Subject Information and Consent Form

Sponsor / Study Title:	**Flexion Therapeutics, Inc. / "An Open-Label Study to Evaluate the Effect of the Administration of FX006 on Synovial Inflammation in Patients with Osteoarthritis of the Knee"**
Protocol Number:	**FX006-2017-014**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Additional Contact(s): (Study Staff)	**«AdditionalStaffMemberContacts»**
Address:	**«PiLocations»**

READ THE FOLLOWING CAREFULLY

You are being invited to participate in a drug research study. Before you give your consent to be part of this study, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve.

PURPOSE OF STUDY

The study doctor is participating in a research study being conducted by Flexion Therapeutics, Inc. (the Sponsor) evaluating a drug called FX006. FX006 is approved in the United States to manage Osteoarthritis (OA) pain of the knee. OA produces pain in the knee (and other joints) that typically is worsened by activities such as long distance walking and is alleviated by rest. You are being asked to take part in this research study because you have OA of the knee.

The purpose of this research study is to evaluate the effect of a single intra-articular (IA) (into the joint) injection of FX006 to control inflammation in the knee. This will be measured by checking the fluid volume in the study knee by an imaging technique called Magnetic Resonance Imaging (MRI).

Be aware that this consent form refers to FX006 as "study drug."

FX006 is approved in the United States under the trade name Zilretta for single injection in the knee for osteoarthritis.

Initials _____ Date _____

Subject Information and Consent Form

About 100 participants will participate in this study at approximately 10 different research sites. The expected length of time of your participation in the study will be up to 28 weeks (including the screening period).

If you agree to participate in this study, you will be asked not to take the following medications during the study:

- Topical (applied to the skin) or oral NSAIDs [aspirin] (from 5 days prior to Pre-treatment MRI through Week 6, and again from 5 days prior to Week 24 MRI)
- Intravenous (IV), Intramuscular (IM) or oral corticosteroids
- Intraarticular (IA) corticosteroids in any joint
- Any IA intervention in the study knee including aspiration (removing fluid) or the injection of any approved or investigational agent, including viscosupplementation (hyaluronic acid, which acts as a lubricating fluid)
- Any investigational drug, device or biologic
- Immunomodulators, immunosuppressives, or chemotherapeutic agents (all of which can alter your body's ability to fight off foreign substances)
- Live or attenuated (weakened) vaccines

PROCEDURES TO BE FOLLOWED DURING THE STUDY

The study involves a Screening period (which may occur up to 28 days prior to Study Day 1) and 5 study visits following the Study Day 1 visit, for a total of 4 visits at the study site and 2 follow-up telephone calls. If you agree to participate in this study, you will need to sign this form. The study doctor will then need to determine whether this study is suitable for you. If you do not meet the requirements of this study, your participation will end with the screening visit. Below is a description of what will be expected to occur.

If you decide to be in this study, you might have to stop taking or change the dose of your regular medication(s) during the entire study as noted above.

Screening Period

Screening for this study will occur up to 28 days before you receive study drug. This visit to your study doctor should not take more than 3 hours.

During Screening the following information will be reviewed with you to determine whether you are eligible to participate in this study:

- Medical history, including a detailed review of your OA medical history in your study knee

Initials _____ Date _____

Subject Information and Consent Form

- Medications and treatments you have taken including any surgeries or therapy you have had. For your safety, it is very important to tell the study doctor about all medications you are taking, including herbal or "natural" remedies, and to check with the study doctor before you begin taking a new medication while on this study.

