A Phase 3, 12-Week, Double-Blind, Placebo- and Active-Controlled, Double Dummy Efficacy and Safety 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-OMON38161

Source
ToetsingOnline

Brief title
Parkinson disease Protocol p04938

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinsin 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 compared with placebo 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 compared with placebo in subjects with moderate to severe PD experiencing motor fluctuations and receiving a stable dose of L-dopa as measured by the proportion of responders and *on* time without troublesome dyskinesia.

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 placebo- and active-controlled dose-range-finding study which is also designed to assess the efficacy and safety of preladenant 2, 5, 10 mg twice daily versus placebo 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 12-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.

AM

Preladenant Groups
2 mg Preladenant Tablet +Placebo Capsule
5 mg Preladenant Tablet +Placebo Capsule
10 mg Preladenant Tablet +Placebo Capsule

Placebo
Group

Placebo Tablet + Placebo
Capsule

Rasagiline
Group

1 mg Rasagiline Capsule +Placebo Tablet

PM (Approximately 8 hours after AM dose)
Preladenant Groups
2 mg Preladenant Tablet
5 mg Preladenant Tablet
10 mg Preladenant Tablet

Placebo Group
Placebo 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 15 to 18 weeks from the
time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of
up to 5 weeks, each subject will be receiving assigned treatment for approximately 12 weeks. After the End of
Treatment, the subject may choose to enroll in an extension trial (up until the maximum number of subjects for
that extension trial has been reached) or return for a Follow-up Visit 2 weeks after the last dose of study drug.

Contacts

Public
Merck Sharp & Dohme (MSD)

2015 Galloping Hill Road
Kenilworth, NJ 07033
US
Scientific
Merck Sharp & Dohme (MSD)

2015 Galloping Hill Road
Kenilworth, NJ 07033
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Each subject must have a diagnosis of idiopathic Parkinson disease (PD) based on the United Kingdom Parkinson's Disease Society Brain Bank Criteria and the inclusion/exclusion criteria for this protocol.
Each subject should have bradykinesia and at least one of the following symptoms:
i) Muscular rigidity
ii) Resting tremor (4 to 6 Hz, Please note that for the purposes of this study, a diagnosis based
solely on bradykinesia and postural instability is insufficient for diagnosis of idiopathic Parkinson's Disease, and subjects diagnosed in this manner cannot be enrolled in the study).
• Each subject must have received prior therapy with L-dopa for approximately 1 or more years immediately before Screening and must continue to have a beneficial clinical response to L-dopa at Screening.
• Each subject must have been on a stable, optimal dopaminergic treatment regimen, defined as maximum therapeutic effect achieved with available anti-parkinsonian treatment, for at least the 5 weeks immediately before Randomization.

• Subjects receiving the adjunct PD medications listed in the list below are permitted to enroll in this trial. Each subject who is receiving one or more of the adjunct PD medications listed below must have been on a stable regimen of treatment for at least the 5 weeks immediately before Randomization.
Amantadine
Anticholinergics
Dopa decarboxylase inhibitors
Dopamine agonists
Entacapone
L-dopa
• Each subject*s Hoehn and Yahr stage must be >=2.5 and <=4 in de optimum "on" state at Screening.
• Each subject must be experiencing motor fluctuations with or without dyskinesias following optimum titration of treatment medications and within the 5 weeks immediately before Screening.
• Each subject must be experiencing a minimum of 2 hours/day of *off* time as estimated by the investigator and supported by the 3-day symptom diary (Daily Diary) at the Randomization.
• Each subject, with or without help of their caregiver, must be capable of maintaining an accurate and complete symptom diary (Daily Diary) as assessed at the Diary Training Visit.
• Each subject must be willing and able to provide written informed consent for the trial. Subjects who are unwilling to provide written informed consent for exploratory pharmacogenetic testing may be included in the trial; however, exploratory pharmacogenetic samples must not be obtained.
• Each subject must be >=30 to <=85 years of age. A subject may be of either sex, any race/ethnicity.
• Each subject must have results of Screening clinical laboratory tests (hematology, blood chemistries, and urinalysis) drawn within 5 weeks prior to Randomization, clinically acceptable to the investigator, and not within the parameters specified for exclusion.
• Each subject must have results of a physical examination within normal limits or clinically acceptable limits to the investigator.
• Each subject must be able to adhere to dose and visit schedules.
• All subjects that are sexually active or plan to besexually 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 also not donate sperm during the trial and within 2 weeks after the last dose of study drug. Complete details regarding contraceptive requirements are specified in protocol section 7.7.2.7.

