Conservative iron chelation as a disease-modifying strategy in Parkinson*s disease

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Objectives The main objective of the FAIR-PARK II trial is to demonstrate an effect of DFP on the course of PD (including both disease-modifying and symptomatic effects). The trial's overall objective can be summarized as follows: to...

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

Summary

ID

NL-OMON47754

Source
ToetsingOnline

Brief title
FAIRPARK II

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson's, Parkinson□s disease

Research involving
Human

Sponsors and support

Primary sponsor: Centre Hospitalier Régional Universitaire (CHRU) de Lille
Source(s) of monetary or material Support: European Union's Horizon 2020

Intervention

Keyword: Deferiprone, iron chelation, Parkinson's disease

Outcome measures

Primary outcome

We expect to observe a significantly lower mean total MDS-UPDRS score at weeks 36 and 40 in the DFP group (relative to the placebo group). This will enable us to demonstrate the efficiency of iron chelation as the first non-dopaminergic disease-modifying strategy in PD. This will be the first in class treatment to slow down the disease progression. The results will be obtained during the four year of the project, and the main paper will be published before the end of the fifth year.

We do not expect to observe anaemia (or other iron metabolism disorders) with 30 mg/kg/day; anaemia was not a problem in the two independent pilot studies of smaller numbers of patients. We expect to see a good safety profile, with a low drop-out rate due to adverse events in all European centres and a low rate of neutropenia/agranulocytosis (with no harmful consequences), thanks to close monitoring with weekly blood counts. DFP has been on the EU market since 1999, with a favourable risk/benefit balance at 100 mg/kg/day (< 3% of neutropenia). This will enable us to demonstrate the safety of the new therapeutic concept of conservative iron chelation in PD.

We aim to demonstrate a positive impact on the quality of life by the PDQ39 questionnaire.

To date, there is no theranostic biomarker. We intend to demonstrate the theranostic value of the clinical, radiological, biological and genetic

biomarkers for the response to DFP - notably the ferric iron overload measured by ultrasound and MRI, the level of degeneration measured by DaT imaging, the COMT genotype for symptomatic improvements at week 36 and the ceruloplasmin genotype for the disease modifier effect at week 40 and the blood and CSF levels of ferritin. The results will be obtained at the end of fourth year of the project and separated publications will be made at the end of the fifth year.

To date, there is no surrogate biomarker. We expect to demonstrate the surrogate value of clinical, radiological, biological and/or genetic biomarkers for monitoring PD progression by analysing the large population of de novo patients in the placebo group for 40 weeks and comparing them with the advanced PD population in the PREDISTIM PHRC-2012 multicentre study (led by the applicant), the BADGE-PD-PHRC 2010 and DIGPD-PHRC 2008 (two PD cohorts led by JC. Corvol), the population of patients with Alzheimer*s disease (AD) in the FP7 NILVAD study, led by Professor Lawlor) and the population of patients with amyotrophic lateral sclerosis (ALS) in the JPND SOPHIA study (led by Professor Van den Berg). Results will be obtained at end of the fourth year of the project and publications will be made at the end of the fifth year.

We intend to demonstrate that DFP has favourable impact on health economics aspects, as measured by a specific questionnaire.

We also expect to see a concomitant, positive impact on the activities of daily living by performing the continuous assessment of the PD-relevant domains with an unobtrusive, quantitative, continuous measurement tool (SENSE-PARK, FP7).

We expect to set up an efficient European clinical trial network in PD, in

order to promote the forthcoming European studies. This will be reinforced through many teleconferences and meetings with the study group, the efficient completion of the study within 5 years, the many papers generated by the study group and the activities led by different work package leaders and investigators. The collaboration with the three FP7 studies (NILVAD, SOPHIA and SENSE-PARK) will also reinforce the European PD network.
We expect to widely disseminate the demonstration of this new therapeutic concept, in order to promote and support the clinical development of DFP and future other iron chelators (i.e. hydroxypyridinones) for PD and other neurodegenerative diseases (i.e. Alzheimer, ALS, multisystem atrophy, etc.).

Secondary outcome

NA

Study description

Background summary

Background and overall aim
The problem: Parkinson*s disease (PD) is a common, chronic, fast-progressing, non-communicable disease. As the second most frequent neurodegenerative disorder worldwide, PD affects millions of people - about 1% of the over-60s and up to 4% of people in the oldest age groups. It is estimated that the prevalence will at least double by 2030. None of the currently available drugs can slow down the dramatic progression of the motor handicap (e.g. falls) and non-motor handicap (dementia), which generally lead to institutionalization and death. At present, only symptomatic treatments are available (i.e., drugs that partially and transiently reduce the patient*s level of handicap). None of the treatments has demonstrated the ability to decrease the long-term progression of handicap. Today, most patients with PD irremediably progress to a severe state of dependence. In Europe, the cost of PD was estimated to be at least ¤13.9 billion in 2010. The huge and increasing socio-economic impact of PD and the immense emotional burden placed on patients and their caregivers represent a great challenge to society. There is an urgent need for a *game-changer*