You will also have the following evaluations performed to determine whether you are eligible to participate in this study:

- Physical Exam (including weight and height)
- X-ray of your study knee
- Assessment of your study knee
- Electrocardiogram (ECG) – measures the electrical activity of your heart
- Vital signs – blood pressure, heart rate, breathing rate and temperature
- Blood sample collection (about 1 teaspoon) to perform routine laboratory tests, including kidney function, and a pregnancy test (only if you are a woman able to become pregnant, that means, you are not surgically sterile or have not been postmenopausal for at least 1 year),
    - An additional 2 teaspoons of blood will be sampled for infectious diseases including Human Immunodeficiency Virus (HIV), Hepatitis B and C.In order to take part in this study, you must agree for the HIV and Hepatitis tests to be performed on samples of your blood. Depending on local laws, you may have to sign a separate consent form before this testing can start. If you do not want to have the tests, or if you do not wish to be told in the event that some of these tests are abnormal, you should not take part in this study. Accordingly, local laws may require the reporting of positive results. You may prefer to discuss the HIV and Hepatitis tests further with an independent counselor. Your study doctor can arrange this for you. If a positive result for hepatitis or HIV is found, your study doctor will inform your family physician and the local public health authority as required by law. The results of these tests must be negative in order for you to be in the study.
    - The study doctor or study staff will tell you if the pregnancy test results are positive. The results of the pregnancy test must be negative in order for you to be in the study.
- Questionnaire about how much pain, function and stiffness you have in your study knee

Initials _____ Date _____

Subject Information and Consent Form

If your study doctor determines that you are eligible after the screening evaluations are completed and all results are received, you will be invited to take part in the study. You will be expected to make every effort to keep your scheduled visits in the study. If you think you will be unable to meet this responsibility, please inform the study doctor as soon as possible.

Pre-Treatment

You will attend the study clinic within 10 days prior to the planned injection in order to have the following procedures completed:

- Ultrasound examination of your study knee – an ultrasound examination uses high frequency sound waves to look at structures inside the body.
- MRI of your study knee – This test uses powerful magnets, radio waves, and a computer to take pictures inside your body. You will lie on a table inside the MRI machine which is a large tube with a hole at both ends. The MRI test will include administration of contrast agent (dye) to provide special pictures of your knee. Contrast agent is administered through an intravenous catheter (a small tube placed in your vein) inserted in your arm.

Once it is confirmed that the MRI is acceptable, you will be scheduled to come in for the Study Day 1 visit.

Treatment Period

Study Day 1

You will attend the study clinic on the day that your study knee will be injected with the study drug (Study Day 1). On Study Day 1, your study doctor will perform several evaluations to make sure you are still eligible for the study. These procedures and tests include:

- Review of eligibility criteria
- Updated medical history
- Review of prior treatment and medications
- Examination and assessment of your study knee
- Vital signs - blood pressure, heart rate, breathing rate and temperature
- Blood sample collection (about 1 teaspoon) for testing of markers (Interleukin-1 Beta) for the presence of inflammation phenotypes (observable traits) that may be associated with your OA.

Initials _____ Date _____

Subject Information and Consent Form

- Urine sample collection to perform a pregnancy test (only if you are a woman able to become pregnant)
- Questionnaires about how much pain, function and stiffness you have in your study knee and quality of life

After those assessments are complete, a study doctor will clean your study knee with a bactericidal solution and a numbing agent will be used based on standard of care at your study site. The study doctor will place a needle inside your knee joint and withdraw (aspirate) any joint fluid from your study knee. You will then receive your study drug given as a single direct injection into the study knee joint through the same needle used to aspirate your knee.

The Joint fluid removed from your knee will be kept for a maximum of 5 years for potential future testing of biomarkers that may be associated with your OA. There is no plan to complete genetic testing as part of this potential testing. You will be able to withdraw your consent at any time that these samples are held in storage by sending a letter to your study doctor.

The study staff will assess how you are feeling during and after you receive study drug. You will be advised to avoid strenuous activities or prolonged weight-bearing activities for approximately 24 to 48 hours following the injection. You may need to stay at the study clinic after the injection if the study doctor feels you need to be monitored longer.

Follow-up Period (Through Week 24)

You should contact the study doctor if you think you may be having a side effect of the study drug at any time during the course of this study.

