REGENERON

Participant Information Sheet/Consent Form

Title	A Phase 3 Randomized, Double-Blind, Multi-Dose, Placebo and NSAID-Controlled Study to Evaluate the Efficacy and Safety of Fasinumab in Patients with Pain Due to Osteoarthritis of the Knee or Hip
Protocol Number	R475-OA-1688
Global Sponsor / Local Sponsor	Regeneron Pharmaceuticals, Inc. / ICON Clinical Research Pty Limited
Principal Investigator	Professor Graeme Jones
Institution	Menzies Institute for Medical Research

1. Introduction

You are invited to participate in a research study of the investigational drug, fasinumab (also known as REGN475), for the treatment of pain due to osteoarthritis (OA) of the hip or knee.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor. You can take as much time as you like to make your decision.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information Sheet/Consent Form to keep.

2. What is the purpose of this research?

This study is being done to see if fasinumab is safe and effective for pain due to osteoarthritis of the hip or knee.

The purpose of this study is to determine how effective and how safe fasinumab is for the treatment of pain compared to placebo (an inactive substance), diclofenac, and celecoxib over a 24-week treatment period. Diclofenac and celecoxib are commonly prescribed medicines which belong to a class of medications called non-steroidal anti-inflammatory drugs (NSAIDs). This class of medication is routinely given as standard-of-care for the treatment of moderate-to-severe pain due to OA.

You are eligible for the study if you have pain due to OA of the hip or knee and have a history of at least 12 weeks of use of the types of medication described below:

1. Inadequate pain relief from paracetamol (examples: Panadol® or Herron Paracetamol®) AND
2. Intolerance to or inadequate pain relief from opioid or tramadol. If you are unwilling to take opioids or tramadol or do not have access to this type of medication you also may be eligible AND
3. Currently using regularly prescribed doses of NSAIDs for at least 4 days per week over the last 4 weeks.

Fasinumab is a fully-human monoclonal antibody (a type of protein) that blocks a substance called nerve growth factor (NGF). Nerve growth factor is a protein that causes pain. Blocking NGF may reduce pain due to OA of the hip and knee.

Fasinumab is an experimental treatment. This means that it is being tested and is not approved in Australia for use in pain management by Therapeutic Goods Administration.

This research is being conducted by Regeneron Pharmaceuticals, Inc. ("Regeneron") and sponsored in Australia by ICON Clinical Research Pty Limited.

3. What does participation in this research involve?

Your participation in this study may last up to 77 weeks (if you have a total joint replacement during the follow-up period it could be longer)

This study has different phases. They are:

Screening & Pre-randomisation	Up to 40 days Screening (up to 30 days) and Pre-randomisation (7 to 10 days) The Study doctor will perform some procedures and evaluate if you are eligible to take part in this study.
Treatment phase	Day 1 to Week 24 (24 weeks) You will receive study treatment.

Participant Information Sheet/Consent Form

Follow-up Phase	Week 25 to 44 (20 weeks) After study treatment ends, you will return to study site for some evaluations.
EOS-Phone contact	Up to Week 72 (Final phone call approximately 52 weeks after the last SC dose of the study drug)

If you participate, you will be asked to do the following things at different times

Procedure Name	
Questionnaires: Answer questions such as how you feel, your age, gender, race, ethnicity, height, weight, medical and surgical history (including infections such as hepatitis B, C, and Human Immunodeficiency Virus), substance abuse history and alcohol and smoking habits, menopausal history (females only), physical activity and previous and current medications. You will also be asked to answer questions regarding your activity level, the amount of joint pain you are experiencing, your quality of life and possible side effects of the study medication. It will take about 30 minutes to complete	
Electrocardiogram (ECG): Which is an electrical measurement of your heart function.	
Collection of Vital Signs: Blood pressure and pulse measurement in the lying, seated and standing position. Body temperature and respiration rate measurement.	
Blood samples for laboratory testing: <u>Your blood will be collected:</u> • To check your health • To check the amount of Fasinumab in your blood (if you are assigned to receive the study drug) Certain blood samples will require fasting for 8 hours prior to being drawn.	
Collection of Urine Samples: Provide urine samples for laboratory testing including drug testing.	