Exclusion criteria

• A subject must not have a form of drug-induced or atypical parkinsonism, cognitive impairment (ie, Montreal Cognitive Assessment [MoCA] score <22), bipolar disorder, schizophrenia, or other psychotic disorder.(Subjects with non-troublesome hallucinations, stable on low dose quetiapine or clozapine are allowed to enroll.)
• A subject must not have a history of any of the following:

- repeated strokes with stepwise progression of Parkinsonian features
- repeated head injury
- definitive encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one first degree relative affected
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- severe symptomatic autonomic involvement unrelated to medications
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign with clear, clinically significant pyramidal tract involvement
- presence of cerebral tumor or communicating hydrocephalus on neuroimaging (by history)
- negative response to large doses of L-dopa (if malabsorption excluded)
- MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) or known neurotoxin exposure
- hallucinations unrelated to medications
- stroke within 6 months of Screening or persistent neurological deficit that may interfere with study assessments
- surgery for PD
• A subject must not have an untreated major depressive disorder meeting Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV-TR) criteria. (A subject who is successfully treated [Beck Depression Inventory-II {BDI-II} score <19] with stable doses of allowed antidepressant medications for at least the 4 weeks immediately before Screening is eligible to enroll in the trial.)
• A subject must not be at imminent risk of self-harm or harm to others, in the investigator*s opinion based on clinical interview and responses provided on the Columbia Suicide Severity Rating Scale (CSSRS). Subjects must be excluded if they report suicidal ideation of Type 4 or 5 in the past 2 months or suicidal behavior in the past 6 months as measured by the CSSRS during Screening or at Randomization visits.
• In the judgment of the investigator, a subject must not have sleep attacks or compulsive behavior
that would interfere with the integrity of the trial or would pose a risk to the subject in participating
in the trial.
• Blood Pressure: A subject must not have a systolic blood pressure (BP) >=150 mm Hg OR diastolic BP >=95 mm Hg at Screening and at a BP recheck prior to Randomization. Should the BP remain elevated, the subject may not enter the trial until the BP has been adequately controlled with antihypertensive medication as demonstrated by 2 BP measurements meeting this criterion at consecutive separate scheduled or unscheduled visits within 5 weeks prior to Randomization. If antihypertensive medications are used to control a subject*s BP, the subject*s BP and doses of antihypertensive medications must be stable for at least 2 weeks prior to randomization.Note: during the course of the study antihypertensive medication may be initiated or increased to control a subject's BP at any time during treatment in P04938 as needed.
• Cardiovascular Disease: A subject must not have had any clinically significant

