A 12-Week Efficacy and Safety Evaluation of Budesonide/Formoterol SPIROMAX® 160/4.5 mcg Inhalation Powder Versus SYMBICORT® TURBOHALER® 200/6 mcg in Adult and Adolescent Patients with Persistent Asthma.

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The overall study objective is to assess the efficacy, safety, and tolerability of 2 laquinimod doses, 0.6 mg/day or 1.2 mg daily (QD), in a double-blind design compared to Avonex® (rater blinded) once weekly (QW)Study objectives:* To evaluate the...

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

Summary

ID

NL-OMON38727

Source
ToetsingOnline

Brief title
LIBRETTO

Condition

- Neurological disorders NEC

Synonym
chronical illness of the central nerve system, multiple sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: TEVA Pharma
Source(s) of monetary or material Support: Teva Pharmaceutical Industries Ltd.

Intervention

Keyword: atrophy, brain, Multiple, Sclerosis

Outcome measures

Primary outcome

The primary endpoint of the study is change in whole brain atrophy as

defined by the percent change in total brain volume from Month 0

(Baseline) to Month 12 between laquinimod 0.6 mg versus Avonex® and

laquinimod 1.2 mg versus Avonex®.

Secondary outcome

The cumulative number of influenza-like symptoms experiencedfrom baseline to

Month 3 on each dose of laquinimod (0.6 mg and 1.2 mg) versus Avonex®

The cumulative number of new T2 lesions measured at Month 6 and Month 12

between the 2 laquinimod doses

Study description

Background summary

Laquinimod is an experimental medicine that has not been approved by regulatory authorities (the agencies that are responsible for approving the use of a medicine in a country; such as the European Medicines Agency [EMA]). This study will compare daily oral treatment with laquinimod capsules of 2 doses (0.6 mg or 1.2 mg) to once weekly intramuscular injection treatment with Avonex®.

Avonex® (beta Interferon-1a) is an approved therapy for RRMS. It is indicated for use by patients with Relapsing (stable or progressive) Multiple Sclerosis as a once-weekly intramuscular injection. This medication contains a form of protein called beta interferon, which is present naturally in the body. Avonex® is indicated to slow the accumulation of physical disability and decrease the frequency of clinical attacks.

Animal and human studies suggest that laquinimod works in a different way than other medicines. With data available to date laquinimod has not been shown to reduce your immune*s system ability to function properly. Instead, it works within the brain, possibly by controlling certain cells that cause damage to brain tissue. In this way, it may result in a slower accumulation of disability over time.
Two large clinical trials in RRMS patients were recently completed. The first study "ALLEGRO" tested the effect of laquinimod 0.6mg against placebo (dummy medication), and showed that laquinimod 0.6 mg reduced the number of relapses, the rate of disease progression (measured by increase in disability) and loss of brain volume (measured by MRI) compared to placebo. The second study "BRAVO", tested the effect of laquinimod 0.6mg against placebo compared to the known marketed product Avonex® 30 mcg (weekly injections). It failed to show a statistically significant effect of laquinimod 0.6mg on the number of relapses compared to placebo.
Another large study, *CONCERTO* started in 2012. This study is testing two different doses of laquinimod (0.6mg and 1.2mg) against placebo.

Study objective

The overall study objective is to assess the efficacy, safety, and tolerability of 2 laquinimod doses, 0.6 mg/day or 1.2 mg daily (QD), in a double-blind design compared to Avonex® (rater blinded) once weekly (QW)
Study objectives:
* To evaluate the effect of 2 laquinimod doses (0.6 mg/day or 1.2 mg/day) compared to Avonex® QW on brain atrophy.
* To evaluate the effect of 2 laquinimod doses (0.6 mg/day or 1.2 mg/day) on new T2 lesions.

