CLINICAL STUDY PROTOCOL

A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of FX006 in Patients with Hip Osteoarthritis

PROTOCOL NUMBER: FX006-2018-015

PHASE: 3

STUDY MEDICATION(S): FX006

INDICATION: Osteoarthritis of the hip

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Clinical Study Protocol Version 3.0 (Amendment 2.0) (dated 31JUL2019)

Sponsor Safety Officer Approval

Signature: _____ **Date:** 31 Jul 2019

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

Title: Chief Medical Officer

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

Signature: _____ **Date:** _____

Name (print): _____

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1. ABBREVIATIONS AND DEFINITION OF TERMS

ACR	American College of Rheumatology
ADaM	Analysis Data Model
ADP	Average Daily Pain
ADRG	Analysis Data Reviewer's Guide
AE	Adverse Event
ANCOVA	Analysis of Covariance
APR	Accurate Pain Reporting
AUE	Area Under the Effect Curve
BMI	Body Mass Index
CBD	Cannabidiol
CDISC SDTM	Clinical Data Interchange Standards Consortium Study Data Tabulation Model
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CI	Confidence Interval
CMC	Carboxymethylcellulose Sodium
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EOS	End of study
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels questionnaire
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
FBR	Foreign Body Response
FDA	Food and Drug Administration
GAD-7	General Anxiety Disorder questionnaire-7
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HEENT	Head, ears, eyes, nose, throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HOOS	Hip injury and Osteoarthritis Outcome Score
HPA	Hypothalamic-pituitary-adrenal
IA	Intra-articular
IB	Investigator's Brochure
IM	Intramuscular
IRB/EC	Institutional Review Board/Ethics Committee
ISI	Insomnia Severity Index

IV	Intravenous
JSN	Joint Space Narrowing
kg	Kilogram
KL	Kellgren-Lawrence
KOOS	Knee injury and Osteoarthritis Outcome Score
LSM	Least square mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MMRM	Mixed model for repeated measures
n	Number
NaCl	Sodium Chloride
NaCMC	Sodium carboxymethylcellulose
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
NSRI	Non-selective serotonin reuptake inhibitors
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OLE	Open Label Extension
OMERACT	Outcome Measures in Rheumatology
PCS	Pain Catastrophizing Scale
PD	Pharmacodynamic
PD-Q	PainDETECT Questionnaire
PGIC	Patients' Global Impression of Change
PHQ-9	Patient Health Questionnaire-9
PLGA	Poly[lactic-co-glycolic acid]
PK	Pharmacokinetic
PRP	Platelet Rich Plasma
PRR	Placebo Response Reduction
QOL	Quality of Life
RBC	Red Blood Cells
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDRG	Study Data Reviewer's Guide
SI	Sleep Interference
SNRI	Serotonin and norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent Adverse Event
TENS	Transcutaneous electrical nerve stimulation

TA[1]	Triamcinolone Acetonide
TAcs[2]	Triamcinolone Acetonide Injectable Suspension, Immediate-Release (commercially available)
TSQM	Treatment Satisfaction Questionnaire for Medication
USA	United States of America
USP	United States Pharmacopeia
VAS	Visual analogue scale
w/w	weight by 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: A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of FX006 in Patients with Hip Osteoarthritis

Study Centers: Multiple centers, approximately 40-50

Study Phase: Phase 3

Objectives

Part I

Double-Blind Objectives

Primary:

- To assess the treatment effect of FX006 on pain following an intra-articular (IA) injection in patients with hip osteoarthritis (OA)

Secondary:

- To assess the effect of FX006 on function, global impression of change, stiffness, quality of life, treatment satisfaction, sleep quality and consumption of rescue medication in patients with hip OA
- To assess the safety of FX006 in patients with hip OA

Part II

Double-Blind Phase Objectives

Primary:

- To assess the efficacy of FX006 on pain following an intra-articular (IA) injection in patients with hip osteoarthritis (OA)

Secondary:

- To assess the efficacy of FX006 on function, global impression of change, stiffness, quality of life, treatment satisfaction, sleep quality and consumption of rescue medication in patients with hip OA
- To assess the safety of FX006 in patients with hip OA

Open Label Extension (OLE) Phase Objectives

Primary:

- To assess the overall safety of a second injection of FX006 in patients with hip OA

Secondary:

- To examine efficacy following a second injection of FX006 in patients with hip OA

Study Design and Methodology:

This is a two-part, multi-center, randomized, double-blind, placebo-controlled, parallel-group study in patients with hip OA. Approximately 70 patients will be enrolled in Part I and approximately 440 patients will be enrolled in Part II of the study. In each part, patients will be randomized to one of two treatment groups (1:1) and treated with a single IA injection of either 32 mg FX006 or normal saline.