cardiovascular event or procedure for 6 months prior to Randomization, including, but not limited to, myocardial infarction, prolonged QTc interval [a subject must not have a QTcf result > 500msec], angioplasty, unstable angina, or heart failure; and a subject must not have heart failure staged New York Heart Association Class III or IV.
• Liver Enzymes: A subject must not have an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >=3 x the upper limit of normal (ULN) or total bilirubin (T-BIL) >=1.5 x ULN. Should a liver function test (LFT) be abnormal (AST/ALT >ULN but <3 x ULN, T-BIL >ULN but <1.5 x ULN) at Screening. No repeat testing allowed. Subjects with suspected Gilbert's Syndrome who have isolated T-BILI >= 1.5 x ULN may enter the study upon genetic confirmation (UGT1A1 assessment).
• Liver Disease: A subject must not have known Gilbert*s syndrome or active serologically confirmed hepatic dysfunction (defined as viral infection [Hepatitis B, C or E; Epstein-Barr virus {EBV}; cytomegalovirus {CMV}]) or a history of diagnosis of drug- or alcohol-induced hepatic toxicity or frank hepatitis.
•If a subject has abnormal ALT or AST at Screening (>1,5 x ULN), the subject must have serology testing to rule out active viral hepatitis. A subject who has a history of serologically confirmed EBV or CMV may be enrolled in the trial as long as the viral infection was not associated with hepatitis in the past, and the ALT or AST are normal at Screening. Types of serology assays to be performed are specified in the table of Laboratory Tests in the section on Trial Procedures.
• 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 received any treatment listed in the table below more recently than the indicated period before Randomization.
• A subject must not need to continue to receive any treatment listed in the table below during the trial.
Tolcapone - 4 weeks
Irreversible MAO inhibitors, eg, rasagiline, selegiline, Zydis selegiline - 90 days
Reversible MAOB or MAOA inhibitor - 4 weeks
Centrally acting dopamine antagonist (including metoclopramide, sulpiride, etc.) - 4 weeks
α-methyldopa - 4 weeks
Methylphenidate - 4 weeks
Reserpine - 4 weeks
Amphetamines - 4 weeks
Flunarizine - 4 weeks
Cinnarizine - 4 weeks
Diphenhydramine used to treat parkinsonism - 4 weeks
Theophylline - 4 weeks
Meperidine, tramadol, methadone, propoxyphene, cocaine, or local anesthesia containing sympathomimetic vasoconstrictors - 2 weeks
Dextromethorphan - 2 weeks
Mirtazapine (a tetracyclic antidepressant), and cyclobenzaprine (a tricyclic muscle relaxant) - 2 weeks
Sympathomimetic amines including cold products, nasal and oral decongestants, and weight-reducing preparations that contain vasoconstrictors (eg, ephedrine,

pseudoephedrine, phenylephrine, and phenylpropanolamine) - 2 weeks
St. John*s wort tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors with the following exceptions: citalopram <= 20 mg/day, escitalopram <= 20 mg/day, paroxetine <= 30 mg/day, amitriptyline
or nortriptyline <= 50 mg/day, trazodone or sertraline <= 100 mg/day - 2 weeks
High tyramine-containing aged cheeses (eg, Stilton) - 2 weeks
Other potentially hepatotoxic drugs (including amiodarone, azathioprine, felbamate, imatinib, isoniazid, isotretinoin, leflunomide, methotrexate, nevirapine, pioglitazone, rosiglitazone, pyrazinamide, valproic acid, and voriconazole) - 4 weeks
Potent CYP3A4 inhibitors (eg, ritonavir, nelfinavir, indinavir); macrolide antibiotics (eg, erythromycin, clarithromycin, troleandomycin, telithromycin, [azithromycin is allowed]); and systemically administered antifungal agents (eg, ketoconazole, itraconazole) - 4 weeks
CYP3A4 inducers (eg, phenytoin, phenobarbital, barbiturates, systemic glucocorticoids) - 4 weeks
Atypical and typical neuroleptics (including depot formulations) except low dose quetiapine fumarate and clozapine - 4 weeks (12 weeks for depot formulations).;• Note: Warnings and Contraindications detailed in the Prescribing Information for the allowed medications (listed in the inclusion criteria describing stable dopaminergic treatment) should be followed.

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):	02-11-2011
Enrollment:	60
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:	19-08-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-12-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-03-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-04-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-04-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	11-08-2011
Application type:	Amendment
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:	16-12-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-01-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-02-2012
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	EUCTR2009-015161-31-NL
ClinicalTrials.gov	NCT01155466
CCMO	NL32827.060.10