strategy, with the development of disease-modifier treatments with neuroprotective and/or neurorestoration effects that can help to avoid this dramatic situation in PD and, more generally, in other neurodegenerative diseases with common physiopathological mechanisms. For many years, the excess oxidative stress related to mitochondriopathy has been considered as one of the main mechanisms involved in cell death (Schapira and Patel, 2014). Oxidative stress is exacerbated by free iron. Chelation of this free iron is known to dramatically increase cell survival. Indeed, iron deposition and oxidation are two major pathways involved in the physiopathology of PD and have been extensively studied (for a review, see Cabantchik et al. 2013). There is a large body of evidence that shows that iron chelation-based antioxidants greatly enhance cell survival in PD cell models and that iron chelators have therapeutic potential in mouse models of PD. However, we reasoned that to develop this therapeutic approach in humans, chelation strategies that target local and regional iron overload (i.e. siderosis) in the brain will necessarily need to avoid systemic iron depletion via the redistribution of iron to endogenous acceptors (i.e. in order to prevent harmful systemic metal loss): this is the new concept of *conservative iron chelation*. We recently demonstrated (for the first time) the feasibility, efficacy and acceptability of the conservative iron chelation approach in pilot translational studies in PD with a prototype drug: deferiprone (1,2-dimethyl-3-hydroxypyridin-4-one, DFP) (in the FAIR-PARK-I project led by the applicant and funded by French Ministry of Health). The only available blood-brain-barrier-permeable iron chelator DFP is approved for treating systemic iron overload in transfused patients with thalassemia. DFP has been on the EU market since 1999, with a favourable risk/benefit balance at dose of 75 to 100 mg/kg/day. We shall adopt a repositioning strategy by using DFP at a lower dose of 30 mg/kg/day in this new indication for local iron overload in PD. DFP will be the first-in-class drug for this novel therapeutic strategy. On the basis of our preclinical and clinical data from FAIR-PARK-I, the present FAIR-PARK-II project should constitute a model for future cytoprotection strategies in neurodegenerative diseases; if DFP treatment is associated with significant slower disease progression, it would be the first non-dopaminergic drug to have a proven disease-modifying effect in PD.

Conservative iron chelation was assessed in cell-based models, corroborated in an animal model of regional siderosis and then translated into a clinical setting (Devos et al., 2014). These preclinical, translational and pilot clinical studies (Devos et al., 2014; details of our results are specified elsewhere in this application): have demonstrated that iron chelation with DFP:

(i) induced greater neuroprotection in cell models (dopaminergic neurons: LHUMES model, patients* lymphocytes) than deferoxamine (used as a reference iron chelator) through a powerful antioxidant effect.

(ii) reduced regional siderosis of the brain and the motor handicap in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxin mouse model.

(iii) reduced regional siderosis of the brain in PD patients

(iv) reduced motor handicap of PD patients (possibly through central and peripheral inhibition of catechol-O-methyl transferase (ICOMT) in a

double-blind, placebo-controlled study in 40 patients.
(v) slowed the progression of motor handicap in a pilot study in early-stage PD patients (thus suggesting a disease-modifying effect) in a double-blind, placebo-controlled study in 40 patients with a delayed start paradigm.
(vi) had a good safety profile, although weekly blood counts are required during the first six months to detect the (reversible) neutropenia that typically occurs in 2-3% of treated patients.
Thus, DFP appears to have disease-modifying potential and also inhibits dopamine metabolism through ICOMT (Waldmeier et al. 1993; Devos et al., 2014; Dexter et al., 2014). The latter associates a more direct symptomatic benefit for the patients, together with the expectation of slower disease progression. The ICOMT activity could be also of high value because there is a lack of well-tolerated drugs with central ICOMT. Entacapone has only peripheral ICOMT activity (and thus a lower efficacy). Although tolcapone has both central and peripheral ICOMT activity, its prescription is restricted indicated by a high risk of hepatitis.
Interestingly, these clinical results were recently confirmed by another independent pilot study on 18 PD patients, which showed a reduction in brain iron overload and a better clinical effect for DFP at 30 mg/kg/day than for placebo and DFP at 20 mg/kg/day (Dexter et al., 2014). Thus, the two pilot studies have been used to calculate the required sample size to lead our project based upon a large randomized clinical trial to demonstrate this new therapeutic concept
Moreover, by taking advantage of collaborations and involvement in other European studies, we shall assess DFP's impact and the prognostic value of biomarkers obtained from large-scale, on-going studies. This will increase the scientific impact and dissemination of our study (i.e. publications) and limit the risk of failure and negative results.
Finally, the health economics and societal impacts will be monitored because it is increasingly acknowledged that conclusions based on conventional clinical trials may not be useful for making decisions on management in a "real-life" clinical setting. If DFP is associated with significant slowing of disease progression in FAIR-PARK-II, it would be the first non-dopaminergic drug to have a proven disease-modifying effect. As such, DFP would also have a huge socio-economic impact. In order to move towards an assessment of DFP's potential real-world benefits data, we shall concomitantly analyse the drug's impact on health economics aspects and the PD patients' and caregivers' quality of life via questionnaires and the continuous quantitative monitoring of PD-associated handicaps in the home environment (i.e., bradykinesia, gait and balance, tremor, sleep) using the SENSE PARK device (developed in the frame of FP7).
At present, no neuroprotective drugs are available. If our academic proof-of-concept study demonstrates a disease modifying effect, this new therapeutic strategy could be offered to the population of patients with PD as a whole. This would represent a considerable market and would have a huge socio-economic impact.