Eligible patients will be randomized within strata defined by Baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) A (pain) (0-10 numeric ratings scale (NRS) average of Screening 2 and Day 1 with the following classifications: 5.0 to < 6.0, 6.0 to < 7.0, and ≥ 7.0 to 9.0 (see Section 9 for details).

FX006 or saline placebo will be administered as a single IA injection with a 12-week follow-up period in the double-blind phase.

Patients participating in Part I of the study will be treated with a single IA injection of either 32 mg FX006 or normal saline and will return for follow up visits at Weeks 12, 16, 20, and 24 or up until the time of this amendment. The patients will be discontinued at the time of notification by the Investigator. Patients participating in Part II of the study will be treated with a single IA injection of either 32 mg FX006 or normal

saline and will return for follow up visits at Weeks 12, 16, 20, and 24. Patients who are eligible for the second injection in the open-label phase at Week 12 will receive an open-label injection of FX006 at Week 12 and return for follow-up visits at Weeks 16, 20, and 24. These patients will complete the study at Week 24.

Patients participating in Part II of the study that are not clinically indicated for a second injection at Week 12 will return to the clinic at Weeks 16, 20, and 24 and will receive an open-label injection of FX006 at the first evaluation where the patient has been determined to meet all criteria. Patients will then return for follow-up visits every 4 weeks for 12 weeks post second injection and will complete the study 12 weeks post second injection (e.g., Week 24, 28, 32, or 36 depending on when the patient receives the open-label injection).

Patients participating in Part II of the study who are not eligible for a second injection after evaluation at Weeks 12, 16, 20, and 24 will complete the study at the Week 24 visit and complete the End of Study (EOS) assessments.

Number of Patients:

Approximately 70 patients in Part I and approximately 440 patients in Part II will be randomized and treated in the double-blind phase of the study.

Test Product, Dose and Mode of Administration:

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

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

Normal saline, sodium chloride (0.9% NaCl) solution, IA, administered as a 5 mL injection into the index hip OA joint under fluoroscopy guidance per injection procedure.

Duration of Dosing:

Single IA injection for all enrolled patients at Day 1 (Parts I and II) and a second IA injection for those patients enrolled in Part II of the study who meet second injection eligibility criteria at either Week 12, 16, 20, or 24.

Inclusion Criteria

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

1. Written informed consent has been obtained prior to initiating any study specific procedures
2. Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions
3. Patients 40 to 80 years of age, inclusive, on the day of consent
4. Body Mass Index (BMI) ≤ 40 kg/m^2
5. Symptoms (including pain) associated with OA of the index hip for ≥ 3 months prior to Screening visit (patient self-report is acceptable).
6. Moderate to severe index hip pain due to OA for >15 days over the last month (as reported by the patient)
7. Currently meet the American College of Rheumatology (ACR) Criteria (clinical and radiological) for OA of the index hip (Altman et al, 1991):
    - Hip pain **and** radiographic femoral and/or acetabular osteophytes;
      OR
    - Hip pain **and** erythrocyte sedimentation rate (ESR) < 20 mm/hour **and** radiographic axial joint space narrowing
8. Kellgren-Lawrence (KL) Grade 2 or 3 in the index hip as confirmed by X-ray during Screening visit (centrally read)
9. WOMAC A (pain) score in index hip ≥ 5.0 and ≤ 9.0 (0-10 NRS scale) at Screening 2 visit **and** at Day 1
10. WOMAC C (function) score in index hip ≥ 4.0 (0-10 NRS scale) at Screening 2 visit **and** at Day 1
11. Ambulatory and no change in use or addition of assistive devices within 3 months prior to screening
12. Agree to maintain the similar activity level and stable non-pharmacological therapies throughout the study
13. Willingness to abstain from use of protocol-specified restricted medications. (see Section 7.6.2)

