Patient's Initials_____

Patient Information and Consent Form

TITLE:	COAST-1: Clinical Knee Osteoarthritis Symptom Treatment 1 Study A Randomized, Double-blind, Placebo-controlled Trial to Assess the Efficacy and Safety of AXS-02 (Disodium Zoledronate Tetrahydrate) Administered Orally to Subjects with Knee Osteoarthritis Associated with Bone Marrow Lesions.
PROTOCOL NO.:	**AXS02-K301**
SPONSOR:	Axsome Therapeutics, Inc.
INVESTIGATOR:	Professor Graeme Jones Menzies Institute for Medical Research Medical Sciences Building 1, Level 3 17 Liverpool Street Hobart, TAS 7000 Australia
STUDY RELATED PHONE NUMBER(S):	Kathy Buttigieg (Clinical Trial Coordinator) +61 3 6226 6909

1. Introduction and Purpose of the Study

You are being asked whether you want to participate in a clinical research study. First we want you to know that taking part in a clinical research study is entirely voluntary. Second, you need to know that there are important differences between being cared for in a clinical research study and being cared for by your doctor outside of a clinical research study. Being in this study does not replace your regular medical care. The purpose of regular medical care is to improve or stabilize your health. The purpose of a clinical research study is to gather information. A clinical research study is designed to answer specific questions about a medication's safety and its effect on a disease or condition. Therefore, it is important that you understand the difference between the regular care you receive from your doctor and what is involved in the clinical research study and why the clinical research study is being done.

This consent document gives you important information about your potential involvement in the clinical research study. Please read this information carefully before deciding to take part. No one can make you take part and you can stop at any time. If you choose to take part in this research study, you will need to sign this consent document and you will receive a copy of this signed and dated document for your records.

This research study is being conducted for Axsome Therapeutics, Inc. Axsome is sponsoring the study and will be paying the study doctor to conduct the study.

The following sections describe the clinical research study. Before you decide to participate, please take as much time as you need to read the information carefully and ask questions and discuss with the study site staff, with your family and friends, or with your personal physician or other healthcare professionals. The study site staff will explain and answer any questions you have before you make a decision.

2. PURPOSE OF THE CLINICAL RESEARCH STUDY

You are being asked to participate in this clinical research study because you have a condition known as **osteoarthritis of the knee**. The purpose of this research study is to determine whether a study medication called AXS02 (disodium zoledronate tetrahydrate) can relieve the pain from osteoarthritis of the knee and whether it causes any safety issues in people with knee osteoarthritis.

AXS02 is an investigational drug. The term "investigational drug" means that the drug being tested has not been approved by the U.S. Food and Drug Administration (FDA).

The study drug that you will take if you are in this study is a tablet that contains either AXS02 or placebo (an identical-looking pill that does not contain any active drug; a placebo is sometimes called a "sugar pill"). The reason for having people take placebo in this study is to see if taking AXS02 is better than taking placebo.

Because this is a clinical research study, AXS02 will be given to you only during this study and not after the study is over.

3. HOW LONG WILL MY PARTICIPATION IN THIS STUDY LAST?

Your maximum participation will be 28 weeks and may include up to 14 visits to the study center. A total of approximately 346 subjects are planned for enrollment in this study in Australia and The United States.

4. WHAT WILL HAPPEN BEFORE THE CLINICAL RESEARCH STUDY BEGINS?

Your participation in this study is entirely voluntary. It is up to you to decide whether to take part or not. If you decide to withdraw from the study or not to take part your future medical care will not be affected in any way.

If you do decide to take part, you will be asked to sign this consent form and you will be given a signed copy of the consent form to keep. You are free to leave the study at any time without giving a reason.

5. WHAT WILL HAPPEN DURING THE STUDY?

The study will begin with you signing and dating the informed consent form, and study procedures will be carried out in the following time periods:

- The first part of this study is called a Screening Period (which begins at your first visit (Visit 1)) which can last up to 21 days. During this period, the study doctor will decide if you qualify to be in the first part of the study. You will also need to stop taking certain medications that you may currently be receiving.

