Clinical Study Protocol

Protocol Title	A Single-arm, Open-label Study to Evaluate a Procedure for Intra-articular (IA) Injection of FX006 in Patients with Osteoarthritis (OA) of the Hip
Protocol Number	FX006-2019-017
Phase	**2**
Study Medication(S)	FX006
Indication	Osteoarthritis of the Hip
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Sponsor	Flexion Therapeutics 10 Mall Road, Suite 301 Burlington, Massachusetts 01803 Tel: 781-305-7777
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SIGNATURE PAGE

Clinical Study Protocol Version 2.0 (dated 11 July 2019)

Sponsor Safety Officer Approval

Signature: _____ **Date:** 11 Jul 2019

Name (print): Scott Kelley, M.D.

Title: Chief Medical Officer

Principal Investigator Agreement: I have read the protocol and agree to conduct the study as outlined herein.

Signature: _____ **Date:** _____

Name (print): _____

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1. ABBREVIATIONS AND DEFINITION OF TERMS

ACR	American College of Rheumatology
ADRG	Analysis Data Reviewer's Guide
AE	Adverse Event
AUE	Area Under the Effect Curve
BMI	Body Mass Index
CBD	Cannabidiol
CDISC SDTM	Clinical Data Interchange Standards Consortium Study Data Tabulation Model
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CI	Confidence Interval
CMC	Carboxymethylcellulose Sodium
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EOS	End of study
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
FBR	Foreign Body Response
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HEENT	Head, ears, eyes, nose, throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-pituitary-adrenal
IA	Intra-articular
IB	Investigator's Brochure
IM	Intramuscular
IP	Investigational Product
IRB/EC	Institutional Review Board/Ethics Committee
IV	Intravenous
JSN	Joint Space Narrowing
kg	Kilogram
KL	Kellgren-Lawrence
LSM	Least square mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
n	Number
NaCl	Sodium Chloride

NaCMC	Sodium carboxymethylcellulose
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
NSRI	Non-selective serotonin reuptake inhibitors
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PD	Pharmacodynamic
PLGA	Poly [lactic-co-glycolic acid]
PK	Pharmacokinetic
PRP	Platelet Rich Plasma
RBC	Red Blood Cells
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDRG	Study Data Reviewer's Guide
TEAE	Treatment-emergent Adverse Event
TENS	Transcutaneous electrical nerve stimulation
TA[1]	Triamcinolone Acetonide
TAcs[2]	Triamcinolone Acetonide Injectable Suspension, Immediate-Release (commercially available)
USA	United States of America
USP	United States Pharmacopeia
w/w	weight by weight
WBC	White Blood Cells

[1.] Abbreviated in past protocols and documents as TCA

[2.] Abbreviated in past protocols and documents as TCA IR

2. SYNOPSIS

Title of Study

A Single-arm, Open-label Study to Evaluate a Procedure for Intra-articular (IA) Injection of FX006 in Patients with Osteoarthritis (OA) of the Hip

Study Centers

Multiple centers, up to 6

Study Phase

Phase 2

Objectives

Primary

- To evaluate the ability of injection procedures to achieve successful intra-articular (IA) injection of FX006 into the hip joints of patients with OA of the hip

Secondary:

- To assess the safety of FX006 administered by IA injection in patients with hip OA

Number of Patients

A maximum number of approximately 30 patients may be enrolled in this protocol.

Initially, up to 22 patients will be enrolled.

In the event there is one (1) unsuccessful IA administration of FX006, 7 additional patients may be enrolled.

Test Product, Dose and Mode of Administration

FX006 – an extended release formulation of triamcinolone acetonide (TA) in 75:25 poly (lactic-co-glycolic) acid (PLGA) microspheres. Nominal 32 mg TA, administered as a single 5 mL IA injection into the index hip under image guidance per injection procedure.

Reference Compound(s), Dose and Mode of Administration

None (single-arm, open-label study)

Blinding

Not applicable (single-arm, open-label study)

Duration of Participation

All enrolled patients will receive a single IA injection on Day 1 and be followed for 8 weeks.

Study Rationale

During clinical trials, FX006, now marketed as Zilretta®, was administered without difficulty by IA injection into the knee joint to >800 patients with knee OA and demonstrated an acceptable safety profile and clear therapeutic effect (see Section 5.2). In two recent studies of patients with hip OA, incomplete IA injections of FX006 into the hip joint occurred. A Sponsor-conducted investigation identified procedural factors as potentially contributing to these incomplete injections in the hip. Specifically, (a) vertical orientation of the syringe of resuspended FX006; and (b) restriction at the outflow from the needle. Notably, during IA injection into the knee joint the FX006 syringe is generally in the horizontal orientation during injection; further, the patient positioning routinely used for injection of the knee joint readily relaxes the surrounding structures.

The approach being investigated in this study addresses these factors by (a) providing tubing as an accessory connector that enables the syringe of FX006 to be kept in a horizontal orientation during injection and (b) specifies positioning the patient and supporting the leg to minimize tension on the hip joint. The goal is to confirm if such procedural changes can result in reliable successful clinical IA administration of FX006 in the hip joint.

Study Design and Methodology

This is a prospective, multicenter, single-arm, open-label study to evaluate the feasibility of an IA injection procedure of 32 mg FX006 under image guidance in patients with hip osteoarthritis (OA). The study will be conducted at up to 6 sites with approximately 22 patients. If one (1) unsuccessful IA administration is observed, 7 additional patients will be enrolled. Eligible subjects will be administered a single IA injection of FX006 on Day 1 and then followed for safety for 8 weeks.

Inclusion Criteria

To be eligible for this trial, a patient must meet all of the following criteria:

1. Provides written informed consent prior to initiating any study specific procedures
2. Is willing and able to comply with the study procedures and visit schedule and to follow verbal and written instructions
3. Is 40 to 80 years of age, inclusive, on the day of consent
4. Has Body Mass Index (BMI) ≤ 40 kg/m^2
5. Has a documented clinical diagnosis of unilateral or bilateral hip OA for at least six (6) months.
6. Has Kellgren-Lawrence (KL) Grade 2 or 3 in the index hip (i.e., the hip identified by the Investigator as appropriate for injection) confirmed by local read of X-ray obtained during Screening or ≤ 6 months of Screening visit.
7. Has clinically significant pain in the index hip (≥ 4.0 (0-10 NRS scale)) at Screening as reported by patient
8. Sexually active males and females of child-bearing potential (defined as neither surgically sterile nor post-menopausal, i.e., age >45 years and no menstrual periods for at least 1 year) must agree to use, from Screening through 14 weeks post-injection for females and through 23 weeks post-injection for males, a highly effective method of contraception, defined as one of the following: abstinence; oral, injected or implanted hormonal methods of contraception; intrauterine device or intrauterine contraceptive system; condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; sexual intercourse only with man ≥6 months post-vasectomy.

Exclusion Criteria

Patients meeting one or more of the following criteria are excluded from the study:

1. Has a history of hypersensitivity to triamcinolone acetonide, PLGA or lidocaine.
2. Is receiving anticoagulants, including warfarin, dabigatran, rivaroxaban, apixaban or low molecular weight heparin), ritonavir or cobicistat. (Aspirin for cardio-protection is permitted at a maximum dose of 325 mg per day provided the dose has been stable at least 3 months prior to Screening.)
3. Has had any previous surgery on the index hip.
4. Presence of surgical hardware or other foreign body in the index hip.
5. Has a history of infection of the index hip.
6. Has a diagnosis of other disorders in the index hip that can cause pain (e.g. trochanteric bursitis, avascular necrosis, pain referred from back).

7. Has received any intra-articular injection in the index hip of corticosteroids, investigational (including FX006) or marketed (including Zilretta) within the 3 months prior to Screening.
8. Has received intra-articular treatment in the index hip with any of the following agents: any biologic agent (e.g., platelet rich plasma (PRP), stem cells, prolotherapy, amniotic fluid) or hyaluronic acid within the 6 months prior to Screening.
9. Has had trauma to the index hip in the past 3 months requiring immobilization.
10. Has a history or evidence of active or latent systemic fungal or mycobacterial infection (including tuberculosis), or of ocular herpes simplex
11. Has within the past 3 months received corticosteroids by mouth, or by parenteral injection. Multiple courses or chronic intermittent use of inhaled, intranasal, or topical steroids is also exclusionary. Single courses of 14 days or less by those routes are permitted
12. Has received a live (e.g., MMR vaccine, chicken pox vaccine, rotavirus vaccine) or live-attenuated vaccine (e.g., FluMist, Zostavax) within 12 weeks of Day 1.
13. Has, at screening, a positive test for hepatitis B surface antigen, HIV or hepatitis C.
14. Has, at screening, any abnormal laboratory value(s) that in in the opinion of the Principal Investigator (PI) (or other authorized clinical delegate) precludes trial participation.
15. Has, at screening, or any time prior to day of scheduled injection (Day 1), clinical suspicion of local or systemic infection, including any infection in the index leg.
16. Has a history of or active significant concomitant illness (known or suspected) including, but not limited to:
    - Inflammatory joint disease, e.g. rheumatoid arthritis, seronegative spondyloarthropathy, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, inflammatory-bowel disease associated inflammatory arthritis.
    - Systemic inflammatory disease, e.g., polymyalgia rheumatica, systemic lupus erythematosus
    - Sarcoidosis or amyloidosis
    - Cushing's syndrome
    - Malignancy requiring systemic therapy within the past five (5) years (excludes basal cell carcinoma or cervical cancer treated only with surgical removal more than one (1) year ago.)
    - Other autoimmune disease.
17. Any infection requiring parental antibiotics within 4 weeks of Day 1 or oral antibiotics within 2 weeks of Day 1
18. Has a history or current diagnosis of any other medical illness which in the opinion of the local Principal Investigator (PI) (or other authorized clinical delegate) precludes trial participation
19. Is a woman who is pregnant, nursing, lactating, or plans to become pregnant during the study
20. Is a man who plans to conceive during the study
21. Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.

