A Phase 3, 40-Week, Active-Controlled, Double-Blind, Double Dummy Extension Study of Preladenant in Subjects With Moderate to Severe Parkinson*s Disease

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON38067

Source
ToetsingOnline

Brief title
Parkinson*s Disease P06153

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson Disease

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Parkinson□s Disease, Phase 3, Preladenant

Outcome measures

Primary outcome

Primary Efficacy Objective: to evaluate the efficacy of a range of preladenant doses during long term use in subjects with moderate to severe Parkinson*s disease (PD) experiencing motor fluctuations and receiving a stable dose of levodopa (L-dopa), as measured by *off* time. Primary Safety Objective: The Primary Safety Objective of this trial is to assess the safety and tolerability of preladenant compared with placebo in subjects with moderate to severe PD experiencing motor fluctuations and receiving a stable dose of L-dopa.

Secondary outcome

Key Secondary Trial Objectives: to evaluate the efficacy of a range of preladenant doses during long term use in subjects with moderate to severe PD experiencing motor fluctuations and receiving a stable dose of L-dopa as measured by *on* time without troublesome dyskinesia and by the proportion of Responders

Study description

Background summary

Parkinson's disease (PD) is an age-related, progressive, neurodegenerative

disease characterized by specific abnormal motor behaviors (resting tremors, increased muscle tone [ie, muscular rigidity], and slowness of movements [bradykinesia or akinesia]) associated with a progressive degeneration of the nigrostriatal dopaminergic pathway. When a patient is initially treated with Levo-dopa or dopamine agonists, the symptoms of PD improve or disappear. After several years of taking L-dopa or dopamine agonists, patients notice that their PD medications wear off sooner than when they first started taking them. This *wearing off* is characterized by the return of symptoms (ie, tremor, slowness, and rigidity) and may occur over the course of a few minutes to an hour. When a patient*s PD symptoms have returned, the patient is said to be in the *off* state. When the patient takes another dose of medication, and his/her PD symptoms improve or resolve, the patient is said to be in the *on* state. One potential novel approach to the treatment of PD is the use of adenosine receptor antagonists. Adenosine exerts its biological actions through a class of G-protein-coupled receptors.Numerous functional studies support the hypothesis that blockade of striatal A2a receptors may provide relief of PD symptoms. Adenosine 2a receptor antagonists have been shown to activate dopaminergic pathways and to reverse motor impairment in rodent models of PD. Preladenant (SCH 420814) is a potent and selective competitive antagonist of the human A2a receptor being developed by Schering-Plough as a treatment for PD. It has an inhibition constant (Ki) of 1.1 nM and >1000-fold selectivity for the A2a receptor over the other three adenosine receptor subtypes (A1, A2b, and A3) and a variety of other receptors and ion channels.

Study objective

This is a active-controlled dose-range-finding study which is also designed to assess the efficacy and safety of preladenant 2, 5, 10 mg twice daily during long term use as an adjunct therapy to L-dopa when administered to subjects with moderate to severe PD.

The dose-range-finding for preladenant is being performed to clarify the findings of the Phase 2 study, P04501, where preladenant was generally well tolerated and improved motor function in subjects with moderate to severe PD. In P04501, 246 subjects received preladenant 1, 2, 5, or 10 mg or placebo twice daily. There was a dose response in reduction in "off" time from Baseline to endpoint (increasing response associated with increasing dose) and similar responses for the two highest doses, 5 and 10 mg of preladenant twice daily, which were statistically superior to placebo. Due to small sample sizes, it was unclear whether the 2 mg twice daily dose might also be effective, and therefore a larger study is being performed. More liver enzyme elevations occurred at the 10 mg twice daily dose than at the 5 mg twice daily dose. Criteria meeting Hy*s law, 5 subjects out of 54 subjects treated with 10 mg of preladenant twice daily experienced increments above the normal reference range of ALT and/or AST (<3 x ULN except for one subject whose AST peaked at between 3 and 4 x ULN 2 weeks after discontinuation of treatment). Therefore, the 10-mg dose is included in this study to more fully characterize its efficacy and

safety. The placebo arm is included as a control. The current standard of care for subjects still experiencing motor fluctuations while on optimal dopaminergic therapy is to add a catechol-O-methyltransferase (COMT) inhibitor, such as entacapone or a monoamine oxidase (MAO) inhibitor such as rasagiline in an effort to prolong the dopaminergic benefits of L-dopa and reduce motor fluctuations. Rasagiline 1 mg once daily is included to allow for benefit/risk assessment. The rasagiline arm is being included as an active control to provide descriptive comparative data for the relative efficacy and safety of the current standard of care and preladenant.

Study design

Preladenant is a tablet. Rasagiline will be supplied as a capsule. A placebo tablet matching preladenant tablet will be available; and a placebo capsule matching rasagiline capsule also will be available. During the 40-week Treatment Period, subjects will receive one tablet and one capsule orally each morning and one tablet orally each evening in a double-blind, double-dummy design as shown in the table below:

Morning
Preladenant Group
2 mg Preladenant Tablet + Placebo Capsule
5 mg Preladenant Tablet + Placebo Capsule
10 mg Preladenant Tablet + Placebo Capsule

Rasagiline Group
1 mg Rasagiline Capsule + Placebo Tablet

Evening (about 8 hours after morning dose 8)

Preladenant Groups
2 mg Preladenant Tablet
5 mg Preladenant Tablet
10 mg Preladenant Tablet

Tablet Rasagiline Group
Placebo Tablet

Intervention

Take study medication, filling out questionaires and draw blood for blood tests.

