A Double-Blind, Placebo-Controlled, Randomized, 18-Month Phase 2a Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Oral UCB0599 in Study Participants With Early Parkinson*s Disease

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

Summary

ID

NL-OMON52354

Source
ToetsingOnline

Brief title
PD0053

Condition

- Movement disorders (incl parkinsonism)

Synonym
Early Parkinson's Disease

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Early Parkinson Disease, phase 2a, UCB0599

Outcome measures

Primary outcome

Primary Efficacy Objective

- To demonstrate the superiority of UCB0599 over placebo with regard to

clinical symptoms of disease progression over 12 and 18 months in participants

diagnosed with early-stage Parkinson*s Disease (PD)

Primary Safety Objective

- To assess the safety and tolerability of UCB0599 in participants diagnosed

with early stage PD

Secondary outcome

Secondary Efficacy Objectives

- To demonstrate the superiority of UCB0599 over placebo with regard to

neurodegeneration of dopaminergic neurons over 12 and 18 months in participants

diagnosed with early stage PD

- To assess the effect of UCB0599 versus placebo with regard to intake of ST

over 18 months in participants diagnosed with early stage PD.

Exploratory PK Objective.

-To assess the pharmacokinetics (PK) of UCB0599 and its N-oxide-metabolite in

participants diagnosed with early-stage PD.

Study description

Background summary

Parkinson*s disease is a progressive neurodegenerative disorder that presents with a spectrum of motor and non-motor signs and symptoms. The mean age at onset is 60 years. The incidence of PD is approximately 20/100,000 persons per year; however, it is much higher in the population aged 65 years or older (>100/100,000 persons per year) (Twelves, 2003). Similarly, the prevalence of PD increases with age. It is estimated to be 1.4% in the population aged 55 years or older and 4.3% in the population aged 85 years and older (de Rijk, 1995).
The clinical diagnosis of PD relies on the presence of the cardinal motor signs: bradykinesia, rigidity, tremor, and postural instability. However, non-motor symptoms such as loss of smell, depression, constipation, and rapid eye movement sleep behavior disorder can occur several years before the onset of motor symptoms.

Early PD is characterized by mild, manageable motor symptoms that may not require
symptomatic treatment (ST), or that show a good response to levodopa, which represents the standard of care. Other commonly used standard of care medications include dopamine agonists, monoamine oxidase B inhibitors, and catechol-O-methyl transferase inhibitors. As PD progresses, the motor and non-motor symptoms become more bothersome, and patients may start experiencing motor complications. After 2 to 5 years of treatment with levodopa, 30% to 50% of patients develop motor fluctuations. Advanced PD is characterized by marked motor disability with loss of independent ambulation. After 210 years since onset, most patients suffer from difficult-to-treat motor symptoms (eg, falls, freezing of gait, dysarthria, and dysphagia) and from non-motor symptoms for which treatment options are limited (eg, dementia, psychosis, depression, autonomic dysfunction, and pain). Patients are often bedridden after 10 to 14 years (Poewe, 2006). To this day, slowing disease progression remains the main unmet medical need in PD.

Parkinson*s disease is pathologically characterized by the loss of dopaminergic neurons in the substantia nigra, associated with ASYN pathology (neuronal cytosolic inclusions called Lewy bodies which consist of misfolded,

pathological aggregates of ASYN). Although the majority of PD cases are sporadic, a small proportion are caused by mutations in PD-related genes, including copy number variations and point mutations of the ASYN-coding gene (SNCA) (Siddiqui, 2016). The gene copy number variations are of particular interest, as they indicate that an increased frequency of the wild-type ASYN is sufficient to cause PD. This is further reinforced by the observations in families with SNCA copy number variations where the pathogenic effect depends on the gene dosage (Devine, 2011). Furthermore, single nucleotide polymorphisms in SNCA that have been associated with PD in genome-wide association studies have been shown to increase ASYN expression, highlighting the relevance of genetic variation in SNCA in sporadic PD (Soldner, 2016; Nalls, 2014). The 140-amino acid ASYN protein is highly expressed in the brain but is also found in the cerebrospinal fluid (CSF) and periphery (ie, red blood cells and plasma). As an intrinsically disordered protein, ASYN exists in a soluble monomeric form in the cytoplasm and in the extracellular compartment. When it adopts a partially ordered, extended helical structure, ASYN also has a natural affinity for membranes, such as synaptic vesicles. Under certain conditions, ASYN can convert into oligomeric, beta-sheet rich structures where such aggregation is driven through the central region of the molecule, rich in hydrophobic residues (residues 61 to 95) known as the nonamyloid beta component region. These oligomeric structures are believed to be the toxic species responsible for the spread of pathology from neuron to neuron (Chen, 2015). Treatments that prevent misfolding and aggregation of ASYN may slow the neurodegeneration in PD, resulting in slower progression of motor symptoms, thus providing a therapeutic benefit to patients with PD.

