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Conservative iron chelation as a disease-modifying strategy in Parkinson's disease (FAIR-PARK II)

Submission date
19/06/2017

Recruitment status
No longer recruiting

Registration date
03/07/2017

Overall study status
Completed

Last Edited
03/10/2023

Condition category
Nervous System Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Parkinson's disease is a long-term condition most commonly associated with changes in movement. It is classed as a neurodegenerative disorder because it is linked to progressive damage of nerve cells (neurons) in the brain. It is the second most common neurodegenerative disorder worldwide affecting millions of people including about 1% of people in their 60s and up to 4% of people in the oldest age groups. It is estimated that the number of people with a Parkinson's disease diagnosis will double, at least, by 2030. Current medications for Parkinson's disease treat only a person's symptoms and do not slow down the worsening of the disease. Neurons are responsible for making a chemical called dopamine which passes messages to the brain for many functions including movement, memory and sleep. The symptoms seen in Parkinson's disease such as slowness of movement, stiffness and tremors are thought to be due to loss of neurons. From the early stages of Parkinson's disease, an excess amount of iron is seen in a part of the brain that contains neurons and this may contribute to their loss. The aim of this study is to investigate whether reducing excess iron using the medication deferiprone might decrease neuron loss and slow down the progression of Parkinson's disease.

Who can participate?
Adults aged 18 and older with a Parkinson's disease diagnosis who have not yet received any treatment.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group receive the treatment tablets with deferiprone. Those in the second group receive a dummy tablet. All participants take the tablets by mouth twice a day, once in the morning and once in the evening, 30 minutes before a meal. This is done daily for nine months and participants are followed up with for one month after treatment. During this period, participants visit the study centre six times to provide information about their health, medications, side effects. They also undergo a physical examination, heart monitors, mobility assessments, and provide blood and urine samples. Participants also provide extra blood samples weekly for the first six months of the trial and then monthly for the last three months of the study. There are also optional tests that

participants can undergo and these include blood samples and lumbar puntures to collect spinal fluid (to analyse any biological effects of the treatment).

What are the possible benefits and risks of participating?
There are no direct benefits with participating. There are always risks when taking medication, however, Deferiprone is a widely prescribed treatment and is well tolerated. There is a risk of a drop of white blood cell count, which is corrected by stopping taking the medication. Participants will be monitored for this. Other risks are side effects such as fatigue, headaches, dizziness, nausea, muscular pain and diarrhoea. Participant may experience discomfort when providing blood samples. Participants who undergo optional lumbar puncture may experience headaches during the procedure and can be allergic to the anaesthetic used during the procedure. There is a risk of infection, damage to the nerves in the spine and bleeding.

Where is the study run from?
This study is a European clinical trial that is being run in France, Spain, Austria, the Czech Republic, Portugal, Germany, the Netherlands and the United Kingdom. In the United Kingdom the trial is being run from the Centre for Aging and Vitality (UK) in Newcastle upon Tyne and Addenbrooke's Hospital (UK)

When is the study starting and how long is it expected to run for?
February 2016 to September 2020

Who is funding the study?
European Commission (EU)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)

2015-003679-31

ClinicalTrials.gov (NCT)
NCT02655315

Protocol serial number
31933

Study information

Scientific Title
Conservative iron chelation as a disease-modifying strategy in Parkinson's disease

Acronym
FAIRPARK II

Study objectives
The aim of this study is to establish whether conservative iron chelation with the prototype drug deferiprone slows down the progression of Parkinson’s disease and to determine the associated risk benefit balance.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North East – Tyne & Wear South Research Ethics Committee, 19/07/2016, 16/NE/0200

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment, Efficacy

Health condition(s) or problem(s) studied
Parkinson's disease

Interventions
Participants are randomly allocated to one of two groups. Those in the first group receive the treatment tablets with deferiprone (15 mg/kg). Those in the second group receive a dummy tablet. All participants take the tablets by mouth twice a day, once in the morning and once in the evening, 30 min before a meal. This is done daily for 9 months and participants are followed up for 1 month after treatment.

During the trial participants will attend visits for screening, randomisation (visit V0), week 12 (visit V1), week 24 (visit V2), week 36 (visit V3) and week 40 (visit V4). During visits V0, V3 and V4 participants have three comprehensive examinations (i.e. rating of the total Movement Disorder Society-Sponsored Revision of the Unified Parkinson’s Disease Rating Scale [MDS-UPDRS] and all

secondary criteria), at visits V1 and V2 assessments will include rating the total MDS-UPDRS and a check on all the safety criteria during a brief consultation. A weekly complete blood count (CBC, with the white blood cell count [WBC]) performed for the first 24 weeks and then monthly until week 36. Deferiprone or the placebo is taken from the day following randomisation until the morning dose on the day of the visit at week 36.

Participants may also be asked whether they would like to have additional, optional, tests performed. These include:
1. Cerebrospinal fluid (CSF) analysis at the randomization visit and at week 36, in order to perform a full set of CSF biochemistry assays and with a view to determining the biological benefits of deferiprone treatment at the central nervous system level and to identifying biological markers. For the patient's comfort, lumbar puncture will be performed under local anaesthesia and with administration of a 1:1 mixture of nitrous oxide and oxygen.
2. Additional blood analysis (extra volume of 40 ml)
This is done to assess mitochondrial function, with functional assays on lymphocytes: mitochondrial membrane potential and reactive oxygen species production (flow cytometry). This is also done to evaluate the neural, endothelial and platelet microparticles.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Deferiprone

Primary outcome(s)
Motor symptoms, non-motor symptoms and daily life activities are assessed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), the change in the total score is measured between baseline and 36 weeks (i.e. the end of the placebo-controlled phase for analysis of both disease-modifying and symptomatic effects).

