i>additional urine -HCG in women of childbearing potential at PET facilities (Only in a subgroup of patients)</i></li> <li>Ascertaining use of effective contraception</li> </ul> ...	New bullet in baseline procedures describing pregnancy testing in women of child bearing potential randomized to the PET ancillary study.
<b>Section 3.11.3.1.5 (Other sections affected by this change: Table 2; 3.11.2; 8.2.4.2)</b>		
... <ul style="list-style-type: none"> <li>serum -HCG in women of childbearing potential</li> <li>urine -HCG in women of childbearing potential</li> <li>Ascertaining use of effective contraception</li> </ul> ...	... <ul style="list-style-type: none"> <li>serum -HCG in women of childbearing potential</li> <li>urine -HCG in women of childbearing potential</li> <li><i>additional urine -HCG in women of childbearing potential at PET facilities (Only in a subgroup of patients)</i></li> <li>Ascertaining use of effective contraception</li> </ul> ...	New bullet in Month 12 procedures describing pregnancy testing in women of child bearing potential randomized to the PET ancillary study.
<b>8 ASSESSMENT OF PHARMACOKINETICS/PHARMACOGENOMICS/OTHER ANCILLARY STUDIES</b>		
<b>Section 8.2.4</b>		
At selected sites, patients will be referred to a PET scan at baseline and end of treatment (Month 12). Each participant in the ancillary study will undergo a TSPO tracer PET scan at baseline and at the end of treatment (Month 12).	<del>At selected sites, patients will be referred to a PET scan at baseline and end of treatment (Month 12). Each participant in the ancillary study will undergo a TSPO tracer PET scan at baseline and at the end of treatment (Month 12).</del>	Clarification regarding the PET imaging location.  New text excluding patients, who will exceed exposure to ionizing

Previous approved wording	Amended or new wording	Reason/justification for change
<p>The 18-kDa TSPO is expressed within microglia and macrophages and has been used as a target for PET ligands to study neurodegenerative disease processes that involve microglial activation, such as HD, Parkinson’s disease (PD) and Alzheimer's disease (AD) (Politis et al, 2012)<sup>41</sup> The PET radioligand <sup>11</sup>C-PK11195 has been used most frequently for this purpose, but signal quantification is limited by poor specific signal-to-background ratio.</p>	<p><i>At selected sites, patients will be referred to the Imperial College in London, where PET Imaging will be performed at the Imanova Imaging Centre on the Hammersmith Hospital site. The PET imaging will be performed at baseline and after treatment with laquinimod over a 12-month period of time.</i></p> <p><i>All patients participating in the PET arm of the study will be exposed to additional ionizing radiation due to the PET/CT scans. There are no alternatives methods available to explore neuroinflammation in vivo. While any ionizing radiation exposure increases the risk of future malignancy, for the radiation exposure in this study such exposure is small and the increased risk is minimal. Patients who recently took part in clinical studies or underwent medical procedures involving ionizing radiation, such that participation in this study would lead to an exposure of &gt;10mSv in the last 12 months, will be excluded from participation in this ancillary study. This will not affect the patient's participation in the main study.</i></p> <p>The 18-kDa TSPO is expressed within microglia and macrophages and has been used as a target for PET ligands to study neurodegenerative disease processes that involve microglial activation, such as HD, Parkinson’s disease (PD) and Alzheimer's disease (AD) (Politis et al, 2012)<sup>41</sup> The PET radioligand <sup>11</sup>C-PK11195 has been used most frequently for this purpose, but signal quantification is limited by poor specific signal-to-background ratio.</p>	<p>radiation of &gt;10mSv in the last 12 months, from participation in the PET ancillary study.</p>
<p><b>Section 8.2.4.1</b></p>		
<p>Genomic DNA will be collected at the screening visit as described in Section 8.3.1 and used to genotype the rs6971 polymorphism within the TSPO gene on chromosome 22q13.2 (Owen et al, 2011<sup>46</sup>, Kreisl et al, 2013<sup>45</sup>).</p>	<p>Genomic DNA will be collected at the screening visit as described in Section 8.3.1 and used to genotype the rs6971 polymorphism within the TSPO gene on chromosome 22q13.2 (Owen et al, 2011<sup>46</sup>, Kreisl et al, 2013<sup>45</sup>).</p> <p><i>Patients who have A/A genotype for rs6971 polymorphism on the TSPO gene, which has been shown to result in low affinity binding (LAB) of the <sup>11</sup>C-PBR28 radioligand, will be excluded from the PET ancillary study. Patients with LAB for TSPO can participate in the main study even if they are excluded from the PET ancillary study. Patients with G/G and A/G rs6971</i></p>	<p>New text regarding inclusion and exclusion of patients with the various genotypes for the rs6971 polymorphism from participation in the PET ancillary study.</p>