- The next two visits will be 10 days apart and are called the Baseline Period (Visit 2 and 3). If based on the results of the tests and procedures from Visit 1 you qualify to continue participation in the study, a number of tests and procedures will be conducted to gather data prior to taking your first dose of study medication. At the second Baseline Period visit (Visit 3) you will begin taking double-blind study medication, which will be either AXS02 or placebo. "Double-blind" means that neither you nor the study doctor will know what treatment medication you are getting.

- The next part of the study is the Double-Blind Active Treatment period (Visits 4, 5, 6, 7, 8), which will consist of up to 5 visits over a maximum of 5 weeks. In this active treatment period, you will take AXS02 or placebo at the beginning of each visit. You will be asked to stay in an upright position for 30 minutes after dosing and wait at least 120 minutes before consuming the first food or beverage of the day.

- The second part of the Double-Blind Period has six visits (Visits 9, 10, 11, 12, 13, 14) over 19 weeks. At these visits you will not receive AXS02 or placebo. A number of tests and procedures will be conducted to gather data.

6. STUDY PROCEDURES

If you agree to be in the study and qualify to participate based on the screening assessments, you will be randomly assigned by chance (like the flip of a coin) to one of the following groups:

- AXS02 tablets 1 time per week for 6 weeks
- Placebo tablets 1 time per week for 6 weeks

A placebo looks like the study medication but does not contain any active drug. You will have a 50% (1 in 2) chance of receiving either AXS02 or placebo. Neither you nor your doctor will know whether you receive AXS02 or placebo. You will receive the dose of your blinded study medication or placebo on 6 separate visits (Study visits 3, 4, 5, 6, 7, and 8).

This is a double-blinded study, which means neither you nor your study doctor will know which study group you are in. However, this information is available in case of an emergency.

If you are currently taking pain medications to help alleviate (temporarily relieve) your pain, you will need to stop taking these medications after Visit 2 and will need to remain off of these medications throughout the duration of the study.

If you experience an injury or increased pain (flare) due to your osteoarthritis, short term use of acetaminophen or ibuprofen may be used as directed by your doctor. You will need to carefully track your use of these pain medications. Pain Medications are not allowed between Visit 2 and Visit 3 (baseline period) or after Day 159, which is 10 days prior to the last study visit (Visit 14).

You will need to take Citrical (Calcium/ Vitamin D supplement) every day starting at your first visit, except for the days where you visit the study doctor and receive study medication. These supplements will be provided to you.

During your Screening visit (Visit 1), the site will register you in the daily telephone and web diary (also known as an interactive voice/web response system), and train you on how to use the diary for collection of information on pain and medication use. You will be given instructions for using the telephone or web diary and will be told to start using it beginning on the evening after your Screening visit.

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Visit 1 – Screening

After reading and signing this informed consent document, the following tests and procedures will be performed to determine if you qualify to participate:

- Review of inclusion/exclusion criteria
- Collect personal information from you, such as your initials, date of birth, sex, and race
- Review of your medical and medication history. You may be asked to provide permission for the study doctor to obtain copies of your medical records from your primary care physician.
- You will be asked permission to collect your email address or phone number so that appointment reminders and reminders to complete your diary can be sent to you.
- Physical exam including an assessment of your dental health (teeth and gums) and measurement of weight, height and vital signs (blood pressure, heart rate, breathing rate and temperature).
- The study doctor will assess your osteoarthritis symptoms
- A blood sample will be collected (25 mL, or about 5 teaspoons) and a urine sample (about a half cup, 100 mL) for clinical laboratory tests. The urine test will include a check for opioids and other drugs.
- You will be asked to complete the BDI-II, which is a 21 question questionnaire to assess how you are currently feeling.
- You will be scheduled to have an X-ray and an MRI of your knee. Both of these procedures will be conducted before you return for Visit 2. The X-Ray and MRI will confirm the presence of your osteoarthritis.
- You will have an electrocardiogram (test that measures and records the electrical activity of the heart) conducted (12-Lead ECG).
- You will also be instructed how to use your daily telephone/web diary to collect daily average pain assessment and use of rescue medications.
- You will be given a bottle of Citrical (Calcium/ Vitamin D supplement). This supplement will be taken every day, except on the days when you return to the clinic for dosing of study medication.

During the study you will be asked to track your use of pain medications, and to take Citrical (Calcium/ Vitamin D supplement). At each study visit, it is very important that you bring back all bottles of study medication that you have been given (even empty bottles), since your study doctor will need them to make sure that you are taking your study medication correctly.