Other objectives:
* To assess the effect of 2 laquinimod doses (0.6 mg/day or 1.2 mg/day) compared to Avonex® on the following patient reported outcomes (PRO):
- Physical and psychological well-being (Multiple Sclerosis Impact Scale; MSIS-29)
- General health status (36-Item Short Form Health Survey; SF 36)
- Treatment satisfaction (Treatment Satisfaction Questionnaire for Medication; TSQM-9)
- Cognitive performance (Symbol Digit Modalities Test; SDMT)
- Disability (Patient-Determined Disease Step; PDDS)

- Effect on work (Work Productivity and Activities Impairment * General Health; WPAI-GH)
* To assess the rate of influenza-like symptoms in the 2 laquinimod doses (0.6 mg/day or 1.2 mg/day) compared to Avonex®.
* To assess the effect of 2 laquinimod doses (0.6 mg/day or 1.2 mg/day) compared to Avonex® on thalamic volume, cortical volume, and white matter (WM) volume.
* To assess the dose-response effect of 2 laquinimod doses(0.6 mg/day or 1.2 mg/day) on magnetic resonance imaging (MRI) and clinical parameters.
* To assess the safety and tolerability of 2 laquinimod doses(0.6 mg/day or 1.2 mg/day).

Study design

This is a multinational, multicenter, randomized, double-blind, parallel-group, active-control (rater blinded) study, to evaluate the efficacy, safety and tolerability of 2 doses of oral administration of laquinimod (0.6 mg/day or 1.2 mg/day) compared to interferon *-1a administered intra muscular once weekly in subjects with relapsing remitting multiple sclerosis (RRMS).

Intervention

-Laquinimod 0.6 mg arm: 2 capsules, 1 containing 0.6 mg laquinimod and the other containing matching placebo, to be administered orally QD.
-Laquinimod 1.2 mg arm: 2 capsules containing 0.6 mg laquinimod to be administered orally QD
Avonex® arm: self administered injection of Interferon *-1a (Avonex®) 30 *g/ 0.5mL solution for injection to be administered IM weekly (QW, ie, every 7 days)

Eligible subjects will be randomized in a 2.5:2.5:1 ratio into one of the following treatment arms:
-Oral laquinimod 0.6 mg
-Oral laquinimod 1.2mg
-IM Interferon *-1a (Avonex®) 30 *g/0.5mL solution for injection

Study burden and risks

The study will be comprised of 2 periods as follows:
-Screening period: up to 1 month.
-Treatment Period: 12 months of QD oral administration of either laquinimod 0.6 mg, laquinimod 1.2 mg, or QW IM administration of Interferon *-1a (Avonex®) 30 *g/0.5mL solution for injection.

The Sponsor may consider an extension phase for which all subjects randomized

to Avonex® will be switched to laquinimod 0.6 mg, while all subjects on laquinimod will continue on their initial assignment.

Eligible subjects will be randomized in a 2.5:2.5:1 ratio into 1 of the following treatment arms:
1. Oral Laquinimod 0.6 mg
2. Oral Laquinimod 1.2 mg
3. IM Interferon *-1a (Avonex®) 30 *g/0.5mL solution for injection

Scheduled visits will be done at Months -1 (Screening), 0 (Baseline), 1, 2, 3, 6, 9, and 12 (Termination)
Subjects that stopped treatment with the study drug before Month 12 (Termination) will be considered Early Treatment Discontinuation (ETD) subjects. ETD subjects will continue follow-up according to complete follow up, for any reason, will be considered Early Study Discontinuation (ESD) subjects.