Previous approved wording	Amended or new wording	Reason/justification for change
	<i>genotype have been shown to have high (HAB) and mixed (MAB) affinity binding, respectively, and will be included in the PET ancillary study.</i>	
<b>Section 8.2.4.2</b>		
<p>Specific activity, chemical purity, and radiochemical purity of <sup>11</sup>C-PBR28 will be determined by radio high performance liquid chromatography (HPLC) coupled with a gamma detector. Specific activity will be determined by counting an aliquot in a dose calibrator and determining the mass by HPLC against a calibration curve of the cold standard. Identity will be confirmed by co-injecting the standard.</p> <p>Approximately 600 MBq of <sup>11</sup>C-PBR28 as intravenous bolus will be injected, and a two-hour emission scan will be acquired on a Siemens HiRez 6 PET/CTI scanner (Siemens Healthcare, Erlanger, Germany). A low dose CTI scan will be performed immediately before each PET study for subsequent attenuation and scatter correction. Imaging data will be reconstructed with filter backprojection (direct inversion Fourier transform) with a 128 matrix, a zoom of 2.6, a transaxial Gaussian filter of 5 mm, scatter correction and attenuation correction. All subjects will have a volumetric T1-weighted MR sequence for co-registration purpose with PET images.</p>	<p><b><i>For women of child bearing potential, a urine pregnancy test will be performed on the same day, and prior to, the PET scan at Imperial College in London. If the result of this test is positive, the PET procedure will not be performed and the patient will be monitored as outlined in Section 7.2.</i></b></p> <p>Specific activity, chemical purity, and radiochemical purity of <sup>11</sup>C-PBR28 will be determined by radio high performance liquid chromatography (HPLC) coupled with a gamma detector. Specific activity will be determined by counting an aliquot in a dose calibrator and determining the mass by HPLC against a calibration curve of the cold standard. Identity will be confirmed by co-injecting the standard.</p> <p>Approximately <del>600</del> <b>400</b> MBq of <sup>11</sup>C-PBR28 as intravenous bolus will be injected, and <del>a two-hour</del> <b>an approximately 90 minutes</b> emission <b><i>PET-CT</i></b> scan will be acquired on a Siemens HiRez 6 PET/CTI scanner (Siemens Healthcare, Erlanger, Germany). A low dose CTI scan <b><i>of the head</i></b> will be performed immediately before each PET study for subsequent attenuation and scatter correction <b><i>of PET signal</i></b>. Imaging data will be reconstructed with filter backprojection (direct inversion Fourier transform) with a 128 matrix, a zoom of 2.6, a transaxial Gaussian filter of 5 mm, scatter correction and attenuation correction. All subjects will have a volumetric T1-weighted MR sequence for co-registration purpose with PET images.</p> <p><b><i>Patients will be advised that they should not participate in further research studies involving ionizing radiation for a year following the last performed scan.</i></b></p>	<p>New text describing pregnancy testing in women of child bearing potential randomized to the PET ancillary study.</p> <p>Updated information regarding the PET procedure.</p> <p>Advice to patients to refrain from participation in studies involving ionizing radiation for a year following the last scan has been added.</p>

## **16.12. SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01 DATED 10 SEPTEMBER 2014**

The revisions listed below have been made to the protocol, and synopsis as appropriate, and are considered substantial by the Teva Authorized Representative.

