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Research into Osteoarthritis in Manchester (ROAM)
Principle Investigator: Professor Terence O'Neill

PARTICIPANT INFORMATION SHEET.

Study title: *The Effect of Denosumab on Pain and Bone Marrow Lesions in Knee Osteoarthritis*

The DISKO study.

You are being invited to take part in a research study. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please ask the research team if there is anything that is not clear, or if you would like more information.

Please take as much time as you need to read the following information carefully and discuss it with friends, relatives or your GP if you wish.

What is the purpose of the study?

Osteoarthritis (OA) is the most common type of arthritis and causes joint pain, swelling and difficulties with day to day activities. DISKO is a study looking at OA affecting the knee. Current treatments for knee OA are limited as they have been shown to only work for short periods and are not effective for all patients. In addition, some people find that many of these treatments have side-effects and so they have to stop taking the medication.

Denosumab is a treatment which is now used to treat people with fragile bones (Osteoporosis). It is given as an injection under the skin and has relatively few side-effects. There is some evidence that certain drugs which have been used to treat osteoporosis may also help reduce knee pain in people with knee osteoarthritis.

The purpose of this study is to find out whether denosumab is effective at reducing pain and structural damage in knee OA.

Why have I been invited to take part?

You have been chosen because your doctor or a health care professional who has been involved in your care, feels that you may be eligible for the study, or you may have responded to an advertisement or

mailing about the research.

You will **not** be able to take part in this study if:

- You are pregnant, breastfeeding, or are considering pregnancy
- Have a history of inflammatory arthritis (e.g. rheumatoid arthritis) or any other form of arthritis other than osteoarthritis affecting the knee
- Have been on treatments recently, either by injection or tablet, for other bone conditions
- Have planned or recent invasive dental surgery or hip / knee surgery
- Have pre-existing cellulitis
- Certain pre-existing medical conditions
- You are not able to have a magnetic resonance imaging scan

Do I have to take part?

It is up to you to decide whether or not to take part. You can also withdraw from the study at any point without giving any reason. A decision not to take part, or to withdraw at any time, will not affect the standard of care you receive, or count against you in any way.

What are the alternatives to taking part in the trial?

If you choose not to take part in this study, then you would receive usual treatments for osteoarthritis. Your doctor will be able to advise on the best treatment for you. Treatments may include painkillers (e.g. paracetamol) or anti-inflammatory medications (e.g. ibuprofen).

What is the drug being tested in this study?

There are no experimental drugs involved in this study. The drug being tested is called 'Denosumab' and it is routinely used in the treatment of another bone disease called 'Osteoporosis'.

What will happen if I take part?

If you are interested in taking part in the study we will arrange a time for telephone screening with you. This will be carried out by the team at the University of Manchester and will take approximately 10 to 15 minutes. The purpose of the telephone screening is mainly to check that there are no medical reasons why you might not be able to take part. We will let you know if this is the case. Once you have completed the telephone screening, and if you are happy to proceed, we will arrange for you to attend a clinical screening visit, this will take place at Salford Royal Hospital. During the clinical screening visit your eligibility for the study would be assessed in more detail. You will begin by signing a consent form and will be given a copy to keep. You will be asked some questions about your past medical history and knee symptoms, and undergo a clinical assessment which includes a physical examination of your knee joint. You would also have a blood test to check your eligibility to take part. This appointment will take up to 1 hour. If you have not had an x-ray of your knees within the previous 2 years we will arrange for you to have an x-ray at the hospital.

If the blood tests show a mild reduction in your level of vitamin D we will arrange for you to have treatment for this in the form of capsules. If your vitamin D level is very low you will not be able to continue in the study. In this case we will write and inform your GP about your low vitamin D level and recommend appropriate treatment.

If your levels of vitamin D are normal we will arrange for you to have a magnetic resonance image (MRI) of your affected knee where we will look for bone bruising (called 'bone marrow lesions'). If you do not have a bone marrow lesion in your knee then you will not be able to continue in the study. This is because one of the ways treatment with denosumab may work is by reducing bone bruises. If the scan shows that you have one or more bone bruises then you would be eligible to take part in the study and your participation will mean coming to the hospital for a further 3 visits over the next 6 months – one at the start of the study (baseline), the second after 3 months and the third after 6 months.