The following assessments will be performed at the specified time points:
-Vital signs will be measured at each scheduled visit.
-Physical examination will be performed at all visits.
-The following safety clinical laboratory tests will be performed:
- Complete blood count (CBC) with differential * at each scheduled study visitb.
- Serum chemistry including fibrinogen, electrolytes, liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase [GGT], and alkaline phosphatase [ALP]), urea, creatinine, glucose, total protein, albumin, total bilirubinc, Creatine phosphokinase (CPK), serum conventional C-reactive protein (CRP), and pancreatic amylase) * will be done at each scheduled visit;
- Glomerular Filtration Rate (GFR) will be calculated by the site at Month -1 (Screening) and before the Baseline MRI scan.
- Serum thyroid stimulating hormone (TSH), triiodothyronine (T3), and free tyroxine (T4) at Months -1 (Screening), 6, ETD (if applicable), and 12 (Termination).
- Fasting Lipid profile (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL], and triglycerides) at Months 0 (Baseline), ETD (if applicable), and 12 (Termination).
- Urinalysis at Month -1 (Screening visit).
- Serum *-hCG (Human chorionic gonadotropin beta) in women of child-bearing potential will be done at each scheduled visit.
- Urine *-hCG test in women of child-bearing potential at Month 0(Baseline) and at each scheduled study visit thereafter.
- Starting after visit Month 3, between scheduled visits, urine *-hCG test will be performed in women of child-bearing potential every 28 (±2) days. The subject will be contacted by telephone within 72 hours after the 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 instruct the subject to arrive at the site as soon as possible
(within 10 days) with all remaining study drug * either capsules or injections.
- *-hCG tests will not be required of women who are ETD and are
in the study for the purpose of follow up if the last study drug dose was taken more than 30 days prior to the visit .
- Electrocardiogram (ECG) will be performed at Months -1 (Screening), 0 (Baseline, 3 recordings 10 minutes apart, before first
dose), and all subsequent visits.
-Chest X-ray will be performed at Month -1 (Screening), (if not performed within 6 months prior to the screening visit; unless locally
not applicable).
-Adverse events (AEs) will be monitored throughout the study.
-Concomitant medications will be monitored throughout the study.
-The subjects will undergo MRI scans at Months 0 (14 to 7 days before Baseline), 6, and 12 (Termination). In case of ETD, an
additional MRI will be performed, provided no study MRI was done within the previous 3 months.
In case of steroid treatment, study MRI scans should be performed before such treatment or delayed to allow a minimum of 14 days,
but not more than 28 days from the completion of the steroid course.
-Neurological evaluations, including Expanded Disability Status Scale (EDSS), Functional Systems (FS) and Timed 25-foot walk
(T25FW) will be performed at Months -1 (Screening [excluding T25FW]), 0 (Baseline), ETD (if applicable), 3, 6, and 12
(Termination).
-History of influenza-like symptoms will be queried and assessed at Month 0 (Baseline) and at each scheduled visit thereafter. At Months 0 through 3, between scheduled visits, the subjects will be
asked to fill a diary reporting influenza-like symptoms on a weekly basis.
-The Multiple Sclerosis Impact Scale (MSIS-29), General health status (SF-36), Treatment Satisfaction Questionnaire for Medication
(TSQM-9), Symbol Digit Modalities Test (SDMT), Patient-Determined Disease Step (PDDS) tests, and assessment of the effect
of general health and symptom severity on work, using the Work Productivity and Activities Impairment * General Health (WPAIGH)
questionnaire will be performed at Month 0 (Baseline), ETD (if applicable), and Months 3 and 12.
-Relapses will be confirmed/monitored throughout the study.
-Additional 10 mL of blood for possible analysis of protein serum levels via the Rules-Based Medicine biomarker discovery platform
or similar will be collected at each study visit, concomitant with other blood draw procedures

Relapse treatment

Treatment of a relapse acceptable per study protocol includes a short course of glucocorticosteroids (eg, intravenous methylprednisolone up to 1 g/day for up to 5 consecutive days). Extended courses of steroids beyond 5 days constitute a protocol violation.

