CLINICAL STUDY PROTOCOL

An Open-label Study to Assess the Safety of Repeat Administration of FX006 to Patients with Osteoarthritis of the Knee

PROTOCOL NUMBER: FX006-2016-011

PHASE: 3b

STUDY MEDICATION(S): FX006

INDICATION: Osteoarthritis of the Knee

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Clinical Study Protocol Version 2.0 (dated 16 October 2017)

Sponsor Safety Officer Approval

Signature: _____ **Date:** 17 Oct 2017

Name (print): *Neil Bodick, MD, PhD, Chief Medical Officer*

Title:

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
ADL	Activities of daily living
ADaM	Analysis Data Model
ADP	average daily pain
ADRG	Analysis Data Reviewer's Guide
AE	adverse event
ANOVA	analysis of variance
AUC	area under the concentration-time curve
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CI	confidence interval
CMC	Carboxymethylcellulose sodium
CTCAE	Common Terminology Criteria for AEs
CSR	Clinical Study Report
CV	coefficient of variation
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
GPAQ	Global Physical Activity Questionnaire
HIV	Human Immunodeficiency Virus
HPA	hypothalamic-pituitary-adrenal
IA	intra-articular
IB	Investigator's Brochure
IRB/EC	Institutional Review Board/Ethics Committee
IM	intramuscular
IV	intravenous
K-L	Kellgren-Lawrence
KM	Kaplan-Meier
KOOS	Knee injury and Osteoarthritis Outcome Score
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
NaCl	sodium chloride
OA	osteoarthritis

OARSI	Osteoarthritis Research Society International
PGIC	Patients' Global Impression of Change
PLGA	poly[lactic-co-glycolic acid]
PK	pharmacokinetic
PRP	platelet rich plasma
PTOA	post-traumatic osteoarthritis
QOL	Quality of Life
QTc	QT interval corrected for heart rate
RBC	red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
SDRG	Study Data Reviewer's Guide
SDTM	Study Data Tabulation Model
TEAE	treatment-emergent adverse event
TA[1]	triamcinolone acetonide
TAcs[2]	triamcinolone acetonide injectable suspension, immediate-release (commercially available)
US	United States
USP	United States Pharmacopeia
w/w	weight/weight
WBC	white blood cells
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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

2. SYNOPSIS

Title of Study: An Open-label Study to Assess the Safety of Repeat Administration of FX006 to Patients with Osteoarthritis of the Knee

Study Centers: Approximately 20 centers

Study Phase: 3b

Objectives:

The primary objective of this study is to assess the overall safety and general tolerability of repeat administration of FX006 (two doses of 32 mg FX006) in patients with symptomatic osteoarthritis (OA) of the knee.

Exploratory objectives of this study include the following:

- examine efficacy signals for sustained pain reduction following two doses of 32 mg FX006.
- collect synovial fluid samples to enable potential future examination of synovial fluid biomarkers that may contribute to the pathogenesis of OA and/or be associated with responsiveness to FX006 treatment.

Study Design and Methodology:

This study is an open-label, repeat administration design of 32 mg FX006. The study will be conducted in male and female patients ≥ 40 years of age with symptomatic OA of the knee.

Eligible patients will be offered participation to receive an initial IA injection of FX006 administered to the index knee at Day 1.

Patients who receive an initial injection of FX006 will return at Weeks 4 and 8 before being evaluated at 12, 16, 20, and 24 weeks following the initial administration of FX006 for repeat administration. At the first visit where the patient has been determined to meet repeat administration eligibility criteria described in Section 7.4.3, the patient will be eligible to receive a second IA injection of FX006 administered to the index knee.

Patients who are eligible to receive a second injection will be evaluated for a total of 52 weeks post initial injection at: Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, regardless of the visit at which they receive their second injection.

Patients that do not benefit from the initial treatment as determined by evaluation at Week 12 will complete the study at the Week 12 follow-up visit. These patients will be evaluated for a total of 12 weeks post initial injection at: Weeks 4, 8, 12.

Patients who are not eligible for a second injection of FX006 after evaluation at Weeks 12, 16, 20, and 24 will complete the study at the Week 24 follow-up visit. These patients will be evaluated for a total of 24 weeks post initial injection at: Weeks 4, 8, 12, 16, 20, and 24.

Refer to Appendix 2 Study Visit Flow Chart.

The study is expected to enroll over approximately 6 months.

Number of Patients:

Approximately 200 patients will be enrolled to ensure that at least 100 patients receive two doses of 32 mg FX006 and complete the study through Week 52.

Test Product, Dose and Mode of Administration:

FX006 – extended release formulation of TA in 75:25 poly(lactic-co-glycolic) acid (PLGA) microspheres.

Nominal 32 mg TA, IA, administered as a single 5 mL injection

Reference Compound(s), Dose and Mode of Administration:

Not applicable

Duration of Dosing:

Single IA injection for all enrolled patients at Day 1/Baseline, and a second IA injection for those meeting repeat administration requirements at either Week 12, 16, 20, or 24.

Screening Inclusion Criteria:

To be included in the trial, patients must fulfill the following criteria to participate in the study

1. Written consent to participate in the study
2. Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions
3. Male or female ≥40 years of age
4. Symptoms associated with OA of the index knee for ≥ 6 months prior to Screening (patient self-report is acceptable)
5. Currently meets ACR Criteria (clinical and radiological) for OA (Altman et al, 1986) as follows:
   - Knee pain
   - at least 1 of the following:
     - Age > 50 years
     - Stiffness < 30 minutes
     - Crepitus
   - Osteophytes
6. Kellgren-Lawrence (KL) Grade 2, 3 or 4 in the index knee based on X-ray performed during Screening (locally read)
7. WOMAC A total sum score of ≥ 6 at Screening and Day 1/Baseline
8. Index knee pain for >15 days over the last month (as reported by the patient)
9. If bilateral OA exists, pain in the contralateral knee must be less than pain in the index knee as reported by the patient
10. Body mass index (BMI) ≤ 40 kg/m^{2s}
11. Ambulatory and in good general health
12. Willingness to abstain from use of the following protocol-restricted medications during the study:
    - Intravenous (IV), intramuscular (IM) and oral corticosteroids (Note: inhaled, intranasal and topical corticosteroids are allowed)
    - IA corticosteroids in any joint
    - IA viscosupplementation (hyaluronic acid) or any IA intervention (IA injection, IA aspiration, etc.) in the index knee
    - Opiates
    - Any investigational drug, device or biologic
    - Immunomodulators, immunosuppressives, or chemotherapeutic agents
    - Live or live attenuated vaccines

Screening Exclusion Criteria:

Patients fulfilling at least one of the following criteria may not be included in the study:

Disease-related criteria

1. Reactive arthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or arthritis associated with inflammatory bowel disease
2. History of infection in the index knee joint
3. Clinical signs and symptoms of active knee infection or crystal disease of the index knee within 1 month of Screening
4. Presence of surgical hardware or other foreign body in the index knee
5. Unstable index knee joint (such as a torn anterior cruciate ligament) within 12 months of Screening

Previous or concomitant treatment-related criteria

6. IA corticosteroid (investigational or marketed) in index knee within 3 months of Screening
7. IA hyaluronic acid (investigational or marketed) in the index knee within 6 months of Screening
8. IV or IM corticosteroids (investigational or marketed) within 3 months of Screening
9. Oral corticosteroids (investigational or marketed) within 1 month of Screening
10. Any other IA drug/biologic use within 6 months of Screening or 5 half-lives (whichever is longer) (e.g., platelet rich plasma (PRP) injection, stem cells, prolotherapy and amniotic fluid injection)
11. Prior administration of FX006
12. Prior arthroscopic or open surgery of the index knee within 12 months of Screening
13. Planned/anticipated surgery of the index knee during the study period

Patient-related criteria

14. Known hypersensitivity to any form of triamcinolone
15. History of sarcoidosis or amyloidosis
16. Active or history of malignancy within the last 5 years, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or effectively managed cervical carcinoma
17. Known active or quiescent systemic fungal, bacterial, mycobacterial (including tuberculosis), viral or parasitic infections, or, shingles, herpes zoster and ocular herpes simplex
18. Any infection requiring IV antibiotics within 4 weeks of Screening or oral antibiotics within 2 weeks of Screening
19. History of osteomyelitis
20. Known or clinically suspected infection with human immunodeficiency virus (HIV), hepatitis B or C viruses
21. Any clinically significant electrocardiogram (ECG) abnormality as judged by the Investigator
22. Patients requiring or likely to require chronic treatment with corticosteroids during the study period based on patient medical history
23. History of, or active Cushing's syndrome
24. Active substance abuse (drugs or alcohol), history of chronic substance abuse within the past year, or prior chronic substance abuse judged by the investigator as likely to recur during the study
25. Skin breakdown at the knee where the injection would take place
26. Women who are pregnant or nursing or plan to become pregnant during the study; men who plan to conceive during the study
27. Women of child-bearing potential (not surgically sterile or post-menopausal for at least 1 year as documented in medical history) not using a highly effective method of contraception [abstinence; oral, injected or implanted hormonal methods of contraception; intrauterine device or intrauterine system; condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; or male sterilization (vasectomy)]

28. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents within 5 years of Screening
29. Has received a live or live attenuated vaccine within 3 months of Screening
30. Use of any other investigational drug or device within 30 days of Screening or within 5 half-lives (whichever is longer) or an investigational biologic within 60 days of Screening or within 5 half-lives (whichever is longer)
31. Any other clinically significant acute or chronic medical conditions (e.g., bleeding disorder) that, in the judgment of the Investigator, would preclude the use of an IA corticosteroid or that could compromise patient safety, limit the patient's ability to complete the study, and/or compromise the objectives of the study

Repeat Administration Inclusion Criteria:

To be eligible to receive a repeat administration, patients must fulfill the following criteria:

1. Benefit from the initial dose of FX006 in the opinion of both the patient and the Investigator
2. No major safety concerns during the initial dose period as assessed by the Investigator
3. Clinically indicated to receive a second dose of FX006 in the opinion of both the patient and the Investigator
4. WOMAC A total sum score of ≥ 6 or a clinical rationale as to why a second dose is indicated
5. Compliant with study procedures and visit schedules through at least Week 12 and the willingness and ability to continue to comply through Week 52
6. Willingness to abstain from use of protocol-restricted medications during the study

Repeat Administration Exclusion Criteria:

Patients fulfilling at least one of the following are not eligible to receive a repeat administration:

1. Clinical signs and symptoms of active knee infection or crystal disease of the index knee
2. Received a non-protocol specified IA intervention (IA injection, IA aspiration, etc.) in index knee during study participation
3. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents during study participation
4. Received a live or attenuated vaccine during study participation
5. Use of any other investigational drug, device or biologic during study participation
6. Allergic reaction to initial dose of 32 mg FX006
7. Any infection requiring IV antibiotics within 4 weeks or oral antibiotics within 2 weeks of second dose of FX006
8. Skin breakdown at the knee where the injection would take place
9. Women who are pregnant or nursing or plan to become pregnant during the study; men who plan to conceive during the study
10. Women of child-bearing potential (not surgically sterile or post-menopausal for at least 1 year as documented in medical history) not using a highly effective method of contraception [abstinence; oral, injected or implanted hormonal methods of contraception; intrauterine device or intrauterine system; condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; or male sterilization (vasectomy)]
11. Any other clinically significant acute or chronic medical conditions (e.g., bleeding disorder) that, in the judgment of the Investigator, would preclude the use of an IA corticosteroid or that could compromise patient safety, limit the patient's ability to complete the study, and/or compromise the objectives of the study

Procedures and Assessments:

The study will involve a Screening period (a minimum of 7 days, up to 21 days), dosing at Day 1/Baseline and up to 13 additional outpatient visits (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52) depending if the patient is eligible for and receives a second injection.

At specified times throughout the study, patients will undergo physical examinations, index knee assessments and index knee X-rays; blood samples will be collected for laboratory safety tests and vital signs will be collected or measured. Information regarding AEs and concomitant medications will be collected.

Patients will have index knee synovial fluid collected at baseline and the week at which the second dose is administered (if the patient is eligible to receive a second dose). Patients that are not eligible to receive a second dose will not have synovial fluid drawn at their final study visit. These samples will be preserved for potential future OA biomarker analyses.

Steps per day will be captured using a measured function device. Patients will be provided with a device at the Screening visit to be worn for at least 7 days prior to Baseline/Day 1 through Week 12. The site will confirm patient compliance with wearing the device to capture steps per day data at each patient visit from Day 1 through Week 12. As well, patients will complete the Global Physical Activity Questionnaire (GPAQ) at Screening and at Week 12.

During out-patient visits, patients will complete the Western Ontario and McMaster Universities (WOMAC®) Osteoarthritis Index Likert (LK) 3.1 and the Knee injury and Osteoarthritis Outcome Score (KOOS) Quality of Life (QOL) Subscale.

Blinding:

This is an open-label study.

IP Administration Procedure:

IA injections will be performed by the assigned injector. The injector may choose the position of the knee (e.g., extended or flexed), the approach for the injection (e.g., medial or lateral) and the numbing agent to be used (e.g., ethyl chloride, subcutaneous lidocaine; IA anesthetics are not allowed) based on standard of care. Sterile technique should be used.

Prior to injection, the index knee should be thoroughly cleansed using a bactericidal solution. The index knee will be aspirated in all cases prior to administration of study medication. Following attempted aspiration, 5 mL of the reconstituted FX006 will be injected into the synovial space. Refer to the Pharmacy Binder for detailed instructions on how to prepare FX006.

The same needle used for IA injection of the study medication may also be used for synovial fluid aspiration, thereby allowing for a single injection with syringe replacement. The injector will use a 21 gauge or larger needle for injection and aspiration of fluid.

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.

In the event that the patient has an immediate reaction (e.g., tenderness, increased pain, swelling, effusion, decreased mobility of the index knee), the patient should be treated according to local clinical guidelines and physician experience

Concomitant Medications:

The exclusion criteria indicate that a patient may not be enrolled if he/she has used any of the following within the specified windows. In addition these medications should not be taken or used throughout the study:

- IV, IM or oral corticosteroids
- IA corticosteroids in any joint
- IA viscosupplementation (hyaluronic acid) or any IA intervention (IA injection, IA aspiration, etc.) in the index knee
- Opiates
- Any investigational drug, device or biologic
- Immunomodulators, immunosuppressives, or chemotherapeutic agents
- Live or live attenuated vaccines

Criteria for Evaluation:

Safety Variables

Safety and tolerability will be evaluated on the basis of AEs spontaneously reported by the patient or discovered by the Investigator and findings from the following assessments: physical examinations, index knee assessments, vital signs, and clinical laboratory evaluations. In addition the index knee will be evaluated by X-ray and assessed by a central imaging vendor for joint space narrowing, chondrolysis, subchondral bone changes, bone infarcts, avascular necrosis, joint swelling, and insufficiency fracture.

Exploratory Efficacy Variables

- Western Ontario and McMaster Universities (WOMAC®) Osteoarthritis Index (Likert (LK) 3.1, 5-point scale): pain, stiffness and function domains independently and collectively (Bellamy et al, 1988).
- Knee injury and Osteoarthritis Outcome Score (KOOS) Quality of Life (QOL) Subscale
- Daily activity measured as steps per day
- Global Physical Activity Questionnaire (GPAQ) domains for Occupational physical activity, Transport-related physical activity, and Physical activity during discretionary or leisure time)

Sample Size Considerations:

A sample size of approximately 100 patients who receive two doses of 32 mg FX006 is considered a reasonable sample size in order to assess the safety profile of repeat administration of FX006. No formal power and sample size calculations have been made as the analysis of the efficacy data collected from this study will be considered exploratory and hypothesis-generating for future multiple dose studies of FX006. In order to ensure at least 100 patients who receive two doses of 32 mg FX006 are enrolled and followed for 52 weeks, approximately 200 patients will be enrolled based on an estimate that approximately 66% of patients enrolled will be eligible to receive a second dose of 32 mg FX006 and approximately 75% of subjects who receive a second dose will complete the study through Week 52.

Statistical Methods:

A comprehensive statistical analysis plan (SAP) will be written and approved prior to database lock for this study that describes the final analyses to be completed for safety and exploratory efficacy endpoints.

No formal interim analysis is planned for the primary safety endpoints in this open-label study to assess the safety and tolerability of FX006 after repeat administration. However, interim analysis may be conducted with exploratory endpoints to examine efficacy signals following administration of one or two doses of 32mg FX006. These interim analyses on exploratory endpoints may be completed for data review, regulatory updates, and/or publication (or presentation at congresses) for this open-label study. Any interim analysis completed will have an interim analysis plan written and approved to describe the purpose and analytical objectives of the interim analysis. Final analyses, described in the protocol and statistical analysis plan, will be conducted after completion of the study, when all subjects have either discontinued the study early (prior to Week 52) or completed the study through Week 52.

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

Treatment exposure will be listed by study site and patient, and will be summarized by treatment and dose.

The examination of efficacy is exploratory in this study. Data from the WOMAC® questionnaire will be presented in by-patient listings with summary presentation of the data and exploratory analyses.

Analysis of the magnitude of pain relief observed with WOMAC A (pain), stiffness (WOMAC B), and function (WOMAC C) will be explored between patients who receive one dose and those receiving a second following the first and second doses of 32 mg FX006 will be explored with a mixed model for repeated measures (MMRM) with fixed effects of number of doses (1 or 2) received, and a dose by time interaction. Model covariates will include study site, and potentially other variables. Subject will be a random effect in the model. Time points of interest for this analysis are those when a subject is eligible for a second dose.