Prior Therapy

Exclusionary medications are noted in the Exclusion Criteria.

Other medications reported at Screening will be recorded as Concomitant Medications and may be continued during the study if, in the judgement of the Investigator, usage and the underlying condition have been stable and are expected to remain stable for the duration of the study.

During the study, any changes in prior concomitant medications and the associated reasons for the changes will be recorded in source documentation and reported in the eCRF.

Concomitant Therapy Allowed During the Study

Concomitant medication required for the treatment of a treatment-emergent AEs is permitted and both the AE and the treatment will be recorded and reported.

Prohibited Medications/Non-Pharmacologic Therapies

The following medications should not be taken from consent through the EOS visit:

- Aspirin (>325 mg per day)
- Any treatment administered by IA injection in the index hip, including hyaluronic acid, plasma, cell therapies, local anesthetics through 8 weeks post injection.
- IV, IM, or oral corticosteroids. Inhaled, intranasal and topical steroids are prohibited from Screening through Week 1 visit.
- Any investigational drug, device or biologic
- Immunomodulators, immunosuppressives, or chemotherapeutic agents
- Live (e.g., MMR vaccine, chicken pox vaccine, rotavirus vaccine) or live-attenuated vaccines (e.g., FluMist, Zostavax) for 8 weeks post injection.

Criteria for Evaluation:

Safety

- Adverse Events
- Vital signs
- Index hip examinations

Sample Size Considerations:

Approximately 22 patients will be treated in this study. If there are no incomplete IA administrations, the study may be considered complete. Observing 0 incomplete injections (0%) in 22 patients gives 90% confidence that the true incomplete IA injection rate is between 0 and 10%. If one (1) unsuccessful IA administration of study drug is observed, 7 additional patients may be enrolled. Observing 1 incomplete IA injection in 29 patients (3%) gives 80% confidence that the true incomplete IA injection rate is between 0 and 10%.

Statistical Methods:

Complete details of the statistical analysis will be specified in the statistical analysis plan (SAP).

Data collected in this study will be presented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics; specifically, the mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized using frequencies and percentages. Confidence intervals may also be provided. Figures may be used to support the presentation of certain data.

Safety analyses will be performed on the Safety Population. AEs will be coded using MedDRA. Incidences (number and percent) of TEAEs, those events that start after dosing or worsened in severity after dosing, will be presented. Incidences of TEAEs will also be presented by maximum severity and relationship to study medication.

Similar presentations will be provided for serious AEs, AEs leading to withdrawal from the study, or AEs leading to death. Analysis of AE data will include examination of the incidence rates of index hip TEAEs. Laboratory data, vital signs and X-ray KL grade will be presented as descriptive summary statistics. Vital sign data will also be presented as change from Baseline at each individual time point.

Table 1: Schedule of Study Assessments

List of Assessments	Screening[1]	Day 1	Week 1	Week 4	Week 8
Window	-14 to -1	–	±2 days	±5 Days	±5 days
Informed consent	X				
Inclusion/Exclusion Review	X	X[2]			
Medical History/Update	X	X[2]			
Patient Demographics	X				
OA Medical History	X				
Prior Treatments and Medications	X	X[2]			
Physical examination	X				
Vital signs	X	X[2]	X		X
Height	X				
Weight and BMI	X				
Index Hip Assessment	X	X[2]	X		X
Index Hip X-ray [3]	X				
Hematology, Chemistry[4]	X				
HIV, Hep B/C[4]	X				
Pregnancy Test[5]	X[5]	X[2,5]			
Index Hip Aspiration[6]		X			
IP administration[7]		X			
AE/SAE & ConMeds[8]	X	X	X	X[9]	X

[1] Screening period is up to 14 days.
[2] To be completed on Day 1 prior to injection procedure
[3] A weight-bearing anterior-posterior view for index hip is recommended. Screening X-ray will be read locally for radiologic findings of OA meeting criteria for Kellgren-Lawrence Grade 2-3.
[4] To be performed via local laboratory.
[5] Pregnancy test will be done in women of childbearing potential. *Serum Pregnancy Test* to be performed at Screening visit by local lab; *Urine Pregnancy Test* to be performed on Day 1 by study site or local lab with result available prior to injection of study medication.
[6] Aspiration must be attempted prior to IP administration. Synovial fluid volume aspirated will be recorded prior to discard.
[7] To be performed under image guidance in compliance with protocol specified procedure.
[8] AE/SAE's and concomitant medications will be captured from signing of informed consent through EOS visit.
[9] To be conducted via telephone

3. ETHICS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

3.1. Institutional Review Board/Ethics Committee

This study will be conducted in compliance with current Good Clinical Practices (GCP) and Title 21 Part 56 of the United States of America Code of Federal Regulations (CFR) relating to Institutional Review Board (IRB)/Ethics Committee (EC).

This study protocol and other related study documents will be submitted to the IRB/EC by the site or the Sponsor for review and approval as dictated by local regulations. IRB/EC approval must be obtained before commencement of any study procedures. The study will be conducted only at sites where IRB/IEC approval has been obtained.

3.2. Ethical Conduct of Study

This study will be conducted in accordance with the protocol, GCP guidelines and applicable national regulatory requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have originated in the Declaration of Helsinki and that the clinical study data are credible.

3.3. Patient Information and Consent

Prior to initiation of any study related procedures, patients will give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation and termination conditions, and risks and benefits.

An IRB/EC-approved informed consent document must be signed by the patient or the patient's legal guardian before his or her participation in the study. A copy of the informed consent document must be provided to the patient or the patient's legal guardian. If applicable, it will be provided in a certified translation of the local language.

Signed informed consent forms must remain in each patient's study file and must be available for verification by study monitors at any time.

4. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

4.1. Investigators

A Principal Investigator will be responsible for study conduct at each center and may delegate study-related activities to appropriately qualified and trained staff. This delegation will be documented in a study-specific Clinical Site Responsibilities and Signature Log.

The contact information for all Principal Investigators participating in the trial will be kept in the Trial Master File.

4.2. Study Administrative Structure

The study will be managed by the Sponsor with specific responsibilities delegated to contract research organizations.

5. INTRODUCTION

5.1. Osteoarthritis

Osteoarthritis (OA) is a painful and debilitating musculoskeletal disease that is characterized by intra-articular (IA) inflammation, deterioration of articular cartilage, and degenerative changes to peri-articular and subchondral bone (Creamer and Hochberg, 1997; Goldring and Goldring, 2006). Arthritis is the most common cause of disability in the United States of America (USA), and OA is the most common joint disease, affecting 27 million Americans, with numbers expected to grow as a result of aging, obesity and sports injuries. Recent data suggest that OA accounts for over $185 billion of annual healthcare expenditures in the US, which does not include loss of productivity costs. It is estimated that by 2030, 45 million people will have OA. OA commonly affect large weight-bearing joints like the knees and hips, but also occurs in the shoulders, hands, feet and spine. Patients with OA suffer from joint pain, tenderness, stiffness and limited movement. As the disease progresses, it becomes increasingly painful and debilitating, culminating, in many cases, in the need for total joint arthroplasty.

Current Guidelines from the American College of Rheumatology (ACR), Osteoarthritis Research Society International (OARSI) and the European League against Rheumatism (EULAR) recommend the use of IA corticosteroids for short-term acute pain relief (Hochberg et al, 2012; Jordan et al, 2003; Menge et al, 2014).

The prevalence of hip osteoarthritis is estimated to range from 6.7% to 9.2% among adults ≥45 years of age and increases with age (Lawrence et al, 2008; Murphy et al, 2012). It is recognized that chronic inflammation occurs in all stages of OA (Benito et al, 2005; Sellam and Berenbaum, 2010; Wenham and Conaghan, 2010). As inflammation is correlated with clinical symptoms and joint degeneration, it should be an important target for corticosteroid intervention.

5.2. Background

5.2.1. Investigational Medicinal Product: FX006

FX006 is an extended-release formulation of triamcinolone acetonide (TA) for IA administration. It is approved in the US under the trade name ZILRETTA® (triamcinolone acetonide extended-release injectable suspension) for the management of pain of osteoarthritis of the knee. FX006 is intended to deliver TA to the synovial and peri-synovial tissues for a period of approximately 3 months (Bodick et al, 2013). FX006 contains TA, United States Pharmacopeia (Ph. Eur/USP), formulated in 75:25 poly (lactic-co-glycolic acid) (PLGA) microspheres with a nominal drug load of 25% (weight by weight [w/w]) 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 (NaCl; 0.9% w/w), carboxymethylcellulose sodium (CMC; 0.5% w/w) and polysorbate-80 (0.1% w/w) to form a suspension prior to IA injection.

Further details of the physiochemical properties of FX006 can be found in the Investigator's Brochure (IB).

5.2.2. Rationale for FX006 in Hip Osteoarthritis

Similar as in knee OA, hip OA patients are confronted with insufficient management of their symptoms (Zhang et al, 2008). Conventional corticosteroids have demonstrated clinical benefits in patients with hip OA (Lambert et al, 2007; Qvistgaard et al, 2006; Atchia et al, 2011), but with short duration of effect (approximately 4-8 weeks) and side effects from burst release of steroids into systemic circulation (Habib et al, 2011). Due to its slow release formulation, FX006 has the potential to offer longer duration of efficacy and minimized systemic exposure, thus, an improved benefit/risk profile for hip OA patients.

5.2.3. Non-Clinical Toxicology

Overall, single or repeat IA administration of FX006 at the clinical dose of 32 mg has no new safety liabilities compared to TAcs in healthy animals:

- Systemic findings were similar among TAcs and FX006 groups following single and repeat dosing and were generally reversible. Initial effects on clinical pathology parameters were more pronounced for the immediate-release form. The incidence and/or intensity of steroid associated systemic histopathological findings at the later time points were slightly higher for high dose FX006 than for TAcs at the same dose level of TA (18.75 mg/mL/joint), as expected based on the sustained release of TA. Microspheres were not detected in tissues outside of the synovial space
- Local findings were similar among the TAcs and the FX006 groups and were reversible. The single and repeat dose dog toxicity studies recapitulated known, previously published, effects of TA in normal animal joints following prolonged exposure. These include decreased Safranin O staining (single or repeat dose) and changes in structure and cellularity of articular cartilage (repeated dosing only)
- An expected, mild, reversible Foreign Body Response (FBR) was noted to the PLGA component of FX006 microspheres
  - The local tissue response to the presence of blank microspheres as well as FX006 microspheres consisted of an expected FBR of macrophage and multinucleated giant cell infiltration involving the synovium. Following a single dose, the FBR was evident at Day 4, peaked at approximately 6 weeks and was completely resolved by 6 months in all FX006-dosed animals. Occasional lymphocyte and plasma cell infiltrates and sporadic focal-to-multifocal areas of minimal-to-slight fibrosis resolved by 9 months. Following repeat IA dosing, a similar local, reversible FBR was noted
  - Further, the dogs in these studies showed no local signs of inflammation on or around the joint and did not display pain, discomfort or difficulty in ambulation in any treatment group; hence, this local response was considered to be non-adverse.

Information available for TA from the literature, corticosteroid product labels and clinical experience suggest that the potential of genetic toxicity, reproductive toxicity and carcinogenic potential of TA are well understood. Similarly, the biocompatibility and local safety of PLGA microspheres, and genotoxic, reproductive toxicological and carcinogenic potential of PLGA have been described in a combination of literature and product information packages. Therefore, no new risks relative to TAcs are presented by FX006 as intended for use.

5.2.4. Systemic and Local Pharmacokinetics (PK) in Patients with OA of the Knee

Overall, FX006 displayed a favorable plasma PK profile relative to that of TAcs. Pharmacokinetic observations resulted in a controlled and stable release of TA from PLGA microspheres into synovial tissues, where concentrations remained high relative to plasma concentrations for at least 12 weeks. Triamcinolone acetonide was absorbed systemically, with a plateau in plasma TA concentrations occurring in the first 24 hours post dose, and slow elimination from the systemic circulation observed in the weeks thereafter (Kraus et al, 2018; Bodick et al, 2013).

Relative to TAcs, 32 mg FX006 produced substantially lower peak plasma levels and decreased pharmacodynamic effects on glucose metabolism and adrenal-cortical axis. FX006 performed as expected, prolonging the residence of TA in the joint while minimizing acutely elevated levels of TA.

5.2.5. Pharmacodynamics (PD) in Patients with Osteoarthritis of the Knee

In a Phase 2 PK/ PD study evaluating three dose levels of FX006 (10 mg, 40 mg, 60 mg) administered as a 3 mL injection, suppression of cortisol in the days following injection produced by the 10 and 40 mg dose of FX006 was less than that produced by injection of TAcs; the 60 mg dose of FX006 produced effects similar to 40 mg TAcs. Cortisol suppression subsequent to Day 1-2 associated with all doses of FX006 would not be expected to be of clinical consequence in adult patients without otherwise compromised hypothalamic-pituitary-adrenal (HPA) axis function.

In a Phase 2 study in diabetic patients with knee OA, treatment with 32 mg FX006 resulted in a statistically significant ($p=0.0452$) reduction in blood glucose elevation relative to TAcs over a 72-hour period following IA injection. The time in glycemic target range (70-180 mg/dL) (American Diabetes Association, 2016) was greater for FX006 as compared to TAcs over the 48 hours post IA injection, providing another indication of the improvement in glycemic control. Over the entire time course of the 15-day post injection glucose monitoring period, blood glucose levels associated with FX006 remained at levels similar to or lower than those produced by TAcs. This observation is consistent with PK studies demonstrating low systemic exposure to TA associated with FX006.

5.2.6. Efficacy in Patients with Osteoarthritis of the Knee

Efficacy data from three studies provide substantial evidence supporting the effectiveness of 32 mg FX006 in the management of OA knee pain (Bodick et al, 2015; Conaghan et al, 2018a; Conaghan et al, 2018b). Results of the primary endpoint from the Phase 3, multi-center, adequate, and well-controlled trial showed that patients treated with 32 mg FX006 had a rapid, durable, and meaningful analgesic response that was statistically significantly better than placebo treated patients ($P<0.0001$). This finding was supported by a second smaller Phase 2b study, where a highly similar pattern of response to 32 mg FX006 was demonstrated.

Robustness of the primary outcome in the Phase 3 study was further supported by the internal consistency demonstrated in favor of 32 mg FX006 through secondary analyses utilizing the primary outcome data (average daily pain [ADP]) to evaluate durability and magnitude of response. These included least square mean (LSM) testing at each week and area under the effect curve (AUE) analyses for Weeks 1 through 12 and Weeks 1 through 24. Results

demonstrated that the analgesic effect of 32 mg FX006 is significant at Week 1, increases through Week 7, and is sustained through at least Week 16. Responder analyses further suggested that FX006 provides clinically relevant improvement from Weeks 1 through 16 relative to placebo.

Analyses utilizing data collected from other instruments or measures, i.e., Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Patients' Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), and Knee injury and Osteoarthritis Outcome Score (KOOS) Quality of Life (QOL), provided additional insight into effects on pain relief as well as physical function and global well-being. At 32 mg, FX006 provides clinically relevant improvement relative to placebo through Week 12 for WOMAC and KOOS QOL and through at least Week 16 for PGIC and CGIC. Additionally, significant reduction of rescue medication utilization in patients treated with 32 mg FX006 is of potential important clinical consequence and adds a meaningful element to the overall effectiveness profile of 32 mg FX006. Collectively, these results provide substantial evidence to support 32 mg FX006 as an effective therapy for the management of OA knee pain.

5.2.7. Systemic and Local Safety in Patients with Osteoarthritis of the Knee

The evaluation of 687 patients treated with a single IA injection of FX006 at any dose in the FX006 clinical studies suggest that it was well tolerated with systemic and local safety profiles similar to those of TAcs and placebo.

Key safety observations from the FX006 clinical studies of OA of the knee are largely consistent.