Monitoring
The study will be closely monitored throughout its course by the Sponsor*s personnel as well as by

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

a. Informed consent/assent: For adult patients, written informed consent signed and dated by the patient before conducting any study related procedures; for minor patients, written

informed consent signed and dated by the parent/legal guardian and written assent signed and dated by the patient before conducting any study related procedure.
b. Male or female patients 12 years and older as of the screening visit. Male or female patients 18 years and older, as of the screening visit, in countries where local regulations or the regulatory status of study medication permit enrollment of adult patients only.
c. General good health, and free of any concomitant conditions or treatment that could interfere with study conduct, influence the interpretation of study observations/results, or put the patient at increased risk during the study.
d. Asthma Diagnosis: The asthma diagnosis must be in accordance with the Global Initiative for Asthma (GINA).
e. Patient has an ACQ score of *1.0 at the screening visit.
f. Severity of Disease: Persistent asthma, with an FEV1 40-85% predicted for age, height, gender and race, as per the third National Health and Nutrition Examination Survey (NHANES III) reference values, with adjustments to predicted values for African American patients, for a minimum of 3 months duration, and that has been stable for at least 30 days before the screening visit, as defined by clinical history.
g. Reversibility of Disease: Demonstrated a *12% reversibility of FEV1 within 30 minutes after 2-4 inhalations of albuterol/salbutamol (if required, spacers are permitted for reversibility testing) at the screening visit. Documented historical reversibility of *12% to a beta-agonist in the 12 months before the screening visit is also acceptable.
h. Current Asthma Therapy: Patients will be required to be on a short-acting *2 agonist (SABA) and inhaled corticosteroid (ICS) for a minimum of 8 weeks before the screening visit and have been maintained on a stable dose of inhaled corticosteroids for 4 weeks before the screening visit at on of the doses specified in the protocol.
i. Short-Acting *2-Agonists: All patients must be able to replace their current SABA with albuterol/salbutamol at the screening visit for use as needed for the duration of the study. Nebulized albuterol/salbutamol will not be allowed at any time during the study. Patients must be able to withhold all inhaled short-acting *2-sympathomimetic bronchodilators for at least 6 hours before all study visits.
j. If female, is currently not pregnant, breast feeding, or attempting to become pregnant, and is of Nonchildbearing potential, defined as:
* Pre-menarche
* *1 year post-menopausal
* Surgically sterile (tubal ligation, bilateral oophorectomy, or hysterectomy)
* Congenital sterility
* Diagnosed as infertile and not undergoing treatment to reverse infertility or is of:
Childbearing potential, must have a negative serum pregnancy test and be willing to commit to using a consistent and acceptable method of birth control as defined below for the duration of the study:
* Systemic contraception used for *1 month prior to screening, including birth control pills, transdermal patch, vaginal ring, levonorgesterel, or injectable progesterone
* Double barrier methods (condoms, cervical cap, diaphragm, and vaginal contraceptive film with spermicide)
* Intrauterine device (IUD)
Childbearing potential and not sexually active, willing to commit to using a consistent and acceptable method of birth control, as defined above, for the duration of the study, in the event the patient becomes sexually active.

If male, is willing to commit to using 2 consistent and acceptable methods of birth control for the duration of the study, and for a period of 3 months after dosing
k. Capable of understanding the requirements, risks, and benefits of study participation, and, as judged by the investigator, capable of giving informed consent/assent and being compliant with all study requirements (visits, record-keeping, etc.).