UCB0599 is an orally available inhibitor of ASYN misfolding and downstream ASYN aggregation. Nonclinical pharmacology studies have provided evidence that UCB0599 inhibits ASYN misfolding in the presence of lipid membranes. In vivo pharmacology studies demonstrated that UCB0599 reduced total brain ASYN levels as well as proteinase K-resistant (ie, aggregated) ASYN in a transgenic mouse model overexpressing SNCA. Moreover, it reduced glial fibrillary acidic protein, a marker of neuroinflammation, and normalized dopamine transporter loss observed in this model, which are both considered a functional consequence of ASYN aggregation. These data suggest UCB0599 may slow neurodegeneration in PD, resulting in slower disease progression, thus providing a therapeutic benefit to patients with PD. To date, slowing PD disease progression remains the main unmet medical need in PD.

UCB0599 has not been approved by any health authorities worldwide as of the date of this document. UCB has conducted five Phase 1 clinical studies to support the development of UCB0599: 1 study, conducted with the UCB1332 racemate and a single microdose of the UCB0599 R-enantiomer (UP0023), and 4 studies with UCB0599 administration at clinically relevant doses (UP0030, TM0017, UP0077, and UP0078).
In the UCB0599 Phase 1 clinical development program, UP0023, UP0030, TM0017, and UP0077 demonstrated that UCB0599 has good PK properties (dose-exposure

linearity, rapid absorption, t1/2 of approximately 11 to 13 hours, and no time-dependent PK behavior observed) and an acceptable safety and tolerability profile for further clinical development. UP0078 demonstrated that food had a minimal effect on the PK profile for UCB0599. Coadministration of the strong cytochrome P450 3A4 (CYP3A4) inhibitor, itraconazole, had a significant effect on UCB0599 disposition, demonstrating a strong drug-drug interaction effect.

Study objective

The main objective of PD0053 is to provide POC for the efficacy of the ASYN misfolding inhibitor UCB0599 in reducing disease progression in study participants with early-stage PD, and to instruct later stage development. The ultimate goal is to provide novel treatment options to PD patients which have the potential to modify the progression of the disease.

Study design

PD0053 is a randomized, double-blind, placebo-controlled, 18-month Phase 2a study to evaluate the efficacy, safety, tolerability, and PK of orally administered UCB0599 in study participants with early-stage PD who are not treated with symptomatic medications targeting motor symptoms of PD at the time of inclusion. The primary objective of the study is to demonstrate the superiority of UCB0599 over placebo with regard to clinical symptoms of disease progression over 12 and 18 months in this patient population. The difference between UCB0599 and placebo will be evaluated for both the low and high doses of UCB0599 (180mg/day and 360mg/day). The comparison of the high dose of UCB0599 with placebo will be considered as the primary evaluation. Oral UCB0599 capsules or matching placebo capsules will be administered twice per day (BID), approximately 12 hours apart.

PD0053 includes a Screening Period (including, where available, a wearable sensor familiarization period for those participants who consent to its use), an 18-month Treatment Period, (including, where available, a wearable sensor familiarization period for those
participants who consent to its use after the Screening Period), and a Safety Follow-up (SFU) Period. Study participants who complete the Treatment Period will have the option to transition into an open-label extension study (OLE; PD0055). In this case, participants will not enter the SFU Period of PD0053.

The study will be conducted utilizing a decentralized model, ie, study visits will be composed of a combination of site visits and remote visits. During remote visits, study assessments will be conducted with the study participant from his/her home. This is done to reduce study participant burden and encourage greater study participation.

In a decentralized model, video communication technology will be integrated

into the clinical research process to support management of research activities, including data collection and providing study participants with a channel for direct feedback. Mobile healthcare personnel (ie, a qualified nurse) may visit the study participant*s/caregiver*s home to complete certain study assessments. Video and communication technology will be used for interactions among the Investigator, mobile healthcare personnel, and study participants/caregivers for remote visits. All data will be collected electronically using purpose-built technology and will be monitored remotely by clinical research associates while complying with all data privacy standards.

Intervention

The UCB0599 doses are 180mg/day or 360 mg/day, to be taken orally in a dose regimen of 90 mg BID or 180 mg BID, approximately 12 hours apart. UCB0599 and placebo are formulated as capsules. Treatment duration is up to 18 months. There is no dose modification allowed.