A second within subject analysis will be completed for subjects who receive two doses of FX006 to examine the improvement in WOMAC scores within a subject after receiving the second dose: WOMAC after the first dose, compared to WOMAC following the second dose. The change from baseline to the last WOMAC score for the first dose will be compared to the change from the last score prior to the second dose to the last WOMAC score following the second dose. The increment difference in the overall change for the first dose compared to second dose will be explored with a linear model.

Evaluation of dose-response will be assessed descriptively with an examination of WOMAC A responses at the time (in weeks) of second dose administration to assess the magnitude of scores at each week that a second dose may be administered. The time to maximal pain relief response with WOMAC A following the first and second doses of 32 mg FX006 will be examined using a Kaplan-Meier (KM) procedure.

Questionnaire data from the Global Physical Activity Questionnaire (GPAQ) domains (occupational physical activity, transport-related physical activity, and physical activity during discretionary or leisure time) will be described descriptively at the two time points collected (Screening and Week 12). The change in GPAQ domain scores and total score will be examined with an analysis of variance (ANOVA) model with summaries comparing patients who receive one dose to those receiving two doses of 32 mg FX006. GPAQ information collected at Screening will be utilized to normalize steps per day based on lifestyles activity. GPAQ information will be a model covariate in subsequent analyses.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Incidences (number and percent) of treatment-emergent adverse events (TEAEs), those events that started after dosing or worsened in severity after dosing, will be presented by treatment group. 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 TEAEs and index knee related TEAEs following the first dose and second dose, as well as the cumulative incidence of TEAEs after all doses of 32 mg FX006. Both the number of events and the number of patients experiencing an event will be examined to assess the by patient cumulative incidence of TEAEs associated with repeat administration.

Clinical laboratory data and vital sign information will be presented as descriptive summary statistics for value and change from Baseline at each individual time point.

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 patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients 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, conditions of participation and termination, 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 (US) 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. We estimate 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 (ACR Subcommittee 2000; Hochberg et al, 2012; Jordan et al, 2003).

While historically OA has been considered a non-inflammatory disease, it is increasingly being recognized that chronic synovitis occurs in all stages of knee OA (Benito et al, 2005; Sellam and Berenbaum, 2010; Wenham and Conaghan, 2010). As synovial inflammation is correlated with clinical symptoms and joint degeneration, it should be an important target for therapeutic intervention. The inflamed synovium may well be the target for IA corticosteroids which are widely used in knee OA (Ayral et al, 2005).

5.2. Background

5.2.1. Investigational Medicinal Product: FX006

FX006 is an extended-release formulation of triamcinolone acetonide (TA) for IA administration that is being developed for the treatment of patients with pain attributed to OA of the knee. FX006 is intended to deliver TA to the synovial and peri-synovial tissues for a period of approximately 3 months depending on the dose administered (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% (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 OA of the Knee

Available clinical and nonclinical data indicate that FX006 is likely to be safe and well tolerated and has the potential to provide pain relief that is meaningfully better and more persistent than that provided by immediate release triamcinolone acetonide (TAcs). Nonclinical data and the literature suggest that this potential could extend to limiting structural progression in patients with inflammatory joint disorders. The near term clinical development program for FX006 focuses on the analgesic effects in patients with OA of the knee.

5.2.3. Non-clinical

The safety of FX006 was evaluated following single IA injection in one non-GLP rat toxicity study and two GLP-compliant dog toxicity studies, and following repeated IA injection in one GLP-compliant dog toxicity study. In the repeat dose study, dogs were dosed once every 3 months (1Q3M) for a total of 3 doses, or once every month (1Q1M) for a total of 3 doses); local and systemic (steroid target tissues) toxicity were assessed.

The systemic effects of repeat IA administration of FX006 containing up to 18.75 mg of TA and 75 mg of PLGA microspheres were consistent with known TA/corticosteroid affects and were similar for the 1Q3M and 1Q1M dose regimens. Regarding local toxicity, at 1 month after the last dose following I.A. administration every 3 months (1Q3M), the only effect on cartilage observed at 1-month post-dose was loss of Safranin-O staining, reflecting reduced levels of glycosaminoglycan. At 6-months post-dose, there were additional changes in the structure and cellularity of articular cartilage in both the TAcs and FX006 groups (in males only). These effects are consistent with the known effects of corticosteroids in normal joints. Occasional FX006-treated animals show slower recovery for cartilage changes compared to TAcs-treated animals, as expected based on the longer exposure to TA in the joints of these animals. After monthly dosing (Q1M), small changes in structure and cellularity were present at 1-month post-dose in both FX006 and TAcs groups, in addition to loss of Safranin-O staining. This is consistent with the more intensive dosing regimen. By 6 months after the cessation of dosing there was clear evidence of recovery. Again, these effects are consistent with the known effects of corticosteroids in normal joints.

A local foreign body tissue response was observed 1-month following repeated IA injection of FX006 or blank microspheres. This effect was characterized by macrophage and multinucleated giant cell infiltration to the presence of the microspheres in the synovium. The local foreign body response was partially or fully reversed by 6 months post dosing. An increased incidence and/or intensity of lymphocyte and plasma cells, and minimal fibrosis were also observed in the blank microsphere and FX006 groups at 1 and 6 months post dosing. Overall, these changes suggest a host tissue response, which is an expected reaction to PLGA products and is consistent with a foreign body response.

Additional details on non-clinical pharmacology, pharmacokinetics (PK) and pharmacodynamics in animals and toxicology information for TA, PLGA, and FX006 can be found in Section 4 of the IB.

5.2.4. Clinical Experience

The clinical development of FX006 to date consists of eight completed studies (FX006-2011 001, FX006-2011-002, FX006-2013-005, FX006-2014-006, FX006-2014-007, FX006-2014-008,

FX006-2015-009 and FX006-2015-010) conducted in patients with pain associated with OA of the knee. A brief summary of each study and data from the completed and fully analyzed studies is presented below.

NOTE TO REVIEWER: Subsequent to completion of the human pharmacology, efficacy, and safety studies reported herein (as of September 2017), extensive in-house testing was performed to assess the actual FX006 dose removed and delivered under the conditions of the dose preparation procedure. This in-house testing determined that the FX006 delivered dose to the patient from an FX006 40 mg vial is 32 mg. Hence, past clinical studies using a FX006 40 mg dose under the current resuspension conditions (5 mL of diluent) should be considered to have delivered a 32 mg dose of TA. All future studies performed with FX006 from the date of Investigator's Brochure Version 7.0 forward will reflect a 32 mg dose.

Completed studies

Study FX006-2011-001 was a Phase 2b, multi-center, randomized, double-blind, dose-ranging, active comparator study. The primary objectives of this study were to assess the magnitude and duration of pain relief of a single 3 mL IA injection of FX006 (10, 40, or 60 mg) relative to 40 mg of TAcs and assess the general tolerability of FX006.

Study FX006-2011-002 was a Phase 2, double-blind, randomized, parallel-group, active comparator study. The primary objectives of this study were to assess the safety and tolerability of a single 3 mL IA injection of FX006 (10, 40, or 60 mg), characterize the systemic PK profile of TA from FX006 relative to 40 mg of TAcs, and characterize the effects on the hypothalamic-pituitary-adrenal (HPA) axis of FX006 relative to 40 mg of TAcs.

Study FX006-2013-005 was a Phase 2, open-label, single administration study. The objectives of this study were to characterize the local duration of exposure of TA and to assess the safety and general tolerability of a single 3 mL IA injection of FX006 (10 or 32 mg) relative to 40 mg of TAcs.

Study FX006-2014-006 was a Phase 2b, multi-center, randomized, parallel group, dose-ranging study. The primary objectives of this study were to assess the magnitude and duration of pain relief of a single 5 mL IA injection of FX006 (20 mg or 32 mg) relative to placebo (normal saline) and assess the safety and general tolerability of FX006.

FX006-2014-007 was a prospective, double-blind, randomized, parallel-group, proof of concept, active comparator-controlled study. The primary objective of this study was to assess the analgesic effect of a single 5 mL IA injection of FX006 (32 mg) relative to 40 mg of TAcs (active control) in patients with moderately symptomatic post-traumatic osteoarthritis (PTOA) of the knee. Due to the challenges of enrolling military personnel with PTOA, this study was discontinued early.

Study FX006-2014-008 was a Phase 3, multi-center, double-blind, randomized, placebo- and active comparator-controlled study. The primary objective of this study was to assess the magnitude and duration of pain relief of a single 5 mL IA injection of FX006 (32 mg), relative to normal saline (placebo control) and 40 mg of TAcs (active comparator).

Study FX006-2015-009 was a Phase 2, open-label, single administration study. The objectives of this study were to characterize the local extent and duration of exposure of TA from FX006 and TAcs, characterize the systemic PK of FX006 and TAcs, and assess the safety and general

tolerability of a single 5 mL IA injection of 32 mg FX006 relative to 40 mg of TAcs in patients with OA of the knee.

Study FX006-2015-010 was a Phase 2, multi-center, double blind, randomized, parallel group study. The primary objective of this study was the assessment of the effects of a single 5 mL IA injection of FX006 (32 mg) on blood glucose levels in patients with type 2 diabetes mellitus, relative to 40 mg of TAcs.

5.2.5. Clinical Pharmacokinetics

Overall, FX006 displayed a favorable plasma PK profile relative to TAcs.

The PK observations in Study FX006-2015-009 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. TA 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.

Relative to TAcs, FX006 32 mg produced substantially lower peak plasma and systemic exposure to TA. FX006 performed as expected, prolonging the residence of TA in the joint while minimizing systemic exposure to TA.

5.2.6. Clinical Pharmacodynamics

In Study FX006-2011-002, 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 TAcs 40 mg. 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 comprised HPA axis function.

In Study FX006-2015-010, treatment with FX006 32 mg 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.

5.2.7. Clinical Efficacy

5.2.7.1. Study FX006-2011-001

In Study FX006-2011-001, a dose-ranging, active comparator trial of a single IA injection of FX006 in patients with OA of the knee:

- The 40 mg dose of FX006 produced a statistically significant ($p<0.05$, 1-sided) and potentially clinically meaningful improvement in pain relief relative to TAcs between Weeks 5 and 10 and also demonstrated significant improvement over TAcs ($p<0.05$,

1-sided) at Week 8 in secondary outcomes that assessed pain, stiffness, function, PGIC, and CGIC.

- The 60 mg dose did not provide additional benefit relative to the 40 mg dose of FX006.
- The median time to onset of pain relief was similar across all treatments, occurring 1 to 2 days following injection. (Bodick et al, 2015)

5.2.7.2. Study FX006-2014-006

In Study FX006-2014-006, a Phase 2b dose-ranging, placebo-controlled trial of a single IA injection of FX006 in patients with OA of the knee:

- The 20 and 32 mg doses of FX006 achieved maximal analgesic effect of similar magnitude at Week 5 post-injection. A dose effect was evident in the maintenance of maximal effect, which persisted through Week 9 with FX006 20 mg and through Week 13 with FX006 32 mg. In secondary outcomes that assessed pain, stiffness, function, and Patient and Clinical Global Impressions of Change, 32 mg FX006 demonstrated significantly better or trending better outcomes versus placebo at Weeks 4, 8, and 12.
- The 32 mg FX006 dose was associated with rapid onset of action, larger magnitude of analgesic effect, and prolonged duration of action relative to placebo.

5.2.7.3. Study FX006-2014-008

In Study FX006-2014-008, a Phase 3 double-blind, randomized, single-dose study to assess the safety and efficacy of FX006 for the treatment of pain in patients with OA of the knee:

- 32 mg FX006 administered as a single IA injection provided more rapid onset of action, increased magnitude of analgesia, and prolonged duration of effect relative to placebo.
- When compared to 40 mg TAcs, 32 mg FX006 was numerically superior at Weeks 2 through 19 on the weekly mean of average daily pain (ADP) scores, although it did not achieve statistical significance, likely as a result of an unexpected loss of assay sensitivity in that measure. However, in pre-specified exploratory OA specific measures, compared to 40 mg TAcs, 32 mg FX006 achieved statistical significance through 12 weeks on WOMAC A (pain), WOMAC B (stiffness), and WOMAC C (function) and the validated KOOS QOL subscale.
- A single IA injection of 32 mg FX006 was well tolerated, with systemic and local safety profiles generally similar to placebo and 40 mg TAcs

5.2.8. Clinical Safety

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

The safety data from the completed FX006 clinical studies 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 Study FX006-2014-008, 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.

- 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 FX006 32 mg, placebo, and TAcs 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 FX006 32 mg 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.

Please refer to the current Investigator's Brochure for further safety details.

5.2.9. Conclusion

These data provide a strong rationale for further clinical study of FX006 and these data also provide the ethical basis for future clinical studies.

6. THESE DATA PROVIDE BASES FOR CONTINUED CLINICAL STUDY OF FX006.STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to assess the overall safety and general tolerability of repeat administration of FX006 (two doses of 32 mg FX006) in patients with symptomatic OA of the knee.

6.2. Exploratory Objective

Exploratory objectives of this study include the following:

- examine efficacy signals for sustained pain reduction following two doses of 32 mg FX006.
- collect synovial fluid samples to enable potential future examination of synovial fluid biomarkers that may contribute to the pathogenesis of OA and/or be associated with responsiveness to FX006 treatment.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This study is an open-label, repeat administration design of 32 mg FX006. The study will be conducted in male and female patients ≥ 40 years of age with symptomatic OA of the knee.

Eligible patients will be offered participation to receive an initial IA injection of FX006 administered to the index knee at Day 1

Patients who receive an initial injection of FX006 will return at Weeks 4 and 8 before being evaluated at 12, 16, 20, and 24 weeks following the initial administration of FX006 for repeat administration. At the first visit where the patient has been determined to meet repeat administration eligibility criteria described in Section 7.4.3, the patient will be eligible to receive a second IA injection of FX006 administered to the index knee.

Patients who are eligible to receive a second injection will be evaluated for a total of 52 weeks post initial injection at: Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, regardless of the visit at which they receive their second injection.

Patients that do not benefit from the initial treatment as determined by evaluation at Week 12 will complete the study at the Week 12 follow-up visit. These patients will be evaluated for a total of 12 weeks post initial injection at: Weeks 4, 8, 12.

Patients who are not eligible for a second injection of FX006 after evaluation at Weeks 12, 16, 20, and 24 will complete the study at the Week 24 follow-up visit. These patients will be evaluated for a total of 24 weeks post initial injection at: Weeks 4, 8, 12, 16, 20, and 24.

Refer to Appendix 2 Study Visit Flow Chart.

The study is expected to enroll over approximately 6 months.

7.2. 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 in a study-specific 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.

Pharmacist/coordinator

- must be a registered pharmacist or an individual with the qualifications and training required to handle and prepare study medications
- is responsible for handling and preparing all study medications and maintaining investigational product accountability records

Injector/Aspirator

- must be a medical doctor, a physician's assistant, or nurse practitioner experienced in administering IA injections and performing synovial fluid aspirations of the index knee
- is responsible for performing IA injections of study medication and synovial fluid aspirations of the index knee

Assessor

- must be a medical doctor, a physician's assistant, or nurse practitioner
- must have relevant OA experience
- responsible for performing the physical examination and index knee assessments and assessing causality of an adverse event (AE) or SAE.

The same individual may serve in multiple roles (e.g., a physician sub-investigator may serve as both the Injector/Aspirator and/or Assessor).

7.3. Discussion of Study Design

7.3.1. Rationale for Study Population

Patients with pain associated with OA of the knee as defined by clinical and radiologic criteria that are otherwise in good health or that have chronic conditions (for example, hypertension) that are well controlled are included. In general this population tolerates IA injections of commercially available corticosteroids (Habib 2009). In prior clinical studies of FX006 in this population, single injections of up to 60 mg of FX006 were well tolerated.

7.3.2. Rationale for Dose Selection

The rationale supporting dosing at this level couples nonclinical data summarized in the Investigator Brochure (Section 4), and clinical experience with FX006. In study FX006-2011-001, the prior dose-ranging study that included 10, 40, and 60 mg doses of FX006 and TAcs (e.g., Kenalog®-40 Injection), a dose response was evident between 10 and 40 60 mg doses over the entire 12 weeks of therapy. At no point in the course of therapy did the 60 mg dose provide additional improvement relative to the 40 mg dose. Thus, it was assumed that the minimum dose to achieve maximal efficacy was >10 and ≤40 mg. As well, 40 mg FX006 has been shown to be well tolerated in previous single dose clinical trials.

7.3.3. Rationale for Study Design

Evidence from non-clinical repeat dose studies, the overall safety profile of 32 mg FX006 being well tolerated and the common practice of repeating corticosteroid injections support the evaluation of repeat administration of 32 mg FX006.

7.3.4. Rationale for Study Parameters

The clinical safety parameters to be assessed (adverse events, physical examinations, index knee examinations, index knee X-rays, vital signs, and clinical laboratory evaluations) are standard

safety and tolerability assessments and support the clinical monitoring necessary based on the toxicology profile for FX006.

The efficacy parameters to be assessed are recommended outcome measures for the assessment of chronic pain (Dworkin et al, 2005).

7.4. Selection of Study Population

7.4.1. Number of Patients

Approximately 200 patients will be enrolled to ensure that at least 100 patients receive two doses of FX006 and complete the study through Week 52.

7.4.2. Screening Criteria

7.4.2.1. Screening Inclusion Criteria

To be included in the trial, patients must fulfill the following criteria:

1. Written consent to participate in the study
2. Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions
3. Male or female ≥40 years of age
4. Symptoms associated with OA of the index knee for ≥ 6 months prior to Screening (patient self-report is acceptable)
5. Currently meets ACR Criteria (clinical and radiological) for OA (Altman et al, 1986) as follows:
    - Knee pain
    - at least 1 of the following:
        - Age > 50 years
        - Stiffness < 30 minutes
        - Crepitus
    - Osteophytes
6. Kellgren-Lawrence (KL) Grade 2, 3 or 4 in the index knee based on X-ray performed during Screening (locally read)
7. WOMAC A total sum score of ≥ 6 at Screening and Day 1/Baseline
8. Index knee pain for >15 days over the last month (as reported by the patient)
9. If bilateral OA exists, pain in the contralateral knee must be less than pain in the index knee as reported by the patient
10. Body mass index (BMI) ≤ 40 kg/m2s
11. Ambulatory and in good general health

12. Willingness to abstain from use of the following protocol-restricted medications during the study:
    - Intravenous (IV), intramuscular (IM), and oral corticosteroids (Note: inhaled, intranasal, and topical corticosteroids are allowed)
    - IA corticosteroids in any joint
    - IA viscosupplementation (hyaluronic acid) or any IA intervention (IA injection, IA aspiration, etc.) in the index knee
    - Opiates
    - Any investigational drug, device, or biologic
    - Immunomodulators, immunosuppressives, or chemotherapeutic agents
    - Live or live attenuated vaccines

7.4.2.2. Screening Exclusion Criteria

Patients fulfilling at least one of the following criteria may not be included in the study:

Disease-related criteria

1. Reactive arthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or arthritis associated with inflammatory bowel disease
2. History of infection in the index knee joint
3. Clinical signs and symptoms of active knee infection or crystal disease of the index knee within 1 month of Screening
4. Presence of surgical hardware or other foreign body in the index knee
5. Unstable index knee joint (such as a torn anterior cruciate ligament) within 12 months of Screening

Previous or concomitant treatment-related criteria

6. IA corticosteroid (investigational or marketed) in index knee within 3 months of Screening
7. IA hyaluronic acid (investigational or marketed) in the index knee within 6 months of Screening
8. IV or IM corticosteroids (investigational or marketed) within 3 months of Screening
9. Oral corticosteroids (investigational or marketed) within 1 month of Screening
10. Any other IA drug/biologic use within 6 months of Screening or 5 half-lives (whichever is longer) (e.g., platelet rich plasma (PRP) injection, stem cells, prolotherapy, and amniotic fluid injection)
11. Prior administration of FX006

12. Prior arthroscopic or open surgery of the index knee within 12 months of Screening
13. Planned/anticipated surgery of the index knee during the study period

Patient-related criteria

14. Known hypersensitivity to any form of triamcinolone
15. History of sarcoidosis or amyloidosis
16. Active or history of malignancy within the last 5 years, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or effectively managed cervical carcinoma
17. Known active or quiescent systemic fungal, bacterial, mycobacterial (including tuberculosis), viral or parasitic infections, or, shingles, herpes zoster, and ocular herpes simplex
18. Any infection requiring IV antibiotics within 4 weeks of Screening or oral antibiotics within 2 weeks of Screening
19. History of osteomyelitis
20. Known or clinically suspected infection with human immunodeficiency virus (HIV), hepatitis B or C viruses
21. Any clinically significant electrocardiogram (ECG) abnormality as judged by the Investigator
22. Patients requiring or likely to require chronic treatment with corticosteroids during the study period based on patient medical history
23. History of or active Cushing's syndrome
24. Active substance abuse (drugs or alcohol), history of chronic substance abuse within the past year, or prior chronic substance abuse judged by the investigator as likely to recur during the study
25. Skin breakdown at the knee where the injection would take place
26. Women who are pregnant or nursing or plan to become pregnant during the study; men who plan to conceive during the study
27. Women of child-bearing potential (not surgically sterile or post-menopausal for at least 1 year as documented in medical history) not using a highly effective method of contraception [abstinence; oral, injected, or implanted hormonal methods of contraception; intrauterine device or intrauterine system; condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; or male sterilization (vasectomy)]
28. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents within 5 years of Screening
29. Has received a live or live attenuated vaccine within 3 months of Screening

30. Use of any other investigational drug or device within 30 days of Screening or within 5 half-lives (whichever is longer) or an investigational biologic within 60 days of Screening or within 5 half-lives (whichever is longer)
31. Any other clinically significant acute or chronic medical conditions (e.g., bleeding disorder) that, in the judgment of the Investigator, would preclude the use of an IA corticosteroid or that could compromise patient safety, limit the patient's ability to complete the study, and/or compromise the objectives of the study

7.4.3. Repeat Administration Criteria

Patients who receive an initial injection of FX006 must meet the following criteria in order to receive a repeat administration.

7.4.3.1. Repeat Administration Inclusion Criteria

To be eligible to receive a repeat administration, patients must fulfill the following criteria:

1. Benefit from the initial dose of FX006 in the opinion of both the patient and the Investigator
2. No major safety concerns during the initial dose period as assessed by the Investigator
3. Clinically indicated to receive a second dose of FX006 in the opinion of both the patient and the Investigator
4. WOMAC A total sum score of ≥ 6 or a clinical rationale as to why a second dose is indicated
5. Compliant with study procedures and visit schedules through at least Week 12 and the willingness and ability to continue to comply through Week 52
6. Willingness to abstain from use of protocol-restricted medications during the study

7.4.3.2. Repeat Administration Exclusion Criteria

Patients fulfilling at least one of the following criteria may not receive repeat administration:

1. Clinical signs and symptoms of active knee infection or crystal disease of the index knee
2. Received a non-protocol specified IA intervention (IA injection, IA aspiration, etc.) in index knee during study participation
3. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents during study participation
4. Received a live or attenuated vaccine during study participation
5. Use of any other investigational drug, device, or biologic during study participation
6. Allergic reaction to initial dose of FX006
7. Any infection requiring IV antibiotics within 4 weeks or oral antibiotics within 2 weeks of second dose of FX006
8. Skin breakdown at the knee where the injection would take place

9. Women who are pregnant or nursing or plan to become pregnant during the study; men who plan to conceive during the study
10. Women of child-bearing potential (not surgically sterile or post-menopausal for at least 1 year as documented in medical history) not using a highly effective method of contraception [abstinence; oral, injected, or implanted hormonal methods of contraception; intrauterine device or intrauterine system; condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; or male sterilization (vasectomy)]
11. Any other clinically significant acute or chronic medical conditions (e.g., bleeding disorder) that, in the judgment of the Investigator, would preclude the use of an IA corticosteroid or that could compromise patient safety, limit the patient's ability to complete the study, and/or compromise the objectives of the study

7.4.4. Removal of Patients from Therapy or Assessments

Each patient will be informed of his/her right to discontinue from the study at any time for any reason and without prejudice to alternative treatment. The Principal Investigator may also discontinue a patient from the study at any time if, for example, he/she considers the patient's health to be compromised by remaining in the study, or the study is prematurely terminated. In these cases the Principal Investigator will:

1. attempt to complete the study assessments defined for the Early Termination Visit*
2. determine whether the patient is willing to be contacted to follow ongoing or new AEs through Week 12 for patients who only receive a single injection, or through Week 52 for patients who receive a second injection (if reason for discontinuation is not "withdrew consent") and contact patient as necessary (via phone or in-person). Concomitant medications associated with any AE will also be captured.
3. document patient consent in the source document for continued follow-up

**Note: Early Termination visits should follow the Week 52 visit schedule*

Data collected from discontinued patients will be included in the clinical study report. Patients who discontinue from the study may be replaced at the discretion of the Sponsor.

7.4.5. Screen Failures

Minimal data for patients who fail screening, such as demographic information and the reason for screen failure will be collected.

Patients who fail to meet eligibility criteria may be re-screened at the discretion of the Medical Monitor. The Medical Monitor will clearly document the rationale for any re-screening decision. Patients that are allowed to re-screen will be assigned a new screening number, re-consented and may have screening assessments repeated if necessary.

7.5. Treatment Administered

7.5.1. Study Medication Treatment Arms

Investigational Medicinal Product Arm:

FX006 – extended-release formulation of TA formulated in in 75:25 PLGA microspheres.

Nominal 32mg TA, administered as a single 5 mL IA injection

Reference Compound:

Not applicable

7.5.2. Identity of Investigational Product(s)

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.

7.5.3. Receipt, Dispensing, and Storage

Study medication will be shipped to the site from the drug supply distribution center as a packaged kit. Receipt and dispensation of study medication will be properly documented within the Drug Tracking Module. Any temperature excursions should be documented in the Drug Tracking Module for Sponsor assessment and authorization for continued use.

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

7.5.4. Packaging and Labeling of Study Medication

The packaged kit will contain one (1) vial of FX006, one (1) vial of Diluent, and a vial adapter. The FX006 and diluent vials will be labelled with their respective unique lot numbers within the packaged kit, which will be affixed with its own label and kit number.

7.5.5. Return of Study Medication

All study medications (packaged kits /used and unused vials) will be returned to the Sponsor. Return of study medications will be properly documented.

7.5.6. Method of Assigning Patients to Treatment Groups

This is a single-arm, open-label study. All eligible patients will receive one or two doses of FX006.

7.5.7. Blinding

This is an open-label study.

7.5.8. Intra-articular Injection Procedure

IA injections will be performed by the assigned injector. The injector may choose the position of the knee (e.g., extended or flexed), the approach for the injection (e.g., medial or lateral) and the numbing agent to be used (e.g., ethyl chloride, subcutaneous lidocaine; IA anesthetics are not allowed) based on standard of care. Sterile technique should be used.

Prior to injection, the index knee should be thoroughly cleansed using a bactericidal solution. The index knee will be aspirated in all cases prior to administration of study medication. Following attempted aspiration, 5 mL of the reconstituted FX006 will be injected into the synovial space. Refer to the Pharmacy Binder for detailed instructions on how to prepare FX006.

The same needle used for IA injection of the study medication may also be used for synovial fluid aspiration, thereby allowing for a single injection with syringe replacement. The injector will use a 21 gauge or larger needle for injection and aspiration of fluid.

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.

In the event that the patient has an immediate reaction (e.g., tenderness, increased pain, swelling, effusion, decreased mobility of the index knee), the patient should be treated according to local clinical guidelines and physician experience (see also Protocol Section Section 8.1.5).

7.5.9. Treatment Compliance

Study medication will be administered by the injector in the clinic. Details regarding study medication administration will be documented in the electronic Case Report Form (eCRF). The receipt, dispensation, and return 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.

7.6. Prior and Concomitant Therapy

During the study, all existing (prior to study entry), new, or changes in concomitant medications and the associated reasons for use or change will be documented and reported.

7.6.1. Allowable Medications/Therapies

The following medications may be taken or used throughout the study:

- Any treatment for a pre-existing condition or for an AE, including the study indication (e.g., analgesic medications), that is not listed as restricted below
- Physical therapy for index knee
- Bracing of index knee

7.6.2. Restricted Medications

The exclusion criteria indicate that a patient may not be enrolled if he/she has used any of the following within the specified windows detailed in the Exclusion criteria (Section 7.4.2.2). In addition these medications should not be taken or used throughout the study:

- IV, IM, or oral corticosteroids (Note: inhaled, intranasal, and topical corticosteroids are allowed)
- IA corticosteroids in any joint
- IA viscosupplementation (hyaluronic acid) or any IA intervention (IA injection, IA aspiration, etc.) in the index knee
- Opiates
- Any investigational drug, device, or biologic
- Immunomodulators, immunosuppressives, or chemotherapeutic agents
- Live or live attenuated vaccines

7.7. Study Variables

7.7.1. Safety Variables

Safety and tolerability will be evaluated on the basis of AEs spontaneously reported by the patient or discovered by the Investigator and findings from the following assessments: physical examinations, index knee assessments, vital signs, and clinical laboratory evaluations. In addition the index knee will be evaluated by X-ray and assessed by a central imaging vendor for joint space narrowing, chondrolysis, subchondral bone changes, bone infarcts, avascular necrosis, joint swelling, and insufficiency fracture.

7.7.2. Exploratory Efficacy Variables

- Western Ontario and McMaster Universities (WOMAC®) Osteoarthritis Index (Likert (LK) 3.1, 5-point scale): pain, stiffness and function domains independently and collectively (Bellamy et al, 1988).
- Knee injury and Osteoarthritis Outcome Score (KOOS) Quality of Life (QOL) Subscale (http://www.koos.nu/).
- Daily activity measured as steps per day.
- Global Physical Activity Questionnaire (GPAQ) domains for occupational physical activity, transport-related physical activity, and physical activity during discretionary or leisure time (http://www.who.int/chp/steps/GPAQ/en/)

7.7.3. Pharmacodynamic Variables

Synovial fluid samples will be preserved for potential future analyses of biomarkers that may contribute to the pathogenesis of OA and/or be associated with responsiveness to FX006 treatment.

7.8. Schedule of Study Assessments

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

Refer to Section 7.9 for details of each assessment.

Table 1: Schedule of Study Assessments

Procedures	Screen[1]	Baseline Day 1	Week 4[2]	Week 8[2]	Week 12, 16, 20, 24[2]	Week 28, 32, 36, 40, 44, 48[2]	Week 52[2]/End of Study
Informed consent	X[3]						
Inclusion/Exclusion Review	X	X[4]					
Medical History/Update	X	X[4]					
OA Medical History	X						
Prior Treatment & Medications	X[5]	X[4]					
Physical Examination	X				X[6]		X
Index Knee X-ray[7]	X						X[8]
Index Knee Assessment[9]	X	X[4]			X[6]		X
12-Lead ECG	X						
Vital Signs	X	X[4]			X[6]		X
Height	X						
Weight and BMI	X						X
Hematology & Chemistry[10]	X				X[6]		X
HIV, Hepatitis B/C[10]	X						
Serum Pregnancy Test[10,11]	X						
Urine Pregnancy Test[9,10, 11]		X[4]			X[6]		X
WOMAC[12]	X	X[4]	X	X	X	X	X
KOOS QOL[12]		X[4]	X	X	X	X	X
GPAQ[13]		X[4]			X[13]		
Measured Function Device[14]	----------X----------						
Index knee aspiration and collection of synovial fluid		X[4]			X[15]		
1st treatment administration		X					
Evaluation for repeat administration					X		
2nd (repeat) treatment administration					X[16]		
AEs & ConMeds[17]		----------X----------					

[1] Screening period is a minimum of 7 days, up to 21 days.
[2] Visit should be conducted within +/- 7 days from scheduled date.
[3] Consent must be obtained prior to any study-specific procedures.
[4] Complete assessment prior to dosing.
[5] Record any prior medications received within 30 days prior to the Screening visit.
[6] To be completed prior to dosing only if patient is to receive the 2nd dose of FX006. For patients not eligible to receive 2nd dose, complete at the final study visit.
[7] Standing, fixed flexion PA view, weight bearing X-ray of the index knee will be taken using a standardized knee positioning device. The Screening X-ray will be read locally for K-L grade. The Screening and Week 52 X-rays will be sent to central imaging vendor for safety assessment.
[8] End of Study x-ray will only be performed if patient has received a repeat administration of FX006.
[9] Index knee will be assessed for tenderness, heat/redness, swelling, effusion, and Baker's cyst. New clinically significant findings or findings that worsen for the patient's baseline condition should be recorded as AEs.
[10] Via Central Laboratory.
[11] Conduct for women of childbearing potential only.
[12] Patient questionnaires to be completed prior to all other assessments.
[13] Complete GPAQ at Week 12 only regardless of when and if second dose is given.
[14] Steps per day will be captured using a measured function device. Patients will be provided with a device at the Screening visit to be worn for at least 7 days prior to Baseline/Day 1 through Week 12. The site will confirm patient compliance with wearing the device to capture steps per day data at each patient visit from Day 1 through Week 12.
[15] To be completed prior to dosing only if patient is to receive the 2nd dose of FX006.
[16] Repeat administration may occur at either Week 12, 16, 20, or 24.
[17] AEs and Concomitant Medications will be captured from Day 1 (post injection) to Week 12 or 24 for patients who only receive a single injection or to Week 52 for patients who receive a second injection or to Early Discontinuation Visit for patients who discontinue the study early.

7.9. Study Procedures

7.9.1.1. 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.

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

Eligibility criteria (inclusion and exclusion criteria), medical history (including OA history), prior treatment and medications are reviewed during screening and again at Baseline/Day 1.

OA medical history includes ACR diagnosis details, OA diagnosis date (if available), K-L grade (See Appendix 1), number of days with index knee pain in the last month, and previous IA steroid or hyaluronic injections.

7.9.3. Physical Examination

The physical exam will assess the following body systems:

1. General Appearance
2. Skin
3. Lymphatics
4. HEENT (head, ears, eyes, nose, throat)
5. Cardiovascular
6. Respiratory
7. Abdominal
8. Musculoskeletal
9. Neurological

Any clinically significant findings must be documented in the source and added to the medical history if found at Screening or recorded as an AE if new or worsened from baseline at one of the post-baseline visits.

7.9.4. Index Knee X-ray

A diagnostic quality X-ray of the index knee is required (standing, fixed flexion PA view; weight-bearing; use of standardized knee positioning device is required) at Screening and Week 52 (for patients that receive a second injection). The Screening X-ray will be read locally for K-L grading by a radiologist or clinician with rheumatology or orthopedic specialty. In addition, the Screening and Week 52 X-rays will be sent to the central imaging vendor for safety assessments. An image acquisition protocol will be distributed to sites with simple instructions for radio-anatomic positioning for reliable grading.

7.9.5. Index Knee Assessment

The index knee assessment will be performed by the designated assessor at the days indicated in Table 1. The index knee will be assessed for tenderness, heat/redness, swelling, effusion, and Baker's cyst. If there is a clinically significant finding outside of the patient's typical disease state at the Screening or Baseline Visit, add to the Medical History. At time points post-baseline, if there are new clinically significant findings outside of the patient's typical disease state or findings that worsen from the patient's baseline condition, record as AEs.

7.9.6. 12-lead ECG

At Screening, a 12-lead ECG will be obtained in the supine position. Measures of heart rate, PR interval, RR interval, QT interval, QTc (corrected for Bazett's or Fridericia's) interval and QRS duration will be obtained. If QTc > 450 msec for male patients or > 470 msec for female patients on the first 10-second 12-lead ECG recording, two additional 10-second 12-lead ECG recordings must be collected approximately 1 minute apart. ECGs will be locally read and a copy of each recording will be kept with the patient's source documentation.

7.9.7. Vital Signs

Vital signs are to be taken at the days indicated in the Table 1. The following measurements will be taken: sitting blood pressure, heart rate, respiration rate, and temperature.

7.9.8. Height, Weight, and BMI determination

Height and weight are to be taken at the days indicated in the Table 1. Height will be measured in centimeters or inches. Weight will be measured in kilograms or pounds. BMI will be calculated using the formulas in Table 2 (reference: www.cdc.gov):

Table 2: BMI Calculations

Measurement Units	Formula and Calculation
Kilograms and meters (or centimeters)	**Formula: weight (kg) / [height (m)]^2** With the metric system, the formula for BMI is weight in kilograms divided by height in meters squared. Since height is commonly measured in centimeters, divide height in centimeters by 100 to obtain height in meters. Example: Weight = 68 kg, Height = 165 cm (1.65 m) Calculation: 68 ÷ $(1.65)^2$ = 24.98
Pounds and inches	**Formula: weight (lb) / [height (in)]^2 x 703** Calculate BMI by dividing weight in pounds (lbs) by height in inches (in) squared and multiplying by a conversion factor of 703. Example: Weight = 150 lbs, Height = 5'5" (65") Calculation: [150 ÷ $(65)^2$] x 703 = 24.96

7.9.9. Central Clinical Laboratory Evaluations

Blood samples will be taken at the days indicated in the Table 1. The specific laboratory panels to be run can be found in Table 3. Follow the Central Laboratory Manual for detailed sample collection, handling, storage, and shipping instructions.

Table 3: Clinical Laboratory Panel

HEMATOLOGY	**CLINICAL CHEMISTRY**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	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
INFECTIOUS DISEASES	Total protein
Hepatitis B Surface Antigen	Albumin
Hepatitis C Antibody	Glucose
HIV	
SERUM PREGNANCY TEST (women of child-bearing age only)	
URINE PREGNANCY TEST (women of child-bearing age only) *test provided by central laboratory but read locally*	

7.9.10. Patient Questionnaires

The following questionnaires will be completed by patient prior to all other assessments scheduled for the visit day at the days indicated in Table 1.

- **WOMAC® LK 3.1**
- **KOOS - Quality of Life Subscale (Q1-Q4)**
- **GPAQ**

7.9.11. Daily Activity

Steps per day will be captured using a measured function device. Patients will be provided with a device at the Screening visit to be worn for at least 7 days prior to Baseline/Day 1 through Week 12. The site will confirm patient compliance with wearing the device to capture steps per day data at each patient visit from Day 1 through Week 12.

7.9.12. Synovial Fluid Aspiration

Synovial fluid samples for potential future biomarker evaluation will be obtained from all patients via aspiration on Baseline/Day 1 prior to study medication administration and the week at which the second dose is administered prior to study medication administration (if the patient is eligible to receive a second dose). Patients that are not eligible to receive a second dose will not have synovial fluid drawn at their final study visit. The injector/aspirator will attempt to aspirate synovial fluid from the index knee using sterile technique. The volume of the synovial fluid obtained will be recorded in the eCRF. If no synovial fluid is obtained then 0 mLs should be recorded. Procedures for sample collection, handling, storage and shipment will be described in the Study Laboratory Manual. The synovial fluid samples will be preserved for potential future analyses of biomarkers that may contribute to the pathogenesis of OA and/or be associated with responsiveness to FX006 treatment.

7.9.13. Treatment Administration

At Baseline/Day 1 and the week at which the second dose is to be administered (if the patient is eligible to receive a second dose), the following will occur:

- Study medication will be prepared by the pharmacist/coordinator (Refer to the Pharmacy Binder for instructions on how to prepare FX006).
- Synovial fluid will be aspirated from the index knee just prior to administration of study medication (refer to Section 7.9.12 for more details of the synovial fluid aspiration).
- The injector/aspirator will perform the IA injection of the study medication (refer to Section 7.5.8 for instructions).

7.9.14. Review of Adverse Events and Concomitant Medications

After receiving study medication, the patient will be monitored for any AEs. Review of any Concomitant Medications will also be performed and documented in source documentation. Refer to Section 8.1 for further information in regard to reporting of AEs. Refer to Section 7.6 for further information in regard to allowed and restricted concomitant medication.

8. CLINICAL SAFETY ASSESSMENTS

Safety evaluations will be based on the assessment of AEs occurring after the initiation of study medication on Day 1 through the last study visit. 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. Adverse Events

8.1.1. Definitions

An AE is any untoward medical occurrence in a patient or clinical investigation patient 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 clinical significant adverse change in frequency and/or intensity) of a preexisting condition, which is temporally associated with the use of the medicinal (investigational) product, is also an AE.

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
    - This serious criterion applies if the patient's death is a direct outcome of a reported AE.
- Is life-threatening,
    - This serious criterion 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,
    - This serious criterion applies if the reported AE requires at least a 24-hour inpatient hospitalization or, if in the opinion of the Principal Investigator, prolongs an existing hospitalization. A hospitalization for an elective procedure or a routinely scheduled treatment is not an SAE by this criterion because a "procedure" or a "treatment" is not an untoward medical occurrence.

- Results in permanent or significant disability/incapacity, or
    - This serious criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the patient's ability to carry out normal life functions.
- Is a congenital anomaly/birth defect.
    - This serious criterion applies if a patient exposed to a medicinal (investigational) product gives birth to a child with congenital anomaly or birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events 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 other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.1.2. Evaluating and Recording of Adverse Events

At each visit all AEs that occur from the time of treatment and throughout a patient's study participation that are observed, elicited by the site personnel, or reported by the patient, will be recorded in the source documentation and appropriate section of the AE eCRF and evaluated by an assessor.

Minimum information required for each AE includes type of event, duration (start and end dates), severity, seriousness, causality to investigational medicinal product, action taken, and outcome.

Severity of AEs will be graded by the Principal Investigator using the Common Terminology Criteria for AEs (CTCAE) version 4.0 (refer to the Study Manual or http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

For AEs not listed in the CTCAE, the following definitions should be used:

Grade 1	Mild Symptomatic or mild symptoms Clinical or diagnostic observations only Intervention not indicated
Grade 2	Moderate Minimal, local or noninvasive intervention indicated Limiting age-appropriate instrumental activities of daily living (ADL)*
Grade 3	Severe or medically significant but not immediately life-threatening Hospitalization or prolongation of hospitalization indicated Disabling Limiting self care ADL**
Grade 4	Life-threatening consequences Urgent intervention indicated
Grade 5	Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The relationship of the AE to the investigational medicinal product should be specified by the Principal Investigator, using the following definitions:

1. Not Related: Concomitant illness, accident or event with no reasonable association with treatment.
2. Unlikely: The reaction has little or no temporal sequence from administration of the investigational medicinal product, and/or a more likely alternative etiology exists.
3. Possibly Related: The reaction follows a reasonably temporal sequence from administration of the investigational medicinal product and follows a known response pattern to the suspected drug; the reaction could have been produced by the study medication or could have been produced by the patient's clinical state or by other modes of therapy administered to the patient.
4. Probably Related: The reaction follows a reasonable temporal sequence from administration of study medication; is confirmed by discontinuation of the study medication or by rechallenge; and cannot be reasonably explained by the known characteristics of the patient's clinical state.
5. Definitely Related: The reaction follows a reasonable temporal sequence from administration of study medication; that follows a known or expected

response pattern to the study medication; and that is confirmed by improvement on stopping or reducing the dosage of the study medication, and reappearance of the reaction on repeated exposure.

If discernible at the time of completing an AE eCRF, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the appropriate AE eCRF. 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.

8.1.3. 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 first becoming aware of the SAE. The SAE will automatically be reported to the Medical Monitor or designee electronically.

Follow-up information relating to a SAE must be reported to the Medical Monitor within 24 hours of receipt by the Investigator by entering new information into the electronic SAE form. The updated SAE will automatically be reported to the Medical Monitor or designee electronically.

If one is unable to log into the EDC system, the SAE hotline may be contacted (information located in the Investigator Site File in the Study Contact list).

All SAEs that occur at a given 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 at least possibly related to investigational product) to the investigative sites as notification of new safety findings. If this occurs, the investigative site must report the information to their IRB/EC per local guidelines (may be submitted by the Sponsor or designee for sites that use a central IRB).

8.1.4. Safety Monitoring Roles

The site personnel will carefully monitor each patient throughout the study for possible AEs. All AEs will be documented on the eCRF designed specifically for this purpose, 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 8.1.3.

The Medical Monitor must promptly review all information relevant to the safety of an investigational new product received from any source. The Medical Monitor will also review alert laboratory results in real time and will contact Investigators as needed to ensure that issues are managed in an appropriate manner.

The medical monitor and the Sponsor will review safety data approximately on a quarterly 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.

8.1.5. Clinical Management of Index Knee-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 knee), the patient should be treated according to local clinical guidelines and physician experience.

If the index knee is aspirated at any time after 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 8.1.3.

8.1.6. Pregnancy

All pregnancies occurring during the study will be reported in the same timeframe as SAEs. All reports of pregnancy, including male patients who conceive, must be followed for information regarding the course of the pregnancy and delivery, as well as the condition of the newborn. Follow-up information concerning the outcome of the pregnancy should be provided to the Sponsor in a timely manner. Additional 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 that describes the final analyses to be completed for safety and exploratory efficacy endpoints. If, after the study has been completed, changes are made to the statistical analysis plan 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 those analyses are summarized below.

9.1.1. Interim Analysis

No formal interim analysis is planned for the primary safety endpoints in this open-label study to assess the safety and tolerability of FX006 after repeat administration. However, interim analysis may be conducted with exploratory endpoints to examine efficacy signals following administration of one or two doses of 32mg FX006. These interim analyses on exploratory endpoints may be completed for data review, regulatory updates, and/or publication (or presentation at congresses) for this open-label study. Any interim analysis completed will have an interim analysis plan written and approved to describe the purpose and analytical objectives of the interim analysis. Final analyses, described in the protocol and statistical analysis plan, will be conducted after completion of the study, when all subjects have either discontinued the study early (prior to Week 52) or completed the study through Week 52.

9.1.2. Final Analyses

All final analyses will be completed following database lock. Final analyses specified in the protocol and SAP will be completed and reported in the CSR. Interim analyses conducted with exploratory endpoints to examine efficacy signals prior to database lock will also be reported in the final CSR. Post-hoc, or additional exploratory analyses, not defined in the SAP may be completed to further understanding and elucidation of the 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, figures, and patient data listings. Summary tables will present data by treatment group and, if applicable, by time of collection. Continuous variables will be summarized using descriptive statistics, specifically the number of patients (n), the mean, median, standard deviation, minimum and maximum, and coefficient of variations (%CV). Categorical variables will be summarized by frequencies and percentages. Confidence intervals will be provided where appropriate for derived endpoints. Figures will be used to support the presentation of certain data. Sensitivity analyses may be performed to examine the effect of missing data, as well as the effect of Baseline imbalance for secondary endpoints.

All confidence intervals (CIs), statistical tests, and resulting p values will be reported as 2-sided. Significance will be assessed at $\alpha = 0.05$ level and the significance level will not be adjusted for multiple comparisons in the exploratory efficacy endpoint analyses.

9.2.1. Analysis Populations

Three main analysis populations are planned for this study as follows:

- Safety Population: All patients who received study medication. The Safety Population will be used to assess safety and tolerability for the primary endpoint.
- FAS Population: All patients who received study drug and provide at least one post-baseline efficacy endpoint assessment. The FAS population will be used to examine exploratory efficacy endpoints.
- Biomarker Population: All patients who received study medication and provide at least one synovial fluid sample for biomarker analysis.

During the course of this study interim analyses may be completed to examine efficacy signals. Populations utilized for those interim analyses will be clearly defined in an interim analysis plan, and in the final CSR.

9.2.2. Study Data

Study data identified in this protocol are to be collected, and source verified, on 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 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 Variables for Assessment

Please refer to Section 7.7.1 for study variables for the primary safety endpoint.

9.2.4. Sub-Groups and Covariates

No pre-planned sub-groups are identified for this study. Sub-groups may be defined for interim analyses of exploratory efficacy endpoints. In the final analysis, Sub-groups may also be defined

and explored after all pre-planned analyses have been completed to further elucidate study results.

Covariates for exploratory efficacy analyses will be fully defined in the SAP and interim analysis plans.

9.3. Determination of Sample Size

A sample size of approximately 100 patients who receive two doses of FX006 is considered a reasonable sample size in order to assess the safety profile of repeat administration of FX006. No formal power and sample size calculations have been made as the analysis of the efficacy data collected from this study will be considered exploratory and hypothesis-generating for future multiple dose studies of FX006. In order to ensure at least 100 patients who receive two doses of FX006 are enrolled and followed for 52 weeks, approximately 200 patients will be enrolled based on an estimate that approximately 66% of patients enrolled will be eligible to receive a second dose of FX006 and approximately 75% of subjects who receive a second dose will complete the study through Week 52.

9.4. General statistical Methods

9.4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be listed by study site and patient, and will be summarized by treatment. 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 patient, and will be summarized by doses administered, as well as total exposure to FX006. Time between FX006 exposure (1st and 2nd doses) will be summarized.

9.4.3. Exploratory Efficacy Analyses

The examination of efficacy is exploratory in this study. Data from the WOMAC® questionnaire will be presented in by-patient listings with summary presentation of the data and exploratory analyses.

Analysis of the magnitude of pain relief observed with WOMAC A (pain), stiffness (WOMAC B), and function (WOMAC C) will be explored between patients who receive one or two doses of FX006 will be explored with longitudinal mixed model for repeated measures (MMRM) with fixed effects of number of doses (1 or 2) received, and a dose by time interaction. Model covariates will include study site, and potentially other variables. Subject will be a random effect in the model. The exact configuration for the MMRM will be fully described in the SAP or interim analysis plans.

A within subject analysis will be completed to examine the differences in WOMAC scores following the first dose, and then following a second dose of FX006. Change from baseline for the first dose and change from last assessment prior to second dose will be completed with linear models. The details of the linear model will be specified in the SAPEvaluation of dose-response

will be assessed descriptively with an examination of WOMAC A responses at the time (in weeks) of second dose administration to assess the magnitude of scores at each week that a second dose may be administered. The time to maximal pain relief response with WOMAC A (pain) following the first and second doses of FX006 will be examined using a Kaplan-Meier (KM) procedure.

Questionnaire data from the GPAQ domains (occupational physical activity, transport-related physical activity, and physical activity during discretionary or leisure time) will be described descriptively at the two time points collected (Screening and Week 12). The change in GPAQ domain scores and total score will be examined with an analysis of variance (ANOVA) model with summaries comparing patients who receive one dose to those receiving two doses of FX006. GPAQ information collected at Screening will be utilized to normalize steps per day based on lifestyles activity. GPAQ information will be a model covariate in subsequent analyses.

9.4.4. Safety Analyses

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Incidences (number and percent) TEAEs, those events that started after dosing or worsened in severity after dosing, will be presented by treatment group. 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 and changes in severity of TEAEs and index knee related TEAEs following the first dose and second dose, as well as the cumulative incidence of TEAEs after all doses of FX006. Both the number of events and the number of patients experiencing an event will be examined to assess the by patient cumulative incidence of TEAEs associated with repeat administration. The cumulative TEAE incidence rate will also be compared with total exposure to FX006.

Clinical laboratory data and vital sign information will be presented as descriptive summary statistics for value and 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, ECG recordings, 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 within the Drug Tracking Module.

In the event of a temperature excursion, refer to the Pharmacy Binder for instructions. In the event of a product complaint, complete the Product Complaint Form located in the Pharmacy Binder and send to productcomplaints@flexiontherapeutics.com. The assigned monitor or clinical manager will coordinate with the Sponsor for further guidance.

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, glucose 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 1. KNEE OA DIAGNOSIS ASSESSMENTS

American College of Rheumatology Criteria for Classification of Idiopathic OA of the Knee (Altman et al, 1986)

Clinical and radiological

- Knee Pain
- + at least 1 of 3:
  - Age > 50 years
  - Stiffness < 30 minutes
  - Crepitus
- + Osteophytes

Kellgren-Lawrence Grade of Knee X-ray

- Grade 0: no findings
- Grade 1: doubtful narrowing of joint pace and possible osteophytic lipping
- Grade 2: definite osteophytes and possible narrowing of joint space
- Grade 3: moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends
- Grade 4: large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

APPENDIX 2. STUDY VISIT FLOW CHART