After this visit, you will be told whether you qualify for the next part of the study.

Visit 2 – First Baseline Visit

Your second visit will take place 1-2 weeks after Visit 1. During this visit, which may be completed by telephone, the following will be reviewed:

- Review any changes in your health or medications since your last visit.
- Go over your use of medications for pain and your Citrical (Calcium/ Vitamin D supplement).
- Review your daily diary entries of pain assessments.
- At the end of this visit, you will be asked to stop all pain medications until your next visit (Visit 3).

If you have a below normal amount of vitamin D in your blood, you will be asked to come to the clinic for Visit 2 where the study doctor will administer a once off additional vitamin D supplement to help increase your vitamin D levels. The Vitamin D supplement would be taken while you are in the clinic at Visit 2 and would be in addition to the Citrical (Calcium/ Vitamin D) supplements that you will take every day while participating in the study.

Visit 3 – Second Baseline Visit

Your third visit will take place 10 days after Visit 2. You should not eat or drink anything other than water starting after midnight before this visit. You should also not take your Citrical (Calcium/ Vitamin D supplement). During this visit the following procedures and tests will be performed:

- Review of inclusion/ exclusion criteria
- Vital signs (blood pressure, heart rate, breathing rate and temperature).
- Collect a blood sample (3 mL, 1/2 teaspoon) and a urine sample (about a half cup, 100 mL) for clinical laboratory tests. The urine test will include a check for opioids and other drugs.
- Review your daily diary entries.
- Review any changes in your health or medications since your last visit.
- Go over your use of Citrical (Calcium/ Vitamin D supplement).
- Completion of 3 questionnaires to evaluate your pain and symptoms of osteoarthritis, and how they affect your activities of daily living.
- After completion of the above procedures, if you are found eligible to continue in the study, you will be randomly assigned either to AXS02 or to a matching placebo. As explained above, neither you nor your doctor will know if you are taking AXS02 or placebo since both will look the same.
- The study doctor or staff will give you a pill to take at the site. You should not have eaten or had anything to drink besides water since midnight. After taking AXS02 or placebo you will remain at the clinic and will be required to remain upright (standing or sitting) for 30 minutes, and wait 120 minutes before eating or drinking something other than water.
- You will be give bottles of rescue medication (acetaminophen and ibuprofen). These pain medications should only be taken if you have a surgery, injury or experience increased pain, which is what we call an OA flare. You will be asked to keep track of the medication that you take.

During the study you will be asked to track your use of pain medications, and to take Citrical (Calcium/ Vitamin D supplement). At each study visit, it is very important that you bring back all bottles of study medication that you have been given (even empty bottles), since your study doctor will need them to make sure that you are taking your study medication correctly.

Visits 4-8 – Treatment Period with Dosing

Your next 5 visits will take place every week (Visit 4, Visit 5, Visit 6, Visit 7 and Visit 8). During each of your visits in the study the following procedures and tests will be performed:

- Vital signs (blood pressure, heart rate, breathing rate and temperature).
- Review any changes in your health or medications since your last visit
- Review your daily diary of pain assessments and use of rescue medications.
- Go over your use of medications for pain and your Citrical (Calcium/ Vitamin D supplement) use.
- The study doctor or staff will give you a pill to take at the site. You should not have eaten or had anything to drink besides water since midnight. After taking AXS02 or placebo you will remain at the clinic and will be required to remain upright (standing or sitting) for 30 minutes, and wait 120 minutes before eating or drinking something other than water.

At **Visit 6** the following procedures and tests will also be performed:

- Collect a blood sample (25 mL, or about 5 teaspoons) for clinical laboratory tests.
- Completion of 3 questionnaires to evaluate your pain and symptoms of osteoarthritis, and how they affect your activities of daily living.

During the study you will be asked to track your use of pain medications, and to take Citrical (Calcium/ Vitamin D supplement). At each study visit, it is very important that you bring back all bottles of study medication that you have been given (even empty bottles), since your study doctor will need them to make sure that you are taking your study medication correctly.

Visit 9 and Visit 10 - Treatment Period without Dosing

After completing Visit 8 you will be asked to return to the study center one week later for Visit 9, then two weeks later for Visit 10.