- The number of treatment-emergent adverse events (TEAEs) reported was similar across groups (FX006 46.0%; placebo 49.2%; TAcs 51.0%)
- The majority of TEAEs in FX006-treated patients were mild or moderate (Grade 1 or 2). Severe or life-threatening events occurred in the FX006-treated patients at a rate of 3.0% as compared to 5.0% and 2.6% in the placebo and TAcs groups, respectively
- In the FX006-treated patients (n=687), the most common TEAEs were:
  - Arthralgia (in any joint) 9.8% (n=67)
  - Headache 5.4% (n=37)
  - Upper Respiratory Tract Infection 3.1% (n=21)
  - Joint swelling 2.8% (n=19)
  - Contusion and back pain 2.3% (n=16)
  - Nasopharyngitis 2.2% (n=15)
- The rate of serious adverse events (SAEs) was low and consistent across groups (FX006 1.9%; placebo 1.1%; TAcs 2.3%); none were considered related to the study drug
- Across all studies there were no deaths

In two Phase 3 studies (FX006-2014-008 and FX006-2016-011), qualitative assessments based on X-rays of the index knee at 24 weeks post injection included joint space narrowing (JSN), subchondral bone changes, osteonecrosis, and insufficiency fracture (Conaghan et al, 2018b).

Study FX006-2014-008

- The overall rate of JSN worsening of at least 1 grade between baseline and Week 24 was low and similar among treatment groups (5.0% [7/140], 4.1% [6/148], and 3.5% [5/145] of patients with both baseline and Week 24 X-rays in the 32 mg single dose FX006, placebo, and TCA IR groups respectively); for all but 1 of these 18 patients, JSN worsened by 1 grade only. The remaining patient (in the placebo group) had a 2-grade worsening in JSN (from 0 at baseline to Grade 2 at Week 24).
- No FX006-treated patient had X-ray evidence of treatment-emergent insufficiency fracture, subchondral bone changes, or osteonecrosis at Week 24.
- Eighteen patients discontinued the study prior to Week 24 and completed a final X-ray as part of early termination visit. Of these, 2 patients, 1 in the 32 mg FX006 group and 1 in the placebo group, had a 1-grade increase in JSN. There were no reports of insufficiency fracture, subchondral bone changes, or osteonecrosis.

Study FX006-2016-011

- The overall rate of JSN worsening of at least 1 grade between baseline and end of study (Week 52 or early termination) among patients who received two FX006 doses and had X-ray data at both timepoints (N=165) was low 3.6% [6/165].
- There were no indications of chondrolysis, osteonecrosis, subchondral insufficiency fractures, or clinically significant subchondral bone changes.

5.2.8. Experience with FX006 Administered IA in Patients with OA of the Hip

Studies of FX006 were recently expanded to include studies in patients with symptomatic OA of the hip joint. Among approximately 45 patients administered 32mg FX006 by IA into the hip, the incidence, nature, and intensity of treatment-emergent AEs was indistinguishable from that observed with IA injection into the knee. There were no treatment related SAEs.

However, in contrast with the prior experience in the knee, there were occurrences of incomplete administration of FX006 variously reported as "increased resistance" or "blockage" encountered during injection procedure. Careful review of the cases failed to identify a common factor and initial laboratory studies were inconclusive.

However, subsequent laboratory models suggested two procedural factors potentially contributing to these incomplete injections of the hip. Specifically, if a syringe of resuspended FX006 was attached directly to a vertical spinal needle (as typically encountered during IA injection in the hip) and outflow from the needle was mildly restricted by tubing, then blockage was observed at an appreciable rate. If the syringe was held horizontally or if the restricting tubing was omitted (giving conditions similar to IA injection in the knee), such events did not occur.

The approach being investigated in this study addresses these factors by (a) providing tubing as an accessory connector that enables the syringe of FX006 to be kept in a horizontal orientation during injection and (b) specifies positioning the patient and supporting the leg to minimize

tension on the hip joint (Kumar et al, 2017). The goal is to confirm if such procedural changes can result in reliable successful clinical IA administration of FX006 in the hip joint.

5.2.9. Conclusion

Intra-articular administration of FX006, an extended-release microsphere formulation of triamcinolone acetonide, demonstrated safety and efficacy in the relief of pain in patients with pain associated with osteoarthritis of the knee. Given the insufficient symptomatic management of hip OA patients and similar pathogenesis between knee and hip OA, it is anticipated that FX006 will provide similar benefit to these patients. However, to fully assess the safety, efficacy and determine a benefit/risk profile for administration of FX006 to patients with hip OA, the procedure for intra-articular administration of FX006 into the hip joint needs to be addressed. Thus, the sponsor is proposing a specific study to evaluate the ability of injection procedures to achieve successful intra-articular (IA) injection of FX006 into the hip joints of patients with OA of the hip.

6. STUDY OBJECTIVES

6.1. Primary Objective

To evaluate the ability of injection procedures to achieve successful intra-articular (IA) injection of FX006 into the hip joints of patients with OA of the hip

6.2. Secondary Objectives

The secondary objective of this study is to assess the safety of FX006 administered by IA injection in patients with hip OA.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a prospective, multicenter, single-arm, open-label study to evaluate and confirm feasibility of an IA injection procedure of 32 mg FX006 under image guidance in patients with hip osteoarthritis (OA). The study will be conducted at up to 6 sites with approximately 22 patients. If one (1) unsuccessful IA administration is observed, 7 additional patients will be enrolled. Eligible subjects will be administered a single IA injection of FX006 on Day 1 and then followed for safety for 8 weeks.

7.2. Flow of Study Participation

The study will involve the following segments:

- A Screening period of up to 14 days
- IA administration of FX006 in the index hip on Day 1
- Follow-up visit on Week 1 (±2 days)
- Follow-up contact conducted by telephone to monitor AE/SAEs and Con Meds on Week 4 (±5 days)
- End-of-Study (EOS) visit on Week 8 (±5 days)

7.3. Site Staffing Requirements

The Principal Investigator is responsible for overseeing the conduct of the study at his/her site, ensuring that sufficient and appropriately experienced staff are available to conduct the trial and ensuring that activities are appropriately delegated and documented. Any delegation of responsibilities will be documented on the Clinical Site Responsibilities and Signature Log. The term 'Principal Investigator' is used throughout this protocol to refer to the actual Principal Investigator and/or his/her delegated team member(s) for the specific responsibility being described.

At a minimum, additional study staff should consist of:

Pharmacist/Coordinator

- Must be a registered pharmacist or an individual with the qualifications and training required to handle and prepare study medications. Can also be the PI or Injector. The responsibilities itemized below may be fulfilled by one person or by two different persons.
- Responsibilities:
  - Receiving and storing investigational product and maintaining accountability records
  - Preparing FX006 for injection
  - Documenting injection procedure activities

Injector

- Must be a medical doctor, doctor of osteopathy, or certified physician assistant with experience in administering IA injections of the hip using image guidance
- Is responsible for performing all IA injections of study medication in compliance with the standardized protocol injection procedure, using image guidance

Assessor

- Must be a medical doctor, doctor of osteopathy, certified physician assistant, or nurse practitioner
- Must have relevant OA experience
- Is responsible for performing the physical examination and index hip assessments
- Is responsible for the overall safety of the patient, including assessing all adverse events for seriousness, severity, and relationship to study medication

Note: The Injector, Assessor, and PI may be the same or different individuals.

Delegation of responsibilities will be documented at each site and specified in each site's Clinical Site Responsibilities and Signature Log.

7.4. Discussion of Study Design

7.4.1. Rationale for Study Population

The safety profile of FX006 has been demonstrated to be well-tolerated in over 800 patients with knee OA and 45 patients with hip OA in clinical trials. Given the similar pathogenesis between knee and hip OA and demonstrated efficacy in knee OA, it is hypothesized that FX006 should be beneficial to hip OA patients, and thus supports FX006 evaluation in this patient population.

7.4.2. Rationale for Dose Selection

FX006 at IA doses up to 60 mg has been tested in knee OA patients with acceptable safety profile. FX006 has been approved to manage knee OA pain at dose of 32 mg. The hip joint is a large weight-bearing synovial joint, like the knee. There is no apparent pathological difference between hip OA and knee OA. Therefore, 32 mg IA dose for hip OA is selected.

7.4.3. Rationale for Study Parameters

During clinical trials, FX006, now marketed as Zilretta, was administered without difficulty by IA injection into the knee joint to >800 patients with knee OA and demonstrated an acceptable safety profile and clear therapeutic effect (see Section 5.2). In two recent studies of patients with hip OA, incomplete IA injections of FX006 into the hip joint occurred. A Sponsor-conducted investigation identified procedural factors as potentially contributing to these incomplete injections in the hip. Specifically, (a) vertical orientation of the syringe of resuspended FX006; and (b) restriction at the outflow from the needle. Notably, during IA injection into the knee joint the FX006 syringe is generally in the horizontal orientation during injection; further, the patient positioning routinely used for injection of the knee joint readily relaxes the surrounding structures.

The approach being investigated in this study addresses these factors by (a) providing tubing as an accessory connector that enables the syringe of FX006 to be kept in a horizontal orientation during injection and (b) specifies positioning the patient and supporting the leg to minimize tension on the hip joint. The goal is to confirm if such procedural changes can result in reliable successful clinical IA administration of FX006 in the hip joint.

7.5. Selection of Study Population

7.5.1. Number of Patients

A maximum number of approximately 30 patients may be enrolled in this protocol.

Initially, up to 22 patients will be enrolled.

In the event there is one (1) unsuccessful IA administration of FX006, 7 additional patients may be enrolled.

7.5.2. Inclusion Criteria

To be eligible for this trial, a patient must meet all of the following criteria:

1. Provides written informed consent prior to initiating any study specific procedures
2. Is willing and able to comply with the study procedures and visit schedule and to follow verbal and written instructions
3. Is 40 to 80 years of age, inclusive, on the day of consent
4. Has Body Mass Index (BMI) ≤ 40 kg/m^2
5. Has a documented clinical diagnosis of unilateral or bilateral hip OA for at least six (6) months.
6. Has Kellgren-Lawrence (KL) Grade 2 or 3 in the index hip (i.e., the hip identified by the Investigator as appropriate for injection) confirmed by local read of X-ray obtained during Screening or ≤ 6 months of Screening visit.
7. Has clinically significant pain in the index hip (≥ 4 (0-10 NRS scale) at Screening as reported by patient
8. Sexually active males and females of child-bearing potential (defined as neither surgically sterile nor post-menopausal, i.e., age >45 years and no menstrual periods for at least 1 year) must agree to use, from Screening through 14 weeks post-injection for females and through 23 weeks post-injection for males, a highly effective method of contraception, defined as one of the following: abstinence; oral, injected or implanted hormonal methods of contraception; intrauterine device or intrauterine contraceptive system; condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; sexual intercourse only with man ≥6 months post-vasectomy.

7.5.3. Exclusion Criteria

Patients meeting one or more of the following criteria are excluded from the study:

1. Has a history of hypersensitivity to triamcinolone acetonide, PLGA or lidocaine.
2. Is receiving anticoagulants, including warfarin, dabigatran, rivaroxaban, apixaban or low molecular weight heparin), ritonavir or cobicistat. (Aspirin for cardio-protection is permitted at a maximum dose of 325 mg per day provided the dose has been stable at least 3 months prior to Screening.)
3. Has had any previous surgery on the index hip.
4. Presence of surgical hardware or other foreign body in the index hip.
5. Has a history of infection of the index hip.
6. Has a diagnosis of other disorders in the index hip that can cause pain (e.g. trochanteric bursitis, avascular necrosis, pain referred from back).
7. Has received any intra-articular injection in the index hip of corticosteroids, investigational (including FX006) or marketed (including Zilretta®) within the 3 months prior to Screening.
8. Has received intra-articular treatment in the index hip with any of the following agents: any biologic agent (e.g., platelet rich plasma (PRP), stem cells, prolotherapy, amniotic fluid) or hyaluronic acid within the 6 months prior to Screening.
9. Has had trauma to the index hip in the past 3 months requiring immobilization.
10. Has a history or evidence of active or latent systemic fungal or mycobacterial infection (including tuberculosis), or of ocular herpes simplex
11. Has within the past 3 months received corticosteroids by mouth or by parenteral injection. Multiple courses or chronic intermittent use of inhaled, intranasal, or topical steroids is also exclusionary. Single courses of 14 days or less by those routes are permitted
12. Has received a live vaccine (e.g., MMR, chicken pox, rotavirus) or live- attenuated vaccine (e.g., FluMist, Zostavax) within 12 weeks of Day 1.
13. Has, at screening, a positive test for hepatitis B surface antigen, hepatitis C antibody, HIV antibody.
14. Has, at screening, any abnormal laboratory value(s) that in in the opinion of the Principal Investigator (PI) (or other authorized clinical delegate) precludes trial participation.
15. Has, at screening, or any time prior to day of scheduled injection (Day 1), clinical suspicion of local or systemic infection, including any infection in the index leg.
16. Has a history of or active significant concomitant illness (known or suspected) including, but not limited to:
    - Inflammatory joint disease, e.g. rheumatoid arthritis, seronegative spondyloarthropathy, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, inflammatory-bowel disease associated inflammatory arthritis.

- Systemic inflammatory disease, e.g., polymyalgia rheumatica, systemic lupus erythematosus
- Sarcoidosis or amyloidosis
- Cushing's syndrome
- Malignancy requiring systemic therapy within the past five (5) years (excludes basal cell carcinoma or cervical cancer treated only with surgical removal more than one (1) year ago.)
- Other autoimmune disease.

17. Any infection requiring parental antibiotics within 4 weeks of Day 1 or oral antibiotics within 2 weeks of Day 1
18. Has a history or current diagnosis of any other medical illness which in the opinion of the local Principal Investigator (PI) (or other authorized clinical delegate) precludes trial participation
19. Is a woman who is pregnant, nursing, lactating, or plans to become pregnant during the study
20. Is a man who plans to conceive during the study
21. Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.

7.5.4. Removal of Patients from Therapy or Assessments

Each treated patient receives study medication as a single administration on Day 1. Therefore, subsequent discontinuation from treatment is not applicable. Patients may be discontinued from study follow-up as detailed below. Data collected from discontinued patients will be included in the clinical study report. Patients who discontinue the study may be replaced at the discretion of the Sponsor.

Withdrawal of Consent

Each patient will be informed of his/her right to withdraw from the study at any time for any reason and without prejudice to alternative treatment. If a patient decides to withdraw from the study, effectively withdrawing his/her informed consent, the Principal Investigator will:

- Document in patient's source their withdrawal of consent and reason for withdrawing from the study
- Assess the patient's clinical condition and take appropriate therapeutic measures if necessary
- Attempt to complete the study assessments defined for the Week 8 (EOS) Visit
- Determine whether the patient is willing to be contacted on a periodic basis (via phone or in person) to follow ongoing or new AEs (including concomitant medication(s) associated with an AE) through the patient's scheduled final visit

Discontinuation of Follow-up by Investigator

The Principal Investigator may discontinue the patient for safety and poor compliance to study procedures. The Principal Investigator should contact the Medical Monitor prior to discontinuing the patient.

7.5.5. Screen Failures

Minimal data will be collected for patients who fail screening (e.g., demographic information, the reason for screen failure).

Patients that fail to meet eligibility criteria may be re-screened with the approval of the Medical Monitor by request through the General Log in the EDC system. The Medical Monitor will document the rationale for any re-screening decision.

Patients that are re-screened will be assigned a new screening number, re-consented, and will have screening assessments repeated if necessary.

7.6. Treatment Administered

7.6.1. Study Medication Treatment Arms

Investigational Medicinal Product Arm:

FX006 – an extended release formulation of triamcinolone acetonide (TA) in 75:25 poly (lactic-co-glycolic) acid (PLGA) microspheres. Nominal 32 mg TA administered IA as a single 5 mL injection into the index hip OA joint under image guidance per injection procedure.

7.6.2. Identity of Investigational Product

FX006 is supplied as a sterile, white to off white powder in a single unit dose 5 mL vial with a butyl rubber stopper, aluminum seal and plastic cap. FX006 is reconstituted in diluent containing an isotonic, sterile aqueous solution of sodium chloride (NaCl; 0.9% w/w), carboxymethylcellulose sodium (CMC; 0.5% w/w) and polysorbate-80 (0.1% w/w) to form a suspension prior to IA injection. Diluent will be supplied as a sterile liquid in a 5 mL vial with a butyl rubber stopper, aluminum seal and plastic cap. FX006 will be reconstituted in 5.0 mL of diluent to form a suspension immediately prior to IA injection. FX006 will be administered as a single 5 mL IA injection.

7.6.3. Receipt, Preparation, Dispensing and Storage

Study medication will be shipped to the site from the drug supply distribution center. Receipt and dispensation of study medication will be properly documented in compliance with the Pharmacy Binder instructions. Any temperature excursions should be documented as specified in the Pharmacy Binder.

Dispensing, preparation and administration of investigational products occurs under the supervision of the Principal Investigator and in compliance with the Pharmacy Binder. The Principal Investigator may only delegate these activities in accordance with state licensing board requirements, and local institutional policies, and applicable law. Before delegating this activity, the Principal Investigator should also ensure that the delegate is trained on and understands the requirements of the protocol.

The packaged kits of FX006 will be stored in a secure area and will be stored refrigerated at 2 to 8 °C.

7.6.4. Packaging and Labeling of Study Medication

The study medication will be labeled in accordance with local guidelines, as applicable.

7.6.5. Return of Study Medication

All study medications (packaged kits/used and unused vials) will be returned to the drug supply distribution center and will be documented in compliance with the Pharmacy Binder instructions. Return of study medications will be properly documented.

7.6.6. Method of Assigning Patients to Treatment Groups

Not Applicable (single arm, open-label study).

7.6.7. Blinding

Not Applicable (single arm, open-label study).

7.6.8. Breaking the Blind

Not Applicable (single arm, open-label study).

7.6.9. Standardized Procedure of IA Administration of FX006 in the Hip

Refer to Appendix A.

7.6.10. Post-Injection Care

Patients should be advised to avoid strenuous activities or prolonged weight-bearing activities for approximately 24 to 48 hours following the injection and to also maintain a stable lifestyle with regard to physical activity throughout the duration of the study.

7.6.11. Treatment Compliance

Study medication will be administered by the Injector. Details regarding study medication administration will be documented in the electronic Case Report Form (eCRF). The receipt, dispensation and return/destruction of any study medication will be properly documented.

If for any reason the administration of study medication is stopped before the entire volume is injected, the Injector should document the reason for stopping administration and refer to Pharmacy Binder for instructions.

7.7. Prior and Concomitant Therapy

7.7.1. Prior Therapy

Exclusionary medications are noted in the Exclusion Criteria.

Other medications reported at Screening will be recorded as Concomitant Medications and may be continued during the study if, in the judgement of the Principal Investigator, usage and the

underlying condition have been stable and are expected to remain stable for the duration of the study.

During the study, any changes in prior concomitant medications and the associated reasons for the changes will be recorded in source documentation and reported in the eCRF.

7.7.2. Concomitant Therapy Allowed During the Study

The following medications/non-pharmacological therapies may be taken or used throughout the study:

- Concomitant medication required for the treatment of a treatment-emergent AEs that is not listed as restricted.

7.7.3. Prohibited Medications/Non-Pharmacologic Therapies

Per the exclusion criteria, a patient is not eligible for this study if he/she has received any of the indicated treatments within the specified windows detailed in the Exclusion criteria (Section 7.5.3 Exclusion Criteria).

Changes to lifestyle with regard to physical activity, physical therapy, acupuncture, TENS, or bracing are prohibited for the first 4 weeks after injection.

In addition, the following medications should not be taken or used from the time of obtaining consent to the End of Study visit:

- Aspirin (>325 mg per day)
- Any treatment administered by IA injection in the index hip, including hyaluronic acid, plasma, cell therapies, anesthetics through 8 weeks post injection.
- IV, IM, or oral corticosteroids. Inhaled, intranasal and topical steroids are prohibited from Screening through Week 1 visit.
- Any investigational drug, device or biologic
- Immunomodulators, immunosuppressives, or chemotherapeutic agents
- Live (e.g., MMR vaccine, chicken pox vaccine, rotavirus vaccine) or live-attenuated vaccines (e.g., FluMist, Zostavax) through 8 weeks post injection

7.8. Study Variables

7.8.1. Procedure Variables

- Compliance with standardized procedure for Study Drug Administration
  - Patient position
  - Attempted aspiration of hip joint fluid with documentation of volume, if any, collected
  - Total volume administered; inclusive of FX006, contrast dye, if used, and saline
- Outcome of Standardized Procedure for Study Drug Administration

7.8.2. Safety Variables

- Adverse events
- Vital signs
- Index hip examinations

7.9. Study Procedures

7.9.1. Schedule of Study Assessments

A summary of the schedule of assessments is provided in Table 1.

7.9.2. Informed Consent

Prior to initiation of any study related procedures, patients will review and sign the study's informed consent form to participate in the study after having been informed about the nature and purpose of the study, participation and termination conditions, and risks and benefits.

7.9.3. Review of Eligibility, Medical History, Prior Treatment and Medications

Eligibility criteria (inclusion and exclusion criteria), medical history (including OA history, prior trauma, infection), prior treatment and medications are reviewed during Screening and at Day 1.

OA medical history includes Kellgren-Lawrence (K-L) Grade, OA diagnosis date (if available), presence of OA in other joints, previous IA injections in the index hip or other joints (e.g., steroids, PRP, hyaluronic injections, investigational), prior procedures, or surgeries involving the index hip.

At Day 1, eligibility should be confirmed (inclusion/exclusion criteria review against any new information/findings through Day 1 assessment).

7.9.4. Physical Examination

The physical exam will assess the following body systems:

- General Appearance
- Skin
- Lymphatics
- HEENT (head, ears, eyes, nose, throat)
- Cardiovascular
- Respiratory
- Abdominal
- Musculoskeletal
- Neurological

Complete physical exam will be conducted at Screening.

Any clinically significant findings observed at Screening must be documented in the source and added to the medical history; new or worsening findings observed subsequently will be recorded as an AE with physical exams conducted by the Investigator as relevant to the adverse event.

7.9.5. Index Hip Assessment

The index hip assessment will be performed by the Principal Investigator, or designee, at the days indicated in Table 1. The index hip will be assessed for tenderness, warmth, redness, swelling, and effusion, limitation on range of motion (directions: flexion, extension, abduction, adduction, internal rotation or external rotation; severity: mild, moderate or severe). Clinically significant findings will be recorded as detailed for other physical exam observations.

7.9.6. Index Hip X-ray

A diagnostic quality X-ray of the index hip is required at Screening. A weight-bearing, anterior-posterior pelvic view with the lower limbs in 10-degree internal rotation is recommended if an existing X-ray obtained ≤ 6 months of Screening is not available.

The Screening X-ray will be read locally for Kellgren-Lawrence (KL) grading.

Kellgren-Lawrence (KL) grading is a global scoring method that considers osteophytes, JSN, subchondral bone sclerosis and/or bone attrition. Grading criteria for the hip are (Rheumatology 2005;44 (Suppl 4):iv42:

- Grade 0: Normal appearance.
- Grade 1: Possible osteophytes, possible JSN medially.
- **Grade 2**: Definite osteophytes, definite JSN, slight sclerosis.
- **Grade 3**: Mild osteophytes, marked JSN, moderate sclerosis, cysts and deformity
- Grade 4: Large osteophytes, severe JSN, cysts sclerosis and deformity

Patients will be considered radiographically eligible for enrollment in the study if the index hip meets criteria for Kellgren-Lawrence Grade 2 or 3.

7.9.7. Vital Signs

Vital signs are to be taken at the days indicated in Table 1.

- Blood pressure (taken after sitting at rest for five minutes with feet flat on the floor)
- Heart rate
- Oral temperature
- Weight (with BMI calculated by the EDC system).
- Height (required for calculation of BMI) will be measured and recorded only at Screening.

7.9.8. Local Clinical Laboratory Evaluations

Blood samples for clinical laboratory testing as detailed below will be obtained on the visit days indicated in Table 1 and analyzed by the local laboratory.

If the PI feels that any subsequent clinical laboratory tests are required to evaluate AEs, those laboratory tests will be performed locally.

Table 2: Clinical Laboratory Panel

Clinical Laboratory Panels	
Hematology	**Clinical Chemistry**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume (MCV)	Chloride
Leukocytes (WBC)	Calcium
Absolute counts of:	Total bilirubin
Neutrophils	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase
Monocytes	Aspartate aminotransferase
Eosinophils	Blood urea nitrogen
Basophils	Creatinine
Platelets	Uric acid
	Glucose
Infectious diseases Serology[1]	Total protein
Hepatitis B Surface Antigen	Albumin
Hepatitis C Antibody	
HIV Antibody	
Pregnancy Tests (women of childbearing potential only) Serum: Screening – submitted to and performed by local laboratory Urine: On Day 1 prior to injection using test provided by local laboratory and read at the site	

[1.] Patients positive for any serology will be excluded and referred to their PCP for further management.

7.9.9. Index Hip Aspiration

Aspiration of the index hip joint must be attempted prior to injection of contrast and study medication at Day 1. If an effusion is detected, synovial fluid will be withdrawn to near dryness prior to injection. The synovial fluid volume, if any, will be documented prior to discarding.

7.9.10. Study Drug Administration

FX006 will be prepared in compliance with the Dose Preparation Procedure for FX006 Hip Studies located in the Pharmacy Binder. IA administration to the index hip will be performed according to Appendix A.

7.9.11. Review of Adverse Events and Concomitant Medications

After signing informed consent and at all visits, the patient should be monitored for any AEs by the Principal Investigator. Review of any Concomitant Medications should also be performed and documented in source documentation. Refer to Section 8.4.1 for further information in regard to reporting of AEs. Refer to Section 7.7 for further information in regard to allowed and restricted concomitant medication.

8. ADVERSE EVENTS

Subjects will be monitored for adverse events from the time of informed consent through the end of their participation in the study.

Results of clinical safety assessments are to be recorded in the patient's medical records and transcribed to the appropriate eCRF, including the AE eCRF for clinically significant findings.

8.1. Definitions

Adverse Event (AE): An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product
- Any clinically significant abnormality found on an ECG, laboratory test, or physical examination
- Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition, which is temporally associated with the use of the medicinal (investigational) product
- Pregnancy is not an AE; however, if a female patient or the female partner of a male patient who has received at least one dose of study medication becomes pregnant during the conduct of the study, the Investigator must notify the Sponsor according to the procedures in Section 8.4.1.

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 do not meet this criterion. A planned 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

Planned Hospitalization:

A hospitalization planned prior to dose of study medication is considered a therapeutic intervention. If the planned hospitalization or procedure is executed as planned, it should be recorded in the patient's medical history. However, if complications arise during the planned hospitalization or procedure or the patient experiences an AE during the planned hospitalization or procedure, it must be reported as an AE.

8.2. Monitoring of Adverse Events

Each patient will be monitored for the occurrence of AEs, including SAEs, beginning with informed consent. Each patient will be followed for safety monitoring until the last follow up visit in the trial as described in the Schedule of Assessments.

Patients will be questioned and/or examined by the Principal Investigator or a qualified designee for evidence of AEs. The questioning of patients with regard to the possible occurrence of adverse events should be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from patients.

The Principal Investigator is required to follow SAEs until resolution or withdrawal of consent. Resolution is defined as:

- A return to baseline for a pre-existing condition
- Resolved with or without residual effects
- The Principal Investigator does not expect any further improvement or worsening of the event
- Fatal outcome: If an autopsy is performed on a deceased patient, the autopsy report should be provided to the Sponsor as soon as it is available

8.2.1. Monitoring of Laboratory Assessments and Other Diagnostic Tests

The Investigator will review results of laboratory and other diagnostic tests for clinical significance and consideration as an AE.

8.2.2. Adverse Events That Occur During the Injection Procedure

If an adverse event occurs during the injection procedure, the Injector will record the details of the AE in the patient's chart and provide a full report of the event to the Principal Investigator, or designee. Reporting procedures in the event of any difficulties with preparing or administering the study drug are detailed in the Pharmacy Binder.

8.3. Assessment of Adverse Events

8.3.1. Assessment of Seriousness

Each adverse event should be assessed for seriousness against the definition of Serious Adverse event in Section 8.1 above.

8.3.2. Assessment of Severity

Each adverse event should be evaluated for severity or intensity. 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:

- 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

8.3.3. Assessment of Relationship to Study Medication

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, and may include consideration of the following factors:

- Possible alternative causes of the AE, 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
- 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:

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 (e.g., the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the investigational product)

8.4. Recording of Adverse Events

All AEs, regardless of seriousness, severity, or causal relationship to study medication, will be recorded on the AE page of the eCRF.

When possible, adverse events should be reported as a specific disease or syndrome rather than individual signs and symptoms. Additionally, procedures and diagnostic tests results should not be reported as AEs unless their underlying diagnosis is unknown. For example, the diagnosis of 'influenza' should be reported as an AE instead of the symptoms of fever, fatigue, malaise, and positive flu test when the Investigator believes that those are all associated with influenza.

However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the appropriate AE eCRF.

Since all enrolled patients are required to have a certain level of arthralgia in the index hip before they receive study drug, the Investigator must take care to fully assess any patient reports of index hip arthralgia that occurs during the study. Incremental return of preexisting index hip arthralgia following post-injection pain relief does not meet the criteria for an adverse event, unless the arthralgia is clinically significantly worse from baseline (before study drug administration).

8.4.1. Reporting of Serious Adverse Events

When an SAE occurs, the Investigator or designee, must log into the electronic data capture (EDC) system and complete the SAE report form within 24 hours of becoming aware of the SAE. The EDC system will notify the Medical Monitor and other appropriate study personnel of the SAE.

If the EDC SAE form is not available, the Investigator should complete and sign the paper SAE form and email it to the Sponsor within 24 hours of becoming aware of the SAE. When the EDC system is available again, the SAE should be input into the EDC SAE form.

Follow up information relating to an SAE must be reported to the Sponsor within 24 hours of receipt by the Investigator by entering new or updated information into the EDC SAE form.

All SAEs that occur at your site should, in addition, be reported by the Investigators to the responsible IRB/EC without undue delay, if applicable according to IRB/EC requirements.

During the conduct of the study, the Sponsor will provide expedited safety reports (AEs classified as serious, unexpected and related to study medication) to the investigative sites. If this occurs, the investigative site must report the information to their IRB per local guidelines (may be submitted by the Sponsor or designee for sites that use a central IRB).

8.5. Safety Monitoring Roles

The site personnel will carefully monitor each patient throughout the study for possible AEs. All AEs will be reviewed and assessed by the Principal Investigator. All AEs will be documented on

the eCRF and will be followed until either completely resolved or until a stable chronic outcome is determined by the Principal Investigator. SAEs will be reported in accordance with Section 8.4.1. The Medical Monitor must promptly review all information relevant to the safety of an investigational new product received from any source.

The Medical Monitor and the Sponsor will review AE data on an ongoing basis, accessed through the EDC system and associated reporting tools, in order to identify potential safety issues/trends that may not be apparent through individual AE reporting. If systematic review identifies a pattern of concern, Sponsor will take steps to address the issues including but not limited to modifying the protocol and/or notifying investigator, authorities and IRB/ECs. Each review will be documented and filed in the Trial Master File.

Principal Investigators will receive prompt notification of any adverse experience associated with the use of the study medication that is both serious and unexpected, or any finding that suggests a significant risk for patients. The Investigator will promptly inform the IRB/EC of the notification and insert the notification in the Investigator's Regulatory Binder in accordance with local regulations.

8.6. Clinical Management of Index Hip-Related Events

In the event that the patient has an immediate reaction following administration of study medication or returns to the clinic with an acute exacerbation (e.g., tenderness, increased pain, swelling, effusion, decreased mobility of the index hip), the patient should be treated according to local clinical guidelines and physician experience.

If the index hip is aspirated at any time other than administration of study medication for any reason, the volume of synovial fluid aspirated must be documented, synovial fluid should be (1) cultured, (2) evaluated for presence of crystals and (3) assessed for white cell count at a local laboratory, and the results should be documented.

Any event that is a change from the patient's baseline status (new or worsening case) should be reported as an AE and those meeting the definition of serious must be reported in accordance with Section 8.4.

8.7. Pregnancy

All pregnancies, female patients or female partners of male patients during the study, must be reported within 24 hours on the Pregnancy Report Form. 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). If not all information on the Pregnancy Report Form is available at the time of the initial report, follow-up reports should be provided to the Sponsor in a timely manner. Additional subsequent follow-up is not needed when a newborn baby is healthy.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical and Analytical Plans

A comprehensive statistical analysis plan (SAP) will be written and approved prior to database lock for this study. If, after the study has been completed, changes are made to the SAP referenced below, these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report (CSR). The key aspects of the proposed analyses are summarized below.

9.1.1. Planned Analyses

A final analysis will be conducted when all patients have completed the study. Final analyses specified in the protocol and SAP will be completed and reported in the CSR. Post-hoc, exploratory analyses, may be completed to further understand and elucidate study results. Any post-hoc, exploratory, analyses completed will be clearly identified as such in the final CSR.

9.2. General Considerations and Methods

Data collected in this study will be presented using summary tables and subject data listings. Summary tables will present data by injection procedure connector used and by time of collection, if applicable. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized using frequencies and percentages. Confidence intervals may also be provided. Figures may be used to support the presentation of certain data.

9.2.1. Analysis Populations

The analysis population planned for this study as follows:

- Safety Population: All subjects who received an attempted administration of study drug.

9.2.2. Study Data

Study data identified in this protocol are collected, and source verified, on electronic Case Report Forms (eCRF) at sites completing the study. All study data will be formulated into data sets to provide transparency, traceability, and integrity of trial analysis results from collection source. Observed study data will be mapped to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture.

9.2.2.1. Clinical Data – CDISC Study Data Tabulation Model (SDTM)

Domains will be mapped to CDISC SDTM using implementation guide version 3.2. No derived data required for analysis are included in the SDTM domains. All SDTM domains will be fully documented with define documents (DEFINE.XML) and a Study Data Reviewer's Guide (SDRG) after database lock and final analyses are completed.

9.2.2.2. Analysis Data – CDISC Analysis Data Model (ADaM)

All planned and exploratory analyses will be completed using CDISC compliant ADaM data sets derived from the SDTM domains for this study. Analysis data sets will contain all derived study endpoints required for analysis. All ADaM analysis data sets will be fully documented with define documents (DEFINE.XML) and an Analysis Data Reviewer's Guide (ADRG) after database lock and final analyses are completed.

9.2.3. Study Endpoints for Assessment

9.2.3.1. Primary Endpoint

Successful study drug administration – defined as Injector reporting complete study drug administration.

9.2.4. Sub-Groups and Covariates

Sub-group analyses per aspiration status, KL grade, gender, etc. may be detailed in the SAP.

9.3. Determination of Sample Size

9.3.1. Sample Size Considerations

Approximately 22 patients will be treated in this study. If there are no incomplete IA administrations, the study may be considered complete. Observing 0 incomplete injections (0%) in 22 patients gives 90% confidence that the true incomplete IA injection rate is between 0 and 10%. If one (1) unsuccessful IA administration of study drug is observed, 7 additional patients may be enrolled. Observing 1 incomplete IA injection in 29 patients (3%) gives 80% confidence that the true incomplete IA injection rate is between 0 and 10%**.**

9.4. General Statistical Methods

9.4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be listed by study site and subject and will be summarized. Frequencies and proportions will be presented for the categorical variables and descriptive statistics will be presented for continuous variables.

9.4.2. Exposure

Treatment exposure will be listed by study site and subject and will be summarized.

9.4.3. Efficacy Analyses

The rate and 90% CI of successful FX006 administration will calculated all subjects dosed.

Exploratory analyses may be conducted to aid in determination of root causes of unsuccessful injections should any occur.

9.4.4. Safety Analyses

Analysis of Adverse Events

Safety analyses will be performed on the Safety Population. AEs will be coded using MedDRA. Incidences (number and percent) of TEAEs, those events that start after dosing or worsened in severity after informed consent, will be presented. Incidences of TEAEs will also be presented by maximum severity and relationship to study medication.

Similar presentations will be provided for serious AEs, AEs leading to withdrawal from the study, or AEs leading to death. Analysis of AE data will include examination of the incidence rates of index hip TEAEs.

Other Safety Analyses

Laboratory data, vital signs and X-ray KL grade will be presented as descriptive summary statistics. Vital signs and lab data will also be presented as change from Baseline at each individual time point.

10. DATA QUALITY ASSURANCE

At the time the study is initiated, the clinical study monitor will thoroughly review the final protocol and the eCRF with the Principal Investigator and staff. During the course of the study, the clinical study monitor will visit the clinical site regularly to check the completeness of the patient records, the accuracy of entries into the eCRF, the adherence to the final protocol and to International Conference on Harmonisation GCP, the progress of enrollment, and the storage, dispensing and accountability of study medication. The Principal Investigator and key study personnel should be available to assist the clinical study monitor during these visits.

The Principal Investigator will give the monitor, auditor(s), Sponsor, Sponsor designee and regulatory authorities direct access to relevant clinical records to confirm their consistency with the eCRF entries. No information in these records about the identity of the patients will leave the clinical site. The Sponsor will maintain the confidentiality of all patient records.

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Independent clinical quality assurance audits may be performed at any time during or following completion of the Study by the Sponsor, or its authorized agents, and Competent Authorities and/or the IRB/EC.

11. DATA HANDLING AND RECORDKEEPING

11.1. Case Report Forms

The eCRF will be supplied by the Sponsor or designee and should be handled in accordance with the instructions provided. All study data should initially be documented in source documents (e.g., patient charts, notes, laboratory reports, etc.) and then subsequently entered from the source into the eCRF. All eCRFs should be filled out completely by examining personnel or the study coordinator. The eCRF is reviewed, signed, and dated electronically by the Principal Investigator.

11.2. Study Medication Accountability

All study medication required for completion of this study will be provided by the Sponsor or designee. Study medication will be acknowledged upon receipt indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study medications received by, dispensed from, or returned by the study site should be maintained per instructions in the Pharmacy Binder.

In the event of a temperature excursion, refer to the Pharmacy Binder for instructions.

In the event of a product complaint, complete the Complaint Notification Form located in the Pharmacy binder.

11.3. Confidentiality of Data

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection by representatives of Competent Authorities, the Sponsor or their representative, and the IRB/EC.

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.4. Retention of Records

In accordance with US federal regulations (21 CFR 312.62[c]), the Sponsor requires that records and documents pertaining to the conduct of this study and the distribution of study medications, including eCRFs, consent forms, laboratory test results, source data, and medical inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the regulatory authorities are notified. The Sponsor or their representative will notify the Principal Investigator of these events. In the event that local regulations are more stringent than that specified above, the local regulations will be adhered to. If local records

retention regulations are more stringent than that specified above, the local regulations will prevail.

11.5. Protocol Adherence

The Principal Investigator must adhere to the protocol as detailed in this document and agrees that any changes to the protocol must be approved by the Sponsor or their representative prior to seeking approval from the IRB/EC. When the changes involved are only logistical and administrative in nature to trial this may not require prior approval by the IRB/EC. The Principal Investigator will be responsible for enrolling only those patients who have met protocol eligibility criteria.

12. PUBLICATION POLICY

12.1. Sponsor's Publication Policy

Sponsor or its designee shall have the right to publish or otherwise publicly disclose the information contained in or related to the Study Drug, the Study Data, or other Confidential Information in any form without the written consent of Site, the Principal Investigator or any other person. Each of Site and Principal Investigator further agrees that Sponsor shall have the exclusive right to commercialize any products or services that are based upon, or derived from the Study Drug, the Study Data, or other Confidential Information.

12.2. Site Publication

After the Study is completed, which means that all completed eCRFs have been received by Sponsor, and the database has been locked at all participating sites and Study closeout visits have taken place at all participating sites, then Site shall have the right, subject to the HIPAA Rules, to publish or otherwise make public data resulting from the conduct of the Study at the Site upon the earlier of (a) the date of publication of a multi-center publication coordinated by Sponsor with respect to the data resulting from the Study, and (b) the date of submission of the data resulting from the Study by Sponsor to the FDA for regulatory approval; provided that Site shall furnish Sponsor with a copy of any proposed publication or release at least 90 days in advance of the proposed submission or presentation date. Within this 90-day period, the Sponsor shall review such proposed publication or release to determine whether it contains any Confidential Information (other than Study Data), or whether Sponsor desires to file patent applications on subject matter contained therein, and to ensure the accuracy of the information contained in the publication or release. Upon receiving any notification from Sponsor requesting deletion of Confidential Information (other than Study Data), requesting correction of inaccuracies, or requesting a delay in publication of up to 90 days to allow the filing of patent applications before publication or release, Site shall take the requested action. The parties acknowledge and agree that Site shall be solely responsible for the editorial content of any such publication or release. In a manner consistent with customary practice, Site shall acknowledge the support and contributions of Sponsor, if requested by Sponsor, in connection with the Study, in any and all publications and presentations reporting and data resulting from the Study. Site and the Principal Investigator shall comply with all applicable federal and state laws and other applicable rules and requirements regarding disclosure of industry support (financial or otherwise) in connection with such publications and presentations.

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14. APPENDICES

APPENDIX A: PROCEDURE FOR IA HIP INJECTION OF FX006

Materials to be provided by Sponsor for use in the injection procedure

- Sterile 3.5" 20 gauge spinal needles with stylet (for the IA injection)
- Sterile mini bore extension tubing set 7 inches (part #: TCBEXT001)
  - Note: Dead space is ≤0.2 mL
- Study Drug Administration Source Documentation form – to be completed and signed by the Injector.

Materials to be provided by the site for use in the injection procedure

- Pillow (non-sterile) to support subject's leg during procedure (see details below)
- Materials for sterile prep and draping of the patient
- Masks and sterile gloves for the Injector
- Materials for administration of local skin/subcutaneous tissue anesthetic (if needed)
- Sterile syringe, empty (for attempting to aspirate joint fluid)
- Sterile syringe for contrast dye (or air)
- Fluoroscopy contrast dye (if to be used; alternative air)
- Sterile syringe for the saline
- Sterile saline for injection (to flush needle before and after injecting study agent)
- Sterile 6" 20 gauge spinal needles with stylet (if Injector's choice for the IA injection)

Preparation of FX006

- See detailed instructions in the Pharmacy Binder for preparation of FX006.
- The syringe with FX006 should be provided to the Injector and used as detailed below.

Notes applicable to all injection procedures:

- Local anesthetic should ***not*** be mixed with the study drug.
- *In the event of difficulties during the procedure* (i.e. needle placement), do ***not*** attempt a second needle placement
  - *Stop the procedure* and report the event to the Principal Investigator and to the Clinical Team at Flexion
- In the event of difficulties with study drug administration,
  - *Stop the procedure* and report the event to the Principal Investigator and to the Clinical Team at Flexion
  - Complete the Complaint Notification Form located in the Pharmacy Binder

FX006 Injection Procedure

1. [redacted]
2. [redacted]

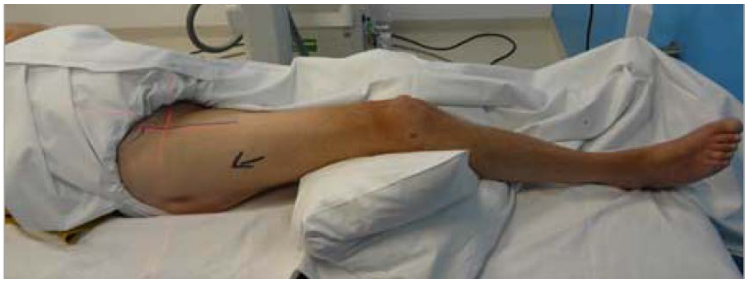

Photo taken from (Kumar et al, 2017).

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