Patient Information Sheet

A randomised trial of zoledronic acid and VOLT01 for osteoarthritis of the knee

Invitation

You are invited to participate in a research study investigating a new treatment for knee pain. The study is being conducted at the Menzies Research Institute Tasmania (Hobart), Alfred Hospital (Melbourne), Royal North Shore Hospital (Sydney), and The Queen Elizabeth Hospital (Adelaide) by Professor Graeme Jones, Professor Flavia Cicuttini, Professor Lyn March, Associate Professor Catherine Hill, Dr Dawn Aitken and Dr Laura Laslett.

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 it with others if you wish.

What is the purpose of this study?

This study will examine a new treatment for knee pain. The treatment is called zoledronic acid. This study will determine whether treating patients with zoledronic acid will improve knee pain and slow down the progression of knee osteoarthritis.

This study is also examining the effect of a new combination therapy of zoledronic acid and a small dose of corticosteroid (VOLT01 substudy) to determine if the new combination is associated with a reduced rate of side effects and a similar effect on knee pain and progression of knee osteoarthritis.

Who is being asked to participate?

We will be studying up to 314 patients. Patients can be included in the study if they:

✓ Are ≥ 50 years;
✓ Have significant knee pain on most days;
✓ Have an abnormality present on a MRI (magnetic resonance imaging) scan; and
✓ Have clinical knee osteoarthritis.

What knee abnormality do I need to be eligible to participate?

We are interested in patients with bone marrow lesions. Bone marrow lesions are bright signals seen on MRI scans adjacent to joints. They have been recently recognised as being a significant contributor to knee pain and are remarkably common in people aged over 50 years. The underlying process and cause is not fully understood.
The diagnosis is confirmed by having a knee MRI scan.

What type of drug is zoledronic acid?

Zoledronic acid is a “bisphosphonate”. Bisphosphonates have been used extensively to treat patients with a wide variety of bone disorders for over twenty years. More than one million patients have now received treatment with zoledronic acid. We have data from a pilot study to suggest that zoledronic acid can be used to treat bone marrow lesions and reduce knee pain.

How is zoledronic acid administered?

Zoledronic acid is given by an infusion or “drip” in a vein in the arm, taking 15 minutes, in 100mL of fluid.

Who will receive zoledronic acid in this trial?

In this study one third of the patients will receive zoledronic acid at months 0 and 12. At the same time, a further one third of patients will receive zoledronic acid with the addition of a small dose of corticosteroid medication (10 mg prednisolone) at month 0 and 12. The remaining one third of patients will receive a dose of a “placebo” (that is, an infusion that looks like zoledronic acid, but has no active ingredients). This is a ‘randomised trial’ which means you will be allocated to one of the three groups randomly, like the flip of a coin. Neither the study investigators nor the study patients can decide which treatment the patients receive. As this is a ‘blind trial’ all study patients will be unaware whether they received zoledronic acid or placebo until we have completed all data collection for the entire study.

What are the adverse or ‘side’ effects of zoledronic acid?

In other clinical trials, the administration of zoledronic acid was followed by a fever or ‘flu-like’ symptoms in about 1 in 4 patients in the first two or three days after the medication was infused. These symptoms can be prevented or reduced by taking common pain relief and/or anti-inflammatory medications, such as either paracetamol or ibuprofen four times a day for up to three days, after each infusion.

Infrequently, patients treated with bisphosphonates have developed impairment in kidney function. This problem is rare, unless a patient has another cause for kidney damage, and usually has been associated with higher doses of bisphosphonate therapy in patients with cancer. If you may have a kidney problem you must let the trial doctor know. Prior to being accepted into this clinical trial, patients will have their kidney function tested. If there is significant impairment zoledronic acid therapy will not be given.

Very rarely patients on bisphosphonate therapy have had problems of poor healing or permanent damage of the bone of the jaw (“osteonecrosis of the jaw”), usually after invasive dental procedures such as tooth extraction. This problem can be very painful. This
complication is more common in cancer patients being treated with bisphosphonates and if there is poor oral hygiene. It is not clear if this problem is related to the use of bisphosphonates or other factors. If you have dental problems, or develop dental problems during the study, you must inform the study doctor.

In other clinical trials, some patients developed low blood calcium levels. This is more likely if you have a low vitamin D level. This may (rarely) cause twitching and muscle spasms, or (very rarely) fits. This complication is prevented/treated by giving patients calcium and vitamin D supplements. Before being included as a participant in this study, blood calcium and vitamin D levels will be checked.

In other clinical trials, some patients also developed mild anaemia, mild dyspepsia (discomfort in the upper abdomen), diarrhoea and eye inflammation (uveitis).

Very rarely, patients are allergic to zoledronic acid. If you think that you might be allergic to zoledronic acid or other “bisphosphonate” drugs, you must inform the study doctor.

The risks to an unborn human foetus or a nursing child from zoledronic acid are unknown. Women who are pregnant or nursing a child cannot participate in this trial. You must confirm that, to the best of your knowledge, you are not pregnant, and that you do not intend to become pregnant during the trial. If you are of child-bearing potential, your doctor will discuss appropriate birth control measures with you and a urine pregnancy test will be performed at visit 1. If you suspect that you have become pregnant during the trial, you must notify the study doctor immediately. If you are pregnant you will be withdrawn from the trial without your consent.

As with any new medication there may be risks currently unknown or unforeseen. If any new or important information regarding the study medication is discovered, you will be notified.

What are the adverse or ‘side’ effects of 10mg prednisolone?

Prednisolone is a corticosteroid medication. Long term use of corticosteroids leads to osteoporosis and other complications.

The single 10 mg dose of prednisolone is too small to cause osteoporosis or to lead to other steroid side effects, but should be sufficient to reduce short-term side effects of zoledronic acid use.

What does this study involve?

If you agree to participate in this study, you will be asked to sign the Patient Consent Form.

Screening visit

All patients will have a blood test to check their general health, kidney function and that they have normal levels of calcium and vitamin D. They will also be asked about their previous medical history and a medical examination will be performed, and they will be asked to provide a urine sample. All patients will be asked to complete a survey relating to knee pain. This survey has questions on symptoms, the degree of knee stiffness and pain and the effect
the condition has on a patient’s daily activities and quality of life. Patients will also be asked
a separate question to assess the amount of knee pain they have. Those with a pain score $\geq$
40 out of 100 on a 100 mm scale will be booked in for a knee MRI scan and a knee X-ray and
will be given a date for visit 2.

If you have a normal MRI scan you will not be asked to continue in the study.

Continuing in the study
This study will go for 24 months. We will need to see you at the start of the study (month 0),
and at 6, 12 and 24 months. Measures will be done at the Menzies Research Institute
Tasmania, Alfred Hospital, Royal North Shore Hospital, and/or The Queen Elizabeth
Hospital.

The following procedures/measures will be performed:
• A blood test will occur at screening and 6 months;
• Urine will be collected at screening and 6 months
• A knee x-ray will occur at screening;
• An MRI scan will occur at screening and months 6 and 24;
• Patients will receive an infusion of either zoledronic acid or a matching placebo
treatment at months 0 and 12;
• Questionnaires about knee pain, knee function, pain at other sites, joint replacement
surgery, and medications will occur at 0, 6, 12, and 24 months;
• Questionnaires about quality of life will occur; height, weight, and leg strength will be
measured at months 0, 6, and 24 months;
• Additional questionnaires (knee pain and function and joint replacement surgery) will
be mailed out at 3 and 18 months.
• Patients will be asked to give consent for medical records to be made available from
the National Joint Registry for the purpose of checking on any knee joint replacement
surgery following study completion.

If you choose to withdraw from this study after 6 months you will be requested to have a
third knee MRI scan.

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.
Is there anything I should do to prepare for zoledronic acid treatment?

All patients are encouraged to have sufficient food and liquid intake prior to administration and for several days following the dose. Patients will be asked to take paracetamol or ibuprofen tablets for the first 3 days after the study infusion. This will lessen the likelihood of a ‘flu-like’ reaction described above. Before and during the study it is important that patients tell the study doctor if they are taking any other medications which are not provided as part of the clinical trial.

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 patients receive any reward for participating in this study?

No, participation in this clinical trial is entirely voluntary. However, the tests and the treatment with zoledronic acid 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 decide to take part in the study you can withdraw (including your data and samples) 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 sponsored by the National Health and Medical Research Council (NHMRC) of Australia (Grant #1045415). Novartis Pharmaceuticals Australia Pty Ltd (the company that manufactures zoledronic acid – one of the treatments being tested) has provided funding for the research team to purchase zoledronic acid and placebo. Voltarra Pharmaceuticals, Inc. is the sponsor for the VOLT01 substudy, which is where we are assessing the effect of the combination of zoledronic acid and prednisolone on the risk of short term side effects of zoledronic acid. Voltarra has provided funding for the purchase of zoledronic acid and prednisolone for the last 50 patients recruited into the study, as well as funding for the cost of identifying and assessing these patients.

All of the money being paid by the sponsor to run the trial will be deposited into an account managed by the Menzies Research Institute Tasmania, Alfred Hospital, Royal North Shore Hospital, and/or The Queen Elizabeth Hospital. 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 patients in the treatment groups may experience reduced knee pain and a reduction in both bone marrow lesion size and cartilage loss. However, it is possible that you may not directly benefit.

How will my confidentiality be protected?

Unless required by law, only your doctor, the study team, and its authorized agents, the Therapeutic Goods Administration (TGA), health authorities where the study drug may be considered for approval (or already approved) 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).

Your details and results will be maintained on confidential password protected databases and access will be limited to the researchers and support staff only. No biological specimens taken from patients will be kept or analysed except as listed.

What happens to the study results?

After 24 months from the last patient entering this clinical trial, patients will be entitled to know whether they received zoledronic acid or placebo treatment. After all patients have completed 24 months in this clinical trial, the overall results of the trial will be collated.

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 patient, 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 zoledronic acid and found it of benefit to you, you may be able to continue the treatment following completion of this study; however, as this drug is currently not covered by the PBS for osteoarthritis, it will be at your own expense. Similarly, if you received placebo you may be able to begin treatment with zoledronic acid at your own expense. This decision should be made in consultation between you and 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 patients 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, Ms Kathy Buttigieg (Menzies Research Institute Tasmania) 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 (Mondays and Fridays). You may also contact the Chief Investigator, Professor Graeme Jones, on 03 6226 7705 or toll free 1800 638 124.
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 7479 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research patients. You will need to quote HREC Reference # H0012941.

Thank you for taking the time to consider this study.

This information sheet is for you to keep.