The primary reasons for this amendment are to ascertain that patients with ongoing alcohol and/or drug abuse are excluded from the study, to clarify the unblinding procedure that can be performed by the investigator in a medical emergency situation, and to further clarify that HIV screening will be done per local requirements at screening.

A comparison table showing substantive changes from the original protocol to Amendment 01 is provided below. Previous text is presented in the column titled “Previous approved wording,” revised or new text is presented in bold italics and deletions are struck through in the column titled “Amended or new wording,” and the reason or justification for the change is presented in the column titled “Reason/justification for change.”

Changes to the synopsis are not detailed in the table but have been made according to the corresponding changes in the body of the protocol.

Previous approved wording	Amended or new wording	Reason/justification for change
<b>COVER PAGE, INVESTIGATOR AGREEMENT, COORDINATING INVESTIGATOR AGREEMENT</b>		
Clinical Study Protocol	Clinical Study Protocol <i>with Amendment 01</i>	Updated to reflect amendment.
Protocol Approval Date: 27 May 2014	Protocol Approval Date: <i>27 May 2014</i> <i>10 September 2014</i>	Date changed to that of amended document.
<b>PROTOCOL AMENDMENTS PAGE</b>		
(Not applicable)	Page 2, describing the document history, has been added.	Page added per sponsor template.
<b>LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS</b>		
(Not applicable)	<i>CDT - Carbohydrate deficient transferrin</i>	New abbreviation added to list following request for CDT testing, where applicable.
<b>3 STUDY DESIGN</b>		
<b>Section 3.8</b>		
In case of a serious adverse event, pregnancy, or in cases when knowledge of the study drug assignment is needed to make treatment decisions, the investigator may unblind the patient's drug assignment as deemed necessary, mainly in emergency situations.  The sponsor should be notified of the event prior to breaking of the code, if possible. If this is not possible, the sponsor should be notified immediately afterwards, and the patient's drug code assignment should not be revealed.	In case of a serious adverse event, pregnancy, or in cases when knowledge of the study drug assignment is needed to make treatment decisions, the investigator may unblind the patient's drug assignment as deemed necessary, mainly in emergency situations. <b><i>Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) or pharmacist(s) at the study center via the IRT, both via telephone and internet. If possible, the sponsor should be notified of the event prior to breaking of the code, if possible. If this is not possible, the sponsor should be notified immediately afterwards, and the patient's drug code assignment should not be revealed. Breaking of the treatment code can always be performed by the site without prior approval by the sponsor.</i></b>	Text has been revised to properly describe the mechanism for unblinding.
<b>Section 3.11 Table 3 (Other sections affected by this change: 3.11.1; 4.2)</b>		
(Not applicable)	New row to indicate drug testing and/or CDT testing at screening.	These tests will be performed, when applicable, to confirm abstinence in former alcohol and/or drug abusers.
(Not applicable)	<b><i>b. When applicable, patients will be screened for drug substances in urine and/or CDT level in blood at screening to confirm abstinence in former (more than 12 months from screening) alcohol and/or drug abusers.</i></b>	New footnote to accompany added procedure.
(Not applicable)	<b><i>d. When applicable per local requirements, patients will undergo an HIV test at screening.</i></b>	Footnote added to specify serology for HIV at screening per exclusion criteria.



