

Information Sheet Parkinson's subjects

You will be given a copy of this Information Sheet

Study title

A pilot clinical trial with the iron chelator Deferiprone (Ferriprox) in Parkinson's Disease

Chief Investigator: Dr David T Dexter

Invitation

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

Parkinson's disease is a progressive neurodegenerative disease. Whilst there are drugs which can treat the clinical symptoms of Parkinson's, there are currently no drugs which can which prevent further nerve cell loss thus the severity of the disease increases with time. However, recently research has provided clues as to how nerve cells die in Parkinson's leading to the development of drugs which may protect the neurons from dying.

There is extensive evidence that iron accumulates in the brain area commonly affected in Parkinson's, the substantia nigra (see diagram below). Whilst iron is vital for several biochemical processes within cells, excessive amounts of iron can trigger the formation of toxic chemicals, called free radicals, which can potentially damage nerve cells within the brain. Indeed, there is growing evidence demonstrating increased levels of free radical damage within the Parkinson's brain. Hence, one way of potentially preventing this damage is to remove the excess iron from the brain. The long term goal of such a therapy would be to slow down the progression of Parkinson's disease.

Drugs capable of mopping up excess iron and removing it from the body, called iron chelators e.g. Deferiprone (Brand name Ferriprox), have been safely used in the hospital clinics for many years to treat diseases where iron accumulates in the body e.g. thalassaemia. This is an inherited disease in which patients are unable to make enough haemoglobin, the protein that is found in red blood cells that carries oxygen

around the body. Such patients require several blood transfusions but when the body breaks down the red cells at the end of their useful life it cannot remove the iron and it builds up in the body causing toxic effects. Deferiprone has also been used in a recent small clinical trial in the brain disorder Friedreich Ataxic, a genetic disease affecting movement, which is also associated with an increase in brain iron. At the same doses to be used in this study Deferiprone was shown to remove brain iron, as assessed by Magnetic Resonance Imaging (MRI), improve clinical symptoms without major side effects in the majority of patients.

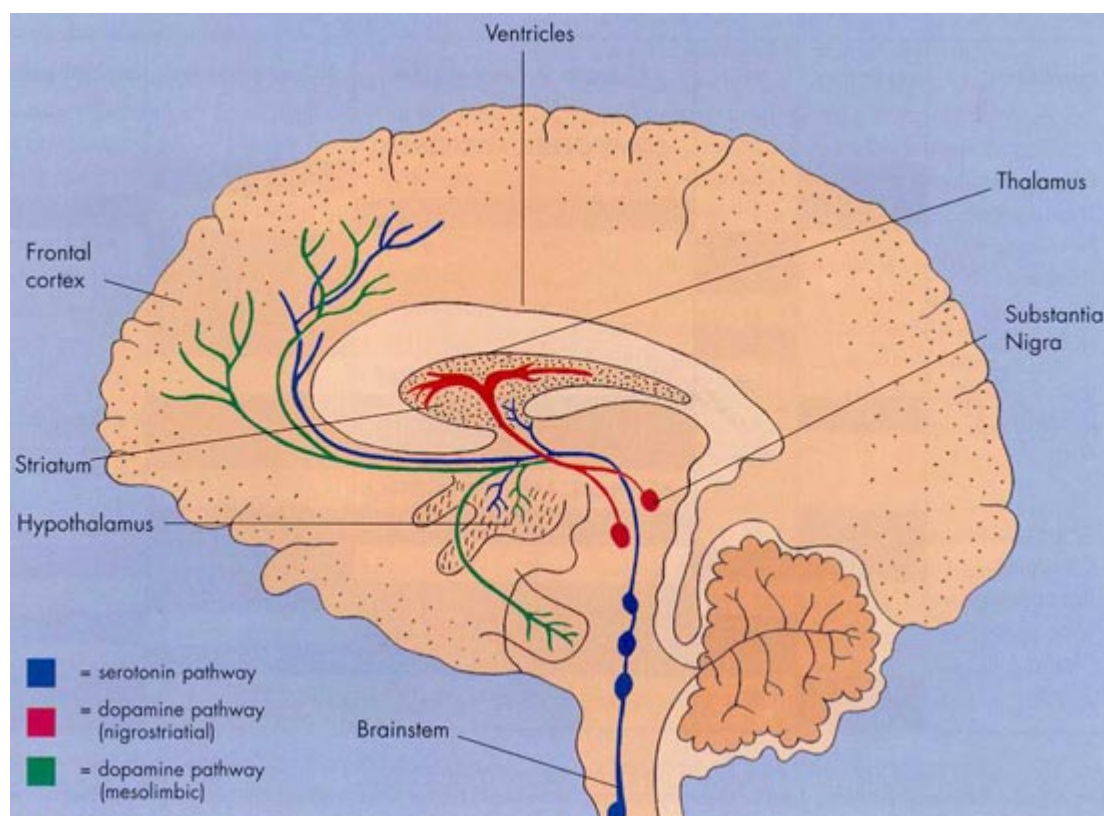


Figure: Diagram showing the neuronal pathway that is principally affected in Parkinson's, the nigrostriatal system that utilizes dopamine as its chemical messenger (red pathway). The nerve cells originate in the substantia nigra, where the increased iron levels have been shown to accumulate in Parkinson's.

However, no studies have so far been carried in Parkinson's disease patients. Hence the aims of this pilot study are to assess whether Deferiprone:- 1) can remove excess iron from the brain area affected in Parkinson's as assessed by MRI, 2) affects the clinical symptoms of Parkinson's disease or other brain functions such as memory etc, and 3) causes any unwanted side effects. It is hoped that this pilot study will provide valuable data to support larger and longer clinical trials with Deferiprone since we will only be able to see whether Deferiprone can slow down the progression of Parkinson's disease with its long term use in patients.

Why have I been chosen?

You have been chosen because you are a patient that has been recently diagnosed with Parkinson's disease and that your standard anti-Parkinson's medication (L-DOPA or dopamine agonists) is successfully treating your clinical symptoms.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you have agreed to take part you are still free to withdraw at any time without giving any reasons and this will not affect the standard of care you receive.

What will happen to me if I take part?

The project consists of two parts, an initial visit (about 3 hours) to the hospital to test your suitability for the study and the study itself which will last 6 months. We will ask for your involvement for approximately 7 months at most.

Initial Visit

The doctor associated with the project will ask you questions about your medical history and discuss with you the purpose of the study and its design. They will also take routine parameters like blood pressure, electrocardiogram (ECG) etc to determine your general state of health. You will also be asked to give blood (about 10 teaspoons or 50ml) and urine samples so that we can assess the numbers of blood cells, liver and immune function, iron and iron binding protein levels. The doctor will also ask you perform a variety of neurological tests to assess the severity of your Parkinson's, very similar to the tests carried out when you were diagnosed. If you consent, you will be videoed whilst you perform such tasks e.g. walking, getting out of a chair etc so that we can have a digital record of how you perform these tasks across the trial period. The videoing will not be intrusive and will allow subsequent assessment of your dexterity and speed of performing specific movements and will allow the research doctor to easily see whether your movement capabilities has changed over the course of the study. In addition, you will be asked to perform a small number of short tests and fill out questionnaires to assess your memory, how happy you are, ability to plan actions and your general quality of life. Finally we will ask everyone to have a magnetic resonance scan (MRI). This gives a detailed structural picture of the brain and allows us to measure the levels of iron in your brain. This type of brain scan does not involve any radiation. This scan takes about 15-30 minutes. If you are claustrophobic you may find MRI difficult to tolerate and should let us know beforehand. Checks will be made before you have the MRI scan to ensure suitability e.g. no pacemaker etc.

From the above tests we will be able to assess whether you are suitable for the study and you will be invited to take part in the main clinical trial study.

Clinical Trial

If you select to enter the clinical trial the clinical staff involved in the study will discuss with you the study design and provide you with a personal diary when are required to attend the hospital. You will be given the option of receiving telephone or text messages to help you remember when your hospital visits are due.

You will be asked to take medication orally every day for the full 6 months of the study. You will be randomly assigned to either take a low (20mg/kg/day) or higher (30mg/kg/day) dose of Deferiprone or a dummy drug (placebo). You will not be told which treatment you will receive nor will the doctors/nurses know which treatment you have been assigned. This is done so that we assess the effects of the drug compared to a dummy drug and to avoid bias in assessment of results.

During the six month study period you will be asked to:-

- 1) Undergo two further MRI scans to assess brain iron content at approximately the 3 and 6 month time points.
- 2) Undergo three sets of neurological tests (as in initial visit) at approximately the 2, 4 and 6 month time points.
- 3) Give a set of blood and urine samples twice per month (at the beginning of each month and in the middle of each month) for 6 months so we can measure the same parameters as in your initial visit (see above) plus test to see how you are metabolizing the drug.

The majority of your visits will be short e.g. to give a blood sample (30mins) and when multiple test will be carried out we will combine them on the same day to limit disruption to your life. We will schedule visits at times which suit you best. A plan of the tests across the 6 months trial period is given below and the length of your visit on each occasion. No lifestyle restrictions are required to take part in this study.

Summary of visits:

Visit Time Points	Type of assessment	Time taken
1)Start of Month 1- start of Trial	Blood/urine samples	30 minutes
2) Middle of Month 1	Blood samples	30 minutes
3)Start of Month 2	Blood/urine samples	30 minutes
4)Middle of Month 2	Neurology tests and Blood samples	2 hours
5)Start of Month 3	MRI Scan and Blood/urine samples	2 hours
6)Middle of Month 3	Blood samples	30 minutes

7)Start of Month 4	Blood/urine samples	30 minutes
8)Middle of Month 4	Neurology tests and Blood samples	2 hours
9)Start of Month 5	Blood/urine samples	30 minutes
10)Middle of Month 5	Blood samples	30 minutes
11)Start of Month 6	Blood/urine samples	30 minutes
12)Middle of Month 6	Blood samples	30 minutes
13)End of Month 6	Neurology tests, MRI scan and Blood tests	3 hours

What are the possible benefits of taking part?

This is a pilot study to investigate whether Deferiprone can remove excess iron in the Parkinson's brain without inducing major side effects. The study will also assess whether Deferiprone affects the symptoms of Parkinson's or general brain function. Hence, apart from increased access to neurological care and helping advance Parkinson's research there may not be any immediate benefit of taking part in the study. However, if this study proves successful we will then investigate whether long term therapy with Deferiprone can slow down the progression of Parkinson's. You will be given the opportunity at the end of this study to continue to Deferiprone if you have not experienced side effects.

What are the possible disadvantages and risks of taking part?

You may experience some disruption to your lifestyle and inconvenience from taking part in the study where you are asked to take medication each day and attend the hospital on multiple visits. You may experience mild discomfort from giving blood samples but this will be comparable to when you may have given blood in the past say at your GP.

You may experience claustrophobia when you are being asked to lie still whilst the MRI scan of your brain is being carried out. The radiographer running the scanner will make you comfortable in the scanner with cushions etc and play you relaxing music for the short duration of the scan.

The drug Deferiprone may induce some side effects in some patients. You will be given a card at the beginning of the study with a day time and out of working hours emergency contact telephone number if you wish to discuss any side effects you may experience. The incidence of side effects given below are, derived from clinical experience in thalassaemia patients where a dose of **100mg/kg/day** Deferiprone is given. In this study the maximum dose we will use is **30mg/kg/day**, some three times less than the dose used to treat thalassaemia, hence the potential incidence of side effects we would expect to be lower than those quoted below. You may experience:-

Minor side effects experienced occasionally in approximately 1 in every 10 of subjects

- 1) Feeling or being sick, abdominal pain. If you experiences this we will recommend you eat little and often and stick to simple foods.
- 2) Red/brown discoloration of your urine. This is a common feature when taking Deferiprone and indicates that the drug is taking iron out of the body, hence the rusty colored urine. This does not indicate that you have blood in your urine and has no medical implication.

Minor side effects experienced occasionally in less than 1 in 10 subjects.

- 1) Diarrhea. If you experience this we will recommend drinking plenty of water to replace any lost fluids.
- 2) Mild joint pain and/or headache. If you experience this and find it troublesome we will recommend you to take painkillers to manage the temporary pain.
- 3) Increased appetite.

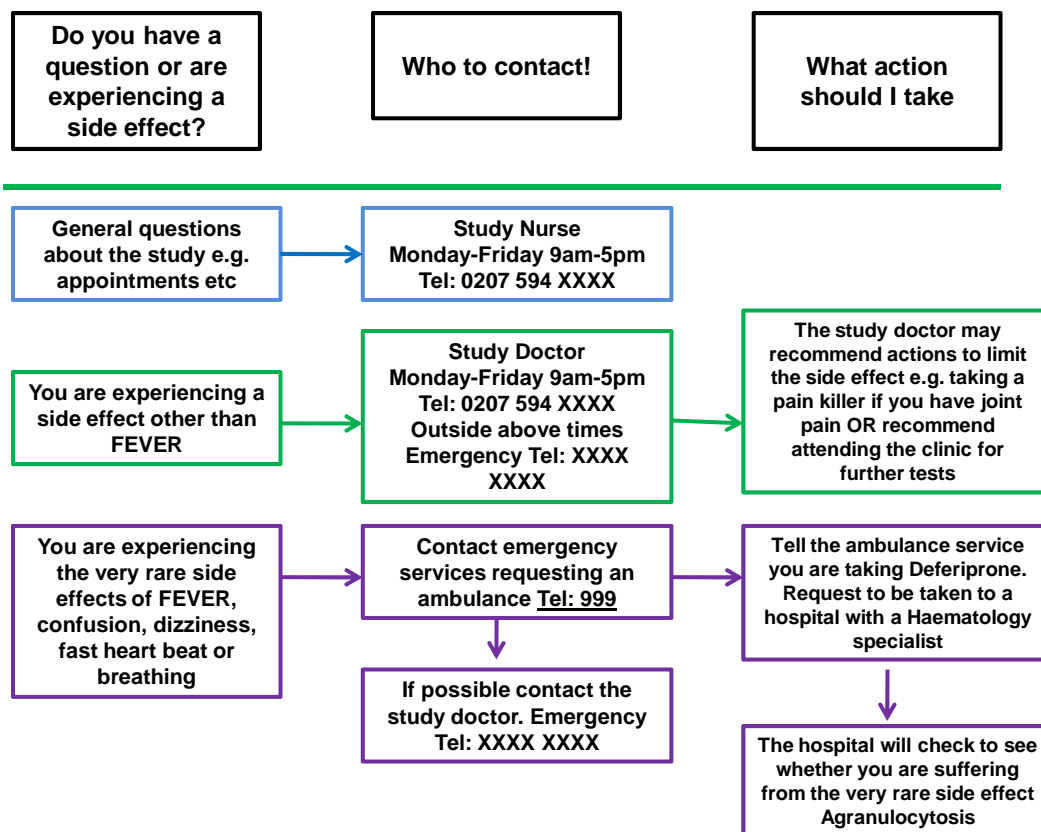
Major side effect experienced in less than 1 in 100 subjects.

Agranulocytosis - a condition in which there are insufficient numbers of white blood cells called neutrophils. This can affect your ability to fight off infection and hence the study will monitor your blood cell count carefully, hence you have been asked to give blood every 2 weeks. If you experience flu-like symptoms or a sore throat we will ask you to contact the study doctor immediately. You will be asked to give an additional blood sample as a precautionary measure to check your numbers of blood white. If your numbers of white cells is abnormally low we may either lower your dose of Deferiprone or withdraw you from the study.

You should be aware that there is a possibility that the methods used in this study may produce an unexpected result that may have relevance for your health. In the unlikely event of this happening, we will discuss this with you and, if necessary, provide any support that you may require, such as arranging follow-up tests and/or treatment.

What should I do if I want advise about the study or I experience a side effect?

Below is a summary chart of who to contact and what actions to take if you have any general questions about the study you are taking part in or you experience a side effect.



Are there any medications I should not take whilst taking part in the trial

Deferiprone does not interact adversely with most medications but we would encourage you to discuss any potential new medications you are considering taking with your GP or the study doctor. You will continue to take your standard anti-Parkinson's medication (e.g. L-DOPA or dopamine agonist) throughout the study. However, since Deferiprone is a metal chelator, antacids (many of which contain the metal aluminum) should not be taken. If you require an antacid the study doctor will recommend on that does not interact with Deferiprone. Standard health supplements e.g. multivitamins, containing low levels of vitamin C (50-300mg) can be taken, however supplements containing over 300mg vitamin C should not be taken during the study.

What if something goes wrong?

Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Lead Investigator (Dr David Dexter, tel 0207 594 6665). The normal National Health Service complaint mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Office.

Will my taking part in this study be kept confidential?

If you consent to take part in the study, any of your medical records may be inspected by the organizations funding the study for purposes of analyzing the results. They may also be looked at by the people from the funding organizations to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital.

If you consent to take part in the research, with your permission we would like to inform your GP that you are participating in this study.

Data collected or generated during your participation in the study, including MRIs, may be sent to the organizations funding the study. Your name, address and other identifying information will be removed from any data that is shared with these organizations and will be replaced with a code number to protect your identity. We call this de-identified data "study data".

The organizations funding the study may use the study data (a) to review the quality of the study conduct or the study data, (b) to better understand Parkinson's disease, (c) to improve the design of future studies, (d) to enable the conduct of scientific discussions or research that furthers the development of therapies for Parkinson's disease or other neurological disorders and (e) for other uses allowed by law.

The organizations funding the study may share study data with others for the sole purpose of conducting research that furthers the development of therapies for Parkinson's or other neurological disorders. For example, study data may be shared with contract research organizations or academic institutions providing services related to the study and with collaborators as part of scientific discussions or for use in research that furthers the development of therapies for Parkinson's or other neurological disorders.

In order to facilitate research that furthers the development of therapies for Parkinson's disease or other neurological disorders, the principal investigator and/or organizations funding the study may also submit study data for inclusion in one or

more research databases. No identifying information will be provided with the study data being included in the database. Any study data included in a database will be treated in accordance with the Data Protection Act or similar laws applicable in other countries. Any future research where the data may be utilized would be subject to ethical review.

By signing this consent form, you are consenting to the use and disclosure of your study data as described above. You can change your mind at any time by providing notice to the principal investigator. Because access to study data is needed for the study, withdrawal of consent means that you will not be able to continue to take part in the study. Any withdrawal of consent will not apply to the use and disclosure of study data that was collected or generated about you as part of the study before your withdrawal of consent.

What happens to my blood and urine samples?

As mentioned earlier, if you take part in the study, you will be asked to give blood and urine samples for studying how well Deferiprone works. Similar to information, samples may be used by the sponsor or shared by the sponsor with other companies or Universities to better understand Parkinson's and to help develop new drugs.

Your blood and urine samples will be given the same code as your other study information and kept in locked storage for up to three years after the last subject completes the study. Anyone who works with your samples will hold the information and results in confidence. Your samples may be used in future research studies but such studies would be subject to ethical review.

What will happen to the results of the research study?

The results of the research are likely to be published in a peer-reviewed scientific journal. You will not be identified in any report/publication.

Who is organising and funding the research?

Imperial College London is organizing the research and Imperial College London Healthcare NHS Trust and the BRC is funding the research. The Trust is a non-profit organization with a mission to rapidly discover and develop drugs to treat medical conditions such as Parkinson's disease.

Who has reviewed the study?

NRES Research Ethics Committee South Central have reviewed the study and given it a favorable ethical approval.

Contact for Further Information

If you have any questions or if there is anything you wish to discuss please contact:

Insert name, telephone number and e-mail address of study doctor when appointed

Insert name, telephone number and e-mail address of study nurse when appointed

If you agree to take part in this clinical trial please sign the consent form. You will be given a copy of the information sheet and a signed consent form to keep for your records.

THIS INFORMATION SHEET IS VALID FOR USE UNTIL :

Signed (REC Chairman) Date:

Centre For Neuroscience

Burlington Danes Building, Hammersmith Hospital Campus,
Du Cane Road. London W12 0NN

Tel: **Insert Tel No of study doctor when appointed**

Study Number	
Centre Name	
Study Subject	

A pilot clinical trial with the iron chelator Deferiprone (Ferriprox) in Parkinson's Disease

Patient Consent Form

A phase II, randomized, double blind study of the safety and efficacy of Deferiprone 20mg/kg/d or 30mg/kg/d compared to placebo over 27 weeks in drug naïve Parkinson's disease subjects.

Name of Principal Researcher: Dr David T Dexter

If you agree with each section below, please INITIAL the box:

NB. Boxes 1, 2, 3, 5, 6, 8 and 9 below need to be initialed in order for the patient to be enrolled into the study.

INITIALS

1)	I have read and understood the information sheet (version 1.0, 17 Feb 2011) for the above study and I confirm that the study procedures and information have been explained to me. I have had the opportunity to ask questions and I am satisfied with the answers and explanations provided	
2)	I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to take part in the study. I understand that my participation in this study is voluntary and that I am free to withdraw from the study at any time, without giving reason, without my medical care or legal rights being affected.	
3)	I understand that sections of my medical notes may be looked at by responsible individuals from Imperial College London and Imperial College Health Care NHS trust, companies acting on their behalf or regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my	

	records.	
4)	I agree to being videoed as part of my neurological examinations	
5)	I agree to giving the blood and urine samples and undergoing the MRI scans necessary to complete the trial. I consent to the retention of the blood and urine samples and the storage of the MRI scan data for potential future use in research. Any such future research on samples will be subject to ethical review.	
6)	I have been given the names of the study staff whom I can call	
7)	I agree to my GP being informed about my participation in this study	
8)	I understand that data collected during my participation in this research project may be stored electronically on one or more research databases. I understand such data will not contain any identifying information so that I cannot be identified on the database. All data so stored will be treated in compliance with applicable privacy laws.	
9)	I freely agree to take part in this study	

Please print and sign your name below and add today's date:

 Name of patient

 Signature

 Date

 Name of person
 Taking consent

 Signature

 Date

N.B. The patient must date his/her own signature

I copy for patient; 1 copy for study files; 1 copy to be kept with the hospital/clinical notes.