Multicenter, parallel-group, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of apomorphine subcutaneous infusion in Parkinson's disease patients with motor complications not well controlled on medical treatment.

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The primary objective of the trial is to investigate the efficacy of apomorphine subcutaneous infusion compared to placebo in PD patients with motor fluctuations not well controlled on medical treatment. The secondary objective is to investigate the...

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

Summary

ID

NL-OMON41299

Source
ToetsingOnline

Brief title
TOLEDO study

Condition

- Movement disorders (incl parkinsonism)

Synonym
parkinsonism, Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Britannia Pharmaceuticals Ltd
Source(s) of monetary or material Support: Farmaceut;BRITANNIA PHARMACEUTICALS LIMITED

Intervention

Keyword: Apomorphine, Efficacy, Parkinson's disease, Safety

Outcome measures

Primary outcome

Primary efficacy variable is the absolute change in time spent *OFF* from

baseline to the end of 12 weeks treatment period based on patient diaries.

Secondary outcome

Secondary Endpoints

The secondary efficacy endpoints are:

- Percentage of patients with response to therapy, defined as an OFF-time

reduction of at least 2 hours, from baseline to end of 12 weeks treatment period

- Patient Global Impression of Change

- Absolute change in time spent *ON* without troublesome dyskinesia*

- Change in oral L-dopa and L-dopa equivalent dose

- Change in Unified Parkinson*s Disease Rating Scale (UPDRS Part III motor

examination) during ON periods

- Change in Quality of Life (using PDQ-8)

Exploratory Endpoints

The exploratory endpoints are:

- Change in Score of the Non-Motor Symptoms Scale for PD

- Change in MDS-UPDRS Part I patient questionnaire = non-motor experiences of daily living

- Change in MDS-UPDRS II, assessed separately for ON and OFF states

- Change in MDS-UPDRS Part IV fluctuations = 4.3 and 4.4 combined

- Drop-outs due to lack of efficacy

- Beck Depression Inventory

- PDSS (PD Sleep Scale)

Safety Endpoints

The safety endpoints are:

- Evaluation of adverse events and local tolerability

- Skin changes

- Full blood count

- Epworth Sleepiness Scale

- QUIP

- C-SSRS

Study description

Background summary

Parkinson`s Disease (PD) is one of the most frequent neurodegenerative disorders. 100-200/100.000 people are affected by PD in Germany. Prevalence increases with age; in the German population >65 years, the prevalence is elevated to 1.800/100.000 (Eggert et al., 2012). Across Europe, prevalence

estimates range between 108 and 257/100.000 (von Campenhausen et al., 2005). PD affects both sexes approximately equally.
Patients with PD suffer from muscle rigidity, resting tremor, postural instability and bradykinesia or akinesia. Flexed posture and freezing (motor blocks) have also been included among the classical features of parkinsonism (Jankovic, 2008). Primarily, the motor symptoms of PD result from the death of dopaminergic neurons in the substantia nigra, leading to striatal dopamine deficiency (Dauer und Przedborski, 2003). The neurotransmitter dopamine modulates post-synaptic signaling in the striatum, influencing motor behavior. Oral administration of the dopamine precursor levodopa (L-3, 4-dihydroxyphenylalanine, L-dopa) reduces the classical motor symptoms. L-dopa is converted to dopamine in the presynaptic dopaminergic nerve endings (Ribaric, 2012). The replacement therapy with L-dopa restores terminal dopamine levels in the striatum. The antiparkinsonian effect is mediated by the stimulation of postsynaptic D2 receptors (Ribaric, 2012). After significant initial improvement, the progression of PD is often accompanied by a progressive shortening of the clinical response to L-dopa. These fluctuations in motor function have been termed ON/OFF fluctuations. Progressive degeneration of the dopaminergic transmission results in a reduced capacity of taking up exogenously administered L-dopa and its conversion to dopamine for storage and release (Chase et al., 1993; Varanese et al., 2011). Erratic gastrointestinal absorption may contribute to the clinical problem of unpredictable motor response or failure of individual doses of L-dopa to induce an ON phase. Complex postsynaptic changes in the striatal expression of neuropeptides and in firing patterns are thought to underlie the formation of dyskinesias, or involuntary movements, which occurs in many of the patients with advanced PD (Obeso et al., 2000).
Motor fluctuations and dyskinesia develop in 50% of patients after 5 years and in 80% of patients after 10 years of L-dopa treatment (Chase et al., 1993; Schrag und Quinn, 2000). Advanced and end-stage PD patients experience an enhanced sensitivity to small changes in plasma L-dopa levels (Lang und Lozano, 1998; Varanese et al., 2011). The transition from good motor (ON state) to poor motor (OFF state) function occurs when brain L-dopa falls below the threshold needed to adequately stimulate striatal dopamine receptors (Dewey et al., 2001). The reduction in the dose of L-dopa often improves dyskinesias, but increases the duration and severity of the OFF periods (Deleu et al., 2004).
The dopamine agonist apomorphine has shown good effect on the ON-OFF phenomenon. Apomorphine directly stimulates the striatal presynaptic and postsynaptic dopamine D1 and D2 receptors (Ribaric, 2012). In contrast to L-dopa, apomorphine is not concentrated and converted in the presynaptic dopaminergic endings. Its motor effects are therefore not dependent on the presence of functional presynaptic nerve endings (Ribaric, 2012).
Two principle approaches are applied for the treatment of patients with fluctuating PD: intermittent subcutaneous *rescue* injections of apomorphine and continuous diurnal subcutaneous apomorphine infusions (Poewe und Wenning, 2000). Intermittent subcutaneous injections produce antiparkinsonian benefit comparable to L-dopa and the efficacy of apomorphine injections has been

demonstrated in placebo-controlled, randomized studies, both as single doses and in a longer-term (4 weeks) study, which showed that 95% of OFF periods could be terminated using apomorphine, compared with 23% on placebo (Dewey et al., 2001).
Continuous subcutaneous apomorphine infusion has been shown to be a highly effective treatment in patients with motor fluctuations in several studies, some of which were long-term (up to 5 years of follow-up). Level 1 evidence from randomized studies, however, is still lacking (Fox et al., 2011).
Clinical practice has shown that, for PD patients with severe motor fluctuations who are poorly controlled by conventional treatment, continuous apomorphine infusion can be an effective and well-tolerated option. It has been noted that this nonaggressive technique is easy to perform and relatively easy to control (Garcia Ruiz et al., 2008).

Study objective

The primary objective of the trial is to investigate the efficacy of apomorphine subcutaneous infusion compared to placebo in PD patients with motor fluctuations not well controlled on medical treatment. The secondary objective is to investigate the safety and tolerability of apomorphine subcutaneous infusion therapy.

Study design

This clinical trial is designed as a randomized, multicenter, multi-national, parallel-group, double-blind and placebo-controlled phase III study in approximately 102 patients. The trial consists of a double-blind treatment phase followed by an open-label phase.
The study will comprise 2 screening visits to confirm patients* eligibility and their ability to handle diary completion followed by hospital admission at baseline with a maximum stay between 5 and 10 days. During the 3-month treatment period, 8 weekly control visits are scheduled. Discontinuation of the blinded drug will be performed at the End of Blinded Treatment Visit. Patients will be offered the possibility to enter the open-label phase starting with the titration of apomorphine at the next visit according to the local standards.
The open-label phase is planned for a maximum of 12 months, including 4 control visits after 12, 24, 36 and 52 weeks and 4 telephone contacts after 6, 18, 30 and 44 weeks .
All efforts should be made to encourage 12 weeks of blinded treatment. Patients discontinuing the blinded treatment of the study due to lack of efficacy (per investigator discretion) prior week 12 will be offered a possibility to enter the open-label phase.
The study will be performed in hospitals specialized in the treatment of PD.

Intervention

Pretreatment prior and during hospitalization

Antiemetic premedication will be administered according to local standards. Recommended pre-treatment use of domperidone is 10 mg tid starting 3 days prior to the infusion. ECGs will be repeated at Baseline and at hospital discharge.
If these ECGs show QTc > 430 ms for male and >450 ms for female, domperidone can be reduced stepwise to 10 mg bid or totally withdrawn, at the discretion of the investigator. ECG will be repeated at week 2. It is recommended to perform ECG before any dose increase and after per investigator discretion. At any time if QTc is > 450 ms a cardiology opinion must be obtained and the decision for continuation or discontinuation of domperidone treatment (QTc > 430 ms for male and >450 ms for female) should be made in accordance with the cardiologist.

Trial medication and adjustments in oral/transdermal antiparkinsonian medication

The hourly flow rate is adjusted during the initial in-patient stay and during the first 4 weeks of treatment, to doses of 3 mg/hour up to 8 mg/hour, depending on individual tolerability and efficacy.
The target dose is each patient*s individual optimized dose or the maximum dose of 8 mg/hour.
Patients will be admitted to hospital on the day of the Baseline visit. On that day, patients will be on their regular medical treatment. On the day following Baseline, patients will take their regular medication and the pump will be initiated.

Each patient will receive a starting dose for apomorphine or placebo as subcutaneous infusion of 1 mg/hour during the first day of infusion.
If no adverse effects occur, the hourly flow rate will then be increased in the following manner:
- During in-patient stay the hourly flow rate will be increased daily by 0.5-1.0 mg/hour until the maximum dose of 8 mg/hour or the highest tolerated dose has been reached, whichever occurs first.
- At the weekly visits up to week 4, the hourly flow rate will be increased by 0.5 to 1 mg/hour per visit until the maximum dose of 8 mg/hour or the highest tolerated dose has been reached, whichever occurs first.

A gradual reduction of concomitant medication is driven by the occurrence of possible adverse events (AEs). During the titration phase (i.e. in the first 4 weeks) concomitant antiparkinsonian medication can be reduced in case of newly emergent or worsened dopaminergic AEs - in particular dyskinesias, nausea, orthostatic hypotension, or sleepiness. Therefore, if dopaminergic adverse effects occur, concomitant medication should be decreased first and the study drug flow rate should be maintained. Upon resolution of the adverse event, the next increase in flow rate should be undertaken.
The investigator will adjust concomitant treatment in a hierarchical way, aiming at the reduction and discontinuation of any oral/transdermal dopamine

agonist first.

Study burden and risks

Risks and side effects of apomorphine administration

Apomorphine hydrochloride should be given with caution to patients with renal, pulmonary or cardiovascular disease and persons prone to nausea and vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients.
Since apomorphine may produce hypotension, even when given with domperidone pretreatment, care should be exercised in patients with pre-existing cardiac disease or in patients taking vasoactive medicinal products such as antihypertensives, and especially in patients with pre-existing postural hypotension (Licher MT GmbH, 2012).
Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia (Licher MT GmbH, 2012).
Apomorphine may be associated with local subcutaneous effects. Most patients experience injection site reactions, particularly with continuous use. These may include subcutaneous nodules, induration, erythema, tenderness and panniculitis. Various other local reactions (such as irritation, itching, bruising and pain) may also occur.
These can sometimes be reduced by the rotation of injection sites or possibly by the use of ultrasound (if available) to areas of nodularity and induration.
Hemolytic anemia and thrombocytopenia have been reported in patients treated with apomorphine. Hematology tests should be undertaken at regular intervals.
Caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range.
Neuropsychiatric problems co-exist in many patients with advanced PD. There is evidence that for some patients neuropsychiatric disturbances may be exacerbated by apomorphine. Special care should be exercised when apomorphine is used in these patients.
Apomorphine has been associated with somnolence, and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with PD. Pathological gambling, hypersexuality and impulsive eating or buying have been reported in patients treated with dopamine agonists for PD, including apomorphine.
Apomorphine (APO-Go PFS) 5 mg/ml solution for infusion in pre-filled syringe contains sodium metabisulphite which may rarely cause severe allergic reactions and bronchospasm.

Precautions and Preventive Measures

The abdominal skin must be checked at each visit. Any skin changes must be documented (counted and described).
Indurations:

- Number
- Size
- Signs of inflammation in these:
o If yes, in how many
o Degree of inflammation: mild, moderate or severe
Ulcerations
Necrosis
Abscess

Before starting the infusion and at each visit, patients are to be reminded of the following measures:
- strict hygiene,
- massages after removing the needle,
- rotation of insertion site, making use of the whole abdomen (if comfortable to the patient),
- do not leave needle in for >18 hours.

If nodule formation is suspected to interfere with the absorption of the study drug, patients should be re-trained in
identifying suitable insertion sites. When necessary and depending on local availability, the following additional methods
are permitted:
- ultrasound
- silicon patches or
- massage devices including creams, as recommended by the national provider of apomorphine or by national treatment
guidelines.

Laboratory tests are performed at Screening, Baseline and at weeks 4, 8, 12 and during open-label phase at weeks 12, 24, 36 and 52. These will include full blood count with differential blood count, haptoglobin, bilirubin and LDH.
In the case of a drop of hemoglobin by >=1.5 g/dl compared to the previous test, hemolytic anemia must be ruled out. The urgency of intervention depends on the degree of the changeand whether there are any concomitant laboratory changes suggestive of hemolytic anemia and must be judged by the investigator in charge of reviewing the blood test results.
The patient must be asked to come for an unscheduled safety visit and have the following assessments:
- clinical assessment for symptoms and signs of anemia,
- full blood count with differential blood count,
- Coombs test,
- haptoglobin,
- bilirubin,
- LDH.

If any findings suggest hemolytic anemia, an internist / hematologist must be consulted. If hemolytic anemia is confirmed, apomorphine must be stopped and

the patient must be managed as advised by the consulted internist / hematologist. The patient must be discontinued from the study.

Anticipated Benefits

For the patients randomized to treatment the benefit lies in the possibility of a positive therapeutic effect, and with their participation in the trial all patients contribute to the scientific understanding of the properties and impacts of apomorphine.

Contacts

Public
Britannia Pharmaceuticals Ltd

Longwater Avenue, Green Park 200
Reading RG2 6GP
GB
Scientific
Britannia Pharmaceuticals Ltd

Longwater Avenue, Green Park 200
Reading RG2 6GP
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male or female patients aged >=30;

- Diagnosis of idiopathic Parkinson*s disease of >3 years* duration, defined by the UK Brain Bank criteria (with the exception of >1 affected relative being allowed), without any other known or suspected cause of Parkinsonism;
- Hoehn & Yahr stage up to 3 in the ON and 2 to 5 in the OFF state;
- Motor fluctuations not adequately controlled on medical treatment including L-dopa which was judged by the treating physician to be optimal;
- Average of OFF time >= 3 h/day based on screening and baseline diary entries with no day with < 2 hours of OFF time recorded;
- Stable medication regimen, with a stable dose of L-dopa administered in at least 4 intakes, for at least 28 days prior to baseline. All oral or transdermal antiparkinsonian drugs are permitted, with the exception of budipine. This regimen may include the use of L-dopa /DDCI rescue medication if this occurs up to 2 times a day, at doses of up to 200 mg L-dopa/day;
- Patients must be able to differentiate between the ON and OFF state and between troublesome and non-troublesome dyskinesias;
- Male and female patients must be compliant with a highly effective contraceptive method (oral hormonal contraception alone is not considered highly effective and must be used in combination with a barrier method) during the study and for 12 months long-term follow-up period, if sexually active;
- Females of childbearing potential must have a negative serum hCG or urine pregnancy test at screening;
- Ability to accurately complete a paper diary on designated days (with assistance from caregivers, if required), recording periods when they are *ON without troublesome dyskinesia*, *ON with troublesome dyskinesia*, OFF, and sleeping;
- Written informed consent prior to enrollment, after being provided with detailed information about the nature, risks, and scope of the clinical trial as well as the expected desirable and adverse effects of the study treatments;
- Patients considered reliable and capable of adhering to the protocol, visit schedule, and medication intake according to the judgment of the investigator.

Exclusion criteria

- History of respiratory depression;
- Hypersensitivity to apomorphine or any excipients of the medicinal product
- High suspicion of other parkinsonian syndromes;
- Presence of severe freezing or clinically relevant postural instability leading to falls during the ON state;
- Concomitant therapy or within 28 days prior to baseline with: apomorphine pen injections; alpha-methyl dopa, metoclopramide, reserpine, neuroleptics, methylphenidate, or amphetamine; intrajejunal L-dopa;
- Previous use of apomorphine pump treatment;
- History of deep brain stimulation or lesional surgery for PD;
- Any medical condition that is likely to interfere with an adequate participation in the study, including e.g. current diagnosis of unstable epilepsy; clinically relevant cardiac dysfunction and/or myocardial infarction or stroke within the last 12 months;
- Symptomatic, clinically relevant and medically uncontrolled orthostatic hypotension;

- Patients with a borderline QT interval corrected for heart rate according to Bazett*s formula (QTc) of >450 ms for male and >470 ms for female at screening or history of long QT syndrome; or >450 ms absolute duration;
- Clinically relevant hepatic dysfunction (total bilirubin >2.0 mg/dL, ALT and AST >2 times the upper limit of normal);
- Clinically relevant renal dysfunction (serum creatinine >2.0 mg/dL);
- Pregnant and breastfeeding women;
- Clinically relevant cognitive decline, defined as MMSE <=24 or according to DSM IV criteria for dementia;
- Active psychosis or history of at least moderate psychosis in the past year, or with medically uncontrolled severe depression; very mild illusions or hallucinations in the sense of *feelings of passage or presence* with fully retained insight are not an exclusion criterion;
- Known history of melanoma;
- Any investigational therapy in the 4 weeks prior to randomization;
- History or current drug or alcohol abuse or dependencies.

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):	05-05-2014
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Apokyn, Ixense, Spontane, Uprima
Generic name:	Apomorphine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-01-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-02-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-08-2015

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2013-000980-10-NL
ClinicalTrials.gov	NCT02006121
CCMO	NL45910.042.13

Study results

Results posted: 29-10-2018

First publication
11-10-2018