A 76-week prospective, open-label, multicenter study to evaluate the long-term effect of Exelon® capsule and transdermal patch on worsening of the underlying motor symptoms of PD in patients with mild to moderately severe dementia associated with Parkinson's disease (PDD).

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Dementia and amnestic conditions
Study type	Interventional

Summary

ID

NL-OMON31692

Source
ToetsingOnline

Brief title
Long-term effect of Exelon in patients with PDD.

Condition

- Dementia and amnestic conditions

Synonym
Dementia associated with Parkinson disease

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: dementia, Exelon, open-label, Parkinson

Outcome measures

Primary outcome

* Predefined adverse events (AEs) due, or potentially due, to worsening of PD

motor symptoms (tremor, muscle rigidity, bradykinesia, fall)

* Study drug discontinuations due to predefined AEs that are due,

Secondary outcome

Secondary safety assessments:

* Adverse events and Serious Adverse Events (SAEs)

* Unified Parkinson*s Disease Rating Scale (UPDRS) Part III (motor subscale)

* Forced Expiratory Volume in one second (FEV1) and Peak Expiratory Flow (PEF)

* Schellong Test (orthostatic hypotension)

* Epworth Sleepiness Scale (ESS)

* Vital signs

* 12-lead ECG

* Concomitant CNS (Central Nervous System) medications

Secondary efficacy assessments:

* Mattis Dementia Rating Scale (MDRS)

* Ten Point Clock Test (TPCT)

* Neuropsychiatric Inventory (NPI-10)

* Alzheimer*s Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)

* Modified Hoehn and Yahr Staging (UPDRS Part V)

Study description

Background summary

Exelon® (rivastigmine) is a drug that has been approved for use in many countries, including the European Union countries and the United States for treating the symptoms of mild to moderately severe Alzheimer*s disease and mild to moderately severe dementia associated with Parkinson*s disease (PDD). Exelon® has been administered to more than 300,000 patients worldwide. The Health Authority approval for Exelon® capsule treatment in PDD patients was based on the results of a large, international study. This study showed that Exelon® improved memory, attention, concentration, and behavior, and patients were able to take a more active role in daily life than those taking placebo (an inactive substance). Treatment with Exelon® capsules was shown to be generally well tolerated.

A thin, opaque, plastic Exelon® patch that sticks to the skin and delivers Exelon® through the skin has been developed. The Exelon® patch has now been approved in the United States for the treatment of mild to moderate Alzheimer's disease and mild to moderate Parkinson's disease dementia. In addition, the Exelon® patch has been recommended for approval in the European Union for the treatment of mild to moderately severe Alzheimer's disease. The Health Authority approval for Exelon® patch treatment in AD patients was based on the results of a large international study in Alzheimer*s disease in which Exelon® 10 cm2 patch was shown to be as effective and safe as Exelon® capsule, and it was very well tolerated. This study also showed that daily Exelon® 10 cm2 patch was the best dose in the first 6 months of treatment of patients with Alzheimer*s disease. Exelon patch has not been tested in patients with PDD.

Study objective

The purpose of this study is to provide long-term safety data for Exelon®

capsule and transdermal patch treatments, in particular the effect of Exelon® on worsening of the underlying motor symptoms of Parkinson*s Disease (PD), in patients with mild to moderately severe dementia associated with PD.

Study design

This study uses a randomized, open-label, parallel-group design to evaluate the longterm effect (76 weeks) of Exelon® capsule and patch on worsening of the underlying motor symptoms of PD and the overall tolerability and safety of both formulations in patients with mild to moderately severe dementia associated with Parkinson*s disease (PDD).
After a 5-week screening period, patients will undergo baseline safety and efficacy assessments and will be randomized to the Open-label Treatment Phase in a 1:1 ratio to either target Exelon® capsule 12 mg/day or target Exelon® 10 cm2 patch. Patients randomized to capsule will begin treatment at 3 mg/day and be titrated in 3 mg/day increments every four weeks to reach a 12 mg/day target dose (or the highest well-tolerated dose). Patients randomized to 10 cm2 patch will begin treatment at 5 cm2 and be titrated after 4 weeks with a single 5 cm2 increment to reach a target patch size of 10 cm2 (or the highest well-tolerated dose). Following the titration period, the target dose (or the highest well-tolerated dose) for each individual patient (Exelon® capsule or patch) should be maintained for the rest of the study duration. However, dose adjustments may be performed at any time (including outside the visit schedule) during the
Maintenance Period.