Participant Information Sheet/Consent Form

Procedure Name	
Pregnancy Testing: Provide urine samples for analysis for pregnancy testing (if you are a woman of child-bearing potential)	
Physical and neurological (nervous system) examination.	
X-rays X-rays will be performed to assess your OA and to determine your eligibility for the study.	
MRI (magnetic resonance imaging): Will be performed on 2 or more joints during the screening period and then may be repeated at a later time in the event of worsening of joint pain beyond your typical pain at the discretion of your study doctor.	

Blood Sample for Optional Pharmacogenetic Study

The maximum amount of blood taken at any single visit will be approximately 33 mL. Approximately 215 mL will be taken from you during the entire study.

If you agree, an optional blood sample will be collected from you for a pharmacogenetic sub-study. Giving this sample is optional; you do not have to agree to give this additional sample to participate in the Main study. A separate Participant Information Sheet/Consent form will be given to you.

The following will be tested: HbA1c (measure of long term blood glucose level), standard hematology (type and number of blood cells), blood chemistries such as sodium, potassium, and calcium, liver panel (function of the liver), creatinine, phosphorous, and CPK (protein found in muscle), pregnancy test will be performed for women of child bearing potential (WOCBP).

Additional procedures: You will also be asked to do the following things at different times:

You will need to stay in the clinic for approximately 1 hour after the study drug is injected so the study doctor can make sure there are no issues with the injection or at the injection site.

Starting from 1 week prior to your first injection until the end of the double-blind treatment period, you will be asked to record your use of rescue medication (paracetamol) and rate your pain level in a diary every day. The study staff will provide the diary and train you on how to record the appropriate information.

If you experience symptoms such as “pins and needles” in your hand or feet you may be required to undergo additional tests as determined by the study doctor or a specialist. If that doctor suspects these symptoms are due to issues with your sympathetic nervous system, you may not be allowed to take any more study drug.

If you experience issues with your blood pressure that indicate a condition called orthostatic hypotension, study drug may be stopped until your symptoms disappear.

Additional X-rays or MRIs may be performed during the study if the study doctor feels that they are necessary.

In the event of total joint replacement surgery, study medication will be stopped and you will be asked to come in to the clinic for a visit before your surgery, and for two visits (at 4 weeks and 20 weeks) after the surgery during which time additional X-rays will be taken of your knees, hips, and shoulders. Pre-operative X-rays and/or MRIs must be performed.

While you are in the study, you must:

- Follow the instructions you are given.
- Stop any prohibited medications.
- Come to the study centre for all visits with the study doctor or study staff.
- Stop paracetamol 24 hours prior to coming to a study visit during the treatment period.
- Maintain current physical activity and exercise levels throughout the study.
- Avoid drinking alcohol while taking paracetamol.
- Avoid alcohol, nicotine, and coffee on the day of your study visits.
- Fast before any scheduled blood tests as instructed by the study doctor except for the Screening visit (Visit 1).
- Drink 0.5 liters / 2 cups of water before your study visits.
- Tell the study doctor or study staff about any changes in your health or the way you feel.

Tell the study doctor or study staff if you want to stop being in the study at any time.

Study Drug

After performing screening procedures, if you are eligible for study participation, you will be randomised (put by chance, like flipping a coin) to receive fasinumab, placebo (an inactive drug substance), diclofenac or celecoxib into one of the following 6 treatment groups:

1. Fasinumab 1 mg SC (subcutaneous, under the skin and above the muscle) injection every 4 weeks and placebo capsules by mouth twice daily.
2. Fasinumab 3 mg SC injection every 4 weeks and placebo capsules by mouth twice daily.
3. Fasinumab 6 mg SC injection every 8 weeks and placebo capsules by mouth twice daily (active fasinumab injections will be given every 4 weeks during study visits; placebo SC injections will be given on alternating 4-week visits).
4. Diclofenac 75 mg by mouth twice daily and placebo SC injection every 4 weeks.
5. Celecoxib 200 mg by mouth once daily, matching placebo capsule by mouth once daily, and placebo SC injection every 4 weeks.
6. Placebo SC injection every 4 weeks and placebo capsules by mouth twice daily.

