Participant Information Sheet

DICKENS - A randomised controlled trial of diacerein to treat knee osteoarthritis with effusion-synovitis

Invitation

You are invited to participate in a research study investigating the effect of a drug called diacerein for the treatment of knee osteoarthritis. The study is being conducted by:

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Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss your intention to participate with someone who is able to support you in making your decision, if you wish.

What is the purpose of this study?

This study is examining whether a drug called diacerein can improve knee pain and decrease knee swelling in patients with knee osteoarthritis. Diacerein is an anti-inflammatory medication which is currently used to treat osteoarthritis. Almost 60% of people with knee osteoarthritis have local joint swelling. In this research study we will test whether diacerein is more effective in knee osteoarthritis patients with local knee joint inflammation.

Who is being asked to participate in this study?

We will be studying up to 260 knee osteoarthritis patients. Patients can be included in the study if they:

- ✓ Are male or female aged 40 to 64 years old;
- ✓ Have significant knee pain on most days;
- ✓ Have knee osteoarthritis (confirmed by a study rheumatologist);
- ✓ Have local swelling in their knee joint (termed effusion-synovitis) present on an MRI scan;
- ✓ Are willing to participate in the study for 24 weeks.

What type of drug is diacerein and how is it taken?

Diacerein is a slow-acting medicine of the class ‘anthraquinones’. It is an anti-inflammatory

medication and works by blocking the actions of a protein (interleukin-1 beta) involved in inflammation. Diacerein is taken orally in the form of a capsule. The recommended starting dosage is 50 mg once daily for the first 2 to 4 weeks of treatment, after which the recommended daily dose is 50mg twice daily. Diacerein should be taken with food, preferably a meal.

Is diacerein approved in Australia?

Diacerein is not currently approved in Australia. It is a prescription medication approved in a number of countries in Europe and Asia for the treatment of joint diseases such as osteoarthritis (swelling and pain in the joints). Our research study could be used to have diacerein approved for therapeutic use in Australia.

Who will receive diacerein in this trial?

In this study one half of participants will be receive diacerein and the other half will receive an identical placebo (that is, a capsule that looks like diacerein but does not contain the active drug being tested). This is a '*randomised trial*' which means you will be allocated to one of the two groups randomly, like the flip of a coin. You will have equal chance of ending up in either group and neither the researcher nor yourself can decide which treatment you will receive. As this is a '*double blind trial*' the researchers, study nurses and study participants will not be aware of which groups participants are randomised to until the study is completed.

What are the adverse or 'side' effects of diacerein?

The use of diacerein has been linked to some side effects which include:

Gastrointestinal symptoms: Common gastrointestinal symptoms include soft stools and diarrhoea. The majority of these are mild to moderate and occur more frequently in the first 2 weeks, and decrease with continuous use, but they may also be severe. To reduce the risk of developing diarrhoea, the treatment will be starting at half the recommended daily dose. It is also strongly advised that you take this study medication with food (preferably a meal), as this will reduce your chances of developing diarrhoea. Intake of diacerein in a fasting state or after very small amounts of food may increase the chances of loose stool and diarrhoea.

Liver function abnormalities: A rare side effect is liver test abnormalities. Around 0.5% of patients on diacerein present with some kind of liver reaction. These are mostly characterised by mild/moderate liver enzyme increases that are reversible. The proportion of patients who develop liver injury following treatment with diacerein is estimated to be 0.03%. We will perform blood tests throughout the trial to monitor your liver function.

Mild skin reactions: While mild skin reactions (rash, pruritus and eczema) have been reported by some patients taking diacerein, the risk is no greater compared to taking a placebo.

The side effects resulting from diacerein treatment have been closely monitored by regulatory agencies such as the European Medicines Agency (EMA's) Pharmacovigilance and Risk Assessment Committee (PRAC). They have concluded that diacerein's benefit on improving pain outweighs its known risks for osteoarthritis treatment.

During the trial, if you experience any other side effects, we ask that you report these to our study staff.

What does this study involve?

If you are interested in taking part in this study, one of our research nurses will contact you over the phone to give you information about the study and assess your eligibility to take participate. This will involve asking you questions about your medical history and knee osteoarthritis symptoms. If you pass the telephone screening questions, you will be asked to make an appointment to attend a face-to-face screening visit or a Telehealth appointment to further determine your eligibility to participate. Face-to-face visits in this study are encouraged but if this is not possible there is the option for you to participate fully via Telehealth.