Previous approved wording	Amended or new wording	Reason/justification for change
<b>Section 3.11.1 (Other sections affected by this change: Table 3; 4.2)</b>		
<p>...</p> <ul style="list-style-type: none"> <li>● HD history</li> <li>● review prior medication history</li> <li>● blood sample for genomic analysis including CAG analysis</li> <li>● perform clinical laboratory tests</li> <li>● clinical hematology</li> <li>● perform urinalysis</li> </ul> <p>perform vital signs measurements (including postural BP changes)</p> <p>...</p>	<p>...</p> <ul style="list-style-type: none"> <li>● HD history</li> <li>● review prior medication history</li> <li>● blood sample for genomic analysis including CAG analysis</li> <li>● <i>when applicable, patients will be screened for drug substances in urine and/or CDT level in blood to confirm abstinence in former (more than 12 months from screening) alcohol and/or drug abusers</i></li> <li>● perform clinical laboratory tests</li> <li>● <i>when applicable per local requirements, patients will undergo an HIV test</i></li> <li>● clinical hematology</li> <li>● perform urinalysis</li> <li>● perform vital signs measurements (including postural BP changes)</li> </ul> <p>...</p>	<p>Drug testing and/or CDT testing (when applicable) added to screening procedures.</p> <p>Serology for HIV specified per exclusion criteria, and to correspond with Table of Study Procedures and Assessments.</p>
<b>4 SELECTION AND WITHDRAWAL OF PATIENTS</b>		
<b>Section 4.2 (Other sections affected by this change: Table 3; 3.11.1)</b>		
<p>Exclusion criterion I: Alcohol and/or drug abuse within the 6 months prior to screening, as defined by Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition Text Revision (DSM-IV TR) criteria for substance abuse.</p>	<p>Exclusion criterion I: Alcohol and/or drug abuse within the <del>6</del> <b>12</b> months prior to screening, as defined by Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition Text Revision (DSM-IV TR) criteria for substance abuse. <i>For former alcohol and/or drug abusers, the abstinence should be confirmed by laboratory tests (drug testing and/or carbohydrate deficient transferrin (CDT) level in blood).</i></p>	<p>History of drug and alcohol abuse updated to 12 months prior to screening.</p> <p>Abstinence should be confirmed by laboratory tests (drug testing and CDT level in blood).</p>
<b>7 ASSESSMENT OF SAFETY</b>		
<b>Section 7.3</b>		
<p>Clinical laboratory tests (serum chemistry and hematology) will be performed at Visits 1-4 and 6-9. Urinalysis will be performed at screening. Specific laboratory tests to be performed are listed below.</p>	<p>Clinical laboratory tests (serum chemistry and hematology) will be performed at Visits 1-4 and 6-9. Urinalysis will be performed at screening. <i>When applicable per local requirements, patients will undergo an HIV test at screening. Also when applicable, patients will be screened for drug substances in urine and/or CDT level in blood at screening to confirm abstinence in former alcohol and/or drug abusers.</i> Specific laboratory tests to be performed are listed below.</p>	<p>Language regarding serology for HIV and drug/CDT testing added to this section.</p>

**16.13. ADMINISTRATIVE LETTER 01 DATED 18 JULY 2014**

July 18, 2014

RE: TV5600-CNS-20007, LEGATO-HD

**Administrative changes to the protocol**

The purpose of this administrative letter is to notify sites of clarifications to the protocol per below:

**1. Healthy Volunteer for MRI qualification, and MRI procedures**

MRI scans will be obtained according to a standard protocol that will be provided by the imaging CRO (iCRO).

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

Detailed instructions are provided in the Site Operation Guide.

Confidential patient information such as patient full name must be omitted from the scan header, the compact disc labels, and any accompanying documentation. MRI scans will be transferred to the iCRO in electronic format, or when not possible by courier. The procedure for sending electronic data and accompanying documentation is specified in the Site Operation Guide.

The MRI reading center will perform QC of all images received. If both scans from one visit fails QC, it will need to be repeated. If the baseline scan fails QC, rescanning of the patient should be performed as soon as possible, but within 30 days from the baseline visit. In cases of failed QC at all other visits, the window for rescanning will be no longer than 30 days. Imaging should be reviewed, by the site, at the time of acquisition so that any sequences affected by obvious artifacts can be repeated immediately.

MRI scans are evaluated locally for any incidental pathology (ie, pathology unrelated to, or inconsistent with, the patient's known HD) according to locally determined procedures. If such pathology is found, the Treating Neurologist should be notified. The MRI reading center will evaluate the scans for the purposes of performing quantitative analyses. In order not to compromise blinding of the study, the MRI Reading Center will not report results from the quantitative analyses back to the clinical site.

2. Temporary discontinuation of study drug treatment.

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

This administrative letter will be an addendum to protocol TV5600-CNS-20007, LEGATO-HD, and is not considered a substantial amendment.

If you have any questions, please contact the study personnel designated for protocol issues on the Clinical Study Personnel Contact Information page of the protocol.

Sincerely,

**Jon Isaacsohn, MD, FACC**  
Chief Medical Officer  
Teva R&D  
Teva Pharmaceutical Industries Ltd.  
Jonathan Isaacsohn, MD  
Chief Medical Officer  
Global Research and Development  
Teva Pharmaceuticals



**Anna Wickenberg, PhD**  
Clinical Lead  
Global Research and Development  
Teva Pharmaceuticals



2017.10.19

## APPENDIX A. 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>4</sup> will be measured at each study visit.

In any case of elevated ALT or AST to a level exceeding of 2xULN (including subjects whose baseline ALT or AST levels are 2x and 3x the ULN, who may be enrolled in the study), a thorough medical history and physical examination with a focus on liver disease should be undertaken<sup>5</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 Treating Physician.

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

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

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

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

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

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

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<sup>4</sup> In case total bilirubin is >ULN, then direct bilirubin will be checked.

<sup>5</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.

**Additional Tests/Evaluations**

- Serology for Hepatitis A (antibody, immunoglobulin M and G), B (core antibody total, core immunoglobulin M, and surface antigen), and C viruses (central laboratory).
- Serology for autoimmune hepatitis: anti-nuclear antibodies (titer), ASMA (Anti Smooth Muscle Antibodies), anti-LKM (Liver Kidney Microsomal) antibodies (central laboratory). Further testing may be required in case of a positive result for Hepatitis B or C.
- An ultrasound examination of the liver and biliary tract.
- Other diagnostic tests/consultations, as deemed necessary by the investigator 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 3x (>3.5x ULN if baseline value is >2.5xULN) but less than 5xULN**

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

- ALT, AST, GGT, ALP, total and direct bilirubin, CBC and differential (to assess for eosinophilia) and INR should be monitored on days 5 ( $\pm 2$ ), 8 ( $\pm 2$ ), 14 ( $\pm 3$ ), and 28 ( $\pm 3$ ). 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 ( $\geq 3xULN$  in case baseline within normal range or  $\geq 2xULN$  in case the baseline value was above ULN, but still  $<5xULN$ ) persist further, the subject will be followed according to the investigator's discretion, but at least once a month a blood sample for ALT, AST, GGT, ALP, and total and direct bilirubin should be sent to the central laboratory.

**1.1.2. ALT or AST 5x but less than 8xULN**

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

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

**1.1.3. ALT or AST 8xULN**

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

- The study drug should be discontinued immediately and the ETD 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  $\geq 3$ xULN, combined with INR  $>1.5$  or total bilirubin  $>2$ xULN
- Any increase in ALT or AST to  $\geq 3$ xULN, which is accompanied by nausea, vomiting, fever, rash, or eosinophilia
- Any increase in ALT or AST to levels  $\geq 5$ x but  $<8$ xULN, which is persistent for 2 weeks of repeated measurements
- Any increase in ALT or AST to levels  $\geq 8$ xULN
- 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. ETD 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 ETD, the minimal follow-up period will be 30 days and will include measurement of liver enzymes at least once 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 B](#).

## 3. Use of CYP3A4 Substrates with Narrow Therapeutic Index

Plasma levels of drugs that are CYP3A4 substrates may increase when combined with laquinimod. Patients taking drugs that are metabolized by CYP3A4, specifically those with a Narrow Therapeutic Index ([Table 6](#) in [Appendix C](#)) should be advised that plasma levels of these drugs could increase when combined with laquinimod.

## 4. Use of CYP1A2 Substrates

Plasma levels of drugs that are CYP1A2 substrates may decrease when combined with laquinimod and within 30 days after the last laquinimod dose, rendering these drugs less effective.

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

For additional information on concomitant use of laquinimod with CYP1A2 substrates, please refer to Section 5.3.2.

## 5. Management of Pregnancy and Pregnancy Testing During the Study

Exposure to laquinimod during pregnancy should be avoided.

Women of child-bearing potential (women who are not post menopausal or who have not undergone surgical sterilization) must practice an acceptable method of birth control for 30 days before taking the study treatment, and 2 acceptable methods of birth control during all study duration and until 30 days after the last dose of treatment was administered.

Acceptable methods of birth control in this study include: Intrauterine device, barrier method (condom or diaphragm with spermicide) and hormonal methods of birth control (e.g. oral contraceptive, contraceptive patch, long-acting injectable contraceptive).

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

To further emphasize the importance of use of acceptable contraception and avoidance of pregnancy under laquinimod exposure, and to reduce as much as possible the exposure to laquinimod if a pregnancy occurs despite all recommended measures, the following measures will be taken:

1. Female subjects of child-bearing potential (women who are not post menopausal or who have not undergone surgical sterilization) will be reminded at each study visit about:
  - a. The importance of using acceptable contraception.  
The importance of immediately stopping the study drug and informing the site in any case of suspected pregnancy (following a positive urine test, absence of menstruation or any other reason suggesting pregnancy).
2. At each scheduled visit, female subjects of childbearing potential (women who are not post menopausal or who have not undergone surgical sterilization) will undergo a urine -hCG test. In addition, a serum pregnancy -hCG test will be performed at each visit.
  - a. In case the the urine test is negative, study drugs will be dispensed according to planned visit tasks (see [Table 3](#)).
    - i. 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 ETD visit.
    - ii. If the blood test is negative – study procedures will be undertaken as planned.
  - b. 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)
    - iii. If the blood test is positive, the subject will be invited to the site for an ETD visit
    - iv. 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.

In case of an established diagnosis of pregnancy, the Treating Physician/Neurologist should discuss with the subject the possible risk to the fetus, including the possibility of termination of the pregnancy. 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 adverse event or serious adverse event, as appropriate.

1. Starting from Visit 3 (Month 1), the following actions will be taken:
  - a. The subject will be provided with home pregnancy urine -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 Treating 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 -hCG pregnancy test should be performed and the rest of the activities will be as in 2b.

## **6. Cancer**

Patients who are diagnosed with malignant solid or liquid tumor while participating in the study should be discontinued from the study.

## **7. Guidance on monitoring subjects with elevated pancreatic amylase levels**

Amylase and pancreatic amylase will be measured at each study visit.

In any case of abnormal pancreatic amylase results to a level exceeding of  $1 \times \text{ULN}$  the subject will be invited to an unscheduled visit to test lipase levels. Lipase will be tested on all follow up visits until normalization of pancreatic amylase levels.

In case of suspected pancreatitis, the subject should undergo a thorough clinical evaluation including an abdominal computed tomography (CT) scan as soon as possible in order to clarify the diagnosis and enable assessment of severity of this condition.

Necessary medical procedures including repeat labs will be performed based on clinical needs determined by the treating physician's judgement.

## **8. Guidance on monitoring subjects with hemoglobin decrease**

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



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

Necessary medical procedures including repeat labs will be performed based on clinical needs determined by the treating physician's judgement.

### **9. Guidance on monitoring subjects with CPK increase**

- In case of CPK results  $>ULN$ , troponin and creatine kinase MB isoenzyme (CK-MB) will be tested by the central laboratory.
- In case of CPK  $>10\times ULN$ , an unscheduled visit to assess urine myoglobin will be required. The following blood tests will be repeated at the unscheduled visit: CPK, blood urea nitrogen, creatinine, electrolytes including potassium, calcium, phosphate.

### **10. Acute Coronary Syndrome, Myocardial Infarction or Any Major Cardiovascular Event**

Patients who experience acute coronary syndrome, myocardial infarction or any major cardiovascular event will permanently discontinue treatment with study medication. Patients will be asked to continue all scheduled visits for safety assessment.

### **11. Liver Impairment**

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

### **12. Renal Impairment**

Patients who develop chronic renal disease associated with moderate-severe functional impairment, defined as estimated CrCl  $<60$  mL/min/1.73 m<sup>2</sup>, while participating in the study should stop study medication temporarily until normalization of renal function or confirmation of renal impairment diagnosis. In case moderate-severe renal impairment is diagnosed, the patient will permanently discontinue treatment with study medication.

## APPENDIX B. LIST OF DISALLOWED MEDICATIONS PRIOR TO AND DURING STUDY

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 4: A Partial List of Moderate/Strong CYP3A4 Inhibitors Disallowed 2 Weeks Prior to Study, During Study and 30 Days After Last Study 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>	Diltiazem, verapamil, mibefradil
<b>Antiemetics</b>	Aprepitant, casopitant, netupitant
<b>Diuretics</b>	Conivaptan
<b>Antineoplastic agents</b>	Imatinib
<b>Antiarrhythmics</b>	dronedarone

**Note:**

- Interactions between drugs and grapefruit juice are documented for drugs with low bioavailability due to pre-systemic gut-wall metabolism. Based on the suggested high oral bioavailability of laquinimod in humans, such interactions are expected with laquinimod.

**Table 5: 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 C. LIST OF OTHER CONCOMITANT  
MEDICATION/THERAPIES****Table 6: A Partial List of Cytochrome P450 3A4 Substrates with a Narrow Therapeutic Index**

*Note: The medications list is considered partial. All medication that fall under prohibited medication classes should be excluded. Please contact the sponsor if you have questions about prohibited medication.*

alfentanil
cyclosporine
diergotamine
ergotamine
fentanyl
pimozide
quinidine
sirolimus
tacrolimus

**Table 7: A Partial List of Drugs That Are Mainly Metabolized by CYP1A2.**

*Note: The medications list is considered partial. All medication that fall under prohibited medication classes should be excluded. Please contact the sponsor if you have questions about prohibited medication.*

Medication class	Drug name
<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 (IBS treatment), Riluzole (ALS treatment), <b>Methadone</b>

Drugs with a narrow therapeutic index appear in bolded text.

Clinical Study Protocol with Am 04

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

## **APPENDIX D. MAGNETIC RESONANCE IMAGING**

The patients will undergo MRI scans at Baseline and Month 12 or Early Termination. The scans will be obtained according to a standard protocol that will be provided by the Imaging CRO (iCRO). The scans will be sent to the iCRO for approval and processing.

MRI scan will be performed using the following schedule:

- Month 0/Baseline: as soon as possible after eligibility has been confirmed but not less than 7 days prior to baseline.
- Month 12: up to 7 days prior to the Month 12 visit.
- Early Termination: as soon as possible, but not more than 7 days after discontinuation of study drug.

Note that the first MRI scan will be performed at least 7 days prior to the baseline visit to enable image approval and to set the reference for comparison to subsequent MRIs.

If a patient terminates within 3 months of the baseline visit, they will not undergo an Early Termination scan.

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

Detailed instructions are provided in the Site Operations Guide.

Confidential patient information such as patient full name must be omitted from the scan header, the compact disc labels, and any accompanying documentation. MRI scans will be transferred to the iCRO in electronic format, or when not possible, by courier. The procedure for sending electronic data and accompanying documentations is specified in the Site Operations Guide.

The iCRO will perform quality control checks of all images received. If both scans from one visit fail QC, the scan will need to be repeated. If the baseline scan fails QC, rescanning of the patient should be performed as soon as possible prior to randomization. In cases of failed QC at all other visits, the window for rescanning will be no longer than 2 weeks. Images should be reviewed, by the site, at the time of acquisition so that any sequences affected by obvious artifacts can be repeated immediately.

MRI scans are to be evaluated locally for any incidental pathology (ie, pathology unrelated to, or inconsistent with, the patient's known HD) according to locally determined procedures. If such pathology is found, the Treating Neurologist should be notified. The iCRO will evaluate the scans for the purposes of performing quantitative analyses. In order not to compromise the blinding of the study, the iCRO will not report results from the quantitative analyses back to the clinical site.

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