Study objective

Objectives
The main objective of the FAIR-PARK II trial is to demonstrate an effect of DFP on the course of PD (including both disease-modifying and symptomatic effects). The trial's overall objective can be summarized as follows: to demonstrate for the first time in a large phase III II, multicentre, parallel-group, placebo-controlled, randomized clinical trial (RCT) that conservative iron chelation, with the prototype drug, DFP, will slow down the progression of handicap in PD patients and will not be associated with a negative clinically benefit/risk ratio. A putative slow-down in the progression of handicap will be monitored in a multicentre, placebo-controlled RCT with 372 patients with de novo PD (169 patients per arm) (the best population for assess a disease-modifying effect without the bias caused by the effects of dopaminergic treatment).

Objective 1: To successfully manage the demonstration of the Investigating DFP efficacy as a treatment for PD in a large placebo-controlled study and thus demonstrate (for the first time in a neurodegenerative disease) the concept of conservative iron chelation as a disease modifier treatment. We aim to demonstrate a lower progression of motor and non-motor handicap at week 36 in PD receiving DFP as compared with placebo.
Objective 2: To demonstrate the feasibility of a multi-site European clinical trial of a potential PD treatment with a demonstrated safety profile, with a specific monitoring.
Objective 3: To fund the larger scale investigation of DFP in PD patients, which the existing preclinical and clinical data strongly mandate and to promote a European clinical trial network of PD clinicians and researchers.
Objective 4: To investigate clinical, radiological, biological and genetic biomarkers of PD progression in response to DFP.
Objective 5: To bring the first data of DFP's potential real-world benefits based upon the drug's impact on health economics aspects and the continuous monitoring of motor and non-motor handicap at home.
Objective 6: To expedite the availability of disease-modifying treatments to PD patients. Based upon our demonstration of efficacy and safety of conservative iron chelation with the only available and prototype drug, DFP, we aim to promote and support the clinical development of iron chelators as a new treatment modality in PD. The following clinical development with large phase III II studies and registration of DFP, the first in class, by ApoPharma could be done within 7 years. We also aim to promote the clinical development (from phase I) of future other iron chelators (i.e. hydroxypyridinones) for PD and other neurodegenerative diseases (i.e. Alzheimer, ALS, multisystem atrophy, etc.).
Objective 7: To evaluate the effect of DFP on the disease progression, taking into account the drop out rate with a combined criterion of disease progression measured by the total score of the MDS-UPDRS and the dropout because of disease

worsening

Study design

A multicentre, parallel-group, randomized, placebo-controlled trial of DFP 15 mg/kg BID. A 9-month treatment period (period 1) will be followed by a 1-month post-treatment monitoring period (period 2), in order to assess the disease-modifying effect in the absence of a symptomatic effect (i.e. an effect of inhibition of catechol-O-methyl transferase (COMT) activity (ICOMT) on dopamine metabolism) of DFP (versus placebo). Considering the short half-life of DFP, one month will be enough to assess the level of handicap of patients in the absence of ICOMT due to DFP treatment.