You will return to the clinic for 2 additional visits after Study Day 1, and you will have 2 follow-up phone calls with the site staff. Each visit will last up to 2 hours, depending on the procedures performed. During each visit, the study staff will discuss with you how you have been feeling, any health problems that you are having, and what medications you have taken since the last visit. You will have the following tests performed:

Week 6 (± 7 days)

- Blood sample collection (about 1 teaspoon) to check your kidney function. This is done within 30 days of the Week 6 to make sure it is safe for you to receive the contrast agent for the MRI at your Week 6 (± 7 days) visit
- Examination and assessment of your study knee
- MRI test of your study knee
- Questionnaires about how much pain, function and stiffness you have in your study knee and about your quality of life

Initials _____ Date _____

Subject Information and Consent Form

Week 12 (± 7 days) Phone Call and Week 18 (± 7 days) Phone Call

- The study staff will ask you questions over the phone about how much pain, function and stiffness you have in your study knee

Week 24/End of Study (± 7 days)

- Blood sample collection (about 1 teaspoon) to check your kidney function. This is done within 30 days of the Week 24 visit to make sure it is safe for you to receive the contrast agent for the MRI at your Week 24/End of Study (± 7 days) visit
- Physical Examination (including height and weight)
- Assessment of your study knee
- MRI of your study knee
- Vital Signs (blood pressure, heart rate, breathing rate and temperature)
- Blood sample collection to perform routine laboratory tests (about 1 teaspoon)
- Urine sample collection to perform a pregnancy test (only if you are a woman able to become pregnant)
- Questionnaires about how much pain, function and stiffness you have in your study knee and about your quality of life

FORESEEABLE RISKS AND DISCOMFORTS

All drugs may cause side effects. There is a risk that your condition may not improve with any treatment received on this study.

The active ingredient in FX006 is triamcinolone acetonide. Triamcinolone acetonide is a corticosteroid that has been injected into the knees of people with osteoarthritis for many years. FX006 keeps triamcinolone acetonide in the joint longer than injections of other forms of triamcinolone acetonide.

Injection of corticosteroids into joints is a common medical procedure, with approximately six million injections in the United States each year. The risks associated with the injection of corticosteroids into joints have been well studied. In completed studies, a total of 687 patients have been injected with a single injection of FX006. To date there have been no new safety concerns compared to the known effects of triamcinolone acetonide.

The most common side effects (two percent or more of the time) seen to date in participants treated with FX006 are the following:

- Joint pain (9.8%)
- Joint swelling (2.8%)
- Headaches (5.4%)
- Upper respiratory infection (3.1%)

Initials _____ Date _____

Subject Information and Consent Form

- Back pain (2.3%)
- Bruising (2.3%)
- Cold symptoms (2.2%)

There is a rare chance that the procedure may not be able to be completed, or that you will not receive the entire amount of the study drug. If this happens, you will be informed by site personnel and will complete all assessments through the end of the study.

Possible side effects of corticosteroids outside of the knee joint: For people with diabetes, there may be a temporary hyperglycemia (increase in blood sugar) associated with injection. There may be temporary elevated blood pressure associated with injection. Injection of corticosteroids is sometimes associated with a flushing (reddening) reaction of the face and upper body. Rarely, corticosteroid injections have been associated with a temporary feeling of numbness and weakness in the limbs. Also rarely, repeated corticosteroid injections have been associated with conditions limiting the body's ability to fight infections or causing low blood pressure, changes in weight and fat deposits, or an allergic reaction. These rare events could possibly be life threatening.

Possible side effects of corticosteroids specific to the knee joint: The most common side effects in the joint from injected corticosteroids are thinning and lightening of the skin at the site of injection. Injection of corticosteroids has been associated with joint infection and joint deterioration has also been reported.

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

Allergic Reaction: Sometimes people have allergic reactions to drugs. If you have a very bad allergic reaction, you could die. Some things that happen during an allergic reaction that could be a sign or symptom of a life-threatening allergic (anaphylaxis) 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 staff if you have any of these or other side effects during the study. Please tell the study doctor if you have ever had allergic reactions that included any of these signs or symptoms in the past.