During these visits, the following procedures and tests will be performed:

- Vital signs (blood pressure, heart rate, breathing rate and temperature).
- Collect a blood sample (25 mL, or about 5 teaspoons) and a urine sample (about a half cup, 100 mL) for clinical laboratory tests.
- 12-lead ECG will be performed **(Visit 9 only).**
- Review any changes in your health or medications since your last visit.
- Review your daily diary of pain assessments and rescue medications.
- Go over your use of medications for pain and your Citrical (Calcium/ Vitamin D supplement) usage.
- Completion of 3 questionnaires to evaluate your pain and symptoms of osteoarthritis, and how they affect your activities of daily living.
- You will be asked to schedule your MRI to occur at the next visit (Visit 11).

Visit 11

You will return for Visit 11 a month later and have the following procedures and tests performed:

- Completion of 4 questionnaires to evaluate your pain and symptoms of osteoarthritis, and how they affect your activities of daily living.
- The study doctor will assess your osteoarthritis symptoms.
- Vital signs (blood pressure, heart rate, breathing rate and temperature).
- A review of your oral health (teeth and gums).
- Review any changes in your health or medications since your last visit.
- Review your daily diary of pain assessments and rescue medications.
- Go over your use of medications for pain and your Citrical (Calcium/ Vitamin D supplement) usage.
- Collect a blood sample (25 mL, or about 5 teaspoons) for clinical laboratory tests.
- 12-lead ECG will be performed.
- An MRI will be performed to review your osteoarthritis.

Visit 12 and Visit 13

After completion of Visit 11 you will return every month for the remainder of the study and have the following procedures and tests performed:

- Completion of 4 questionnaires to evaluate your pain and symptoms of osteoarthritis, and how they affect your activities of daily living.
- Vital signs (blood pressure heart rate, breathing rate and temperature)
- Collect a blood sample (25mL, or about 5 teaspoons) for clinical laboratory tests.
- Review any changes in your health or medications since your last visit.
- Review your daily diary of pain assessments and rescue medications.
- Go over your use of medications for pain.
- At Visit 13, you will be asked to schedule your X-ray and MRI to occur at the final visit (Visit 14).

Visit 14 (Final Study Visit)

After Visit 13 you will return to the clinic one month later for your final visit. The following will be performed:

- Completion of 5 questionnaires to evaluate your pain and symptoms of osteoarthritis, and how they affect your activities of daily living.
- The study doctor will assess your osteoarthritis symptoms.
- Physical exam including measurement of weight, height and vital signs (blood pressure, heart rate, breathing rate and temperature).
- Review any changes in your health or medications since your last visit.
- Review your daily diary of pain assessments.
- Go over your use of medications for pain.
- Collect a blood sample (25 mL, or about 5 teaspoons) for clinical laboratory tests.
- 12-lead ECG will be performed.
- An X-ray and MRI of your knee will be performed to review your osteoarthritis.

Early Termination Visits

If you choose to discontinue taking study medication for any reason, after you have taken at least one dose of study medication, you will be requested to return to the site for an early termination visit so that the study doctor may perform a final evaluation. At that visit all the procedures described above for Visit 14 will be performed.

You may also choose to continue to complete the visits in the study, in order to help provide longer term information on the safety and effect of the study medication.

It is very important that you bring back all bottles of study medication that you have been given (even empty bottles), since your study doctor will need them to make sure that you have been taking your study medication correctly.

Your study doctor may discontinue the study medication, or they may remove you from the study at any time, if he/she does not consider it to be in your best interest to continue. This may occur if:

- you experience an unrelated illness or complication
- you have not complied with the requirements of the study
- you have become pregnant
- your study doctor has received new information about the study medicine in relation to safety or effectiveness.

- you cannot tolerate the study medication

If you withdraw from the study, you will be asked to return to your study doctor for a final visit and final procedures. It is important for your health and safety to have this last visit. Your study doctor will talk to you about any potential medical issues that may arise and arrange for you to receive alternative treatment for your condition.

7. WHAT ELSE SHOULD I KNOW ABOUT THE STUDY PROCEDURES?

Magnetic Resonance Imaging (MRI)

An MRI is a test that takes pictures of your body's organs, tissues, and bones without exposing you to radiation. An MRI uses a powerful magnetic field and a kind of radio frequency energy that makes two and three dimensional computerized images. The MRI is a routinely performed medical procedure. It is completely painless, although there will be loud noises when the machine is on. If you have metal in your body, tell your doctor. Some MRI scanners are very narrow. Tell your doctor if you are uncomfortable in closed spaces.