Exclusion Criteria

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

Disease-related criteria

1. Patients who cannot washout of prohibited medications (Refer to Section 7.6.2) (e.g., opioids or other analgesics)
2. Diagnosed as secondary OA in the index hip including but not limited to articular fracture, major dysplasia or congenital abnormality, osteochondritis dissecans, acromegaly, ochronosis, hemochromatosis, Wilson's disease, or primary osteochondromatosis, etc.
3. Current or any history of ipsilateral chronic knee pain (lasting ≥ 3 months)
4. Contralateral hip and/or knee pain ≥ 4.0 (0-10 NRS scale) within 1 month prior to Screening visit
5. Current or any history of chronic Sciatica (lasting ≥ 3 months)
6. Current or any history of acetabular labrum tear in the study hip
7. Atrophic osteoarthritis, femoral head necrosis and/or collapse, or subchondral bone insufficiency fracture in the index hip joint determined via central reading
8. Current or history of infection in the index hip (e.g., osteomyelitis) or current skin infection at injection site
9. Concurrent chronic pain conditions with pain score ≥ 4.0 (0-10 NRS scale) within 1 month prior to Screening 1 visit, including but not limited to:
    - hip impingement syndrome, trochanteric bursalgia
    - peripheral or central neuropathy that may affect sensation of the index hip
    - non-radicular low back pain
    - peripheral nerve entrapment
    - diabetic neuropathy
    - post-herpetic neuralgia
    - post-stroke pain
    - fibromyalgia
10. Major surgery or clinically significant trauma (e.g., fracture) of lower limbs within 12 months prior to Screening visit or with ongoing sequelae.
11. painDETECT Questionnaire (PD-Q) score > 18 during Screening visit
12. History or current evidence of reactive arthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or arthritis associated with inflammatory bowel disease, systemic lupus erythematosus or other autoimmune diseases
13. Any planned surgeries in the lower limbs during the study period

Previous or concomitant treatment-related criteria

14. Presence of surgical hardware or other foreign body in the index hip
15. Planned/anticipated surgery that would require use of a restricted medication during the study period
16. IA corticosteroid of any joint within 3 months of Screening visit (investigational or marketed, including FX006)
17. IA treatment of index hip with any of the following agents within 6 months of Screening: any biologic agent (e.g., platelet rich plasma (PRP) injection, stem cells, prolotherapy, amniotic fluid injection) or hyaluronic acid (investigational or marketed)
18. Intravenous (IV) or Intramuscular (IM) corticosteroids (investigational or marketed) within 3 months of Screening
19. Oral corticosteroids (investigational or marketed) within 1 month of Screening
20. Inhaled, intranasal or topical corticosteroids (investigational or marketed) within 2 weeks of Screening visit

21. Changes to lifestyle with regard to physical activity, physical therapy, acupuncture, transcutaneous electrical nerve stimulation (TENS), or bracing within 1 month prior to Screening; or planned or expected changes during the study.

Patient-related criteria

22. Patients with a total score of ≥ 15 or >0 on Question #9 on the Patient Health Questionnaire-9 (PHQ-9) at Screening visit
23. Patients with a score of ≥ 15 on the Generalized Anxiety Disorder (GAD-7) at Screening visit
24. Patients with Pain Catastrophizing Scale (PCS) score of ≥ 30 at Screening visit
25. Patients with Insomnia Severity Index (ISI) Questionnaire score ≥ 15 (moderate severity) at Screening visit
26. Known or suspected hypersensitivity to any form of triamcinolone or PLGA
27. Laboratory evidence of infection with human immunodeficiency virus (HIV), positive test for hepatitis B surface antigen (HBsAg) or positive serology for hepatitis C virus (HCV) antibody with positive test for HCV Ribonucleic acid (RNA)
28. A medical history suggesting the patient will or is likely to require a course of systemic corticosteroids during the study period
29. History or evidence of active or latent systemic fungal or mycobacterial infection (including tuberculosis), or of ocular herpes simplex
30. History of sarcoidosis or amyloidosis
31. History of or active Cushing's syndrome
32. Medical therapy for depression, including selective or non-selective serotonin reuptake inhibitors (SSRIs, NSRIs, SNRIs) and tricyclics, if dose/regimen has not been stable for ≥ 6 months prior to Screening
33. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents within 5 years of Screening
34. Active or history of malignancy within 5 years of Screening, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or effectively managed cervical carcinoma
35. Active substance abuse (drugs or alcohol) or history of substance abuse within the past 12 months of Screening
36. Has received a live (e.g., MMR vaccine, chicken pox vaccine, rotavirus vaccine) or live-attenuated vaccine (e.g., FluMist, Zostavax) within 3 months of Day 1
37. Use of any other investigational drug, biologic or device within 3 months of Screening visit
38. Any bacterial or viral infection requiring parenteral antibiotics within 4 weeks of Day 1 or oral antibiotics within 2 weeks of Day 1
39. Any other clinically significant acute or chronic medical conditions (e.g., uncontrolled diabetes) 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
40. Patients contraindicated to the use of acetaminophen/paracetamol (allowed rescue pain medicine) per National Product Labeling and/or Investigator's judgment
41. Patient is the Investigator or any Sub investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study
42. Women who are pregnant or nursing or plan to become pregnant during the study; men who plan to conceive during the study
43. 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)]