Study burden and risks

The study drug being tested may cause some side effects and possible discomforts. The patient may experience none, some, or all of those given below because medicines and their possible side effects can affect individual people in different ways. Studies with new investigational study products generally have the risk that you may experience side effects that are currently unknown and unforeseeable.
Based on clinical studies conducted so far, a total of 98 study participants were given the study drug at doses similar to the dose used in this study. Common (occurring between 1 and 10 in 100 study participants) side effects observed in study participants in previous studies are listed as follows:
• Headache
• Feeling sleepy or lacking energy
• Sleepiness or dizziness
• Involuntary muscle contractions
• Physical weakness or tiredness
• Low or increased blood pressure
• Allergic reaction (to drug)
• Hives or lip swelling as part of an allergic reaction to the drug
• Increased or decreased appetite
• Shingles
• Difficulty seeing clearly
• Frequent loose bowel movement or constipation
• Indigestion or stomach pain
• Frequent urination
• Change of kidney function
• Cough

Drug hypersensitivity:
The most serious side effect(s) that have happened in study participants who have taken the study drug in other research studies were hypersensitivity (allergy like) reactions. These allergy like reactions typically included itching, skin rash (redness, swollen patches or hives) and swelling of hands, feet, lips, or tongue. Severe, allergy-like reactions may cause difficulty breathing, low blood pressure and could be life threatening, if not treated. So far, moderately intense but not severe allergy-like reactions have occurred in three study participants taking the study drug. In these three cases, moderately intense but not severe allergy-like reactions started within a month after starting treatment with the study drug. However, it cannot be excluded that an allergy like reaction may appear at any time during the study.

There is good scientific support to suggest that the study drug could be an effective treatment of your disease. However, currently there is limited knowledge about what side effects may occur. Potential side effects estimated based on animal data and from a first study in healthy volunteers are listed below, although other side effects may also occur.
• Blood effects: Increased chance of forming a blood clot, possibly leading to blocked vein or artery. Increased chance of bleeding, possibly causing bruises or bleeding.
• Heart effects: Slower heart rate, faster heart rate.
• Gastrointestinal effects: Vomiting (being sick and throwing up).
• Effects on the function of the liver.
• Effects on the function of the kidneys.
• Damage to the muscles.

Potential risks of the study procedures:

Blood sampling:
Blood samples will be taken from a vein in the patient's arm or hand during the study. Blood maybe taken using a needle or a cannula (flexible plastic tube) inserted in a vein in the arm. This minimizes the use of needles, though sometimes (if the cannula becomes blocked) a new cannula may need to be inserted or the use of a needle may be necessary. The taking of a blood sample may cause some slight discomfort and bruising, and there is a risk of infection. Other risks, although rare, include dizziness and fainting. In very rare cases, nerve damage may occur.

Electrocardiogram (ECG):
When the patient has an ECG, small sticky pads will be placed on the arms, legs, and chest and a machine will measure the electrical activity of the heart. The study staff may need to clip/shave small patches of the hair in these areas. These sticky pads may cause some local skin irritation and may be uncomfortable to remove. Both female and male participants must undress from the waist up in order to ensure correct ECG recording.

Blood pressure:
When the blood pressure is taken, an inflatable cuff will be placed on the patient's arm and a machine will measure the blood pressure and heart rate after the patient's has been lying down for 5 minutes and while standing up. The patient may experience mild discomfort in his or her arm while the cuff is inflated.

Magnetic Resonance Imaging (MRI; if not done before with an available report):
An MRI is a type of scan that uses magnetic fields and radio waves to take pictures of the inside of the head and/or body. The procedure does not use X-ray radiation. There have been no ill effects reported from exposure to the magnetic or radio waves used in MRI. However, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal that may cause injury. The patient will be asked about metal within his or her body (this includes, for example, body piercings, or a pacemaker). In addition, the MRI scanner makes a loud, knocking noise that in very rare and extreme cases could affect hearing ability. The study staff will provide the patient with ear plugs or other protection for his or her hearing while in the MRI scanner. Lying in the small confined area may case you some discomfort or anxiety. The study doctor may choose to give the patient medication to help him or her relax during the procedure.

DaT-SPECT:
DaT-SPECT is a tool used to confirm the diagnosis of PD. It is a specific type of imaging technique that helps to look at cells in the brain that are important for the action of dopamine (a brain chemical) in the brain. It involves receiving an injection that contains a small amount of a radioactive substance. Side effects can include headache, dizziness, increased appetite and an unusual feeling under the skin.