You will have a 1 in 9 or approximately an 11% chance to be assigned to the placebo group, a 2 in 9 or approximately a 22% chance to be assigned to 1 mg fasinumab treatment group, a 2 in 9 or approximately a 22% chance to be assigned to fasinumab 3 mg treatment group, a 2 in 9 or approximately a 22% chance to be assigned to fasinumab 6 mg treatment group, a 1 in 9 or approximately an 11% chance to be assigned to diclofenac 75 mg treatment group, and a 1 in 9 or approximately an 11% chance to be assigned to celecoxib 200 mg treatment group.

The study medications will be given in a double-blinded manner. “Double-blind” means that neither you nor the study doctor will know who is receiving fasinumab, diclofenac, celecoxib, or placebo. The study doctor will be able to find out what you are taking if needed in case of an emergency.

The SC injections will be performed by the study doctor or study staff at the baseline visit and then every 4 weeks, up to Week 20. If you complete the full study treatment, you will receive a maximum of 6 injections.

Fasinumab and fasinumab-matching placebo will be given by SC injections in the upper arm, abdomen or thigh by the study doctor or study staff. For the injection, a device called a pre-filled syringe will be used.

Diclofenac 75 mg, celecoxib 200 mg, and matching NSAID placebo will be oral capsules.

Because this is a research study, fasinumab, celecoxib or diclofenac (or matching placebo) will be given to you only during this study and not after the study is over.

Study Phases:

Screening

The screening period starts with the screening visit which may be up to 30 days before your next visit;

The following tests and procedures will be done at the Screening:

- Blood and urine samples will be collected and vital signs will be measured (including heart rate) to determine if you qualify to participate in the study.
- You will be examined and asked questions about your health and about your pain.

- You will have X-rays of the shoulders, knees, and hips, and you will have an MRI(s) of several of your joints performed.
- You will also have a physical exam, neurological exam, and an ECG performed.
- During this screening period, you may take your current treatment regimen for OA.

Pre-randomisation Period

If you complete the screening period and meet the requirements to continue, you will have a second visit at the site about 1 week before the baseline visit.

- You will be instructed to stop your current treatment regimen for OA including NSAIDs medications that are not allowed during the study but you will be allowed to take paracetamol as needed (according to the instructions of the study doctor, up to a maximum of 500 mg strength tablets/capsules).
- You will be instructed to report your pain levels in a daily diary. Failure to follow these guidelines will lead to discontinuation from the study.

Double-blind Treatment Period

The double-blind treatment period is up to 24 weeks long and begins at the randomization visit (baseline).

- You will attend study visits every 4 weeks and receive SC injections of fasinumab or placebo every 4 weeks.
- You will also receive diclofenac 75 mg, celecoxib 200 mg, or matching NSAID placebo by mouth, once or twice daily.
- In addition you will receive a telephone call at Week 2 to ask about side effects and your use of any medications.
- You may use paracetamol if you have insufficient pain relief. You will use a diary to report your paracetamol usage during this time.
- At the study visits, your vital signs will be taken and you will be examined.
- If you are a woman of childbearing potential you may need to provide a urine sample at these visits. You will also be asked questions about your health.
- At Week 16, 24, and (if needed) early termination visit, X-rays of the shoulders, knees and hips will be obtained. X-rays and MRIs can be also performed at any visit if a participant complains of worsening joint pain. The decision to perform an X-ray with or without a MRI will be made by your study doctor. Also if you are to have a joint replacement during the study, you will need to have an X-ray and/or MRI prior to the replacement.
- Blood samples and urine samples will be taken at Weeks 1, 4, 8, 16, and 24.

Follow-up Period

After the end of the treatment period (at 24 weeks after the first injection), you will continue to be monitored for an additional 20 weeks. During this follow-up period you will have two in-office visits (at 28 weeks and 44 weeks from the date of first injection).

- The study staff will ask you about any side effects and your use of any medications.
- At the in-office visit, you will undergo safety procedures such as physical (Week 44 visit only) and neurological examinations, vital signs, and X-rays (Week 44 visit only).
- You will also be asked about your pain.
- Blood and urine samples will also be taken at Week 44 visit.
- You will receive a telephone call 52 weeks after your last injection of study drug to check to see if you have had or plan to have a joint replacement surgery.
- You may start regular use of NSAID medications beginning 16 weeks after your last injection of study drug.

The Schedule of Assessments below will show the study procedures to be performed during each study period:

dy period	Screening/Pre-randomization		Treatment period								Follow-up period		EoS
Visit (V)	V1	V2	V3	Phone 1	V4	V5	V6	V7	V8	V9 EoT	V10	V11	Phone 2
Study Day (D)/Week (W)	Up to 30 days	7 to 10 days	D1	D15	W4	W8	W12	W16	W20	W24	W28	W44	W72
Age, gender, ethnicity, race and height recorded	X												
Medical history recorded	X												
Review of medications you are taking	X	X	X	X	X	X	X	X	X	X	X	X	
Review of any side effects	X	X	X	X	X	X	X	X	X	X	X	X	
Blood pressure, pulse rate, respiration rate, temperature measured	X	X[1]	X		X	X	X	X	X	X	X	X	
Weight and physical examination	X									X		X	
Neurologic examination	X		X		X	X	X	X	X	X	X	X	
Study treatment injection administration			X		X	X	X	X	X				
Receive study treatment tablets			X		X	X	X	X	X				
Receive rescue treatment (paracetamol)		X	X		X	X	X	X	X				
Receive instructions for use of diary		X	X										
Record rescue medication in diary[5]		X	X	X	X	X	X	X	X	X			
ECG performed	X									X			
MRI[2] performed	X												X[2]
X-rays[2] performed	X							X		X		X	
Answer questions for your activity level, joint pain, side effects and quality of life	X	X	X		X	X	X	X	X	X	X	X	
Complete pre-operative questionnaire[3]										X		X	
Blood and urine tests:													
-Pregnancy test[4] (blood or urine)	X		X		X	X	X	X	X	X		X	
-General health (blood and urine)	X				X			X		X		X	
-Post-menopausal status (blood)[6]	X												
-Drug test (urine)	X												
-Amount of fasinumab in your blood			X		X	X		X		X		X	

Participant Information Sheet/Consent Form

dy period	Screening/Pre-randomization		Treatment period								Follow-up period		EoS
Visit (V)	V1	V2	V3	Phone 1	V4	V5	V6	V7	V8	V9 EoT	V10	V11	Phone 2
Study Day (D)/Week (W)	Up to 30 days	7 to 10 days	D1	D15	W4	W8	W12	W16	W20	W24	W28	W44	W72
-Antibodies against fasinumab (blood)			X					X		X		X	
-Research samples (blood)			X		X	X		X		X		X	
-Optional sample for DNA testing (blood)			X										

EoT = End of treatment; EoS = End of Study

1. Blood pressure and pulse rate only will be measured at this visit
2. Additional MRI or x-rays may be performed during the study if the study doctor deems necessary. At the EoS phone call you will be asked if you have had or have scheduled a joint replacement, if that is the case you will be asked to come to the clinic for additional imaging.
3. If you have a joint replacement during the study you will be asked to have the assessments for W24 or W44 as a pre-operative visit.
4. The pregnancy test will be done on your blood sample at the Screening visit and on your urine sample in the other visits. Pregnancy test is applicable to women of child-bearing potential only.
5. Will be recorded daily using diaries. Paracetamol use will be reported from pre-randomization visit to week 24.
6. Only to be performed if postmenopausal status has to be assessed for female patients who are ≤59 years of age.

There will be no cost to you for the study doctor's time or certain procedures and supplies related to this study.

The study drugs will be provided to you without charge.

You are responsible for the cost of your standard medication, in addition to any costs related to procedures and supplies not required by the study.

You will not be paid for participating in this study. However, you may be reimbursed for travel to and from the study site, parking, and other expenses associated with the research project visit upon presentation of valid tax invoice. If you do not complete the entire study, you will be reimbursed only for the visits completed while you were in the study.

4. Other relevant information about the research project

This study will include approximately 2700 participants at approximately 150 sites around the world.

5. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information Sheet/Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the Menzies Institute for Medical Research.

6. What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at hospital.

Other options are available; these include:

NSAIDs such as ibuprofen (Nurofen) or naproxen sodium (Naproxen) or opiod drugs.

Risks of alternative treatments include: Ulceration or gastrointestinal bleeding or possible cardiac events or stroke as seen with NSAIDs and drowsiness, dizziness, and nausea and vomiting as seen with opioid therapy.

The benefits of alternative treatments are: Possible alleviation of pain due to OA of the hip or knee. Also, these are not experimental drugs and their side effects are well known.

If you have any questions concerning alternative treatments, please ask your study doctor. You and your doctor can decide what is best for you.

7. What are the possible benefits of participating in the study?

Your participation will provide new information on the effects of this drug in patients. You may or may not personally benefit from your participation in the study.

8. What are the possible risks and disadvantages associated with this study?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Fasinumab

Fasinumab may cause all, some, or none of the side effects listed below. These side effects can be mild but could also be severe or serious. There may also be unknown side effects from taking fasinumab. The risks involved in giving fasinumab are not fully known and may include possible side effects to an unborn child, if you are pregnant or become pregnant.

Risks and Possible Side Effects of Fasinumab

As of January 28, 2017, 746 people have taken fasinumab in unblinded clinical studies.

Based on a study with 419 patients with osteoarthritis of hip or knee, common side effects seen in ≥5% (which may affect 5 or more people in every 100) of fasinumab treated patients during the treatment period were:

- Joint pain
- Headache,
- Upper respiratory tract infection,
- Change in feelings (i.e. numbness and tingling).

Joint damage occurred in patients in all dose groups, but it was more frequent at higher doses. Joint damage occurred in 1/82 (1.2%) patient in placebo, 2/85 (2.4%) in 1 mg, 4/84 (4.8%) in 3 mg , 6/85 (7.1%) in 6 mg and 10/83 (12.0%) in 9 mg fasinumab groups given every 4 weeks subcutaneously.

This joint damage usually occurred in a knee or hip and sometimes occurred in more than one joint. The joint damage often occurred with increased joint pain. For some patients, these events have resulted in joint replacement.

In large clinical studies studying monoclonal antibodies against NGF, joint damage was much more likely to occur if a group of pain medications called non-steroidal anti-inflammatory drugs or NSAIDs (such as ibuprofen) were taken together with the monoclonal antibody to NGF. However, even if you do not take non-steroidal anti-inflammatory drugs, there is still a risk of joint damage with monoclonal antibodies against NGF. Since worsening of joint pain is the most common symptom of this joint damage, if you notice significantly worsening joint pain or increased joint pain that lasts more than two weeks, please notify your study doctor immediately.

From the completed and unblinded studies, joint pain and change in feelings (i.e., numbness, pins and needles, tingling) have been observed in a higher percentage of patients who received fasinumab than those who received placebo. These findings were mainly mild to moderate in severity.

In animal studies, drugs that block NGF have been found to cause abnormalities in the sympathetic nervous system, the part of the nervous system that controls bodily functions such as sweating, heart rate and blood pressure. The risk in humans is unknown, and effects on the nervous system will be monitored closely during the study. If you have changes in your heart rate or blood pressure, please notify your study doctor. Examples of reasons to call your doctor include feeling light headed or dizzy. During the study, your study doctor will check for any signs of nervous system problems.

It is possible that your body may make antibodies against fasinumab. These antibodies may have the effect of causing fasinumab not to work or causing an allergic reaction. As of January 28, 2017, a few patients treated with fasinumab have developed very low amounts of antibodies against fasinumab; these antibodies have not been associated with any known side effect.

Allergic Reaction Risk

There is a chance that you will experience an allergic reaction to the study drug. Common symptoms of a mild to moderate allergic reaction include:

- Headache
- Rash
- Flushing
- Swelling
- Shortness of breath
- Nausea, or vomiting.

Symptoms of a severe allergic reaction include:

- Dizziness
- Difficulty breathing or swallowing
- Decrease in blood pressure, and could be life threatening.

In completed studies there have been no serious systemic allergic reactions reported for patients treated with fasinumab, but regardless, all administrations of fasinumab will be in the

study doctor's office where there is emergency equipment and medication available to treat you if needed.

As low levels of doxycycline (an antibiotic) are used in the production process of fasinumab, you may have an allergic reaction if you are allergic to doxycycline. Please, make sure to inform your study doctor or study staff if you have an allergy to doxycycline or any other medications.

A severe allergic reaction requires immediate medical treatment and could result in permanent disability or death.

If you believe you are having a severe allergic reaction, you should immediately seek emergency medical treatment, and you should alert the study doctor and study staff as soon as possible.

Other Medications that will be given during the Study

Starting about 1 week before getting your first injection, you will need to stop taking your normal OA pain medications (including oral and topical medications). You may continue to use paracetamol.

If you complete the screening period and meet initial eligibility criteria to continue, you will be given paracetamol to take as needed in the event of OA pain. This is rescue medication. You may take 1-2 tablets every 6-8 hours. Do not take more than 2500 mg a day. It is not recommended to take paracetamol at intervals of less than 4 hours. Your study doctor will let you know how much to take.

You will receive this rescue medication (paracetamol) for the entire time that you are in the study receiving study medication.

If you take more than the allowed amount of paracetamol repeatedly, study treatment will be stopped.

A medication to protect your stomach lining may be prescribed if the study doctor believes it is necessary.

Risks and Possible Side Effects of Taking Paracetamol during the Study

When used appropriately, side effects with paracetamol are rare. The most serious side effect is liver damage due to large doses or using it along with alcohol or other drugs that also damage the liver. You should avoid drinking alcoholic beverages if you are taking paracetamol. Chronic alcohol use may also increase the risk of stomach bleeding while taking paracetamol. There is also a small risk of serious allergic and/or skin reactions.

Risks and Possible Side Effects of NSAIDs during the Study

You might be randomised to receive diclofenac or celecoxib.

Possible side effects of NSAIDs being taken in the study include the following:

- Heart attack or stroke or high blood pressure
- Ulcers or bleeding in the stomach or intestines

- Anemia
- Allergic and/or skin reactions and/or asthma attacks in people with asthma
- Liver or kidney problems

Other side effects of NSAIDs include stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Placebo Risks

The type of medication you are assigned to in the study is determined by chance. Some people in the study will receive placebo instead of fasinumab, diclofenac, or celecoxib. Placebo is a substance that looks like a drug but has no drug in it. Please ask the study doctor or study staff if you have any questions about placebo.

If I stop my regular medication, what are the risks?

If you stop your regular medication to participate in the study, your OA pain might get worse. Please tell the study doctor or study staff right away if you have any problems when you stop or change your regular medication.

It is possible that receiving fasinumab may change how your regular medications, vaccines, or supplements work. It is very important that you tell the study doctor about any medications, supplements, or vaccines before you take them during the study.

STUDY PROCEDURES RELATED RISKS

ECG

It could cause some discomfort when the nursing/medical staff remove the electrodes which are sticky patches placed on your chest.

Collection of Vital Signs

Inflation of the blood pressure cuff may be uncomfortable.

Blood Draws/ Study Drug Infusion

Blood collection may cause discomfort at the site where the blood is taken, bruising at the site or infection at site where the blood was collected. Some participants may experience fainting or dizziness during blood collection. Fasting may cause lightheadessness or may affect blood sugar levels.

Radiation Risk

X-rays should not cause any discomfort, however, there is increased exposure to radiation.

This research study involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The total effective dose from this study is up to 7.8 mSv. At this dose level, no harmful effects of radiation have been demonstrated, as any effect is too small to measure. The risk is believed to be minimal.

MRI Scan

Because an MRI can be dangerous for people with metal in their body, you must tell the study doctor whether you have metal in your body, including braces, surgical clip, pin, bullet fragment, splinter, etc, to determine if you are at risk. Otherwise, the effects of magnetic fields in an MRI scanner have been extensively studied, and there are no other known significant risks with an MRI exam. You may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure.

General

You might feel uncomfortable during Physical and neurological (nervous system) Examination.

Some questions in the questionnaires might make you feel uncomfortable.

There are no expected risks during the collection of urine samples for laboratory testing including drug test and analysis for pregnancy testing (if you are a woman of childbearing potential.

Unforeseeable Risks

It is possible that there will be other side effects associated with fasinumab which are unknown at this time, some of which may be serious or life-threatening.

You should tell your study doctor or the study staff about any new health problems that develop while you are in this study and about any new medications you start taking (including over-the-counter medication, herbal remedies, and non-prescription drugs).

If you experience any side effects during the course of this study, you should immediately contact the study doctor.

Reproductive Risk

In animal studies, fasinumab has been found to cause abnormalities in the nervous system of babies if their mothers were treated with fasinumab while pregnant. NSAIDS should not be used by women late in their pregnancy as these drugs may cause a blood vessel in the fetus to close prematurely.

If you are female, you must not be pregnant or become pregnant during this study because fasinumab has not yet been tested in pregnant women; unknown risks to the unborn child are possible if you become pregnant.

You must agree to use a medically acceptable method of birth control from start of study until 20 weeks after the last dose of study drug. Acceptable methods of birth control are listed below.

If you become pregnant, you may no longer participate in this study, and:

- You must tell the study doctor immediately
- Women who become pregnant during the study will have to stop study drug
- Your study doctor will follow-up with you on the outcome of the pregnancy as required by the protocol

As the effects of the fasinumab on a breastfed child are not known at this time, breastfeeding women cannot enroll in the study.

Acceptable methods of birth control include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner[1]
- Sexual abstinence[2]

([1]Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomised partner has received medical assessment of the surgical success.)

([2]Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical research study and the preferred and usual lifestyle of the participant.)

Periodic abstinence, withdrawal, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

Postmenopausal women must be amenorrheic (without their periods) for at least 12 months to be considered not of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

You must notify your study doctor if you get pregnant during the study and up to 20 weeks after the last injection.

9. What will research samples collected from this study be used for?

Additional blood samples will be collected and stored for up to 15 years following the completion of the study, in order to help Regeneron understand the following:

- How much fasinumab is present in your blood.

- How fasinumab works in the body.
- What makes some people respond better to the study drug.
- Why some people develop side effects.
- How the study drug could affect other diseases or conditions.

These additional samples will be stored for in a secure storage space at Regeneron Pharmaceuticals, Inc., USA, which can be reached by email at PrecisionMedicine@regeneron.com. They will only be used for the research purposes described above. Your samples will be destroyed at the end of the storage period (15 years). If you wish to withdraw your consent to use and store your samples, please notify the study doctor in writing.

To protect your privacy, we will only use a participant number, instead of your name or other identifiers, on your sample(s). Your name and other information that directly identifies you will not be disclosed outside of the study site and will not be known by the Sponsor. A unique code will be applied to your samples at the site. The study doctor will keep the key linking your personal information to this code at the study site. We have set up study records to keep your participation and all your test results separate and confidential

If you agree with the collection of a blood sample for the optional pharmacogenetic sub-study, a separate Participant Information Sheet/Consent Form with further details will be given to you.

10. What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.
Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue

11. Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

12. What if I withdraw from this research project?

You may refuse to be in the study or discontinue being in the study at any time. You do not need to give a reason, and your medical care to which you are otherwise entitled will not be affected by your decision.

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

Furthermore, you have the option of withdrawing your consent for the storage of your samples for Additional Future Research without withdrawing your participation in the main study.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information and data/samples already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

13. Could this research project be stopped unexpectedly?

The study doctor or Regeneron Pharmaceuticals, Inc., the sponsor of the study ("Regeneron"), can remove you from the study without your consent at any time for any reason including:

1. To improve your medical care,
2. For your failure to follow the study requirements,
3. If you are experiencing unusual or serious side effects,
4. If the study is stopped by Regeneron, or
5. Other reasons not itemized here.

The same procedures will be followed as those that would happen if you decided to discontinue from the study.

14. What happens when the research project ends?

After the end of the treatment period (at 24 weeks after the first injection), you will continue to be monitored for an additional 20 weeks. During this follow-up period you will have two in-office visits (at 28 weeks and 44 weeks from the date of first injection).

Because this is a research study, fasinumab, celecoxib or diclofenac (or matching placebo) will not be given after the study is completed.

Part 2 How is the research project being conducted?

15. What will happen to information about me?

Participant Information Sheet/Consent Form

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. We will only use a participant number (a code), instead of your name or other identifiers, on information sent outside of the study site. The study doctor will keep the key linking your personal information to this code at the study site. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Regeneron Pharmaceuticals, Inc. and ICON Clinical Research Pty Limited, the institution relevant to this Participant Information Sheet/Consent Form, Menzies Institute for Medical Research, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

Your decision to allow us to collect and use your health information is completely voluntary but if you do not allow us to do so, you may not participate in the study.

Information and results from this study may be presented at meetings or published in journals. Your name and information that can be traced back to you will not be in any presentation or publication.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian and/or Tasmanian privacy and other relevant laws, you have the right to request access to your information collected and stored by the study site. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project and for the additional future research that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

Absolute confidentiality cannot be promised, because information needs to be shared. By signing the consent form, you understand that your personal data may be transferred to countries that may not have the same level of personal data protection as found within Australia.

Your permission to use and/or share your health information does not have an expiration date, subject to applicable law, unless you withdraw your permission in writing. If you allow us to collect this information, you can change your mind at any time and no new data from you will be added

to the study database. However, if you reverse your permission, you will no longer be able to participate in the study.

In addition, even if you reverse your permission, your information that have already been collected may continue to be used and disclosed to protect the integrity of the research and as permitted by this information sheet and consent form.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov* as required by national or international law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

16. Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study doctor as soon as possible who will assist you in arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

There are two avenues that may be available to you for seeking compensation if you suffer an injury as a result of your participation in this research project:

- The pharmaceutical industry has set up a compensation process, with which the Sponsor, ICON Clinical Research Pty Limited, of this research project has agreed to comply. Details of the process and conditions are set out in the Medicines Australia Guidelines for Compensation for Injury Resulting from Participation in a Company-Sponsored Clinical Trial. In accordance with these Guidelines, the sponsor will determine whether to pay compensation to you, and, if so, how much. A copy of the Guidelines is available to you from the research staff on request.
- You may be able to seek compensation through the courts.

17. Who is organising and funding the research?

This research project is being sponsored in Australia by ICON Clinical Research Pty Limited and is being conducted and funded by Regeneron Pharmaceuticals, Inc.

Regeneron may benefit financially from this research project if, for example, the project assists Regeneron to obtain approval for a new drug.

By taking part in this research project you agree that samples of your blood or tissue (or data generated from analysis of these materials) may be provided to Regeneron.

Regeneron may directly or indirectly benefit financially from your samples or from knowledge acquired through analysis of your samples.

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to Regeneron.

By participating in this study, you do not acquire any ownership rights in the samples you contribute or in any medical or genetic tests, drugs or other commercial products we may develop through this research.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to Regeneron, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

The Menzies Institute for Medical Research will receive a payment from ICON Clinical Research Pty for undertaking this research project.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

18. Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Tasmanian Health and Medical Human Research Ethics Committee (Reference number H00…...).

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

19. Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the study doctor, Professor Graeme Jones on (03) 6226 7705 or any of the following people:

Clinical contact person

Name	*Sara Whatling*
Position	*Clinical Trial Coordinator*
Telephone	*(03) 6226 4294*
Email	*Sara.whatling@utas.edu.au*

Participant Information Sheet/Consent Form

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

HREC Executive Officer details

Reviewing HREC name	*Tasmanian Health and Medical Human Research Ethics Committee*
HREC Executive Officer	*Adele Kay*
Telephone	*(03) 6226 7479*
Email	*human.ethics@utas.edu.au*

Research Governance Officer details

Name	*Sarah Bascomb*
Position	*Research Integrity Coordinator*
Telephone	*(03) 6226 1956*
Email	*Sarah.Bascomb@utas.edu.au*

Consent Form

Title	A Phase 3 Randomized, Double-Blind, Multi-Dose, Placebo and NSAID-Controlled Study to Evaluate the Efficacy and Safety of Fasinumab in Patients with Pain Due to Osteoarthritis of the Knee or Hip
Protocol Number	R475-OA-1688

Participant Information Sheet/Consent Form

Global Sponsor / Local Sponsor	Regeneron Pharmaceuticals, Inc. / ICON Clinical Research Pty Limited
Principal Investigator	Professor Graeme Jones
Institution	Menzies Institute for Medical Research

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to the Menzies Institute for Medical Research concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Participant Information Sheet/Consent Form

Name of Study Doctor/ Senior Researcher† (please print)	_____
Signature _____	Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation

Title	A Phase 3 Randomized, Double-Blind, Multi-Dose, Placebo and NSAID-Controlled Study to Evaluate the Efficacy and Safety of Fasinumab in Patients with Pain Due to Osteoarthritis of the Knee or Hip
Protocol Number	R475-OA-1688

Participant Information Sheet/Consent Form

Global Sponsor / Local Sponsor	Regeneron Pharmaceuticals, Inc. / ICON Clinical Research Pty Limited
Principal Investigator	Professor Graeme Jones
Institution	Menzies Institute for Medical Research

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with the Menzies Institute for Medical Research.

I wish to withdraw my consent for (tick as applicable):

[ ] My participation in the main research project described above.

[ ] The optional storage of my blood samples for Additional Future Research.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.