Screening visit/Telehealth Appointment

During screening you will be asked questions about your medical history, asked to fill out questionnaires relating to your knee pain and you will have an assessment by a study doctor to confirm you have knee osteoarthritis. You will also be asked which prescription and over-the-counter medications you are currently taking so they can be documented. If you are a woman of childbearing age and there is any possibility that you are pregnant, you will need to perform a urine pregnancy test before you start in the study. Our research nurse will provide you with more information about the study, answer any questions you may have and ask you to sign your consent if you agree to participate. If you require further time to consider participating in the study, you will be followed-up by a research nurse over the telephone and written informed consent will occur before any other assessments are taken.

Post-screening tests

Following the screening appointment, you will be booked in for a blood test, a knee x-ray and a knee MRI scan. The blood test will be performed to ensure it is safe for you to take the study medication (diacerein). The x-ray will be performed to confirm you have osteoarthritis. If you have end-stage osteoarthritis (i.e. bone on bone x-ray) then the study medication being tested will likely not work for you and you will not be able to take part in this study. The MRI scan will be performed to check that you have local swelling in your knee joint (termed effusion-synovitis). If you pass all the screening tests, you will be eligible to be enrolled in the study.

Continuing in the study

After you have been screened and enrolled in the study, it will go for 24 weeks and you will have to attend three study visits or Telehealth appointments (baseline visit, week 12 visit and week 24 visit). At 2 weeks you will be contacted by telephone and emailed study questionnaires to fill out at weeks 4, 8, 16 and 20.

Baseline visit or Telehealth appointment and requirements as part of being a participant in this study

At this appointment you will be randomised into one of two groups (diacerein or identical placebo). Only one member of the research team will know what group you are in, to ensure you receive the correct capsules. You will be required to take one capsule daily with food, containing 50 mg of diacerein or identical placebo, for the first 2 weeks. This will then be increased to two capsules daily with food, equating to 100 mg of diacerein or identical placebo, to be taken for the remainder of the 24 week trial (provided you have not experienced side-effects and it is appropriate for your dosage to increase).

Below is a summary of the procedures/measures that will also be performed as part of this study:

- At the face-to-face clinic visits we will measure your height, weight, leg strength and perform a count of your study medication at baseline, weeks 12 and 24. If you have a

Telehealth appointment at these timepoints we will ask you self-report your height and weight.

- You will be asked to fill out questionnaires about your knee symptoms at baseline, weeks 4, 8, 12, 16, 20 and 24 weeks. You will also be asked to fill out additional health questionnaires including questions about your medication usage, general well-being, quality of life, occupation and employment, use of health services and the costs you have incurred due to medications, medical appointments, scans, transport, and specialised equipment purchased for your knee pain, your concession/health care card and private health insurance status, osteoarthritis treatments you are using, depressive and anxiety symptoms, treatment side effects and overall satisfaction with the study treatment.
- You will have a repeat MRI scan at 24 weeks.
- You will have a repeat blood test at 12 and 24 weeks to monitor your liver and kidney function.
- Samples of any blood tests you have as part of this study will also be stored for future testing which will help to determine if the study treatment is working. Your blood samples and associated data may be distributed to other researchers, including researchers outside Australia, for this testing.
- You will be asked to give consent to have your medical records made available to us from the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) for the purpose of checking on any knee joint replacement surgery following study completion. We ask that you provide us with your Medicare number for this purpose. Any data linkage that occurs as part of this study is subject to conditions around data security and privacy.
- We advise you to inform your health care professional if you are participating in this study.

Are there any other risks in this study?

A small amount of radiation exposure is associated with a knee x-ray. This amount of radiation is unlikely to be associated with increased risk of disease and is less than the current National Health and Medical Research Council guidelines.

Having blood taken causes minimal risk, but there may be a chance of discomfort, feeling faint and bruising.

MRI scans may be claustrophobic, but are otherwise considered safe.

The effect of the study medication on an unborn or breast fed baby is unknown and women who are pregnant or breastfeeding will not be able to take part in this study. If you are a woman of childbearing age and there is any possibility that you are pregnant, the research nurse will need to perform a urine pregnancy test before you start in the study.

Additional things to note while taking the study medication

Thus far, there is no evidence to indicate that taking diacerein affects the susceptibility or severity to COVID-19. If you are diagnosed with COVID-19, we ask that you stop taking the study medication until your symptoms resolve as a precaution.

Taking the study medication with drugs that modify intestinal transit (e.g. laxatives, excess fibres) may increase the risk of developing diarrhoea. You should exercise caution when combining the study medication with laxatives or excess fibres and not take them at the same time.

Certain antacids containing aluminium hydroxide and/or magnesium hydroxide (e.g. Mylanta) should not be taken with the study medication. A distance of 1-2 hours is recommended.

Temporary treatment modification/suspension should be considered if you are having antibiotic and/or chemotherapy treatment to prevent stomach problems. Please let the study staff know as soon as possible if you plan to start a course of antibiotics or chemotherapy while in the study so that you and the Principle Investigator can make a decision about changing your study medication.

The study medication (both diacerein and placebo) *may* cause a harmless change in your urine colour (yellow or pink). This will not affect your health at all.

The study medication contains lactose (milk sugar). If you are sensitive to lactose you should not take the study medication.

While you are participating in this trial, we ask that you do not donate blood.

What happens if I suffer injury or complications as a result of the study?

If you suffer any injuries or complications as a result of this study, you should contact the investigators as soon as possible, and they will assist you in arranging appropriate medical treatment.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies. You do not give up any legal rights to compensation by participating in this study.

If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

Will participants receive any reward for participating in this study?

No, participation in this clinical trial is entirely voluntary. However, the tests and the treatment with diacerein in this clinical trial will be provided at no cost and reasonable travel expenses may be reimbursed.

What if I don't want to take part in this study, or if I want to withdraw later?

Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

If you stop taking the study treatment or need to withdraw from the study for any reason, we will ask if you are willing to have a continued involvement with the study, such as completing your second MRI, study surveys or study visits. However, you can decline to do this and can fully withdraw (including your data, blood samples and x-ray and MRI scans) at any time without effect. New information about the treatment being studied may become available during the course of the study. You will be kept informed of any significant new findings that may affect your willingness to continue in the study.

Likewise, if your doctor feels that it is in your best interest to withdraw study therapy, he/she will do so immediately without your consent.

How is this study being paid for?

The study is being funded by the National Health and Medical Research Council of Australia (NHMRC, APP1147370). All of the money being paid by NHMRC to run the trial will be deposited into an account managed by the Menzies Institute for Medical Research, University of Tasmania. No money is paid directly to individual researchers.

Will I benefit from the study?

This study aims to further medical knowledge about treating knee osteoarthritis. If the treatment is effective, then the participants in the treatment groups may experience reduced knee pain and a reduction in joint inflammation. However, it is possible that you may not directly benefit.

How will my confidentiality be protected?

Your identity as a participant in this study is confidential. Paper copies of your data will be stored in locked filing cabinets, with restricted access. Electronic data will be kept on password-protected servers, separating your identifying and non-identifying information. These servers are housed at the University of Tasmania. The codes linking data to identifying participant information will be kept separately from the study data, under password protection and with restricted access. Only members of the research team who need to contact study participants, enter data or perform data quality control will have access to identifiable information. The providers used in this study (e.g. pathology services and radiology departments) are accredited and exercise best practices with regard to data security and confidentiality.

Unless required by law, only your doctor, the study team, and its authorized agents, the Therapeutic Goods Administration (TGA), other genuine researchers who agree to preserve the confidentiality of your information and the responsible Human Research Ethics Committee will have access to data which identifies you by name or from which your identity is otherwise apparent or can be reasonably ascertained. All such personal information will be used only for the purpose of administering your participation in this Study, and in accordance with the laws governing protection and privacy of personal information under the Privacy Act 1988 (Cth).

What happens to the study results?

If you give us your permission by signing the consent document, we plan to discuss/publish these study results with the study sponsor, the ethics committee for monitoring purposes, peer-reviewed journals, presentations at conferences and/or other professional forums. You will not be personally

identified in any reports or publications resulting from this study. Any participant, who wishes, may ask their doctor to receive a copy of these results.

What happens to my treatment when the study is finished?

If you received diacerein and found it of benefit to you, you may be able to continue the treatment following completion of the study. Similarly, if you received placebo you may be able to begin treatment with diacerein. While this drug is not currently approved in Australia, there are a number of mechanisms in which you can get access to the drug at your own expense. Our study staff will provide you with guidance about which option is best for you. This decision should be made in consultation with your treating doctor.

Could the study be stopped early?

In rare circumstances, clinical trials of new medications are stopped early. For example, if an unexpected but severe side effect of a new medication is discovered. In the unlikely event that such circumstances occurred in this clinical trial, then doctors would be fully informed and would pass this information on to participants directly.

What should I do if I want to discuss this study further before I decide?

When you have read this information, the Clinical Trials Coordinator, Kathy Buttigieg is available to discuss it with you and answer any queries you may have. If you would like to know more at any stage, please do not hesitate to contact her on 03 6226 6909 (available Monday, Tuesday, Thursday and Friday). You may also contact the Chief Investigator, Dr Dawn Aitken, on 03 6226 7769.

Concerns or complaints?

This study has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study you should contact the Executive Officer of the HREC (Tasmania) Network on (03) 6226 6254 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. You will need to quote HREC Reference #H0017151.

Thank you for taking the time to consider this study.

This information sheet is for you to keep.