Intervention

Patients will be randomized in a 1:1 ratio to either target Exelon® capsule 12 mg/day or target Exelon® 10 cm2 patch

Study burden and risks

Risks are possible side effects of study medicine or another medicine, and those of taking blood. In general, the side effects of this treatment are mild to moderate, and usually resolve without medical intervention. The most common side effects are nausea, vomiting, tremor, diarrhea, loss of appetite, dizziness, fall, and low blood pressure. These effects are usually transient, not severe and usually resolve when you have settled on your best dose. It is possible the patient could experience a skin reaction to Exelon® patch at the application site. Most reactions are minor but rarely they may be more severe or general.

Concerning the PD, as the dose of medication is increased there is an approximately 10% chance that the patient may experience a temporary worsening of his/her tremor or develop a new tremor. The severity of the tremor may

improve after you have reached a stable dose or following a dose reduction. Even if your tremor does temporarily worsen, the patient can still have benefits from Exelon®. The patient's motor symptoms will most likely continue to worsen during the 18-month study, as they would if he/she were not participating in this study, but the PD should not progress at a faster rate because of treatment with Exelon®. Problems or side effects that are now not known could also occur.

The tests done at each visit are standard medical tests. The most unpleasant is often having blood samples taken. The risks of taking blood may include fainting, pain and/or bruising.

Rarely, these may be a small blood clot or infection at the site of the needle puncture. The blood pressure cuff may also cause discomfort or bruising to the upper arm.

Contacts

Public
Novartis Pharma B.V.

Lichtstrasse 35
CH-4056 Basel
CH
Scientific
Novartis Pharma B.V.

Lichtstrasse 35
CH-4056 Basel
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

1. 50-80 years of age (both inclusive);
2. males, and females not of child-bearing potential (surgically sterile or one year postmenopausal);
3. have a clinical diagnosis of idiopathic Parkinson*s disease according to the UK Parkinson*s Disease Society Brain Bank clinical diagnostic criteria (see Appendix 2);
4. have a clinical diagnosis of Parkinson*s disease dementia according to DSM-IV criteria (Code 294.1) (see Appendix 3), with onset of symptoms of dementia at least 2 years after the first diagnosis of idiopathic Parkinson*s disease;
5. have a MMSE score of * 10 and * 24 (at Screening Visit only, Visit 1);
6. have sufficient education to have been able to read, write, and communicate effectively during the premorbid state;
7. be cooperative and willing to complete all aspects of the study, and capable of doing so, either alone or with the aid of a responsible caregiver, according to judgment of the investigator;
8. be residing with someone in the community throughout the study or, if living alone, in regular contact with the primary caregiver;
9. have a single caregiver, paid or unpaid, willing to accept responsibility for supervising the treatment, (e.g. application and removal of the patch daily at approximately the same time of day) and assessing the condition of the patient throughout the study, and for providing input to safety and efficacy assessments in accordance with all protocol requirements;
10. provide, if mentally competent (or if incompetent, their legally acceptable representative will provide) written informed consent prior to their participation in the study. Caregivers also will provide written informed consent.

Exclusion criteria

1. an advanced, severe, or unstable disease of any type that may interfere with the primary and secondary variable evaluations;
2. a score of 5 in the *on*-state on the Modified Hoehn and Yahr Staging (UPDRS Part V) assessment at screening;
3. a current diagnosis of any primary neurodegenerative disorder other than idiopathic PD e.g. Alzheimer*s disease, Frontotemporal dementia, Huntington*s disease, Dementia with Lewy bodies, Parkinson-Plus-Syndromes other than PDD (e.g. progressive supranuclear palsy or olivopontocerebellar degeneration);
4. a current diagnosis of any treatable dementia (hypothyroidism, syphilis, vitamin B12 or folate deficiency, hydrocephalus, chronic subdural hematoma) that is verified by the investigator to be the cause of dementia. Patients receiving stable therapy for hypothyroidism, vitamin B12 and folate deficiency, not considered to be the cause of dementia by the investigator, may be enrolled. Patients with abnormal laboratory diagnostic tests at screening not previously documented or further investigated are not eligible for