Second Injection Inclusion Criteria (Part II Only):

To be eligible to receive the second injection during the open-label phase, patients must fulfill the following criteria:

1. Completed the double-blind phase of the study through Week 12
2. No major safety concerns during the initial dose period (including allergic reaction to initial dose of study medication) as assessed by the Investigator and patient
3. Clinically indicated to receive FX006, in the opinion of the Investigator and patient
4. WOMAC A (pain) score of ≥ 3 (0-10 NRS)
5. Compliant with study procedures and visit schedules up to the open-label injection with FX006 and the willingness and ability to continue to comply for additional 12 weeks after the second injection
6. Willingness to continue abstaining from use of protocol-restricted medications during the study (Refer to Section 7.6.2)

Second Injection Exclusion Criteria (Part II Only):

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

1. Clinical signs and symptoms of active hip infection or crystal disease of the index hip
2. Received a non-protocol specified IA intervention (IA injection, IA aspiration, etc.) in index hip during study participation
3. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents during study participation.
4. Received a live (e.g., MMR vaccine, chicken pox vaccine, rotavirus vaccine) or live-attenuated (e.g., FluMist, Zostavax) vaccine during study participation
5. Use of any other investigational drug, device or biologic during study participation
6. Any bacterial or viral infection requiring parenteral antibiotics within 4 weeks or oral antibiotics within 2 weeks of second injection
7. Skin breakdown at the hip where the injection would take place
8. Women who are pregnant or nursing or plan to become pregnant during the study; men who plan to conceive during the study
9. 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)]
10. 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

Procedures and Assessments:

The study will involve a Screening period (a minimum of 10 days, up to a maximum of 30 days), dosing at Day 1, and four additional outpatient visits at Weeks 1, 4, 8, and 12 during the double-blind phase.

Patients participating in Part I of the study will return to the clinic at Weeks 12, 16, 20, and 24 or up until the time of this amendment. The patients will be discontinued at the time of notification by the Investigator.

Patients participating in Part II of the study who are eligible for the second injection in the open-label phase at Week 12 will receive an open-label injection of FX006 at Week 12 and return for follow-up visits at Weeks 16, 20, and 24. These patients will complete the study at Week 24. Patients participating in Part II of the study that are not clinically indicated for a second injection at Week 12 will return to the clinic at Weeks 16, 20, and 24 and will receive an open-label injection of FX006 at the first evaluation where the patient has been determined to meet all criteria. Patients participating in Part II of the study will then return for follow-up visits every 4 weeks for 12 weeks post second injection and will complete the study 12 weeks post second injection (e.g., Week 24, 28, 32, or 36 depending on when the patient receives the open-label injection).

At specified times throughout the study, patients will undergo physical examinations, index hip assessments and index hip X-rays; blood will be collected for laboratory safety tests, and vital signs will be collected. Information regarding adverse events (AEs) and concomitant medications will be collected.

During out-patient visits, patients will complete accurate pain reporting (APR) and placebo response reduction (PRR) training prior to completing the Western Ontario and McMaster Universities (WOMAC®) Osteoarthritis Index, Patient Global Impression of Change (PGIC), Hip injury and Osteoarthritis Outcome Score (HOOS) Quality of Life (QOL) Subscale, Sleep Interference (SI) question, EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) and the Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9).

See Schedule of Assessments for full details.

Blinding:

The blinded-assessor technique will be used in this study in order to maintain double-blind conditions. Key site staff roles are defined in Section 7.2 and a site specific blinding plan will be developed to ensure the blind is maintained throughout the duration of the study. Treatments will be prepared by an unblinded pharmacist/coordinator who has experience with the preparation of study medication and who has been properly trained by the Sponsor or designee.

IA injections will be performed by an unblinded injector.

Full details are located in Section 7.5.8.

IP Administration Procedure:

IA administration into the hip joint

- IA injections will be performed by the assigned unblinded injector. The injector may choose the numbing agent to be used based on standard of care, if needed
- A 20 gauge or larger, 3.5 inch needle or longer is to be used for injection
- Sterile technique will be used
- Prior to injection, the injection site should be thoroughly cleansed using a bactericidal solution. The injection contents will not be visible to the patient
- Aspiration must be attempted prior to all injections. If effusion is detected by fluoroscopy, withdraw to near dryness prior to injection
- Either 5 mL of the reconstituted FX006 or 5 mL of normal saline will be injected into the index hip joint. Refer to the Pharmacy Binder for detailed instructions on how to prepare FX006. Reconstitution process should not be visualized by any blinded study staff or by the patients.
- Injection into the hip joint will be done with fluoroscopy guidance by the assigned injector (using contrast or air). The injector may choose the position of the hip (e.g., supine position with lower extremity internally rotated) and the approach for injection (e.g., anterior.)

Patients will be observed per standard of care after the procedure.

Refer to the Pharmacy Binder for detailed references on study drug preparation and IA administration.

Post-Injection Care

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

Prior and Concomitant Therapy

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

Allowable Medications/Non-Pharmacologic Therapies

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

- Any treatment for a pre-existing condition or for an AE, outside of the study indication, that is not listed as restricted
- Study-allocated rescue medication
- Aspirin for cardio protection at a maximum stable dose of 325 mg per day provided the dose has been

stable over the 3 months prior to Screening

- Medical therapy for depression, including selective or non-selective serotonin reuptake inhibitors (SSRIs, SNRIs, NSRIs) and tricyclics *provided* the dose has been stable over the 6 months prior to Screening 1 (see Table 7-1)
- Stable lifestyle with regard to physical activity, physical therapy, acupuncture, TENS, or bracing during the 1 month prior to Screening and expected to remain stable throughout the duration of the study

Prohibited Medications/Non-Pharmacologic Therapies

The following medications should not be taken or used for the duration of the study, after the patient signs informed consent. The washout (at least 5 half-lives after the last dose) must be completed at least 2 days prior to Screening 2 visit.

- Oral non-steroidal anti-inflammatory drugs (NSAIDs)
- Aspirin (>325 mg per day)
- Centrally-acting pain medications (e.g., pregabalin, gabapentin)
- Opioids, Marijuana, Cannabidiol (CBD)
- Topical therapies (e.g., NSAIDs, capsaicin, lidocaine patches, other local treatments) applied to the index hip
- Anesthetic medications injected locally in the index hip (other than lidocaine if used for IA injection procedure)
- Muscle relaxants (e.g., cyclobenzaprine, tetrazepam, diazepam)
- IV, IM, oral, inhaled, intranasal or topical corticosteroids
- IA corticosteroids in any joint
- Any IA intervention in the index hip (e.g., IA viscosupplementation (hyaluronic acid))
- Initiation of or change in medical therapy for depression, including selective or non-selective serotonin reuptake inhibitors (SSRIs, SNRIs, NSRIs) and tricyclics; see Section 7.6.1 for examples of specific agents in each class
- Any investigational drug, device or biologic
- Immunomodulators, immunosuppressives, or chemotherapeutic agents
- Live (e.g., MMR vaccine, chicken pox vaccine, rotavirus vaccine) or live-attenuated vaccines (e.g., FluMist, Zostavax)
- Changes to lifestyle with regard to physical activity, physical therapy, acupuncture, TENS, or bracing throughout the duration of the study

Rescue Medication

To standardize pain-relief rescue medication across all patients, starting at screening, patients will discontinue all prohibited medications and follow procedures:

- The designated rescue medication is acetaminophen (paracetamol) 500 mg, one tablet every 4 to 6 hr to a maximum of 6 (six) tablets (3000 mg) per 24 hr period
- Patients may not take any rescue medication during the 48 hr prior to a study visit
- Starting at screening and at each study visit, patients will be provided with a sufficient quantity of rescue medication for the interval to the next scheduled visit
- At each visit, patients will return the bottles provided at the previous visit for rescue medication accountability and be issued a new supply

Criteria for Evaluation:

Efficacy

- WOMAC Osteoarthritis Index (0-10 NRS): pain, stiffness and function domains independently and collectively (Bellamy et al, 1988)
- PGIC: 7-point scale (Farrar et al, 2001; Guy, 1976; Dworkin et al, 2005)
- HOOS QOL Subscale (http://www.koos.nu/)
- Sleep Interference (SI): Question 9F from the Brief Pain Inventory (Short Form)
- EQ-5D-5L: consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS) (https://euroqol.org)
- Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9)
- Responder status as defined by:
  - Proportion of patients experiencing either ≥50%, ≥30% or ≥20% decrease (improvement) in pain) (substantial, at least moderate and minimum clinically important difference, respectively, as defined by (Dworkin et al, 2008)
  - Outcome Measures in Rheumatology (OMERACT) - Osteoarthritis Research Society International (OARSI) criteria (Pham, 2004)
- Consumption of rescue medication