X-RAY

Your participation in this research study involves exposure to radiation (x-rays) in addition to what you may receive as part of your standard care. X-ray produces images of the internal body parts being examined. X-ray is painless, however, radiation is emitted. The benefit from the radiation you receive for your standard care typically outweighs the risk because it allows your doctor to provide appropriate medical care; however, the additional radiation "dose" you receive for research purposes may not benefit you personally. X-ray produces images of the internal body parts being examined. The radiation dose you will receive in one year from this study is less than the average annual "background" dose received by a member of the US population. We cannot say with absolute certainty that there is no risk from the radiation dose in this study.

Blood and Urine Samples

About every three or six weeks 25 mL blood and 100 mL urine samples will be taken. There is a possibility that your study doctor may ask to take an additional blood and / or urine sample from you if they feel it is needed in order to properly evaluate the results of the tests conducted on these samples. If your study doctor requests an additional sample, the size of the sample collected will be 25 mL (about 5 teaspoons) for a blood sample or 100 mL (about half a cup) for a urine sample.

Storage of Blood and Urine Samples

Your samples will be shipped to a central laboratory and will be stored there awaiting analysis. The central laboratory being used in this study is ACM Global Central Laboratory Singapore Pty Ltd (11 Changi North Street 1, #04-05/08, Singapore 498823), who are experienced in handling and testing samples from research studies. All samples will be destroyed once all tests are complete.

The samples will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval. If additional analysis is proposed, your consent will be required. You will have the right to refuse to these additional tests or analysis being carried out and you may at any time request for any retained, identifiable samples to be destroyed. By signing the written informed consent you are giving your permission for storing your samples.

These samples will not be used for genetic or DNA testing.

8. HOW WILL I RECEIVE THE STUDY MEDICATION?

The study medication will be presented as hard white or off-white tablets. Each **active** study medication tablet will contain 50mg AXS02. Matching **placebo** tablets will contain the same ingredients as the active study medication, except that AXS02 will be replaced by an equivalent quantity of non-animal sourced cellulose (inactive substance). The study medication will be given to you at the following visits: 3, 4, 5, 6, 7, and 8. At all visits you may receive either AXS02 or placebo; neither you nor your study doctor will know which you are taking, although this information can be obtained in the event it would be medically necessary to obtain it.

Doses are to be timed such that the dose is taken at the site during your visit. You should not eat or drink anything other than water after midnight before your visit. After taking the dose, you will remain in the clinic and will be required to remain upright (sitting or standing) for 30 minutes, with no eating or drinking anything other than water for 120 minutes.

9. WHAT HAPPENS WHEN I FINISH TAKING THE STUDY MEDICATION?

Your regular medical care might include some of the study tests and procedures. The study doctor or a member of the study staff can answer any questions you may have about which tests and procedures are not part of your regular medical care.

After the study is over, you should talk to the study doctor about your future treatment for osteoarthritis.

10. ARE THERE ANY SPECIAL INSTRUCTIONS TO FOLLOW WHILE PARTICIPATING IN THIS STUDY?

While you are in the study, you must:

- Follow the instructions you are given by the study doctor and study staff.
- Come to the study center for all visits with the study doctor or study staff as scheduled.
- Always contact the study doctor or the study staff before you start taking ANY new prescription or over the counter medication since some medications are unsafe to be taken together with the study medication
- Tell the study doctor or study staff if you want to stop taking study medication or stop being in the study at any time (you do not need to provide a reason for discontinuing treatment or stopping your participation in the study if you do not want to).
- Take your study medication as prescribed and return all study medication bottles
- You will be required to carry a patient card with information about your participation in the study and emergency contact information for the study staff.

It is possible that taking AXS02 with your regular medications or supplements may change how AXS02, your regular medications, or your regular supplements work. Please inform your study doctor if you start, stop, or have any changes in medications that you take, including over-the-counter medications (for example, allergy medications, cough and cold remedies, or pain relievers), herbal supplements, vitamins and minerals, as well as medications you receive as a prescription, before or during the study.