enrollment;
5. a current diagnosis of probable vascular dementia according to the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l*Enseignement en Neurosciences criteria (NINDS-AIREN) criteria (see Appendix 4);
6. a current diagnosis of a major depressive episode according to DSM-IV criteria (Code 296) (see Appendix 5), or any other DSM-IV Axis I diagnosis that may interfere with the response of the patient to study medication, including bipolar disorder or schizophrenia, as assessed by psychiatric evaluation. Patients with major depression at baseline who are clinically stable under therapy may be enrolled;
7. a current diagnosis of active, uncontrolled seizure disorder;
8. a disability that may prevent the patient from completing all study requirements and, in particular, interfere with the assessment of dementia (e.g., blindness, deafness, severe extrapyramidal symptoms during the *on*-state);
9. a history of stereotaxic brain surgery for Parkinson*s disease (e.g. pallidotomy, deep brain stimulation, tissue transplant);
10. a current diagnosis or ECG, at screening or baseline, that displays evidence of bradycardia (<50 bpm), sick-sinus syndrome, conduction defects (sino-atrial block, second or third degree atrio-ventricular block);
11. a current diagnosis of acute, severe, or unstable asthmatic conditions;
12. a clinically significant urinary obstruction;
13. a current diagnosis of active, uncontrolled peptic ulceration or gastrointestinal bleeding within the last 3 months;
14. elevated liver function tests, specifically elevated alkaline phosphatase (AP), ALT (SGPT), AST (SGOT), or gamma-glutamyl-transferase (GGT) greater than 3 times the upper limit of the normal range;
15. a known exaggerated pharmacological sensitivity or hypersensitivity to drugs similar to Exelon® or to other cholinergic compounds;
16. patients receiving antipsychotics who are not on stable doses of atypical antipsychotics for four weeks prior to baseline;
17. patients who have previously participated in any clinical study with anti-dementia drugs;
18. taken any of the following substances during the four weeks prior to randomization:
* cholinesterase inhibitors or cholinergic drugs (e.g., rivastigmine, donepezil, tacrine, galantamine, succinylcholine-type muscle relaxants). Topical pilocarpine will be permitted.
* centrally-acting anticholinergic drugs, including tricyclic and tetracyclic antidepressants
* neuroleptics other than clozapine or quetiapine
* lithium
* paroxetine
* memantine
* an investigational drug
* a drug or treatment known to cause major organ system toxicity
Note: Stable patients on cholinesterase treatment and/or memantine should not be washed out in order to enter the study. However, if patients are on these medications and in the investigator's clinical judgment, there is a legitimate medical reason for discontinuation (i.e., side effect profile, lack of benefit), then it would be appropriate for these patients to undergo the 4-week wash-out period, in order to enter the study.

19. started any new, or change in dose during the four weeks prior to randomization:
* psychotropic medication (clozapine, quetiapine, antidepressants, anxiolytics or hypnotics including benzodiazepines, anticonvulsants);
* anti-parkinsonian medication;
* peripheral anticholinergic drugs: If new-onset urinary urgency or urinary incontinence constitutes a major problem which cannot be adequately managed with non-pharmacological measures, then initiation of treatment with a peripheral anticholinergic drug such as tolterodine or oxybutynin will be permitted.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-07-2008
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Exelon® capsules
Generic name:	Rivastigmine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Exelon® patch

Generic name:	Rivastigmine

Ethics review

Approved WMO Date:	16-11-2007
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	26-02-2008
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	13-03-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	25-03-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	24-04-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	10-06-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	02-08-2008
Application type:	Amendment

Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	13-08-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	29-09-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	04-11-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	14-11-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	19-11-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	06-03-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	12-03-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO	

Date:	14-07-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	16-07-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

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	EUCTR2007-000350-31-NL
CCMO	NL20470.003.07