Cerebrospinal fluid sample (CSF) sample by lumbar puncture:
A lumbar puncture (also known as spinal tap) will be performed for collection of a small amount of CSF, which is the fluid that surrounds the brain and spinal cord. CSF will be used to test for biomarkers. A lumbar puncture is done by inserting a thin, hollow needle between two bones in the lower back. Prior to the lumbar puncture, a local anesthetic may be applied to numb the area. The most frequent side effect of lumbar puncture is a severe headache that may be accompanied by nausea, vomiting, and dizziness. The needle insertion may cause some slight discomfort and bruising, and there is a risk of infection. While extremely rare, the procedure may also cause bleeding into the fluid surrounding the spinal cord and brain or an abnormal movement of the patient's brain inside the skull, either of which can be fatal.

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

- Study participant must be 40 to 75 years of age inclusive, at the time of signing the informed consent
- Study participant has Parkinson*s Disease (PD), with a diagnosis made by a neurologist according to the 2015 Movement Disorder Society criteria within 2 years of Baseline Visit (including diagnosis during Screening)
- The following diagnostic criteria must be met: bradykinesia AND at least ONE of the following: muscular rigidity, or resting tremor
- A Screening Dopamine Transporter Imaging with Single Photon Emission Computed Tomography (DaT-SPECT), or a historical DaT-SPECT within 3 months of the Screening Visit (V1) that has been qualified by the central reader, shows evidence of dopamine transporter deficit per study requirements (see section 4.2 protocol) as determined by a central reader.

- Study participant is in the <=2.5 modified Hoehn and Yahr stage at Screening
- Study participant has never taken medications for the treatment of motor symptoms of PD and is not expected to require starting symptomatic treatment (ST) with a high likelihood in the next 6 months as far as clinical judgement allows
- Study participant has never taken part in disease-modifying treatment studies directed at neurodegenerative disease (NDD)
- Study participant does not take N-acetyl cysteine or other cysteine donors or glutathione precursors on a regular basis as a food supplement.
- Study participant is willing, competent, and able to comply with all aspects of the protocol, including follow-up schedule and biospecimen collection
- A male participant must agree to use contraception during the Treatment Period and for at least 90 days after the last dose of study medication and refrain from donating sperm during this period
- A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
(i) Not a woman of childbearing potential (WOCBP)
OR
A WOCBP who agrees to follow the contraceptive guidance during the Treatment Period and for at least 1 month after the last dose of study medication. The study participant must have a negative serum pregnancy test at Screening (Visit 1), which is to confirmed negative by urine testing prior to the first dose of study medication at Baseline (Visit 3). If oral contraception is used, an additional barrier method will be required during the study

Exclusion criteria

- Study participant has a known hypersensitivity to any components (and/or its excipients) of the study medication or comparative drugs as stated in the protocol
-Study participant has a brain magnetic resonance imaging (MRI) scan performed during Screening indicative of a clinically significant abnormality or a historical MRI scan during the 6 months before Screening Visit 1 of sufficient quality to show such abnormalities. In case of doubt, the significance is determined on a case-by-case basis in close collaboration with the Medical Monitor and should not include abnormalities like age-appropriate brain atrophy, minor white matter signals, or mild vasculopathy
- Study participant has any contraindication for the brain MRI or Dopamine Transporter Imaging with Single Photon Emission Computed Tomography (DaT-SPECT) imaging
- Study participant has a Montreal Cognitive Assessment (MoCA) score less than 23, indicating mild cognitive impairment or other significant cognitive impairment or clinical dementia at Screening that, in the opinion of the Investigator, would interfere with study evaluation
- Study participant has abnormalities in lumbar spine previously known or

determined by a Screening lumbar x-ray (if conducted) that could preclude lumbar puncture, in the opinion of the Investigator. The participant must be excluded from lumbar puncture but not from study participation.
- Study participant has clinically significant electrocardiogram (ECG) abnormality at Screening, in the opinion of the Investigator
- Study participant has past history of use of medications for the treatment of motor symptoms of PD. Short (up to 4 weeks) past use of medications for the treatment of motor symptoms is permitted following a sufficient washout period. Medications included are: levodopa (maximum 400mg per day), dopamine agonists, MAO-B inhibitors, anticholinergics, or amantadine. A sufficient washout period is at least 3 months prior to the Baseline Visit.

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):	08-09-2021
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	UCB0599
Generic name:	UCB0599

Ethics review

Approved WMO Date:	24-02-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-05-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-10-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-11-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-01-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-04-2022

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-06-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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Application type:	Amendment
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Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-08-2023
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	EUCTR2020-003265-19-NL
ClinicalTrials.gov	NCT04658186
CCMO	NL75963.091.21