You must not currently be participating in a study involving an investigational medication or have received an investigational medication within 30 days from the Visit 2.

You must tell your study doctor if you have been sick or injured or if there have been any changes in your treatments and medications during the study.

11. VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. If you decide not to participate in this research study, or if you decide to withdraw from the research study later on, it will not affect your future treatment, nor will there be penalty, prejudice, or loss of any benefits to which you are otherwise entitled.

You may also choose to discontinue taking study medication at any time, but continue to go to the study visits and have the procedures done. This will help with the study as all the information collected is valuable to determine the safety of the study medication.

Should you decide to participate in this research study, you may discontinue participation at any time, for any reason. Should you decide to withdraw from the research study for any reason, please contact the study doctor immediately. You will be asked to see the study doctor or designated study staff for an Early Termination Visit to collect information that may be important for this study, as well as to ensure your safety. You will be asked to continue to complete your daily telephone diary until the date of your final visit.

If you withdraw or are removed from the study, biological samples (for example, blood or urine samples) that have been collected from you (but not yet fully analyzed) can be destroyed by making a request to the study doctor. However, any data already generated from your samples will be kept to preserve the validity of the study.

Your participation in this study may be discontinued at any time with or without your consent by the study doctor or the Sponsor (Axsome Therapeutics, Inc., the company paying for this study). This could occur if your study doctor considers it to be in your best interest, you do not follow instructions given to you by your study doctor, or if you suffer a complication. This could also happen if your study doctor, the IEC, or the Sponsor ends the study.

NEW FINDINGS

Your study doctor will inform you of any significant new findings that may develop during the course of this clinical research study that may affect your willingness to continue as a participant in this study.

12. WHAT ARE THE RISKS AND POSSIBLE DISCOMFORT OF BEING IN THIS RESEARCH STUDY?

Some adverse reactions (harmful effects of medication) can be expected with medication such as AXS02 and some were reported by subjects treated with AXS02 in prior trials.

You should be aware that AXS02 may cause:

- Hypocalcemia (too little calcium in the blood): was observed in about 1% of patients taking medications similar to AXS02. This is a potentially serious condition which may lead to numbness, fainting, seizures, angina or arrhythmia (irregular heartbeat).
- Osteonecrosis of the jaw (degradation of the jawbone); has been reported in some patients treated with medications similar to AXS02. Most cases have been in cancer patients with high doses who then undergo dental surgery.
- Flu-like symptoms; has been reported in patients treated with medications similar to AXS02. These include things like fever, chills, flushing, and musculoskeletal pain.
- When medications similar to AXS02 were given by orally or via I.V., common harmful effects were fever (30-45%), nausea (25-30%), shortness of breath (20-25%), constipation (10-30%), weakness (24%), arthralgia (pain) (24%), cough (22%), weight loss (16%), diarrhea (15%), depression (14%), abdominal pain (10-15%), insomnia (10-15%) and loss of appetite (2%).

In a previous study of AXS02, the following adverse events were seen:

- Headache; was observed in 50% of subjects. Most events were seen at higher doses than will be given in this study.
- Fever; was observed in 47.2% of subjects. Most events were seen at higher doses than will be given in this study.
- Musculoskeletal pain; was observed in 44.4% of subjects. Most events were seen at higher doses than will be given in this study.
- Diarrhea; was observed in 41.7% of subjects. Most events were seen at higher doses than will be given in this study.
- Abdominal pain; was observed in 22.2% of subjects
- Nausea; was observed in 19.4% of subjects

In the post marketing experience there have been side effects such as:

- Unusual upper leg breaks (fractures),
- Atypical femoral fractures,
- Kidney problems, and
- Eye issues like redness, itching, inflammation and infectious conjunctivitis and iritis.

Ask the study doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

Please tell the study doctor or study staff right away if you have any side effects. There may be other risks or side effects associated with AXS02 that are not known at this time. Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think these problems are related to the study medication.

Risks of Allergic Reaction

Sometimes people have allergic reactions to medications. If you have a very bad allergic reaction, you could die. Some things that happen during an allergic reaction are:

- a rash
- having a hard time breathing
- wheezing
- a sudden drop in blood pressure (making you feel dizzy or lightheaded)
- swelling around the mouth, throat, or eyes
- a fast pulse
- sweating

You should get medical help and contact the study doctor or study staff if you have any of these or any other side effects during the study.