In the trial we would like to find out if a one off injection of denosumab is effective at reducing pain and structural damage in people with knee OA. In order to find this out, we will assign people into one of two groups, one of whom will receive the denosumab (give as an injection under the skin) and the other an inactive intervention (placebo), given also as an injection under the skin. Which group you are put in depends on chance. You will have an equal chance of getting either the denosumab or placebo. When the study is completed, the results are compared to see if denosumab is better at reducing pain and preventing further structural progression of knee Osteoarthritis than the placebo.

You will receive your randomised injection at the baseline visit. You will also be given a daily calcium and vitamin D supplement which you should take throughout the trial period. Whichever group you are in you can keep taking your normal treatment for your knee OA, for example any painkillers or anti-inflammatory tablets, that you were already taking when the study began. We will ask you to try and stay on the same dose of these tablets during the study. However, if you felt you needed more painkillers (e.g. a higher dose), this is allowed and we would make a note of the changes of medicine in your study record when you attend for your next follow up appointment. Throughout the trial you should always discuss any new medications with your doctor before starting them. We would ask you also to avoid having a steroid knee injection or beginning treatment with glucosamine or chondroitin and not to start other non-drug treatments such as physiotherapy and splinting unless your doctor considers it to be necessary.

Within the first couple of weeks after your injection we will contact you by telephone to ask about any side effects you may have experienced.

At the 3 month visit we will check the level of calcium in your blood and at the 6 month visit we will ask you to have a repeat MRI of your knee. This is to find out whether bone marrow lesions, identified on the baseline MRI, have changed in response to the treatment you have received.

At each of the 3 study visits we will also ask you to:

- fill out some questionnaires including about your knee pain, and how your knee symptoms affect your life.
- wear an activity monitor for approximately 7 days before each study visit. The monitor is a small device which is secured to your upper leg with adhesive pads (hypo-allergenic).

No matter which group you are assigned to (denosumab or placebo), you will undergo the same tests and questionnaires. These will be with a researcher who does not know which treatment group were in.

We will also ask your permission to collect some additional blood samples and urine at the first and third examination to analyse in the future (subject to separate ethical approval).

Expenses and payment.

We will pay up to £25 for travelling expenses for coming to each visit.

What do I have to do?

The study will be discussed with you and you will be given a copy of this information and a consent form to read. You should read this information carefully and think about whether you wish to participate in this study. Feel free to discuss taking part with family, your GP and the study team if you have any questions. If you decide that you would like to take part in the study or have any questions, please contact a member of the research team using the contact information at the end of this information leaflet.

What are the possible benefits of taking part?

You may not benefit directly from this study. However, the trial will give us useful information which may be of benefit to others in the future and aid the development of new treatments for osteoarthritis.

What are the possible disadvantages and risks of taking part?

Denosumab has been widely used by physicians for over 5 years, however, as with any medication there are always potential risks which are detailed below. You should discuss these risks with your study doctor or GP. Taking part in this study will involve some of your time to complete questionnaires, have blood and urine tests, an X-ray of your knee if required, and having MRI scans of your knee.

Medications

Denosumab has been used for many years and is relatively safe, with side effects being unlikely. In a small minority of people it can be associated with cellulitis (red, hot, swollen, tender/painful skin) in the leg, though this is very uncommon. Very rarely (< 1 in 1000), denosumab has been associated with a condition affecting the jaw bone, known as osteonecrosis of the jaw (ONJ). Invasive dental surgery is a risk for development and we would ask that if you have planned invasive surgery (such as removal of a tooth) that you should not take part in the study. It would be important for you to maintain optimal oral hygiene during the time that you are taking part in the trial and report any pain in the jaw or any open soft tissue lesions in your mouth to your doctor or dentist. There are a small number of reports of a condition affecting the ear, known as osteonecrosis of the ear, however, this is extremely rare and it is not yet established whether it is definitely related to treatment with denosumab. Very rarely (< 1 in 1000) unusual thigh bone fractures may occur though this is usually among people who have taken treatment for at least several years.

In a small proportion of patients the level of calcium in the blood may fall following denosumab injection. In an attempt to reduce this we will arrange to check the level of calcium and vitamin D in your blood and correct any deficiency before you receive the study treatment. We will prescribe calcium and vitamin D supplements throughout the course of the trial and will arrange to check your calcium level at the first follow up visit. We will also contact you directly by telephone, usually within 2 weeks of your receiving the injection, to check for any symptoms or side effects that may suggest low calcium levels. These include tingling around the mouth and fingers and also cramps. Other side effects which may occur include muscle and bone pain and very rarely (< 1 in 1,000) an allergic reaction.

X-rays

Having an X-ray of the knee will expose you to a small amount of radiation. You will have an X-ray of the knee at the start of the study, if you have not had one in the past 2 years. X-ray views of the knee will be performed, one looking from the side of the knee (called a 'lateral'), one from the back (called a 'PA') and one from the front (called a 'skyline'). The PA X-ray will include both your knees.

MRIs

MRI scans are safe and painless procedures used to produce a detailed image of the anatomy and physiology of your knee. An MRI scan will involve lying flat in the scanner for up 90 minutes. Having an MRI scan may be claustrophobic for some patients, but for the purpose of this study only the bottom half of your body will be in the scanner. If you do suffer from claustrophobia you should discuss this with the research team.

Before you go into the scanner, you will need to fill in a patient declaration form in the presence of a radiographer. Please inform us prior to the scan if you have any of the following; heart or nerve pacemaker; previous brain or heart surgery; previous injury to the eye involving metal; cochlear implants; hydrocephalus shunts; artificial joint replacements or any metal objects in the body so we can check that MRI is a safe procedure for you.

The MRI scan and analysis in the study is only designed to look at bone changes in osteoarthritis. It is not like a standard clinical MRI scan which looks for other abnormalities as well. However, if anything potentially serious and unexpected was found on your scan we would need to discuss the results with your GP and/or other doctors and further investigation might be required to know if it was important or not.

Pregnancy and Risk to Foetus?

If you are pregnant, planning on getting pregnant during the course of the study or are breastfeeding then you should not take part in the study.

If you become pregnant, think you are pregnant, or breastfeed while you are taking denosumab and for an additional 5 months after stopping denosumab, you must tell the study doctor or the study staff right away. The study doctor will then notify Amgen (the company that manufacture Denosumab). If you give permission we will ask you for further information on the pregnancy or breastfeeding outcome for you and the baby.

If your partner is pregnant when you enrol in the study or becomes pregnant while you are taking denosumab, or within 5 months after stopping denosumab, you must tell the study doctor or the study staff right away. The study doctor will ask if you and/or your pregnant partner wish to provide contact details and permission for further information to be collected about the pregnancy outcome for both the mother and baby.

Women of childbearing potential must agree to use at least one highly effective form of contraception and to continue until 5 months after treatment. Acceptable methods of contraception include surgical sterilisation, oral, implantable or injectable hormonal methods, intra-uterine devices. or sexual abstinence.

What if new information becomes available?

Sometimes during the course of a trial, new information becomes available on the drug that is being studied. If this happens, we will tell you about it and discuss with you whether you want to, or should continue in the study. If you decide to withdraw, we will let your general practitioner know. If you decide to continue in the study you may be asked to sign an updated consent form.

On receiving new information, we might consider it to be in your best interests to withdraw you from the study. If so, we will explain the reasons for this and also inform your general practitioner.

If the study is stopped for any other reason, you will be told why and we will also inform your general practitioner.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time. We may ask you, if you wish to withdraw, to consider attending for a final assessment (to complete a questionnaire and have a final scan of your knee), but this is entirely optional. You can choose to leave the study at any time without having any further assessments. We would like to use all of your data up to the point of withdrawal as this will help with our analysis. However, if you would prefer us not to use any of your data you may request for all of your data to be removed from the study. A decision not to carry on with the study will not affect the quality of care you receive in any way.

Will my part in this study be kept confidential?

If you consent to take part in this study, the records obtained while you are in this study, as well as related health records will remain strictly confidential at all times.

The University of Manchester 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. The collected personal data will be processed by the Manchester Clinical Trial Unit (MCTU) and the unit will act as the data processor for this study. The legal basis or reason in data protection law

which allows us to use your personal data is “public interest task” and “for research purposes” for the sensitive information collected. For more information about the way we process your personal information and comply with data protection law please see our Privacy Notice for Research Participants. (<http://documents.manchester.ac.uk/display.aspx?DocID=37095>).

The University of Manchester will have access to identifiable information about you for 25 years after the study has finished.

Your rights to access change or move your information may be 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 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 this link:

<http://documents.manchester.ac.uk/display.aspx?DocID=37095> and by contacting the trial team on 0161 306 0545. To find out more about how we use your information please request a copy of our privacy statement from the Research Nurse.

You will be allocated a trial number, which will be used as a code to identify you on all trial forms. The information will be held securely on paper and electronically at Salford Royal NHS Foundation Trust, The University of Manchester (study sponsor) and at The Manchester Clinical Trials Unit under the provisions of the 2018 Data Protection Act.

Your records will be available to people authorised to work on the trial but may also need to be made available to people authorised by the Research Sponsor (the University of Manchester), which is the organisation responsible for ensuring that the study is carried out correctly. A copy of your consent form may be sent to the Research Sponsor during the course of the study. By signing the consent form you agree to this access.

The information collected about you may also be shown to authorised people from the UK Regulatory Authority, the local NHS Trust and Independent Ethics Committee; this is to ensure that the study is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you as a research participant and any identifying information will be kept strictly confidential with access limited to the study research staff and study monitors.

In line with The Medicines for Human Use (Clinical Trials) amendment Regulations 2006 and in accordance with any future updates at the end of the study, your data will be securely archived for 25 years from the completion or discontinuation of the study (the end of the study is defined as the last visit of the last patient in the study). Arrangements for confidential destruction will then be made.

Data collected during the study will be analysed in an anonymous format so that the Researchers will be unable to identify you and, will be stored for analyses in the future. The research team may wish to share your anonymised data (all identifiable data will be removed) with other research groups. Data sharing is an important way of advancing our knowledge about musculoskeletal conditions by optimising the use of good quality research data and by supporting policy and other decision-making in this research field.

Informing your General Practitioner (GP)?

If you agree to take part in this study, with your permission, we will write to your GP to inform them.

What will happen to any samples I give?

During this study we will be collecting blood tests at the screening visit and again at 3 months – this is for the purpose of assessment of eligibility for participation in the study and also safety. Provided you give consent we would collect and store some additional blood and urine samples at the baseline visit and also at the 6 month visit for use in future research. The samples will be coded so they cannot be directly

tracked back to you. There are no immediate plans to analyse the data and it will be used in the future to look at biochemical and other markers, including DNA, in the blood and urine which may help shed light on how the treatment may affect the knee and to help better understand what factors, if any, are linked with response.

What happens when the research study stops?

After the research study you will return to the standard NHS care which you received prior to the study, either with your GP or in a secondary care clinic.

What will happen to the results of this clinical trial?

The results of the study will be available after it finishes and will usually be published in a medical journal or be presented at a scientific conference. The data will be anonymous and none of the patients involved in the trial will be identified in any report or publication. Should you wish to see the results or the publication, please ask your study doctor or research nurse.

Who is organising and funding this clinical trial?

This study is being funded by Versus Arthritis. The treatment being tested 'Denosumab' is being supplied by the manufacturer (AMGEN). The University of Manchester are organising and responsible for the conduct of the study. The study doctor and nurse will not receive any payment for conducting this research study.

Who has reviewed the study?

This study was given a favourable ethical opinion for conduct in the NHS by a Research Ethics Committee.

Further information and contact details.

You are encouraged to ask any questions you wish, before, during or after your treatment. If you have any questions about the study, please contact the study nurse or doctor or any other member of the research team, who will be able to provide you with up to date information about the drug(s)/procedure(s) involved. If you wish to read the research on which this study is based, please ask a member of the study team.

If you would like to take part in the study, require any further information, or have any concerns now or whilst taking part in the study please contact:

Principal Investigator:

Professor Terence O'Neill

Email: Terence.O'Neill@manchester.ac.uk

Research Nurse:

Salford Royal NHS Foundation Trust

Tel: 0161 206 2615

ROAM Research Administrator:

Tel: 0161 306 0545 / 0547

Email: ROAM@manchester.ac.uk

For further information about types of arthritis and its treatment you could also contact the medical research charity Versus Arthritis : Website: www.VersusArthritis.org
Telephone number: 0300 790 0400 e-mail: enquiries@VersusArthritis.org

Complaints

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 275 7583 or 0161 275 8093 or by email to research.complaints@manchester.ac.uk.

Harm

In the event that something does go wrong and you are harmed or suffer loss as a result of taking part in the research you may have grounds for claiming compensation from The University of Manchester or Salford Royal NHS Foundation Trust.

In order to protect you, the University of Manchester has insurance in place that provides:

- compensation for non-negligent harm to research subjects occasioned in circumstances that are under the control of the University,
- cover for legal liabilities for injury, loss of or damage to property, or financial loss arising from the University's actions or those of its staff or supervised students.

If you make a claim in respect of legal liability you may have to pay your legal costs."

If you decide you would like to take part you will be asked to read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the consent form will be filed in your patient notes (if applicable), one will be filed with the study records and one will be faxed to the Clinical Trials Unit who are responsible for managing the study.

You can have more time to think this over if you are at all unsure.

Thank you for taking the time to read this information sheet and to consider this study.