Initials _____ Date _____

Subject Information and Consent Form

Stopping Regular Medication: If you stop or change the dose of your regular medication to be in the study, your osteoarthritis symptoms might come back or get worse. Please tell the study doctor or staff right away if you have any problems when you stop using or change the dose of your regular medication.

Joint Fluid Removal: Joint fluid will be removed from the study knee prior to intraarticular injection of study drug. There is a risk of infection as well as fainting with joint fluid removal.

Injection into the joint: The study drug will be injected into the study knee joint. Injections of corticosteroids into the knee may result in pain, swelling, restriction of joint movement, and infection of the joint. Rarely, there may be a flare reaction that simultaneously produces pain, warmth, joint swelling, and fluid in the joint that will last for days or weeks. In addition, injections carry a risk of damage to blood vessels, muscles, nerves, and other tissues. Rarely, multiple injections of joints have been associated with deterioration of joint structures.

Blood Samples: Blood sampling may cause pain, bleeding and/or bruising at the site where the needle enters the skin. Lightheadedness, dizziness, fainting, and in rare cases, infection, may occur.

Electrocardiogram (ECG): The only known complication from a diagnostic ECG is possible skin irritation from the ECG electrode pads or discomfort when removing the pads.

X-Ray: There is exposure to small amounts of radiation with X-ray. The risk of developing a radiation-induced cancer or cataracts at some time later in life or defects due to damaged ovarian cells or sperm cells is very low.

MRI: During the MRI, you may feel mild vibrations in your body. The machine will produce a loud knocking noise. This is normal. You may receive earplugs or earphones to protect your ears. The scanner used in the MRI is a small space. Some people may feel uncomfortable or become anxious while in the scanner. The scanner has an intercom, which lets you to speak to the staff during the procedure. If you feel ill or anxious during scanning, tell the MRI staff and the scanning will be stopped if you wish. The MRI will require a catheter to be inserted into one of your veins to inject the MRI contrast agent. The contrast agent gadolinium will be injected into your vein to enhance visibility. You may experience coolness, minor swelling, pain, bleeding and/or bruising at the injection site. The most common risks associated with gadolinium are rash and hives. Rarely, mild nausea, headache, temporary low blood pressure, chest pain, back pain, fever, weakness, seizures and shortness of breath from narrowing of the air tubes in your lungs may occur. A rare and severe disease called nephrogenic systemic fibrosis (involves fibrosis/hardening of skin, joints, eyes, and internal organs) has occurred in certain

Initials _____ Date _____

Subject Information and Consent Form

individuals with severe kidney disease who received gadolinium-based contrast agents. There is no risk for this disease in individuals with normal or mild problems in kidney function. Before you undergo the MRI with contrast, your study doctor will determine if the contrast dye is safe for you. The MRI scan does not expose you to x-ray radiation. You may have an allergic reaction to the contrast agent. If you have implants containing metal, you face certain risks. The magnets used in an MRI can cause problems with pacemakers or make implanted screws or pins shift in the body. If you have metal or a device in your body, you must inform your study doctor.

Ultrasound: Diagnostic ultrasound is a safe procedure that uses low-power sound waves. There are no known risks. If your knee is tender, the ultrasound exam could hurt a bit.

Questionnaires: Filling out the questionnaires could lead you to feel uncomfortable or upset. Please tell the study doctor or staff if you feel uncomfortable or upset while filling out a questionnaire at the site or over the phone. You have the right to refuse to answer any questions.

Loss of Confidentiality: There is a risk of loss of confidentiality of your information that is used in this study. You will read more about the protection of your information later in this form. Please ask the study doctor or study staff if you would like to know more about how your information will be protected while you are in this study.

For Men: Specific risks of FX006 to the male reproductive system are unknown at this time. However, the following risks are defined for corticosteroids in general including Kenalog-40®: Corticosteroids may increase or decrease motility and number of spermatozoa in some people. If your partner becomes pregnant during the study or through Week 24 if you discontinue early, you must tell the study doctor immediately. The study doctor will advise you regarding your partner's further medical care and your study participation. The study doctor or study staff will ask for information about the pregnancy and the birth of the baby. The study doctor or study staff will share this information with the sponsor and institutional review board (IRB) (a group of people who review research studies to protect the rights and welfare of research participants).

For Women: Specific risks of FX006 to the female reproductive system and to the human embryo, fetus, or nursing infant are unknown at this time. Some drugs can cause premature (early) birth or birth defects. However, the risks are defined for corticosteroids in general including Kenalog-40®. Corticosteroids taken by the mother have been shown to cause birth defects and affect infant growth.

You cannot take part in this study if you are pregnant or nursing an infant. If you are a woman who is able to become pregnant, you must agree not to become pregnant during your participation in this study or through Week 24 if you discontinue early.

Initials _____ Date _____

Subject Information and Consent Form

Female and male participants must use birth control throughout the study. The form of birth control you use must be discussed with, and approved by, the study doctor before you begin the study. You must agree to use one of the following effective birth control methods: abstinence (if this is consistent with your lifestyle), oral, injected, or implanted hormonal methods of contraception, condoms, a diaphragm or cervical cap with spermicidal foam/gel/film/cream/suppository, intrauterine device (IUD), intrauterine system, or intercourse with a surgically sterile partner (post-vasectomy/hysterectomy, or tubal ligation) are acceptable for use during the study. The birth control methods listed are not totally effective in preventing pregnancy. If you or your partner becomes pregnant during the study, you must tell the study doctor immediately. The study doctor will advise you regarding your further medical care and study participation. The study doctor or study staff will ask for information about the pregnancy and the birth of the baby. The study doctor or study staff will share this information with the sponsor and IRB.

Unknown Risks: There may be risks associated with the injection of FX006 that are not currently known. You could have problems which include your osteoarthritis of the knee getting worse or even death. Significant new findings that develop during the course of the study which may relate to your willingness to continue participation will be provided to you in a timely manner.

Although unlikely, if you suffer a serious or lasting injury as a result of participation in this study, it may affect your ability to obtain private health insurance, your employability, and/or quality of life.

If you experience any side effects, you should contact the study doctor immediately. 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 drug.

COMPENSATION FOR STUDY-RELATED INJURY

If you have any questions during the study or if you experience a side effect or research related injury, contact the study doctor.

In the event of a research-related injury, necessary medical treatment will be provided primarily through the study doctor. The Sponsor will reimburse you the reasonable costs, in excess of what is covered by your private medical health insurance; of any immediate care and/or treatment you receive for injury that is determined by the study doctor to be a direct result of the use of the FX006. The study doctor shall determine the medical care which is necessary and appropriate. If there is an emergency, please seek immediate treatment outside of the study doctor if you are not able to reach the study doctor. Injury or illness resulting from the use of the FX006 does not include the normal progression of your disease or any underlying pre-existing medical conditions.

Initials _____ Date _____

Subject Information and Consent Form

You agree to cooperate in obtaining any proceeds from insurance or other third-party coverage that may be available. There are no plans to provide other financial compensation (including without limitation) for such things as lost wages, disability, or discomfort due to research-related injury.

Be aware that your health care payer/insurer might not cover the costs of study-related injuries or illness. Provision of medical care and/or payment of medical expenses does not imply fault or wrongdoing on the part of the Sponsor, your study doctor, or the study site. If you experience an injury or side effects, you should contact your study doctor listed on page 1.

Please note that you do not give up any of your legal rights by signing this consent form, including your right at law to claim compensation for injury where you can prove negligence.

POTENTIAL BENEFITS OF THE STUDY

No direct benefit is guaranteed to you from taking part in this study. Your condition may improve, remain the same, or worsen during the study. It is expected that new information, which may benefit participants or society in general, will be obtained by this study.

SPONSORING COMPANY

Flexion Therapeutics, Inc. will pay the study doctor (and/or the study clinic) for conducting this study and for your participation.

COSTS

The study drug, clinical evaluations, and study procedures will be provided at no charge to you, your private medical insurance (if any), or the public health insurance plan.

PAYMENT

<<Site Specific Compensation language>>

Your participation in this study may contribute to the development of FX006, from which the Sponsor or others may receive economic benefit. You will have no rights to any patents or discoveries arising from this study and you will receive no economic benefit.

ALTERNATIVE TREATMENT

Instead of taking part in this study, you may choose to receive no treatment or to receive standard treatment, which may include medications such as Tylenol®, non-steroidal anti-

Initials _____ Date _____

Subject Information and Consent Form

inflammatory drugs such as Advil®, other IA steroids like TCA IR (commonly referred to as cortisone shots), hyaluronic acid such as Synvisc-One®, other pain therapies, physical therapy or surgery. The risks and benefits of alternative (other) standard treatments and courses of therapy will be explained to you by the study doctor. The study doctor will answer any questions you have about these other treatments. In addition, you may discuss your options with your regular health care provider.

FX006 is approved in the United States for a single injection in the knee. The study doctor will discuss treatment options with you at the end of the study.

VOLUNTARY PARTICIPATION / WITHDRAWAL FROM STUDY

Your participation in this study is voluntary. You may refuse to participate, or withdraw from the study at any time, without penalty or loss of benefits to which you are otherwise entitled. This will not affect the medical care you receive from the study doctor. You must tell the study doctor if you wish to stop taking part in the study. Your participation in this study may be discontinued, without your consent, at any time by the study doctor if he/she believes that participation in the study is no longer in your best interest or if the study is stopped by the Sponsor. The regulatory authorities (for example, US Food and Drug Administration), or the Sponsor may also discontinue your participation in the study.

If you decide to withdraw from the study or the study doctor requests your withdrawal, you will be asked to have a final visit for safety reasons. If you leave the study, the study doctor and study staff will still be able to use your information that they have already collected.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact**:**

Initials _____ Date _____

Subject Information and Consent Form

By mail:

Study Subject Adviser
Advarra IRB
6940 Columbia Gateway Drive, Suite 110
Columbia, MD 21046

- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00026180.

CONFIDENTIALITY

To the extent permitted by laws and/or regulations, your medical records will be kept confidential and will not be made publicly available. As part of this research, the study doctor will collect the results of your study-related tests, including results of tests for HIV and other communicable diseases and illegal drug use, and procedures and may also access your personal medical records for health information such as past medical history and test results.

Information from this study will be submitted to the Sponsor, Sponsor's representatives or other entities the Sponsor does business with, and to the US Food and Drug Administration and possibly to governmental agencies in other countries where the study drug may be considered for approval. The information obtained from this study, including the results of all tests you undergo, will be held in both computerized and manual filing systems. Except as required by law, you will not be identified on any study form by name, address, telephone number or any other direct personal identifier. Instead, you will be assigned a participant identification number. The study doctor will keep a list that matches participant identification numbers to participant names, but the study doctor will not send that list to the Sponsor. However, the study forms will contain other information about you, such as your age, sex and medical history. It is possible that this other information could be used to identify you even though your name does not appear.

The results of this research may be presented at scientific or medical meetings or published in scientific journals, but your identity will not be made known.

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.

Initials _____ Date _____

Subject Information and Consent Form

AGREEMENT OF DECISION TO PARTICIPATE

I have been given enough time to read this consent. This study has been explained to my satisfaction and all of my questions relating to taking the study drug, the study procedures, possible risks and discomforts, and side effects have been answered. I have been given the opportunity to consider whether or not to participate. If I have any further questions regarding this study, or in the event of a study-related injury, I should contact the appropriate person named above. I voluntarily agree to take part in this study. By signing this document, I have not waived any of my legal rights.

I authorize the collection, access, use and disclosure of my information as described above.

I will receive a copy of this signed informed consent form.

Printed Name of Subject	Time of Signature
Signature of Subject	Date

I have given a verbal explanation of the research study, its procedures and risks and I believe that the participant has understood that explanation. I attest that the participant had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to be in this study.

Printed Name of Person Obtaining Consent	Time of Signature
Signature of Person Obtaining Consent	Date

Initials _____ Date _____