King's College Hospital NHS
NHS Foundation Trust

King's College Hospital NHS Foundation Trust
King's College Hospital
Denmark Hill
London SE5 9RS

Tel: 020 3299 9000
Fax: 020 3299 3445
www.kch.nhs.uk

Patient Information Sheet

Study title

Molecular Imaging of Neurodegenerative Disease – Mitochondria, Associated Proteins & Synapses – Parkinson's disease

Short Title: MIND-MAPS-PD

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 (PD) and parkinsonism are chronic and progressive neurological conditions that cause a variety of symptoms such as slowness of movement, stiffness and shaking. They involve the malfunction and death of vital nerve cells in the brain. Some of these dying nerve cells produce a chemical called dopamine, which sends messages to the part of the brain that controls movement. The exact causes behind the progressive loss of nerve cells are still unknown. We know, however, that a protein called a-synuclein is accumulated in the brains of people with PD and parkinsonim, and has toxic effect on the neurons. A-synuclein interacts with some small cell components called mitochondria. Mitochondria are located in large numbers in all brain cells, and their function is critical for their health. Mitochondria are often referred as the "powerhouses of cells". In animal models of PD and familial forms of PD, scientists have found that a-synuclein interferes with mitochondria and causes death of neurons. A step before the death of neurons in PD and parkinsonism is the loss of synapses in the brains of people with PD and parkinsonism. Synapses are structures that permit a neuron to pass an electrical or chemical signal to another neuron.

Mitochondrial complex 1 (MC1) is a crucial enzyme for mitochondrial function. Sigma receptors type-1 (S1R) are critical regulators of 'communications' between mitochondria and other neuronal cell structures. Scientists have shown that both MC1 and S1R are involved in animal models of PD. Synaptic vesicle glycoprotein 2A (SV2A) is a protein located in neuronal synapses that can be used as a marker of synaptic loss such as happens in PD and parkinsonism.

Positron emission tomography (PET) of the brain is a powerful and safe scanning technique that allows the direct evaluation of small chemical changes in the brain, and consequently study the functions of the brain in people with PD and parkinsonism. Recent advances in PET of the brain allow the direct evaluation of MC1, S1R and SV2A, and consequently of mitochondrial and synaptic function in people with PD and parkinsonism.

In this study, we aim to use MC1, S1R and SV2A specific PET scans and evaluate the function of mitochondria and synapses in people with PD and parkinsonism and compare the findings with a group of healthy volunteers. We will also investigate for associations between mitochondrial and synaptic dysfunction and severity of symptoms in people with PD and parkinsonism. Our findings will provide understanding related to the biological signatures of the disease that will help us track the progression of PD and parkinsonim, and most importantly help the discovery of new targets for the development of novel medications aiming to delay progression of symptoms.

Why have I been chosen?

You have been chosen because you have a diagnosis of PD or parkinsonism with or without dementia.

Do I have to take part?

No, 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 hospital care you receive.

What is involved in this study if I take part?

If you are suitable, and agree to undergo this study, we will ask you to attend King's College Hospital and Imanova Ltd for clinical and imaging assessments. Imanova Ltd is a Clinical Imaging Centre located at Hammersmith Hospital Campus (Du Cane Road, W12 0NN, London), with established expertise in state-of-the-art molecular imaging techniques. Imanova provides a pleasant environment for the patients and world-class capabilities by bringing

together state-of-art equipment and research methodology. In the present study, the role of Imanova Ltd is that of a research facility with no commercial interest. All appointments will be on a weekday.

Screening and clinical assessments will last up to 3 hours and will take place either at King's College Hospital. During this time, you will have the opportunity to discuss the study with the doctor, ask any question you may have and then, if you agree to take part into this study, you will asked to sign the consent form. A copy of which will be given you for your records. No research related activity can take place until you have given your informed consent. We will then assess your suitability to take part in the study and we will conduct a specific neurological examination and questionnaires in order to assess how severe your disease is. This data will help us to understand the relationship between system nervous damage and the wide range of symptoms of PD and parkinsonism. We will ensure all data collected will be anonymized i.e. no researchers will be able to identify you from the data. Stored data may be used in future research. We will also ask you to undertake a blood sample to assess any bleeding disorders. The amount of blood that will be taken will be about 1-2 teaspoons. Additionally, you will be asked to wear patients will wear the Parkinson's KinetiGraph™ (PKG™) watch for six days, this device records a broad range of symptoms including slowness of movements and tremor.

We will then ask you to undertake three PET scan at Imanova Ltd for direct evaluation of MC1, S1R and SV2A in the brain. A PET scan is special type of scan, which can be used to measure chemical changes within the brain. Each imaging visit may take around 4 hours or longer (though we will do our best to make it as short as possible). Before the scan we will need to place two needles: one into a vein and one into an artery in your arm. Arterial cannula is needed to collect a small amount of blood during the PET scan for aiding with the analysis of the data. Prior to inserting a needle into the artery, blood sampling and a medical test (Allen's test) for

evaluating the circulation in the arm will be performed. Women of child bearing potential will undergo a urine pregnancy test. Each PET scan will take about 1.5 hours. During this time you will be asked to lie on your back on a bed with your head resting in the scanner.

The tracer injection will not cause any discomfort; no side effects have been reported following in humans studies with the tracers used in the present study. During each PET scan you will also be asked to undertake up to two low dose brain CT scans, which are necessary to measure data from the PET scan. We will ask you to fast 3-4 hours prior to the PET scan. Refreshments will be offered after the PET scan. If you are taking Parkinson's medication, we will ask you to withdraw your medication from the night before the PET scan. We will ask you to bring with you your medications because, once completed the PET scan, you have to resume your medication regimen.

We will ask everyone to have a magnetic resonance scan (MRI). MRI is a special scan, which gives a detailed structural picture of the brain and does not involve any additional radiation. It is used to help with PET analysis. This scan usually lasts about 1.5 hours (but may take a little longer, if the you need time to settle in comfortably).

If you experience any distress during the study, we will endeavor to provide you support you may require.

Summary of visit

Visit 1	**Visit 2**	**Visit 3**
Screening and clinical assessment (about 3 hours) Blood sample (up to 15	Urine pregnancy test Allen's test Vital signs pre and post PET	Urine pregnancy test Allen's test Vital signs pre and post PET

minutes)	scan Intravenous and arterial cannulation [^{18}F]BCPP-EF PET scan (approximately 1.5 hours) MRI scan (approximately 1.5 hour)	scan Intravenous and arterial cannulation [^{11}C]SA4503 PET scan (approximately 1.5 hours) [^{11}C]UCB-J PET scan (approximately 1.5 hour)

The PET tracer will be produced at Imanova the day of the PET scan. If we have problem with the production of the PET tracer, or other circumstances, additional visits to Imanova Ltd may be arranged. MRI may be performed before the PET scan and the order of the PET scans may change, if needed.

We will reimburse transportation to and from home to the hospital and refreshments throughout your visit. Please keep any travel tickets or parking receipts. You will need to provide those to the research team in order to receive a refund. We will also offer as a small thank you £100.

Medication restrictions: There are some medications, which have the potential of introducing bias in PET ligand quantification. Medications or supplements with known action on MC1, S1R and SV2A must be discontinued prior to PET measurements as follows: (a) For [^{18}F]BCPP-EF PET (MC1): metformin and non-steroidal anti-inflammatory drugs such as aspirin, indomethacin, diclofenac, piroxicam and ibuprofen must be discontinued at least 4 days prior to PET measurement; (b) For [^{11}C]SA4503 PET (S1R): neuroactive steroids such as dehydroepiandrosterone, progesterone, pregnenolone, testosterone and deoxycorticosterone must be discontinued at least 4 days prior to PET measurement, and haloperidol, fluvoxamine and donepezil must be discontinued at least 7 days prior to PET measurement; (c) [^{11}C]UCB-J

PET (SV2A): levetiracetam and bevetiracetam must be discontinued at least 7 days prior to PET measurement. If any of these treatments are essential for your clinical management, you will be excluded from the study.

What are the possible risks of taking part?

Cannulation

Insertion of a cannula into a vein or artery may cause brief discomfort as the cannula penetrates the skin, similar to the discomfort you have when having an injection. To insert the canula into your artery we will use a local anaesthetic to numb the area so you do not feel pain. Detailed instructions on insertion of the arterial line and the care of the site after removal of the arterial line are provided with the leaflet (Arterial Line insertion and care information sheet version 1 dated 10 October 2016) provided to you with this information sheet. Risks of any cannulation include minor local bleeding and bruising. Very rarely, a blood clot could form around the cannula. Most people have no after-effects of cannulation. However, occasionally, a scar may occur. Even when this happens, the scar left over the long term usually is small.

More rarely, there can be some discomfort lingering after the cannula insertion. The full list of potential complications is as follows:

Common complications:

- Temporary artery spasm (20%)
- Bruising (14%)

Less common complications:

- Localised site infection (0.72%)
- Bleeding (0.53%)
- Generalised infection (0.13%)
- Damage to the fingers due to inadequate blood supply (0.09%)

Rare complications:

· Paralysis of median nerve (runs from the forearm into the palm of the hand) (<0.1%)

· Air embolism (air bubble trapped in a blood vessel. When an air bubble travels along an artery, it moves through a system of blood vessels that gradually become narrower. At some point, the embolus will block a small artery and cut off the blood supply to a particular area of the body.) (<0.1%)

· Carpal tunnel syndrome (median nerve becomes pressed or squeezed at the wrist causing pain, weakness, or numbness in the hand and wrist) (<0.1%)

Most arterial cannula insertions are done without any problem. You may notice bruising around the area where the cannula was inserted, which should disappear after a week or two. The place where the cannula was inserted will heal quickly within a few weeks, with any marks fading with time.

If any of the following occur within 72 hours after the cannula was removed, you MUST consult the Study Doctor immediately.

· Intense or sharp thumb or palm pain

· If anywhere on your hand, fingers or thumb appears pale and cold or

· If anywhere on skin to the hand, fingers or thumb appears dark or blackened and cold

· If you notice an unusual ‘lump or bump’ over where the cannula was inserted

· If you develop a fever (raised temperature) and feel unwell

· If you feel a sudden shortness of breath

· The dressing becomes soaked with blood (If you experience heavy bleeding), apply firm pressure to the area with the dressing supplied for 5 minutes and attend Accident & Emergency for advice/ treatment. Please also notify the Study Doctor.

Imaging procedures

The administration of [^{18}F]BCPP-EF, [^{11}C]SA4503 and [^{11}C]UCB-J will entail a maximum

exposure of approximately 7.4 mSv. Exposure to 7.4 mSv of additional annual ionising radiation is equivalent to about 3 years of annual background ionizing radiation exposure (2.3 mSv per year) for an average UK resident. The additional risk of developing a fatal cancer associated with this exposure has been estimated to be about 1 in 3000. The overall UK cancer mortality rate of about 1 in 3.5, and therefore the additional risk due to participation in this study is very low. Along with other procedures involving radiation (including X-rays), PET scans can be hazardous to an unborn child. If you are a woman of childbearing age you should not take part in the study unless you are on a reliable form of contraception, and even if this is the case a urine pregnancy test prior to the PET scan will be performed.

The MRI scan does not expose you to ionizing radiation, but it can be noisy (we can provide you with earplugs to counter this). An MRI is a very strong magnet, so if you think you may have any metal in your body (e.g. as a result of surgery, or an accident, such as metal filings in your eye due to welding accidents) you must let us know, so we can assess if the procedure will pose any risk to you. There is otherwise no discomfort associated with MRI scanning, other than having to lie on your back and try to remain as motionless as you can for about 90 minutes. However, if you are claustrophobic you may find MRI difficult to tolerate, if so please let us know in advance.

You should be aware that the scans used in this study might reveal an unexpected fact about you 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 and informing your GP.

What are the possible benefits of taking part?

PET scans are not a form of treatment and do not provide any direct benefits to you. However, the knowledge acquired from this study will improve our understanding of Parkinson's disease and parkinsonism and may help us to provide the means for the development of better drugs for this disease.

What if something goes wrong?

King's 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 King's College London is at fault. This does not affect your legal rights to seek compensation. Moreover, if you are following a private insurance scheme, you should notify your insurer that you are taking part in this study.

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 investigators (Dr Flavia Niccolini, flavia.niccolini@kcl.ac.uk, 07552079134, 0207 848 5755; Dr George Dervenoulas, georgiosdervenoulas@gmail.com, 0207 848 5682 5755; Dr Gennaro Pagano, gennaro.pagano@kcl.ac.uk, 07949805013 or Dr Marios Politis, marios.politis@kcl.ac.uk, 0207 848 5682). The normal National Health Service complaint mechanisms are also available to you. Our Patient Advice & Liaison Service is located at King's College Hospital, ground floor Hambleden Wing, near the main entrance on Bessemer Road. Opening hours: Mon-Fri 9 am to 5 pm. Tel: 020 3299 3601. If you are still not satisfied with the response, you may contact the King's College Hospital Research and Development office, Telephone 020 3299 3841 Fax 02032995155.

Will my taking part in this study be kept confidential?

All information collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognized from it.

If you consent to take part in the research, with your permission we can write to your GP to inform him/her that you are participating in this study.

All employees working in the NHS are bound by a legal duty of confidence to protect personal information and therefore any information you give during this study will be kept confidential. Should we be concerned about your health or wellbeing we may discuss this with your clinical care team/GP.

Data collected during your participation in this research project may also be stored electronically on a research PET database at King's College London and Imanova Ltd, and may be used in future by both Imanova Ltd and King's College London to compare with results from other studies. However, such data will be anonymised so that you cannot be identified on the database. All data so stored will comply with the provisions of the Data Protection Act and will only be accessible via written permission of the principal investigator of this study. Your anonymised data may be used in future ethically approved research studies.

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.

If you wish, feedback will be sent to you from the research doctor with the results, which will be in a manner understandable to a non-medical person.

Who is organising and funding the research?

The study is funded by Imanova Ltd and King's College London is the sponsor of the study.

This study is part of a collaboration called MIND MAPS between Imanova, King's College, London, Imperial College, London and AbbVie, to develop better ways of imaging neurodegenerative disease. The results of all studies in the MIND MAPS collaboration are going to be shared between all the participants and published in scientific journals.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by the London - South East Research Ethics Committee.

Contact for Further Information

If you have any questions or there is anything you wish to discuss please phone or Dr Flavia Niccolini on 07552079134, or George Dervenoulas on 0207 848 5682 5755, or Dr Gennaro Pagano on 07949805013, or Dr Marios Politis on 0207 848 5682.

If you agree to participate in this study 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.