Key secondary outcome(s))
1. The disease-modifying effect is measured as the changes in the overall MDS-UPDRS score between baseline and week 40
2. The global effect on motor and non-motor symptoms is analysed as the change in the different subscales of the MDS-UPDRS between baseline and week 36 and between baseline and week 40
3. Effects on quality of life and autonomy is analysed as the change in the Parkinson's Disease Quality of Life (PDQ-39, via a 39-item self-questionnaire) and the Clinical Global Impression scored by the examiner and the patient between baseline and week 36 and between baseline and week 40
4. A health economics assessment is performed via a specific questionnaire and EQ-5D questionnaire between baseline and week 36 and between baseline and week 40
5. Safety criteria that is measured include:
5.1. Complete blood count (CBC, including a white blood cell (WBC) count and a differential, absolute neutrophil count (ANC) and platelet count) is assessed using weekly (± 3 days) blood tests from the start of treatment onwards for 24 weeks and then monthly until week 36
5.2. An iron status check (haemoglobin, serum iron, ferritinemia, transferrin, total binding capacity, transferrin saturation coefficient, 24-hour urine iron) is assessed at baseline and week

36
5.3. Clinical chemistry tests (fating glucose, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT)) are assessed at screening and weeks 12 and 24
5.4. General health status and full physical exam (including vital signs, bodyweight, electrocardiogram and blood pressure) are assessed at baseline and weeks 12, 24, 36 and 40
5.5. Adverse events, concomitant medication(s) and observance are measured using questions about the occurrence of adverse events, the use of any medications and the compliance with the study therapy, at each scheduled or unscheduled visit
5.6 β HCG (for women of childbearing potential) is measured monthly through blood tests

Completion date
20/09/2020

Eligibility

Key inclusion criteria
1. Adult patients aged 18 and older
2. Parkinson's disease diagnosed according The Movement Disorder Society Clinical Diagnostic 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

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
372

Key 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 anomalies on MRI suggestive of vascular involvement 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, sulphonamide antibiotics or methotrexate
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 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

Exclusion criteria for the biomarker study and the ancillary study:
1. Subjects for whom MRI is contraindicated (metal objects in the body, severe claustrophobia, pacemaker, incompatible surgical material)
2. Very severe rest tremor, which could induce MRI artefacts
3. Lumbar puncture
4. Blood coagulation disorders, antiplatelet drugs or anticoagulants
5. Intracranial hypertension
6. Contraindications to nitrous oxide
7. Ventilation with FiO2 >50%, emphysema or pneumothorax
8. Altered states of consciousness, non-cooperative patient (need to stop the nitrous oxide)

Date of first enrolment
07/07/2017

Date of final enrolment
31/12/2019

Locations

Countries of recruitment

United Kingdom

England

Austria

Czech Republic

France

Germany

Netherlands

Portugal

Spain

Study participating centre
Centre for Aging and Vitality
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Campus of Ageing and Vitality
Newcastle upon Tyne
United Kingdom
NE4 5PL

Study participating centre
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation
Centre Hospitalier Regional Universitaire de Lille

ROR
https://ror.org/02ppyfa04

Funder(s)

Funder type
Government

Funder Name
European Commission

Alternative Name(s)
European Union, Comisión Europea, Europäische Kommission, EU-Kommissionen, Euroopa Komisjoni, EC, EU

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository: European Clinical Research Infrastructure Network (ECRIN)

Added 01/10/2020:
As specified in the Consortium agreement of FAIR PARK II, the intellectual management board (IMB) oversees intellectual property management and dissemination of the consortium.
The IMB is subdivided into two groups: the intellectual property division (IPD) and the scientific evaluation division (SED).
The SED is subdivided into two groups: the scientific project assessment group (SPAG-SED) and the publication project assessment group (PAG-SED).
The data are available to all the scientific community. People who want to have access to the data generated during THE FAIR PARK II study will address a scientific draft (specifying the types of analyses) to the project management team (pauline.guyon@chru-lille.fr and stephanie.lenaour@inserm-transfert.fr). The project management team will forward the document to the SPAG-SED.
The SPAG-SED duties:
1. Advice and expertise on the opportunity of the submitted project
2. Assessment of the scientific value of the submitted project
3. Control of the validity of the research project proposed
4. Advice on the optimum use of the project resources
5. Advice and support regarding ongoing and validated projects
6. Review the submitted project pursuant to FP II grid
If no written remark or comment has been made within 15 days. the project is approved and people can have access to the data.
The data will be available for the end of April 2021 and for the moment, there is no duration specified regarding their availability.
Patient's consent is obtained to share the data in the scientific community. Data are pseudo-

anonymized (with the patient ID). The sharing of all data will be compliant with all legal and ethical requirements.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/12/2022	03/10/2023	Yes	No
HRA research summary			28/06/2023	No	No
Other unpublished results		13/06/2023	02/10/2023	No	No
Protocol file	version 7	14/10/2019	02/10/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes