University College London Hospitals
NHS Foundation Trust

Participant Information Sheet

A Phase II, Placebo Controlled, Double Blind, Randomised Clinical Trial To Assess The Safety And Tolerability Of 30 mg/KG Daily **U**rsodeoxycholic Acid (UDCA) In Patients With **P**arkinson's Disease (PD)

"The **UP**-Study''

Name of researchers: Professor Oliver Bandmann, Professor of Movements Disorder Neurology, Sheffield Teaching Hospitals NHS Foundation Trust.
Professor Tom Foltynie, Consultant Neurologist and Professor of Clinical Neurology, University College London.

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. Talk to others about the study if you wish.

- **Part 1** tells you the purpose of this study and what will happen to you if you take part.

- **Part 2** gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

PART 1

What is the purpose of this study?
We would like to invite you to take part in our research study as a patient who has been diagnosed with Parkinson's disease (PD) within the last 3 years. We want to assess the safety and tolerability of a drug called ursodeoxycholic acid (UDCA) in PD.

There is strong evidence from our own research and the work carried out by other groups that UDCA rescues the function of the mitochondria (mitochondria are the "powerhouse" of the cell) in PD patient tissue and other models of PD. This suggests that UDCA may slow down the worsening of PD.

UDCA has been in clinical use for the treatment of liver disease (primary biliary cholangitis) for over 30 years. We therefore know that it is safe and well tolerated in patients with liver disease but we don't know yet whether this is also the case in patients with PD. Furthermore, the dose used for patients with liver disease (15 mg/kg) is not high enough for UDCA to get into the brain. We therefore need to double the dose to 30 mg/kg. This higher dose was also safe in clinical trials for liver disease, but is currently not used routinely in clinical practice.

The aim of this study is to now explore the potential of UDCA to slow down the progression of PD in a randomised, double-blind, placebo-controlled, "proof of concept" study. The primary objective of the study will be to determine the safety and tolerability of this drug in patients with PD.

Why have I been chosen?
You have been asked to participate in this study as you have been diagnosed with PD within the past 3 years and have been identified as being potentially suitable for the study.

Do I have to take part?
No, it is entirely up to you to decide whether or not you would like to take part. If you decide you would like to help us with this study, you will be given an information sheet to keep and be asked to sign a consent form. You remain free to withdraw at any time, without giving reason and this will not affect your usual clinical care.

What will be involved if I agree to take part in the study?
If you decide you would like to take part, we will ask you to come to the Clinical Research Facility, O Floor, at the Royal Hallamshire Hospital, Sheffield or the Leonard Wolfson Experimental Neurology Centre, National Hospital for Neurology, London depending on which location is more convenient for you. We aim to recruit 30 people with PD across both sites. 20 of those recruited will be allocated to take capsules containing UDCA, 10 will be given placebo ("dummy") capsules. The placebo capsules look identical to the UDCA capsules but contain no active ingredient and cause no harm. Participants will be asked to take their allocated study medication three times every day for 48 weeks and will continue to take their usual PD medication as normal. If you are suitable and agree to take part, you will be asked to attend 7 visits in total (including the screening visit). The last visit will be 8 weeks after you've stopped taking the medication. We would like to see you again to find out whether UDCA might have had a real effect on the progression of your Parkinson's disease or whether it might have only improved the symptoms of your Parkinson's disease (like your other PD medication). The procedures and time taken for each visit are identified in the table below. A member of the research team will be

accompanying you throughout your visit. You are more than welcome to also be accompanied by a family member or carer, if preferred.

Who decides which treatment I receive?

If you consent to take part in the study, you will be allocated at random (by chance – like tossing a coin) by computer to receive either UDCA or placebo. This is a "double-blind" study which means that neither you nor the research team will know whether you have been allocated to receive UDCA or placebo, since this could affect the results of the study. However, should it be necessary, the research team and other medical professionals will be able to find out what you are taking very quickly. Once you are allocated to either UDCA or placebo, you will remain on the same study treatment throughout the study.

How many capsules do I have to take and for how long?

You will start by just taking one capsule per day for the first three days. The dose will then be further increased by one capsule every three days until the final dose is reached. This final dose/number of capsules will depend on your body weight. We would like you to take 30 mg/kg UDCA (or a similar number of capsules of the placebo). Therefore, if your body weight was 65 kg, we would ask you to take 8 capsules per day, but if your body weight is 85 kg, it would be 10 capsules. You should take the medication three times daily together with food and split the doses as evenly as possible. Your research team will provide you with precise instructions for all this. You would typically reach the final dose within the four weeks of the trial. You would then be asked to stay on this dose for the subsequent 44 weeks so that you would be taking trial medication for a total of 48 weeks.

Does UDCA have any side effects?

With any medication, there is the possibility of unwanted side effects. Loose stools are the most common side effect of UDCA. Patients have also reported headache or mild weight gain on UDCA. Your health and well-being will be monitored at each study visit with additional telephone checks between visits. You will be advised to contact a member of the research team promptly should you develop unexplained diarrhoea or any other unexplained symptoms and will be given details of who to contact in these circumstances.

What if the study medication doesn't suit me or I want to stop taking part in this trial for other reasons?

If the study medication doesn't suit you or causes a problem at any stage, the dose can be reduced or the treatment stopped altogether. You should tell your local research team about any problems or side effects at your study visits and during check-up telephone calls. You can also stop taking part in this trial at any point if you change your mind for other reasons. Even if you discontinue your medication you can still continue with the study visits and have the other procedures listed in this patient information sheet. However if you do decide to withdraw, your withdrawal will not affect your NHS care.

Summary of study visits

The table below will explain what happens at each visit and how long the visit is likely to take.

Visit	Length of study visit (approx.)	Procedures
Visit 0 Screening visit (1-8 weeks before the actual drug treatment would begin)	3 hours	• We will discuss the study with you and answer any questions • You will then sign the consent form if you wish to take part. • A member of the study team will ask you about your medical history and the tablets that you are taking. • We will undertake a detailed neurological physical examination with particular focus on your Parkinson's disease (PD). • We will also check your pulse rate, temperature, respiration rate, and blood pressure. • A member of the study team will complete 2 questionnaires with you. These will help to find out whether you may have developed depression or memory problems. The presence of depression or significant memory problems would exclude you from the trial. • A member of the study team will take a blood sample and ECG to check if it is safe for you to participate in the study. • You will be provided with an activity monitor to wear for 7 days after this visit if no reasons have been identified why you couldn't take study medication after the screening assessment has been completed.

Visit 1 Baseline visit (Week 1)	4 hours	This visit will take place approximately 2-4 weeks after your screening visit. You will be asked to attend this visit in the OFF state (see below for further explanation) • We will use a clinical rating scale called UPDRS (Unified Parkinson's disease rating scale) to assess the motor aspect of your Parkinson's disease • A member of the study team will complete two quality of life clinical questionnaires with you. • Sheffield patients will be asked to undertake a gait analysis test. • You will then be invited to take your PD medication. Typically, 30 – 60 minutes later, you will be re-examined and a member of the study team will complete 3 further questionnaires with you. • You will then have a MR Spectroscopy scan • Blood samples will be taken for safety, genetic testing and storage • You will be 'randomised' to either the study drug (UDCA) or placebo and will be provided with 3 months' supply of this study medication • You will be provided with a patient diary
Visit 2 (Week 12)	1 hour	• We will review of your medication • We will ask you to return any used medication that you may have. • We will review your diary

		• We will ask you about possible side effects • Some safety bloods will be taken • You will be supplied with 3 months' supply of study medication
Visit 3 (Week 24)	1 hour and 20 minutes	• We will review of your medication • We will ask you to return any used medication that you may have. • We will review your diary • We will ask you about possible side effects. • We will then re-assess the motor aspect of your Parkinson's, using the MDS-UPDRS rating scale • Some safety bloods will be taken • An ECG will be performed • You will be supplied with 3 months' supply of study medication.
Visit 4 (Week 36)	1 hour	• We will review of your medication • We will ask you to return any used medication that you may have. • We will review your diary • We will ask you about possible side effects • Some safety bloods will be taken • You will be supplied with 3 months' supply of study medication

Visit 5 (Week 48)	3 hours and 35 minutes	You will be asked to attend this visit in the OFF state (see below for further explanation) • We will review of your medication • We will ask you to return any used medication that you may have. • We will review your diary • We will ask you about possible side effects • Some safety bloods will be taken • We will then use the UPDRS clinical rating scale again to re-assess the motor aspect of your Parkinson's disease • Sheffield patients will be asked to undertake a gait analysis test. • You will then be invited to take your PD medication. Typically, 30 – 60 minutes later, you will be re-examined and a member of the study team will complete 3 further questionnaires with you. • You will then have another MR Spectroscopy scan • 2 questionnaires will be completed with a member of the study team. These will help us to find out whether you may have developed depression or memory problems • A member of the study team will complete two quality of life clinical questionnaires with you at this appointment. These will help us understand how the trial medication has affected your quality of life and whether the trial medication has

		had an effect on non-motor symptoms of Parkinson's such as constipation.
Visit 6 (Week 56)	2 hours	You will be asked to attend this visit in the OFF state (see below for further explanation) • We will review of your medication • We will review your diary • We will ask you about possible side effects • Some safety bloods will be taken • We will then use the UPDRS clinical rating scale again to re-assess the motor aspect of your Parkinson's disease • You will then be invited to take your PD medication. Typically, 30 – 60 minutes later, you will be re-examined and a member of the study team will complete 3 further questionnaires with you. • 2 questionnaires will be completed with a member of the study team. These will help us to find out whether you may have developed depression or memory problems • A member of the study team will complete two quality of life clinical questionnaires with you at this appointment. These will help us understand how the trial medication has affected your quality of life and whether the trial medication has had an effect on non-motor symptoms of Parkinson's such as constipation.

You will be provided with refreshments at each of your study visits.

What does it mean to attend a visit in the OFF state?

It is important for you to understand that at three study visits (baseline visit/visit 1, visit 5 and visit 6), the key assessments need to be conducted in the absence of your regular PD medication. This is so that the assessors are able to get a true picture of your disease without it being masked by your medication. You should therefore be prepared to attend these visits having omitted any prescribed short-acting PD medication from the evening before the clinic visit, and having omitted any slow release medicines the day before the clinic visit and on the day of the clinic itself. Your research team will advise you about this. Once the main assessments have been completed, you will be invited to take your normal morning PD medication.

To reduce any physical discomfort of stopping medication and to facilitate attendance at clinic, your local research team will arrange for you to be provided with some supportive medicines as necessary (e.g. to help you sleep, relieve any discomfort and/or help with any muscle spasms or contractions). You may also be prescribed dispersible Madopar, to be taken in the event of severe difficulty with wearing-off symptoms. If you have significant difficulties in attending visits in the OFF state, it may be that you will be unable to continue in the study. Your research team will be on hand to give you advice throughout. A member of the research team will telephone you approximately 2 days prior to these visits to remind you to stop your medication.

It can be helpful to bath or shower the night before and to have your clothing ready and easily accessible for the next morning. Allow yourself more time than usual for getting dressed.
Think about what you eat for breakfast – too much protein can interfere with how rapidly your medication "kicks-in" or becomes effective which can delay the time it takes for you to complete both sets of assessments, off and on medication.

Telephone Calls
With your permission a member of the research team will contact you weekly by telephone for the first month of the study to ensure you are happy increasing your medication to the maximum dose that you can tolerate. A member of the research team will then telephone you at week 8, 18, 30, 42 and 52 to check how you are getting on with the study medication and discuss any issues that you may have.

Study Diary
At the baseline visit, you will be provided with a patient diary, which will detail how to increase your study medication (dose escalation) during the first month. We will ask you to record any changes to the study medication throughout the trial. We will also ask you to record any changes to the medication that you usually take as part of your standard of care throughout the study. The study nurse or doctor will review the diary at each visit.

We will now describe the different procedures which form part of this trial.

Study Procedures

Blood samples:
We will take a small blood sample (about 5ml or one tea spoon) for genetic analysis. Your genetic material (DNA) will be extracted from the blood, anonymised and sent to our collaborators in the USA for analysis. We are undertaking this part of the project with collaborators in the USA since they will

undertake the analysis for free, but also because of their excellent scientific reputation. The samples will be anonymised prior to being sent to the US collaborators. We will analyse your genetic material (DNA) to find out whether your response to the trial medication may correlate with PD-relevant genetic changes. We will also take a small blood sample (about 5 ml or one tea spoon) at each visit to help us pick up any unwanted effects of the trial medication on the function of other organs such as the liver or your kidneys. If indicated these bloods may need to be repeated and may involve an extra visit to the hospital. We will also take a serum sample to be stored for future research, with your consent.

Electrocardiogram:

You will have 2 electrocardiograms (ECG) which is a simple test that can be used to check your heart's rhythm and electrical activity. Sensors attached to the skin are used to detect the electrical signals produced by your heart each time it beats. These signals are recorded by a machine and are looked at by a doctor to see if they're unusual. You will have this test undertaken at 2 visits (screening visit and visit 3). This test will help us to analyse your heart traces to make sure that we detect any unexpected effects of the trial medication on your heart rhythm.

Home Sensors:

As part of this study we also wish to gather data on how people walk and move in their natural, home environment. You will therefore be asked to wear a small movement sensor for 7 days at the beginning of the study (prior to the baseline visit) and for 7 days, 12 months later at the end of the study (visit 5). This sensor is worn on a strap around the lower back, and is comfortable to wear and will be removed while bathing or swimming. We ask you to keep an activity diary in this period and to go about your routine day to day tasks as you always would. With your permission a member of the study team will send you a daily text during normal working hours to remind you to wear the sensor for 7 days. The information about your contact telephone number for the daily text reminders will be kept in an encrypted file by the Sheffield Trials team.

Additional Tests at Sheffield Teaching Hospitals only

All patients will be invited to have a MR scan at **Sheffield Teaching Hospitals NHS Foundation Trust.** If you are a patient who will attend the Clinical Research Facility at the National Hospital of Neurology, London to participate in this trial, you can still take part in this study even if you cannot, for whatever reason, travel to Sheffield for the MR scan. The Research team will be happy to discuss this option with you.

If you do decide to travel to Sheffield for the MR scan, a member of the Sheffield research team will telephone you prior to your visit to go through some clinical questions to ensure it is suitable for you to have the scan.

Magnetic resonance spectroscopy (MR) scans:

An MR spectroscopy is a detailed type of scan. The scan is based on magnetism and does not involve ionising radiation (which makes it different from an X-ray), so there is no radiation risk. Anyone can have one, as long as they don't have a pacemaker, other non-MR compatible metallic device (the magnetism from the scan can upset such devices), or metallic fragments in the eye, for example, from welding (as the magnetism could make them move and cause damage). You will be asked about these things before you go in the scanner. In the scanner, it is important you lie very still. The scans will take about 60 minutes in total; you will have a break half way through to have a stretch and move around.

We would like you to have MRS of your brain both at the beginning and at the end of the medication period. This will help us determine whether the trial medication has a beneficial effect on the energy metabolism in your brain.

Gait Analysis tests:

We will only undertake the gait analysis in Sheffield patients. The gait analysis will help us to measure objectively whether the trial medication has an effect on your mobility. The gait analysis test will be undertaken when you have not taken your PD medication to make sure that the severity of your Parkinson's disease is not masked by your medication. The gait analysis test involves wearing small sensors on your ankles, trunk and head. The sensors will be attached using Velcro strips and this is a painless and non-invasive process. We will then ask you to walk a defined distance (5 metres) through the gait analysis system (the gait analysis system is called the OptoGait). This consists of a series of infrared beams (like on TV remote control) which are broken as you walk, this gives very detailed information on your walking pattern. You will be asked to walk through this system 3 times at slow, normal and fast speed as selected by you. All data is recorded anonymously on a computer. The gait analysis is painless and non-invasive.

You could certainly have breaks between the different parts of the study. If preferred, we could also do the MR scan on a different day to the gait analysis. You will not have to stay in hospital after any of these procedures.

What are the possible disadvantages and risks of these procedures?

Blood samples:

There are small risks associated with needle injections. For most people, needle injections do not cause serious problems, however some people experience a small amount of swelling, bleeding or pain at the needle site or some people may feel faint. On very rare occasions infection may occur. If we were to detect any relevant genetic changes in your blood we will discuss them with you and offer a referral to our colleagues in Clinical Genetics so that you could be formally tested if required.

ECG:

Rarely, a reaction to the electrode adhesive may cause redness or swelling where the patches were placed.

MRS scans:

Sometimes people can feel claustrophobic, breathless or generally unwell in the scanner, but you will have a buzzer which you can press at any time to be let out for any reason. There is a small chance that having a scan could result in us finding an unexpected abnormality which was causing no major symptoms, for example, an aneurysm or small tumour. If this were to occur, deciding what to do about the abnormality could be difficult. In these circumstances, you would be informed of the abnormality and referred on to the relevant specialist for further assessment and discussion of treatment options. You should consider carefully this potential risk before you decide whether you wish to take part in this study.

Gait Analysis:
All Gait Analysis techniques are safe and non-invasive. We do not anticipate any risks. The gait analysis equipment is manufactured and CE marked to standards for a medical device.

Questionnaires:

The study team will be happy to discuss the results of the depression and memory questionnaires with you and provide you with further support, if required.

What are the possible benefits of taking part?
This study will not be of any direct benefit to the participants who take part. However this could help us in the future to identify mechanisms to slow down the progression of Parkinson's disease.

What will happen at the end of the research study?
Because it is not yet known if the treatment is effective, participants will not continue UDCA study treatment beyond the end of the study. At the end of the study the study doctor will write to your GP with your consent providing advice on further follow-up and treatment.

Is there anything else I need to know?
If you have private medical insurance you should contact the company before agreeing to take part in the study, to check whether participation would affect your insurance cover.

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you would like to consider participating in the study, please continue to read the additional information in Part 2 before making any decision.

PART 2: Additional Information

What if I wish to complain about the way in which this study has been conducted?
If you have any cause to complain about any aspect of the way in which you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you and are not compromised in any way because you have taken part in a research study. If you have any complaints or concerns please contact the local investigator (details to be inserted) Otherwise you can use the normal hospital complaints procedure and contact (PALS details to be inserted)

What if I am harmed?
If you are harmed by your participation in this study, there are no special compensation arrangements. Sheffield Teaching Hospitals NHS Foundation Trust and the University of Sheffield will provide indemnity for this study. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal

action for compensation against Sheffield Teaching Hospitals NHS Foundation Trust or the University of Sheffield, but you may have to pay your legal costs.

NHS bodies and Universities are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team, liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. Sheffield Teaching Hospitals NHS Foundation Trust therefore cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

Will the information obtained in the study be confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Sheffield Teaching Hospitals NHS FT (STH NHS FT) is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. STH NHS FT will keep identifiable information about you for 15 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you and any samples that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information at https://www.sheffieldclinicalresearch.org/ or by contacting the study team.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). Our Data Protection Officer is Peter Wilson and you can contact them by phone (0114 2265153) or email *(Peter.Wilson@sth.nhs.uk).*

[STH NHS FT] or [UCL] ***(delete one paragraph as appropriate)***

STH NHS FT will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from STH NHS FT and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people in STH NHS FT who will have access to information that identifies you will be people who need to contact you for reasons outlined above or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

OR

UCL will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from STH NHS FT and regulatory organisations may look at your medical and research

records to check the accuracy of the research study. UCL will pass these details to STH NHS FT along with the information collected from you and your medical records. The only people in STH NHS FT who will have access to information that identifies you will be people who need to contact you for reasons outlined above or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details. UCL will keep identifiable information about you from this study for the duration of the study (up to 2 years).

Will my General Practitioner/Family doctor (GP) be informed?
With your consent, your GP will be informed of your participation in this research study. If there are any clinically significant results found as a result of you taking part in the study, the study doctor will advise your GP about how these should be dealt with. We may also contact your GP if we need to clarify anything in relation to your medical information.

What will happen to the samples that I give?
The safety blood samples will be analysed at the local hospital laboratory. The blood sample for DNA analysis will initially be transported to SITraN (Sheffield Institute for Translational Neuroscience) at the University of Sheffield for storage and DNA extraction. We will then be sending the anonymised DNA samples to the Laboratory of Neurogenetics, National Institute of Ageing, Bethesda USA. We will also request your consent for additional anonymised samples (serum only) to be stored and used in future research. For example, we may want to use the stored serum samples to help us understand how UDCA affects your Parkinson's disease.

What will happen to the results of the research study?
The results of this research may be presented at scientific meetings in the UK and overseas. It will not be possible to identify you from any of the data that will be presented. The data from the study may also be published in a medical journal. You will not be identified in any report or publication.

Regular newsletters will be available at your clinic visits to keep you up to date with how the study is progressing.

Who is organising and funding the research?
The research project is being organised by Prof Oliver Bandmann. The project is being funded by J P Molten Foundation Charity and has been review by the East of England – Cambridgeshire and Hertfordshire Research Ethics Committee.

Will I be reimbursed?
Your travel expenses will be reimbursed, however you will not be paid for your time in participating in this study.

Whom should I contact if I have any further questions?
Please contact Professor Thomas Foltynie

Thank you for taking the time to read this patient information sheet and considering taking part in this study.

A copy of this information sheet is given to the patient together with a signed consent form for them to keep.