Risks of Taking Placebo

Some people in the study will get placebo instead of AXS02. Taking placebo is the same as not taking anything for your osteoarthritis. If you take placebo during the study, it is possible that your osteoarthritis symptoms may get worse. Please ask the study doctor or study staff if you have any questions about placebo.

Risks of Blood Draws

There are also potential complications resulting from having blood samples taken from your arm. These include pain, bleeding, inflammation of the vein, bruising, light-headedness, and, on rare occasions, infection. This study may involve risks that are currently unknown, so it is important you tell your study doctor of any illnesses and conditions you experience.

Risks of Fasting

Fasting overnight could cause dizziness, headache, stomach discomfort, or fainting. You will be required to fast overnight for all study visits starting at Visit 3, which means that you cannot have had anything to eat or drink (except water) overnight on the days of your study visits. You will be asked to fast for a total of 12 visits (Visit 3 through Visit 14).

Risks of Stopping Your Regular Medications

Participants are not allowed to take certain pain medications, including opioids, during this study. Stopping these medications may lead to increased OA pain.

Risks of Electrocardiogram (ECG)

Skin irritation is rare but could occur during an ECG from the electrodes or gel that is used.

Other Risks

There may be risks or side effects which are unknown at this time.

RISKS OF PREGNANCY

WOMEN

Taking the study drug may involve unknown risks to a pregnant woman, an embryo, fetus (unborn baby) or nursing infant. Therefore, you must be post-menopausal to participate in this study. Post-menopausal means that you are no longer able to become pregnant. You are considered to be post-menopausal if it has been over a year since you last menstruated (had a period) and you have a laboratory test (FSH) that confirms the status. You will also have your blood drawn to confirm that you are post-menopausal to eliminate the risk of becoming pregnant.

MEN

If you are a man, there may be risks to an unborn baby you father during or after the study. The study doctor will talk to you about the birth control options you and/or your partner must use during the study.

PREGNANCY FOLLOW -UP

Should you or your partner become pregnant during the study, you must report it immediately to the study doctor. If this happens, the study doctor will discuss with you what you should do. If you should become pregnant, it is expected that you will obtain and follow good prenatal and postnatal care. You will be responsible for all routine pregnancy-related expenses. If you become pregnant during the study, you will be asked about the outcome of the pregnancy and the health status of your baby. The sponsor would like to follow you through to the end of your pregnancy. You will be asked to sign a consent form before this information is collected. This information may be available to the study doctor, the sponsor, and IRB/IEC Review.

13. WHAT OPTIONS ARE AVAILABLE OTHER THAN BEING IN THIS STUDY?

You do not have to be in this study to receive treatment for your osteoarthritis. Instead of taking part in this study, you may choose to receive treatment with other medications.

These include prescription and over the counter medications and other treatment methods such as physical therapy. The study doctor will discuss with you the risks and benefits of alternative treatments.

14. WHAT ARE POSSIBLE BENEFITS OF BEING IN THIS STUDY?

You may or may not receive a direct benefit from taking part in this study. However, you and future patients may still benefit from this research. The results from this study may help to develop a new treatment for you and others with osteoarthritis and other pain conditions.

15. WHAT WILL I HAVE TO PAY FOR TAKING PART IN THIS RESEARCH STUDY?

While you are in the study, you still need to get regular medical care. You (and/or your health care payer) will still have to pay for the costs of your regular medical care that are not a part of this study. There will be no charge to you for your participation in this study. During the study, the study medication, study-related procedures (X-ray, MRIs, etc.), and study visits will be provided at no charge to you or your insurance company.

16. WILL I BE PAID FOR TAKING PART IN THIS STUDY?

You will be reimbursed up to $50 *per visit* to cover your out-of-pocket and travel expenses. You will be reimbursed an additional $30 for the visits when you have x-rays and MRIs. If you leave the study early for any reason, you will be reimbursed for each study visit you have already completed.

17. WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

Records of your participation in this study will be held confidential except as disclosure is required by law or as described in this informed consent document (under "Authorization to Use and Disclose Protected Health Information"). The study information will be recorded in your medical notes.

All data collected will be identified by a code number and your identity will remain unknown. All information, which is collected about you that leaves the clinic, will have your name and address removed so that you cannot be recognized by it. Personal data, which may be sensitive, e.g. race, ethnic origin, health will be collected and processed electronically but only for research purposes in connection with this study.

Your study doctor is responsible for keeping a code list which makes it possible to link your assigned number to your name. This will be kept in a safe place to ensure that in case of an emergency you can be identified and contacted. The code list will be kept until the last marketing application has been received for the study medication.

Direct access to your medical records will be required by authorized sponsor representatives of Axsome Therapeutics, Inc. and study team to check health related information collected for the study is correct and complete. Your medical records may also be reviewed by the regulatory authorities, ethics committees (US and Australia; United States Food and Drug Administration (FDA) and IRB/IEC) and auditors to check that the study is being carried out correctly. For this reason, the study team will take steps to protect your privacy and will identify you on any study-related documents only with a code.

Only the study team will have the access to the key to the code (the key enables the study team to identify individuals). If the results of this study are published or presented at meetings, you will not be identified.

You have the right to access and correct the information collected about you during the study. You should understand that by signing this consent form you are giving your permission for this to happen. Therefore, absolute confidentiality cannot be guaranteed.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. 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.

18. COMPENSATION FOR INJURY

If you are injured or experience a side effect as a direct result of the product or procedures used in this study, then reasonable and appropriate medical treatment that is not covered by your medical insurance will be provided to you without cost by the study sponsor, Axsome Therapeutics.

During the clinical study, you must only get other medical treatment - except in emergencies - after previously consulting with the study physician. You must inform the study physician immediately about any emergency treatment which has taken place.

By signing this consent form, you will not be waiving any of the legal rights, which you otherwise would have as a subject in a research study.
This commitment for free medical treatment does not include treatment for any other complications or illness experienced during this study if such complications or illness are not a result of your participation in the study.

Be aware that your health care payer might not cover the costs of study-related injuries or illnesses.

19. WHO SHOULD I CONTACT ABOUT MY RIGHTS OR IF I HAVE QUESTIONS?

Before you sign this document, you should ask questions about anything that you do not understand. The study team will answer your questions before, during, and after the study. If you do not think your question was fully answered or do not understand the answer, please continue to ask until you are satisfied.

If you have any questions, concerns or complaints about this study, or how it is being run, or suffer a research-related injury, please do not hesitate to discuss your concerns with the study doctor. The phone numbers to reach the study doctor are on the first page of this document. An Independent Ethics Committee has reviewed the study and has given an approval/favorable opinion of it. This approval does not mean that the study is safe or that you should take part in the study. You must make that decision for yourself.

Tasmanian Health and Medical Human Research Ethics Committee (HREC) is a group of people who perform independent review of research.

This study has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have questions about your rights as a research participant or if you have questions, concerns or complaints about the conduct of this study 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 H0015578.

Please indicate below whether you want us to notify your primary care physician or your specialist of your participation in this study.

Patient's Initials_____

_____ Yes, I want the study doctor to inform my primary care physician/specialist of my participation in this study.

_____ No, I do not want the study doctor to inform my primary care physician/specialist of my participation in this study.

_____ I do not have a primary care physician/specialist.

_____ The study doctor is my primary care physician/specialist.

20. CONSENT

I have read and understand the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily agree to participate in this study until I decide otherwise. I do not give up any of my legal rights by signing this consent document.

A copy of the information sheet and signed consent form will be given to you to keep.

Patient Name	Signature	Date

I have fully informed the patient of all aspects of the trial

Full Name of Investigator conducting consent †	Signature	Date

The study subject has indicated that he/she is unable to read. The consent document has been read to the subject by a member of the study staff, discussed with the subject by a member of the study staff, and the subject has been given an opportunity to ask questions of the study staff.

Name of Witness ‡ (if applicable)	Signature	Date

* Time is needed only if information was provided and consent is given on the same day, or if consent is given and any study-specific activities will be performed on the same day.

† The investigator, or a suitably qualified and trained person designated by the investigator to conduct the informed consent process, must sign and date the consent document during the same interview when the subject signs the consent document.

‡ Impartial Witness: A person, who is independent of the study, who cannot be unfairly influenced by people involved with the study, who attends the informed consent process if the subject cannot read, and who reads the informed consent and any other written information supplied to the subject. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance.