Study to Assess the Safety and Efficacy of FX006 Administered to Patients With Greater Trochanteric Bursitis

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Clinical Research Protocol

Study to assess the safety and efficacy of FX006 administered to patients with greater trochanteric bursitis

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Approval:

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LIST OF ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
PI	Principal Investigator
SAE	Serious Adverse Event
NPRS	Numeric Pain Rating Scale
PGIC	Patient Global Impression of Change
IDS	Investigational Drug Service
MRI	Magnetic Resonance Imaging

PROTOCOL SYNOPSIS

TITLE	Study to assess the safety and efficacy of FX006 administered to patients with greater trochanteric bursitis
SPONSOR INVESTIGATOR	Dr. British Bawa, MD
BACKGROUND/ RATIONALE	Zilretta is approved for intra-articular injection into the knee joint for treatment of osteoarthritis (1). There are ongoing studies for intra-articular injection into the other large joints including the shoulder and hip joints (2). To our knowledge, there has been no prior study to prove efficacy of injection of the extended release steroid into the bursa. The bursae surrounding the hip joint including the iliopsoas and the greater trochanteric bursa are some of the larger bursae in the body. Conventional treatment for inflammation of these bursae is injection of corticosteroids (3). We believe that a long acting corticosteroid, if efficacious, can have a great impact. There is a significant population of patients suffering from chronic bursal pain, who might benefit. At our institute, bursal injection of the steroid in the region of hips is one of the most common locations, second to joint injections. To our understanding, the bursa surrounding the hip are deep enough to avoid side effects associated with subcutaneous injection of steroid. The current proposal is a pilot study.
STUDY DESIGN	This is a prospective, open-label, pilot study, to assess the safety and efficacy of **FX006 (triamcinolone acetonide extended release injectable suspension 32 mg)**, administered to patients with greater trochanteric bursitis.
PRIMARY OBJECTIVE	The primary objective will be to determine the safety and efficacy of this drug in bursal injections by monitoring the improvement in the pain from baseline, as established using the using a Numeric Pain Rating Scale (NPRS) score at the end of 12 weeks.
SECONDARY OBJECTIVES	Secondary objective is to determine any alteration in the Patient Global Impression of Change (PGIC) measure. This is used as an indicator to assess the patient's impression to change in treatments, to their chronic pain.
PRIMARY END POINT	The primary endpoint will be the improvement in the pain from baseline, at the end of week 12, as determined by the NPRS pain score
SECONDARY END POINT	The secondary endpoint will be any alteration in the PGIC measure, at the end of week 12.

NUMBER OF SUBJECTS	24 patients
SUBJECT SELECTION CRITERIA	Inclusion Criteria: • Written consent to participate in the study • Male or female greater than or equal to 18 years of age • Symptoms consistent with greater trochanteric bursitis for greater than or equal to 3 months prior to screening (patient reported is acceptable) • Pain in hip for greater than 15 days over the last month (as reported by the patient). • Hip bursitis as determined by clinical examination and clinical features. Where Magnetic Resonance Imaging (MRI) data is available, it will be used to confirm the bursitis diagnosis. Also, pain relief in subjects that have been treated with bursal injections containing an anesthetic (such as ropivacaine) is in itself indicative of bursitis. • Body mass index (BMI) less than or equal to 40 kg/m2 • Ambulatory and in good general health • Willing and able to comply with the study procedures and visit schedules and able to follow verbal and written instructions. • Willing to abstain from use of protocol-restricted medications during the study Exclusion Criteria: • Hip Arthroplasty • Hip osteoarthritis, iliopsoas bursitis, reactive arthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or arthritis associated with inflammatory bowel disease • History of local infection around the bursa. • Lack of pain relief with the intrabursal treatments containing an anesthetic • Intra-bursal treatment of any bursa with any of the following agents within three (3) months of screening: any corticosteroid preparation (investigational or marketed, including FX006); and/or six (6) months for any biologic agent (e.g., platelet rich plasma (PRP) injection, stem cells, prolotherapy, amniotic fluid injection; investigational or marketed). • Parenteral or oral corticosteroids (investigational or marketed) within 3 months of Screening • Inhaled, intranasal or topical corticosteroids (investigational or marketed) within 2 weeks of screening. • Females who are pregnant or nursing or plan to become pregnant during the study; women who plan to conceive

TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	24 patients will be injected with the 5ml of FX006. This injection may be followed with up to 3ml of ropivacaine (depending on the capacity of the bursa), under ultrasound guidance.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATIO	N/A
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	The study will be completed in week 12 and all recorded patients' NPRS, PGIC and emergent findings, if any will be compiled into a HIPAA compliant database.
CONCOMITANT MEDICATIONS	Allowed. Exclusions are listed below. Prohibited: • Intra-bursal treatment of any bursa with any of the following agents within six (6) months of Screening: any corticosteroid preparation (investigational or marketed, including FX006), any biologic agent (e.g., platelet rich plasma (PRP) injection, stem cells, prolotherapy, amniotic fluid injection; investigational or marketed). • Parenteral or oral corticosteroids (investigational or marketed) within 3 months of Screening • Inhaled, intranasal or topical corticosteroids (investigational or marketed) within 2 weeks of Screening.
EFFICACY EVALUATIONS	Follow up telephone interviews will be performed in 1, 2, 4, 8, and 12 weeks to assess the patient for any adverse events and also to obtain the NPRS and PGIC scores.
SAFETY EVALUATIONS	Subjects will be questioned about any change in their perception of well-being or adverse effects if any, as compared to baseline

STATISTICS **Primary Analysis Plan**	We plan to enroll 24 patients for the pilot study. This sample size is determined by the projected availability of eligible patients within the proposed study period (6 months). Descriptive statistics will be reported for demographics and all clinical variables collected in this study. For the efficacy evaluated by NPRS and PGIC, we will use appropriate summary statistics (e.g. mean + standard deviation for variables with normal distribution or median and interquartile range for variables with skewed distribution) to report NPRS and PGIC at each time point and analyze their changes over time. For safety evaluated, we will report the frequency and percentage of patients who have received any treatment to emergent adverse events within 12 weeks.

1 BACKGROUND/RATIONALE

Zilretta is approved for intra-articular injection into the knee joint for treatment of osteoarthritis (1). There are ongoing studies for intra-articular injection into the other large joints including the shoulder and hip joints (2). To our knowledge there has been no prior study to prove efficacy of injection of the extended release steroid into the bursa. The bursae surrounding the hip joint including the iliopsoas and the greater trochanteric bursa are some of the larger bursae in the body. Conventional treatment for inflammation of these bursae is injection of corticosteroids (3). We believe that a long acting corticosteroid, if efficacious, can have a great impact. There is a significant population of patients suffering from chronic bursal pain, who might benefit. At our institution, bursal injection of the steroid in the region of hips is one of the most common locations, second only to joint injections. To our understanding, the bursa surrounding the hip are deep enough to avoid side effects associated with subcutaneous injection of steroid. The current proposal is a pilot study.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective will be to determine the safety and efficacy of this drug in bursal injections by monitoring the improvement in the pain from baseline, as established using the using a Numeric Pain Rating Scale (NPRS) score at the end of 12 weeks. Safety of the extended-release 32 mg FX006 administered to patients with greater trochanteric bursitis will be evaluated with a follow-up to determine if there were any adverse events within 12 weeks from the time of injection.

2.2 Secondary Objectives

Secondary objective is to determine any alteration in the Patient Global Impression of Change (PGIC) measure. This is used as an indicator to assess the patient's impression to change in treatments to chronic pain.

3. STUDY DESIGN

3.1 Study Overview

This is a consented, pilot study in patients with pain and bursitis involving the greater trochanteric bursa, with administration of 32 mg FX006. The study will be conducted in male and female patients 18 years of age or older with symptomatic greater trochanteric bursitis. Each patient will be screened for eligibility with an ultrasound to confirm the diagnosis of bursitis, in the absence of prior MRI imaging done in the preceding three months. Based on the inclusion/exclusion requirements, they will be offered participation in the study to receive an intra-bursal injection of 32 mg FX006. Eligible and participating patients will receive treatment under ultrasound image guidance to the greater trochanteric bursa. Patients will be followed up by phone at 1, 2, 4, 8, and 12 weeks and mean NPRS pain scores and PGIC scores will be recorded. Adverse events, if any, will be reported immediately to the primary physician and any subsequent follow-up will be reported. The study will be completed in week 12 and all recorded patients' NPRS, PGIC and emergent findings, if any will be compiled into a HIPAA compliant database.

4 CRITERIA FOR EVALUATION

4.1 Primary Endpoint

The primary endpoint will be the improvement in the pain from baseline, at the end of week 12 as determined by the NPRS pain score.

4.2 Secondary/Exploratory Endpoints

The secondary endpoint will be any alteration in the PGIC measure, at the end of week 12.

4.3 Safety Evaluations

Incidence of adverse events will be recorded and reported to appropriate bodies including the UTHealth IRB and FDA, if indicated.

5 SUBJECT SELECTION

5.1 Study Population

Subjects with a diagnosis of bursitis of greater trochanter, who meet the inclusion and exclusion criteria will be eligible for participation in this study.

5.2 Inclusion Criteria

1. Written consent to participate in the study
2. Male or female greater than or equal to 18 years of age
3. Symptoms consistent with bursitis of greater trochanter for greater than or equal to 3 months prior to Screening (patient reported is acceptable)
4. Pain in hip for greater than 15 days over the last month (as reported by the patient)
5. Hip bursitis as determined by clinical examination and clinical features. Where Magnetic Resonance Imaging (MRI) data is available, it will be used to confirm the bursitis diagnosis. Also, pain relief in subjects that have been treated with bursal injections containing an

anesthetic (such as ropivacaine) is in itself indicative of bursitis
6. Body mass index (BMI) less than or equal to 40 kg/m2
7. Ambulatory and in good general health
8. Willing and able to comply with the study procedures and visit schedules and able to follow verbal and written instructions.
9. Willing to abstain from use of protocol-restricted medications during the study

5.3 Exclusion Criteria

1. Patients who have had hip arthroplasty or conditions such as, hip osteoarthritis, iliopsoas bursitis, reactive arthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or arthritis associated with inflammatory bowel disease
2. History of local infection around the bursa;
3. Lack of pain relief with intra-bursal treatments containing an anesthetic
4. Intra-bursal treatment of any bursa with any of the following agents within three (3) months of screening: any corticosteroid preparation (investigational or marketed, including FX006); and/or six (6) months for any biologic agent (e.g., platelet rich plasma (PRP) injection, stem cells, prolotherapy, amniotic fluid injection; investigational or marketed).
5. Parenteral or oral corticosteroids (investigational or marketed) within 3 months of screening; Inhaled, intranasal or topical corticosteroids (investigational or marketed) within 2 weeks of screening;
6. Females who are pregnant or nursing or plan to become pregnant during the study; women who plan to conceive during the study.

6 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies medication.

6.1 Allowed Medications and Treatments

Standard therapy for hip pain is allowed, except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

6.2 Prohibited Medications and Treatments

The following medications are prohibited during the study:

- Intra-bursal treatment of any bursa with any of the following agents within six (6) months of screening: any corticosteroid preparation (investigational or marketed, including FX006), any biologic agent (e.g., platelet rich plasma (PRP) injection, stem cells, prolotherapy, amniotic fluid injection; investigational or marketed).
- Parenteral or oral corticosteroids (investigational or marketed) within 3 months of screening
- Inhaled, intranasal or topical corticosteroids (investigational or marketed) within 2 weeks of screening.

7.1 Treatment Plan

The patient will make a one-time visit to the outpatient radiology department at Memorial Hermann Hospital at the Texas Medical Center, and will be expected to stay for a maximum of 2 hours. Each patient will be consented for the procedure and a baseline assessment using the NPRS and PGIC measures will be made.

24 patients will be injected with the 5ml of FX006. This injection may be followed with up to 3ml of ropivacaine (depending on the capacity of the bursa), under ultrasound guidance. The data collected from the patient and subsequent follow-up will be maintained by the clinical team throughout the 12 weeks of the subject participation.

7.1.1 Formulation of Test Product

FX006 is an extended-release formulation of Triamcinolone Acetonide (TA), developed by Flexion Therapeutics, for the management of pain of osteoarthritis. FX006 contains TA, formulated in 75:25 polylactic-co-glycolic acid (PLGA) microspheres with a nominal drug load of 25% and is provided as a sterile white to off-white powder for reconstitution. The drug product is reconstituted with diluent containing an isotonic, sterile aqueous solution of sodium chloride, carboxymethylcellulose sodium and polysorbate-80 to form a suspension prior to Intra-Articular injection.

7.1.2 Packaging and Labeling

Study drug is supplied in a package kit containing one (1) vial of FX006, one (1) vial Diluent, and a vial adapter.

The FX006 and diluent vials will be labeled with the respective unique lot numbers within the packaged kit, which will be affixed with its own label and kit number.

7.2 Supply of Study Drug at the Site

Flexion Therapeutics, Inc. will ship Study Drug to the investigational sites. The initial FX006 study drug shipment will be made after site activation (i.e., all required regulatory documentation has been received by Flexion Therapeutics, Inc. and a contract has been executed). Subsequent study drug shipments will be made after site request for resupply. All drugs will be stored in the Investigational Drug Service (IDS) pharmacy of the Memorial Hermann Hospital at the Texas Medical Center, prior to use, in a monitored refrigerator, and dispensed as prescribed.

7.2.1 Dosage/Dosage Regimen

FX006 will be reconstituted according to the instructions for use, using aseptic techniques. It will be administered at the standard dosage of 32 mg and injected into the hip bursa using ultrasound guidance. This injection may be followed with up to 3 mL of ropivacaine (the actual volume of ropivacaine injected will be up to the discretion of the radiologist and will be based on the capacity of the bursa). Medication will be administered once per subject.

7.2.2 Dispensing

FX006 will be dispensed by the IDS pharmacy to the research nurse or other study personnel after the prescription is submitted to the pharmacy. Research personnel that are receiving FX006 will sign the chain of custody log in the pharmacy. FX006 will be dispensed in packaging supplied by manufacturer.

7.2.3 Administration Instructions

FX006 will be administered in standard dosage of 32 mg injected into hip bursa using ultrasound guidance using aseptic technique. This injection may be followed with up to 3 mL of ropivacaine (depending on the capacity of the bursa). Medication will be administered once per subject.

7.2.4 Storage

Study drug will be stored by the IDS pharmacy in a designated, monitored refrigerator, 2 to 8ºC. If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this may be reported to Flexion Therapeutics, Inc., for guidance on disposition.

7.3 Study Drug Accountability

An accurate and current accounting of the dispensing study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The study drug dispensed will be recorded on the Investigational Drug Accountability Record. Used study drug vials will be disposed of appropriately according to the site protocols.

8 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is detailed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject.

8.1 Clinical Assessments

8.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at screening and during each follow-up telephone call and upon study discontinuation. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

8.1.2 Demographics

Demographic information (date of birth and gender) will be recorded at screening.

8.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent history, and information regarding underlying diseases will be recorded at screening.

8.1.4 Physical Examination

A focused physical examination will be performed by either the investigator or a sub-investigator who is a physician at screening.

8.1.5 Vital Signs

Measurement of body temperature, blood pressure, pulse and respiration will be performed after the subject has rested for 5 minutes on the treatment date.

8.1.6 Other Clinical Procedures

Subjects will be asked about their Numeric Pain Rating System (NPRS) on a 1 to 10 scale, and will be asked about their Patient Global Impression of Change (PGIC) scores during each follow-up telephone call.

8.1.7 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to the study drug will be recorded on the case report form (CRF).

9 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

9.1 Collection

Adverse events will be collected from the time of medication administration until completion of the follow-up telephone calls at week 12 or until subject participation in study ends.

The Investigator or other medical trained personnel will probe, via discussion with the subject, for the occurrence of Adverse Events during each subject contact and record the information in the source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), outcome, and treatment. The Investigator, or other medical trained personnel will also assess the seriousness and severity of the event, and relationship of the event to study drug according to the definitions below. If unrelated to study drug, the more likely cause of the event will also be assessed and recorded.

9.2 Definitions

Adverse Event (AE): Any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

Serious Adverse Event (SAE): An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, ("Life-threatening" refers to an event in which the patient was at substantial risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization,
    - Note: Adverse events requiring hospitalizations that are less than 24 hours in duration generally do not meet this criterion. A scheduled hospitalization for an elective procedure or a pre-existing condition that has not worsened during participation in the

study does not meet this criterion.

- Results in permanent or significant disability/incapacity; a substantial disruption of the patient's ability to carry out normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event: event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above.

Severity: the intensity of the adverse event. This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. The severity of AEs will be assessed according to the following definitions:

Table 1: AE Severity Grading

Severity	Description
Mild	The AE is noticeable to the patient and/or the Investigator, but does not interfere with routine activity.
Moderate	The AE interferes with routine activity, but responds to symptomatic therapy or rest.
Severe	The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy

Causal Relationship: A medically-qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, as related or not related, based on clinical judgment and using all available information. Possible causes of the AE should be considered, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors, the temporal association between drug exposure and onset of the AE, and whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product. The causal relationship between the study medication and the AE will be assessed using one of the following categories:

Causal relationship	Description
Not Related	An AE is not associated with study medication if: ○ Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the study medication); or ○ Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant treatments).

Related	An AE is attributed to the study medication if: ○ There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of study medication); and ○ The AE is more likely explained by the investigational product than by another cause (i.e., the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the investigational product).

9.3 Serious Adverse Event Reporting

An event that is serious must be recorded on the source document and requires expeditious handling to comply with regulatory requirements.

- Reporting to IRB: In accordance with the standard operating procedures and policies ofthe local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB as soon as possible but not later than 7 days after first knowledge by investigator.
- Reporting to Flexion: All serious adverse events in patients treated with Zilretta must be reported to Flexion within 3 calendar days. The Investigator should attempt to collect as much information about the adverse event as needed to get a complete medical understanding. Any new information collected on an SAE should be forwarded to Flexion as it becomes available.

9.4 Reporting to the US FDA

All serious adverse events which are considered causally related to Zilretta must be assessed for whether it is expected per the Investigators Brochure. An unexpected event means that it is not described within the reference safety information (the Zilretta IB) as associated with Zilretta.
If an event is assessed as serious, related to Zilretta, and unexpected, it must be reported to the FDA according to 21CFR312.32.

9.5 Pregnancy

All pregnancies, female patients or female partners of male patients during the study, must be evaluated by the Investigator and/or other medically qualified personnel. The Investigator must continue to follow the pregnancy until the completion of the pregnancy, including the outcome and the condition of the newborn (if applicable). Additional subsequent follow-up is not needed when a newborn baby is healthy. Information on the pregnancy, including follow up reports, and any data on the birth of the newborn should be reported to Flexion within 3 days.

10 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

10.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or Flexion Therapeutics, Inc. feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

Subject withdrawal of consent (or assent)

Subject is not compliant with study procedures

Adverse event that in the opinion of the investigator would be in the best interest of the subject to

discontinue study treatment

Protocol violation requiring discontinuation of study treatment

Lost to follow-up

Flexion Therapeutics, Inc. request for early termination of study

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 10 for early termination procedures.

10.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

10.3 Replacement of Subjects

Subjects who withdraw from the study treatment will be replaced.

11 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

Failure to meet inclusion/exclusion criteria

Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The CPHS will determine if a protocol violation will result in withdrawal of a subject.

12 STATISTICAL METHODS AND CONSIDERATIONS

Sample size justification:

We plan to enroll 24 patients for the pilot study. This sample size is determined by the projected availability of eligible patients within the proposed study period (6 months). This pilot study will help to establish the safety and efficacy of the investigated treatment FX006, and the data collected in this study will allow us to plan a future efficacy trial.

Statistical analysis plan:

Descriptive statistics will be reported for demographics and all clinical variables collected in this study.