Study burden and risks

Each subject will participate in the trial for approximately 40 to 42 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. Right after a screening, each subject will be receiving the assigned treatment for approximately 40 weeks. The End of Treatment visit from the P04938 study will be combined with the screening visit of the P06153 study,, in order to use the medication in a ongoing stable level. At the end of the treatment the subject will return for a Follow-up Visit after the last dose of study drug.

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

• Subjects must have completed P04938.
• Each subject must be willing and able to provide written informed consent for

the P06153.
• Subjects must be able to adhere to dose and visit schedules.
• Subjects must be taking levodopa (L-dopa).
• Subjects may be taking any of the additional adjunct Parkinson Disease (PD) medications shown in the table below.
Note: Subjects taking only L-dopa are permitted to enroll in this trial.
Amantadine
Anticholinergics
Dopa decarboxylase inhibitors
Dopamine agonists
Entacapone
L-dopa
• Each subject must have results of clinical laboratory tests (hematology, blood chemistries, and urinalysis) within
normal limits or clinically acceptable to the investigator as evidenced by the last available test results from the
parent study (P04938), and no results fall within the parameters for exclusion described below in the
exclusion criterion for liver-related findings.
• There has been no change in, or there has been no finding to warrant checking, serology status (for
cytomegalovirus [CMV], Epstein-Barr virus [EBV], and Hepatitis B, C, and E).
Each subject must have results of a physical examination within normal limits, including blood pressure, within
normal limits or clinically acceptable limits to the investigator, and not within the parameters for exclusion
described below in the exclusion criterion for blood pressure.
• All subjects that are sexually active or plan to be sexually active agree to use a highly effective method
of birth control while the subject is in the study and for 2 weeks after the last dose of study drug. A
male subject must not donate sperm within 2 weeks after the last dose of study drug. Complete details
regarding contraceptive requirements are specified in protocol Section 7.7.1.7.

Exclusion criteria

• A subject must not have discontinued from P04938 for any reason.
• A subject must not have a severe or ongoing unstable medical condition (eg, any form of clinically significant
cardiac disease, symptomatic orthostatic hypotension, seizures, or alcohol/drug dependence).
• A subject must not have poorly controlled diabetes (eg, HbA1c *8.5) or significantly abnormal renal function
(eg, creatinine *2.0 mg/dL) in the opinion of the investigator.

• As a continuation of the liver-related withdrawal criteria from the parent studies (P04938), any
subject with elevated values for alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total
bilirubin (T-BIL), as evidenced by the most recent chemistry panel results in the parent study, meeting any one
of the following criteria:
• ALT or AST *8 x ULN.
• ALT or AST *5 x ULN for more than 2 weeks.
• ALT or AST *3 x ULN and (T-BIL *2 x ULN or international normalized ratio [INR] *1.5 that is not due to
anti-coagulation) at the same visit.
• ALT or AST *3 x ULN with the appearance of worsening fatigue, nausea, vomiting, right upper quadrant
pain or tenderness, fever, rash, and/or eosinophilia (*5%).
• As a continuation of the blood pressure (BP) withdrawal criteria from the parent studies (P04938),
any subject meeting the following criteria for the second of two consecutive visits separated by 7 days (ie, the subject met one of the BP criteria once already, 7 days before the P06153 Screening visit):
• Systolic BP *180 mm Hg or diastolic BP *105 mm Hg, or
• An elevation from Baseline BP in the parent study (P04938) of systolic BP *40 mm Hg or diastolic BP *20 mm Hg.
• A subject must not have a history within the past 5 years of a primary or recurrent malignant disease with the
exception of adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or in situ
prostate cancer with a normal prostate-specific antigen (PSA) post resection.
• A subject must not have an average daily consumption of more than three 4-ounce glasses (180 mL) of wine or the equivalent.
• Prohibited Concomitant Medications: A subject should not take or start taking any treatment listed in the table on page 4 from the protocol.
A subject must not have received any treatment listed in the table below more recently than the
indicated period before Day 1 of P06153.
Note: Warnings and Contraindications detailed in the Prescribing Information for the allowed medications
(shown in the inclusion criteria) must be followed.
• A subject must not have allergy/sensitivity to the investigational products or their excipients.
• A female subject must not be breast-feeding or considering breast-feeding.
• A female subject must not be pregnant or intending to become pregnant.
• A subject must not have any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial.
• A subject must not be a member of or a family member of the personnel of the investigational or sponsor staff directly involved with this trial.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-02-2012
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Preladenant
Generic name:	NA
Product type:	Medicine
Brand name:	Rasagiline Mesylate
Generic name:	Azilect
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	17-03-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	21-10-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-11-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-01-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-03-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-03-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-04-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-06-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2009-015162-57-NL
ClinicalTrials.gov	NCT01155466
CCMO	NL36126.060.11