A randomised, placebo-controlled, multicentre phase IIb study evaluating the efficacy of pirepemat on falls frequency in patients with Parkinson*s disease

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Primary:To evaluate the effects of pirepemat on falls frequency as compared to placebo.Secundary:To evaluate the effects of pirepemat on Parkinson's disease motor symptoms as compared to placebo.To evaluate the effects of pirepemat on apathy as...

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

Summary

ID

NL-OMON56278

Source
ToetsingOnline

Brief title
INRE_pirepemat on falls freq in ptnts with Parkinson

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Integrative Research Laboratories Sweden AB (IRLAB)
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Parkinson, Pirepemat

Outcome measures

Primary outcome

Change in falls frequency from baseline period (1 month prior to randomisation)

to the end of treatment visit as assessed by fall diary.(1 month prior to dose

se-escalation)

Secondary outcome

Secundary:

Change in the total score of MDS-UPDRS part 2 (M-EDL) from baseline to Week 11.

Change in total score (Frequency*Severity) and Caregiver distress of NPI Item G

(Apathy/Indifference) from baseline to Week 11.

Tertiary/exploratory endpoint variables

- Change in MDS-UPDRS part I from baseline to Week 11.

- Change in MDS-UPDRS part II from baseline to Week 11.

- Change in MDS-UPDRS part III from baseline to Week 11.

- Change in MDS-UPDRS part IV from baseline to Week 11.

- Change in MDS-UPDRS part IV item 4.3 (Time spent in the off state) from

baseline to Week 11.

- Change in sum score of MDS-UPDRS items 2.13 (Freezing) and 3.11 (Freezing of

gait) from baseline to Week 11.

- Change in individual scores from baseline to Week 11for the following MDS-UPDRS part I items: 1.2 (Hallucinations and psychosis), 1.3 (Depressed mood), 1.5 (Apathy), 1.6 (Features of dopamine dysregulation syndrome), 1.8 (Daytime sleepiness), 1.9 (Pain and other sensations), 1.13 (Fatigue).

- Change in individual scores from baseline to Week 11for the following MDS-UPDRS part II items: 2.1 (Speech), 2.12 (Walking and balance).

- Change in modified Hoehn & Yahr score from baseline to Week 11.

Change in scores from baseline to Week 11for the following tests:

- Single leg stance test

- Tandem walking test

As measured by subject incident of treatment-emergent adverse events, clinically significant changes in vital signs and physical examination, clinical laboratory safety tests, and ECGs.

Study description

Background summary

Falls are a frequent and serious complication of Parkinson*s disease (PD). Prospective studies report that 60% of people with PD have at least one fall per year and 39% fall recurrently. The risk of experiencing falls in PD increases with disease severity. In a prospective study the 7 year cumulative incidence of falls in non-falling patients diagnosed with PD at baseline was 57.5%, with a relative risk to controls of at least 3.1. Consequences of falls in PD include fractures and injury, fear of future falls, hospital admission, and increased caregiver burden, with falls cited as one of the worst aspects of

the disease.
The cause of the high propensity for falls in PD is likely to be multifactorial. The major contributing risk factors for falls have been shown to be fall history, freezing, impaired postural function and cognitive deterioration.
The major causes underlying falls in PD seem not to be amenable to standard anti-Parkinson therapy. Postural instability is a cause of significant morbidity that worsens as PD advances and rarely improves with dopaminergic or surgical therapy. However, whilst axial motor features such as postural instability and freezing of gait have been associated with falls in PD, the relationship with overall motor severity is complex and there is little available detailed quantitative information on individual axial and nonaxial items and their relative potential to cause falls.
It is suggested that postural instability and other poorly dopa-responsive symptoms in PD are likely to be the results of other *extranigral* lesions, possible involving a lack of cortical control. Affected neurotransmitters include, among others, norepinephrine, acetylcholine and serotonin. In particular, cell loss of noradrenergic input from the locus coeruleus has been implicated to underly postural instability in PD. It is likely that not only subcortical cell loss is underlying axial motor impairment in PD, since cognitive impairment, including measures of global and executive function, have also been associated with falls in PD.
Pirepemat displays a novel pharmacological profile which addresses pathological dysregulations occurring in multiple cortical transmitter systems implicated in axial motor impairment and dementias. Neurochemical data show that pirepemat combines therapeutically useful effects on monoaminergic, cholinergic and glutamatergic neurotransmission in the cerebral cortex leading to activation of synaptic activity both in the cortex and in the basal ganglia suggesting strengthening of cortical and cortico-striatal connectivity. At the integrated level the specific regional effects on biogenic amines, acetylcholine and down-stream effects related to synaptic activation, gives rise to a behavioural profile indicating cognitive and behavioural benefits without psychomotor stimulant like, or antipsychotic like inhibitory, properties. Hence, pirepemat targets several of the key neurochemical features suggested to be underlying risk factors for falls in PD, without causing unwanted adverse effects on the motor system.

Study objective

Primary:
To evaluate the effects of pirepemat on falls frequency as compared to placebo.
Secundary:
To evaluate the effects of pirepemat on Parkinson's disease motor symptoms as compared to placebo.
To evaluate the effects of pirepemat on apathy as compared to placebo.
Other:
To evaluate the effects of pirepemat on Parkinson's disease symptoms and

severity as compared to placebo.
To evaluate the effects of pirepemat on postural dysfunction as compared to placebo.
To evaluate the effects of pirepemat on cognitive function as compared to placebo
To evaluate the safety and tolerability of pirepemat
To examine the relationship between dose and plasma concentration of pirepemat and pharmacodynamic effects.

Study design

This will be a randomised, double-blind, placebo-controlled multi-centre study.

Intervention

Patients will take three daily oral doses (at approximately 8 am, 2 pm and 8 pm) of pirepemat or placebo for 84 consecutive days. Dosing will start with half maximum dose for the first week of treatment and de-escalated according to pre-specified schedule during the last week of study treatment.

Study burden and risks

there are no direct benefits expected for the participant.

The following side effects of the study drug under investigation are common:
- Headache
- Thinking and memory problems
- Confusion
- Hallucinations
- Tremors
- Falls
- Increase in PD symptoms
- Constipation
- Pain in the upper abdomen
- Urinary tract infection
- Pain in the extremities (hands and feet)
- Sweating

The following side effects are uncommon but may be serious:
A few patients with PD who were treated with Pirepemat had short-term increases of certain enzymes in their blood. These enzymes are large molecules that help important chemical reactions in the liver to occur. If the levels of these enzymes in the blood are higher or lower than normal, they can indicate liver problems. All patients will be closely monitored during the study. In case of any abnormal liver values, the participants study participation may be terminated, and they will receive appropriate treatment and be closely followed

up.
Since it is possible for drugs that affect the central nervous system to lead to people feeling depressed or having suicidal thoughts, the study doctor will ask the participant and the participants caregiver at each visit whether the participant has experienced this.

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

1. Male or female 55-85 years of age, inclusive. 2. Diagnosis of idiopathic Parkinson's disease, according to the UK Parkinson's disease Society Brain Bank criteria. 3. Montreal Cognitive Assessment (MoCA) score of >=10 and <26 at screening. 4. A modified Hoehn & Yahr score of >=2.5 in *on*. 5. Having experienced recurrent falls during the past 3 months (based on interview with

the patient and/or caregiver) and at least 2 falls during the past 4 weeks before baseline. 6. On a stable regimen of anti-Parkinson's medications for at least 30 days prior to baseline, and willing to continue the same doses and regimens during study participation. 7. Able to cooperate and participate in study related procedures. This includes the ability to accurately complete a falls diary. The falls diary may also be completed by a responsible caregiver. For patients meeting DSM-IV TR criteria for Parkinson*s disease dementia, the falls diary should be completed by the caregiver. 8. Availability of a responsible caregiver at least five days per week at least 2 hours per day. For patients meeting DSM-IV TR criteria for Parkinson*s disease dementia, availability of a responsible live-in caregiver is required.

Exclusion criteria

1. Any of the following potential hepatic conditions: a. known history of alcohol abuse, chronic liver or biliary disease, with the exception of Gilbert*s syndrome b. total bilirubin greater than the upper limit of the normal range (unless associated with isolated instances of suspected Gilbert*s syndrome) c. alkaline phosphatase (ALP) greater than 1.5 times the upper limit of the normal range d. aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 2 times the upper limit of the normal range e. history of repeated unexplained upper right quadrant abdominal pain and/or nausea, or jaundice 2. A positive Hepatitis B surface antigen or a positive Hepatitis C antibody result. 3. A score of 5 (wheelchair bound or bedridden) in the "on"-state on the modified Hoehn & Yahr scale. 4. Uncontrolled symptomatic orthostatic hypotension. 5. Clinically significant polyneuropathy. 6. Weight <55 kg at Screening. 7. Patients with current or past treatment with deep brain stimulation (DBS) or patients with previous history of stereotaxic brain surgery for PD. 8. A current diagnosis of any primary neurodegenerative disorder other than idiopathic PD. 9. A current diagnosis of any treatable dementia (hypothyroidism, syphilis, vitamin B12 or folate deficiency) that is verified by the investigator to be the cause of dementia. 10. A current diagnosis of a major depressive episode according to DSM-IV criteria. 11. Patient has delirium. 12. Any history of a heart condition, including prolonged QTc (>450 ms for males and > 470 ms for females, QTcF and/or QTcB), cardiac arrhythmias, any repolarisation deficits or any other clinically significant abnormal ECG as judged by the Investigator. 13. Severe or ongoing unstable medical condition including a history of poorly controlled diabetes; obesity associated with metabolic syndrome; uncontrolled hypertension; cerebrovascular disease, or any form of clinically significant cardiac disease; renal failure, history of abnormal renal function. 14. History of seizures within two years of screening. 15. History of cancer within five years prior to screening, with the following exceptions: adequately treated non-melanomatous skin cancers, localised bladder cancer, non-metastatic prostate cancer or in situ cervical cancer. 16. History of severe allergy/hypersensitivity or on-going

allergy/hypersensitivity, as judged by the Investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to pirepemat. 17. Creatinine clearance <30 mL/min (calculated according to the Cockroft-Gault formula). 18. Treatment with Warfarin within three months before study treatment. 19. Treatment with Amantadine within 6 weeks before study treatment. 20. Treatment with Selegiline within 6 weeks before study treatment. 21. Administration of another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment with less than three months between administration of last dose and first dose of IMP in this study. 22. Current or history of drugs of abuse according to DSM-IV criteria. 23. Any planned major surgery within the duration of the study. 24. Any other condition or symptoms preventing the patient from entering the study, according to the Investigator*s judgement. Where the clinical significance of an abnormal Screening test result (lab or any other tests) is considered uncertain, the test may be repeated once, at the discretion of the Investigator, as long as the repeat test result is available within the 6 weeks screening period to determine eligibility.

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:	Completed
Start date (anticipated):	05-04-2024
Enrollment:	3
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Pirepemat
Generic name:	Pirepemat

Ethics review

Approved WMO Date:	17-11-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-03-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-10-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-12-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-02-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-02-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2019-002627-16-NL
Other	IRL752C003
CCMO	NL82410.091.22