For the efficacy evaluated by NPRS and PGIC, we will use appropriate summary statistics (e.g. mean + standard deviation for variables with normal distribution or median and interquartile range for variables with skewed distribution) to report NPRS and PGIC at each time point and analyze their changes over time. For safety evaluated, we will report the frequency and percentage of patients who have received any treatment to emergent adverse events within 12 weeks.

12.1 Data Sets Analyzed

All eligible patients who are randomized into the study and receive at least one dose of the study drug (the Safety Population) will be included in the safety analysis.

12.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized: gender and age.

13 DATA COLLECTION AND RETENTION

13.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel will enter data from source documents corresponding to a subject's contact into the protocol-specific Case Report Form (CRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by Flexion Therapeutics, Inc., but will be identified by a site number, subject number.
If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

13.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.
All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

13.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

13.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained.

Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

13.5 Availability and Retention of Investigational Records

The Investigator will make study data accessible to authorized representatives of Flexion Therapeutics, Inc., IRB and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator will ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, etc.) will be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which Flexion, Inc. is required to maintain study records and, therefore, Flexion, Inc. will be contacted prior to removing study records for any reason.

13.6 Subject Confidentiality

In order to maintain subject confidentiality, only a site number and subject number will identify all study subjects on CRFs and any other documentation that may be submitted to Flexion Therapeutics, Inc. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

14 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

To maintain confidentiality, evaluation forms, reports and other records will be identified by a coded number only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator will comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996).

14.1 Protocol Amendments

Any amendment to the protocol will be written by the Investigator. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

14.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRBs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRBs unconditional approval statement will be transmitted by the Investigator to Flexion Therapeutics, Inc. prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should

identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

14.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25 [a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will send an IRB-approved copy of the Informed Consent Form to Flexion Therapeutics, Inc.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

Pending IRB approval, a research nurse may obtain informed consent remotely including means such as phone, video or other verbal means for the purposes of screening a trial subject. Written informed consent shall be obtained prior to the subject entering the trial

14.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among Flexion Therapeutics, Inc. and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

14.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying Flexion Therapeutics Inc., except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to Flexion Therapeutics, Inc. any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.

7. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
8. Maintain adequate and accurate records in accordance with §21 CFR 312.62.

9. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
10. Promptly report to the IRB and Flexion Therapeutics, Inc. all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
11. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
12. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

15 REFERENCES

1. Effects of a Single Intra-Articular Injection of a Microsphere Formulation of Triamcinolone Acetonide on Knee Osteoarthritis Pain: A Double-Blinded, Randomized, Placebo-Controlled, Multinational Study, Conaghan, P,G; Hunter, D. J.; Cohen, S. B.; Kraus, V. B., Berenbaum, F.; Lieberman, J. R; Jones, D. G.; Spitzer, A, I.; Jevsevar, D.S., Katz, N. P. Burgess, D. J., Lufkin, J.; Johnson, J; Bodick, N.; J. Bone Joint Surg: April 18, 2018, 100(8), 666–677.

2. Study to Compare Exposure of TA Following Administration of FX006 or TAcs in Patients With OA of the Shoulder or Hip, Clinical Trials.gov, NCT 03382262.

3. Greater Trochanteric Pain Syndrome: A Review of Anatomy, Diagnosis and Treatment
Williams, B. S.; Anesthesia & Analgesia: May 2009 - Volume 108 (5) 1662-1670.

16 APPENDIX 1: SCHEDULE OF STUDY ASSESSMENTS

	VISIT 1 (Day 1)	VISIT 2 (Week 2)	VISIT 3 (Week 4)	VISIT 4 (Week 8)	VISIT 5 (Week 12)
Informed Consent	X				
Medical History	X				
Abbreviated Physical Exam	X				
Height	X				
Weight	X				
Vital Signs	X				
Pregnancy Test (Urine)	X				
Dispensing or Administration of Study Drug	X				
Initiate Subject Diary	X				
Subject Diary Review		X	X	X	X
Concomitant Medication Review	X	X	X	X	X
Adverse Events	X	X	X	X	X