Exclusion criteria

a. History of life-threatening asthma, defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest or hypoxic seizures.
b. Culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that is not resolved within 2 weeks before the screening visit. In addition, the patient must be excluded if such infection occurs between the screening visit and the baseline visit.
c. Any asthma exacerbation requiring oral corticosteroids within one month of the screening visit. A patient must not have been hospitalized for asthma within 6 months before the screening visit.
d. Presence of glaucoma, cataracts, ocular herpes simplex, or malignancy other than basal cell carcinoma.
e. Historical or current evidence of a clinically significant disease including, but not limited to: cardiovascular conditions (eg, congestive heart failure, known aortic aneurysm, clinically significant cardiac arrhythmia or coronary heart disease), hepatic, renal, hematological, neuropsychological, endocrine conditions (eg, uncontrolled diabetes mellitus, uncontrolled thyroid disorder, Addison*s disease, Cushing*s syndrome), gastrointestinal conditions (eg, poorly-controlled peptic ulcer, gastroesophageal reflux disease [GERD]), or pulmonary conditions (eg, chronic bronchitis, emphysema, bronchiectasis with the need for treatment, cystic fibrosis, bronchopulmonary dysplasia, chronic obstructive pulmonary disease). Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the patient at risk through participation, or which could affect the efficacy or safety analysis if the disease/condition became exacerbated during the study.
f. Have any of the following conditions that, in the judgment of the investigator, might cause participation in this study to be detrimental to the patient, including, but not limited to:
- Current malignancy, excluding basal cell carcinoma. History of malignancy is acceptable only if the patient has been in remission for one year prior to the screening visit. (Remission is defined as no current evidence of malignancy and no treatment for the malignancy in the 12 months before the screening visit)
- Current or untreated tuberculosis. History of tuberculosis is acceptable only if a patient has received an approved prophylactic treatment regimen or an approved active treatment regimen and has had no evidence of active disease for a minimum of 2 years
- Uncontrolled hypertension (systolic blood pressure (BP) *160 or diastolic BP >100)
- Stroke within 3 months before the screening visit
*- Immunologic compromise
g. History of a positive test for human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection.

h. Clinical visual evidence of oral candidiasis at the screening visit.
i. History of any adverse reaction, including immediate or delayed hypersensitivity to any *2-agonist, sympathomimetic drug, or any intranasal, inhaled, or systemic corticosteroid therapy.
j. Known or suspected sensitivity to the constituents of the DPIs (SPIROMAX or TURBOHALER) used in the study (eg, lactose).
k. History of severe allergy to milk protein.
l. Use of systemic, oral or depot corticosteroids within 4 weeks before the screening visit
*- Use of topical corticosteroids (*1% hydrocortisone cream) for dermatological disease is permitted
- Use of intranasal corticosteroids at a stable dose or as needed may be used during the study for treatment of allergic rhinitis.
m.Use of immunosuppressive medications within 12 weeks before the screening visit and during the study.
n. Immunotherapy at a stable dose for at least 90 days before the screening visit and throughout the study for the treatment of allergies is permitted.
o. Use of potent Cytochrome P450 3A4 (CYP3A4) inhibitors (eg, ritonavir, ketoconazole, intraconzole) within 4 weeks before the screening visit.
p. Use of any prohibited concomitant non-asthma medications, such as treatment with *2-adrenergic receptor antagonists and non-selective *-receptor blocking agents, such as *-blocking anti-hypertensive products (administered by any route), monoamine oxidase (MAO) inhibitors, and tricyclic antidepressants within 1 week before the screening visit.
q. History of alcohol or drug abuse within 2 years preceding the screening visit.
r. Current smoker or a smoking history of 10 pack years or more (a pack year is defined as smoking 1 pack of cigarettes/day for 1 year). A patient may not have used tobacco products within the past 1 year (eg, cigarettes, cigars, chewing tobacco, or pipe tobacco).
s. Patient is a clinical investigator site employee or their immediate relatives.
For exclusion criteria (t) to (v), please refer to the current protocol

Study design

Design

Study phase:	3
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):	09-01-2014
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avonex®
Generic name:	Interferon □-1a 30 µg/0,5ml
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Laquinimod natrium
Generic name:	Sodium 5-chloro-3-(ethyl(phenyl)carbamoyl)-1-methyl-2-oxo-1,2-dihydroquinolin-4-olate

Ethics review

Approved WMO

Date:	17-10-2013
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

Approved WMO

Date:	09-01-2014
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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	EUCTR2013-000081-11-NL
CCMO	NL46265.096.13