Intervention

Pharmacotherapeutic group: iron chelator.
The active substance is 3-hydroxy-1,2-dimethylpyridine-4-one (DFP, FERRIPROX®), a bidentate ligand that binds to iron in a 3:1 molar ratio. DFP decreases excessive iron and ferritin levels. Its low molecular weight and liposolubility enable it to cross the blood-brain barrier. Clinical haematology studies have demonstrated that DFP is effective in promoting iron excretion and that a dose of 25 mg/kg three times per day can prevent the progression of iron accumulation (as assessed by serum ferritin levels) in patients with transfusion-dependent thalassemia. However, chelation therapy may not necessarily protect against iron-induced organ damage. DFP (provided by ApoPharma) is unique among available iron chelators in that it readily penetrates the CNS and has been shown to function as an iron redeployment agent. The drug has been approved for many years in the indication of haemosiderosis in thalassemia major patients undergoing chronic blood transfusion. We intend to reposition DFP, with a disease-modifying effect in PD.
Patients will receive placebo or 30 mg/kg per day DFP divided into two doses (at 08.00 and 20.00). An initial DFP dose escalation will be applied every third day during a period of 15 days
We shall check on tolerability (assessed by interviews and examinations) and compliance (assessed by interviews and tablets counts) every 3 months. Interviews of patients and caregivers will be performed by the investigators.
In the event of poor tolerance, we shall delay the titration phase by 1 week. The dose can be temporarily reduced to 20 mg/kg per day (suspicious of adverse event or variation of blood ANC toward neutropenia). However, we shall ask to the centers to maintain the patients at the dose of 30 mg/kg per day.

Study burden and risks

Expected benefits:
We expect to observe a significantly lower handicap in the DFP group and thus a lower disease progression.

It appears to have no loss of opportunity for the patients under placebo since there is still no validated neuroprotective treatment. Rasagiline has shown a weak disease modifying effect, for which a pure symptomatic effect remains subject of debate. Moreover, it has been specified in the exclusion criteria that *Subjects with a handicap likely to require symptomatic dopaminergic treatment in the coming nine months* in order to avoid patients having a handicap requiring symptomatic effect.
Possible risks:
- Risk of neutropenia (< 3%)
- No anemia expected
- Adverse effect of DFP (see products characteristics).

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. Adult Patients
2. Parkinson*s disease diagnosed according The Movement Disorder Society Clinical Diagnotic Criteria for Parkinson*s Disease (PD).
3. Treatment-naïve, i.e. the best population for assessing a disease-modifying effect without the interaction of dopaminergic treatment (no dopaminergic agonists, L-dopa, anticholinergics, monoamine oxidase B inhibitors (e.g. rasagiline) or deep brain stimulation).
4. Patients covered by a Health Insurance System in countries where required by law
5. Written informed consent dated and signed prior to the beginning of any procedures related to the clinical trial

Exclusion criteria

1. Disease duration greater than 18 months.
2. Patients with high frequency of comorbidity or vital risks that may reasonably impair life expectancy
3. Subject with handicap required dopaminergic treatment at the inclusion and therefore likely not to bear 9 months without symptomatic treatment
4. Hoehn and Yahr stage 3 or more.
5. Significant cognitive impairment (a Mini Mental State Examination score <24 or an equivalent impairment on a similar scale) or dementia diagnosed in accordance with the Movement Disorders Society criteria (Emre et al., 2007).
6. Atypical or secondary parkinsonism (supranuclear palsy, multisystem atrophy, etc.)or significant cortical or subcortical atrophy (i.e. atypical for PD).
7. Progressing axis I psychiatric disorders (psychosis, hallucinations, substance addiction, bipolar disorder, or severe depression), in accordance with the Diagnostic and Statistical Manual of Mental Disorders.
8. Subjects undergoing brain stimulation.
9.Due to the high risk of agranulocytosis caused by the IMP and the unknown mechanism by which this agranulocytosis is induced, it is not allowed to combine Deferiprone with other medicinal products causing agranulocytosis (as described in the IB). Such medicinal products are the already mentioned clozapine and also some NSAIDs (e.g. Phenylbutazone or Metamizole), antithyroid agents, sulfonamide antibiotics or metothrexate.
10. A history of relapsing neutropenia
11. Hypersensitivity to deferiprone.
12. Patients with agranulocytosis or with a history of agranulocytosis.
13. Patients taking a treatment at risk of agranulocytosis (clozapine, Closaril®/Leponex®).
14. Patients with anaemia (regardless of the latter's aetiology) or a history of another haematological disease. Haemochromatosis is not an exclusion

criterion.
15. Pregnant or breastfeeding women or women of childbearing potential not taking highly effective contraception.
16. Kidney or liver failure.
17. Other serious diseases.
18. Inability to provide informed consent.
19. Participation in another clinical trial with investigational medicinal product within 3 months prior to inclusion in the study
20. Patient who has suffered mild or moderate depressive episode and isn*t in remission and on a stable medication for at least 8 weeks
21. Patient > 130kg

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:	Recruitment stopped
Start date (anticipated):	26-10-2016
Enrollment:	38
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ferriprox
Generic name:	Deferiprone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-05-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-08-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-01-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-02-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-09-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-07-2019

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-11-2019
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	EUCTR2015-003679-31-NL
Other	FoxTrialFinder: 004322, ClinicalTrials.gov:NCT02655315
CCMO	NL56625.091.16

Study results

Date completed:	31-07-2020

Actual enrolment: 33