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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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...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON44575

Source
ToetsingOnline

Brief title
TV5600-CNS-20007 (0075/0075) LEGATO-HD

Condition

- Neurological disorders congenital
- Movement disorders (incl parkinsonism)

Synonym

Huntington's Disease, neurodegenerative genetic disorder

Research involving
Human

Sponsors and support

Primary sponsor: TEVA Pharma
Source(s) of monetary or material Support: TEVA Branded Pharmaceutical Products R&D

Intervention

Keyword: Huntington, Laquinimod, TV5600-CNS-20007

Outcome measures

Primary outcome

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 outcome

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)

Study description

Background summary

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.
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 abbearant cytokine production from HD monocytes and microglia, and reports in the scientific literature that abberant inflammatory phenotypic changes are an intrinsic feature in patients with HD and animal models for HD.

Study objective

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 (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.

Study design

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.
It is planned to randomize a total of 330 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.
Number of Investigational Centers Planned: Approximately ~30 centers.
Countries Planned: North America and Europe.

Intervention

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

Investigational Product:
The dose levels of laquinimod are 0.5 mg and 1.0 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 1.0 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:
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 3 treatment groups of the study (2 active treatment groups and placebo, allocation ratio of 1:1:1).
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.

Study burden and risks

See section E9.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients may be included in the study if they meet all of the following criteria: ;a. Documentation of prior positive genetic testing for HD, or a clinical diagnosis of symptomatic HD (Diagnostic Confidence Level 4).;b. Presence of 36-49 CAG repeats, inclusive, in the huntington 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. Women of child-bearing potential (women who are not post menopausal or who have 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

Exclusion criteria

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. Serum levels >=2x upper limit of the normal range (ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at screening ;g. Serum direct bilirubin which is >=1.5xULN at screening ;h. Estimated creatinine clearance < 60 mL/min at screening, calculated using the Cockcroft Gault equation: (140 - age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/dL) ;i. 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 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. 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 design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-05-2016
Enrollment:	10

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Laquinimod
Generic name:	Laquinimod

Ethics review

Approved WMO Date:	15-10-2014
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	04-11-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	17-12-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	09-02-2016

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	03-03-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	23-03-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	05-07-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	20-07-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	04-11-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	02-06-2017

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-000418-75-NL
CCMO	NL50246.058.14