Safety

- Adverse Events
- Physical examinations
- Index hip examinations
- Index hip X-rays
- Vital signs
- Clinical laboratory evaluations (hematology, chemistry)

Sample Size Considerations:

Approximately 70 patients will be randomized in Part I and approximately 440 patients will be randomized in Part II in this study (an estimated 35 and 220 per treatment group, respectively).

For Part I, a sample size of approximately 35 per arm will provide information regarding the treatment effect. For Part II of the study, the expected sample size was determined based on the primary endpoint as follows. A minimum sample size of N=212 per arm for the placebo and the FX006 group has 90% power to yield a statistically significant difference (alpha=0.05, 2-sided) if the true underlying difference at Week 12 is 0.65 and with an assumption of 2.0 for the standard deviation (SD). For the first key secondary endpoint, the sample size of N=220 per treatment group has 90% power to yield a statistically significant difference between FX006 and placebo if the true underlying difference is 0.68 at Week 12, assuming a SD of 2.125. An early discontinuation rate of 6% was assumed. The data from Part I may be used to inform if the above assumptions were appropriate and the planned sample size for Part II should remain at 440, or whether a smaller sample size would be feasible.

Statistical Methods:

Complete details of the statistical analysis will be specified in the statistical analysis plan (SAP). A separate SAP will be prepared for Part I and Part II of the study prior to database lock for each part of the study.

Parts I and II of the study will enroll separate patients, and as such all analyses will be performed independently of one another. Analyses for Parts I and II of the study will be performed in the same manner, as detailed below. The analyses of the Part I data will be performed in an unblinded manner and results may be used to inform the conduct of Part II; as the analyses of Part I will be completed prior to the enrollment of any patients in Part II, this will have no impact on maintaining the blind for Part II. All analyses of Part I data are exploratory in nature.

Data collected in this study will be presented using summary tables, figures, and subject 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 mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages. Confidence intervals may also be provided. 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, should one occur.

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.

All patients who receive study medication and have Baseline and at least one post-dose pain evaluation will be included in the Full Analysis Set (FAS). The FAS will be the primary analysis population for efficacy.

The primary endpoint will be analyzed with a longitudinal mixed model for repeated measures (MMRM) with fixed effects for treatment group, study week, treatment-by-week interaction and Baseline score. Subject will be the random effect. Treatment differences from control will be estimated via least square means from the analysis model along with 95% confidence intervals, and associated 2-sided p-values. This model assumes missing at random and includes only observed data.

Key secondary endpoints will be assessed similarly to the primary endpoint. Multiplicity will be addressed by analyzing the key secondary endpoints sequentially in the order presented in the protocol, testing each endpoint at the nominal alpha=0.05, 2-sided level to ensure overall type I error control at the 2-sided 0.05 level.

Additional continuous secondary efficacy endpoints will also be assessed similarly to the primary endpoint, but are not part of the sequential testing approach. Categorical end points will be compared via chi-square or exact tests depending on incidence rates.

AUE will be calculated and comparisons of the AUE endpoints will be estimated from an Analysis of Covariance (ANCOVA) with model parameters for treatment and covariates of Baseline WOMAC A score and study site. Full details of the AUE analyses will be detailed in the SAP.

Safety analyses will be performed on the Safety Population. AEs will be coded using MedDRA. Incidences (number and percent) of TEAEs, those events that start after dosing or worsened in severity after dosing, will be presented 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 hip TEAEs following the first dose and second dose (Part II only), as well as the cumulative incidence of TEAEs after all doses of FX006 (Part II only).

Laboratory data, vital sign information and X-ray data will be presented as descriptive summary statistics for value and change from Baseline at each individual time point. Categorical variables will be summarized by frequencies and percentages.

3. ETHICS

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

3.1. Institutional Review Board/Ethics Committee

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

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

3.2. Ethical Conduct of Study

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

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

3.3. Patient Information and Consent

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

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

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

4. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

4.1. Investigators

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

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

4.2. Study Administrative Structure

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

5. INTRODUCTION

5.1. Osteoarthritis

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

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

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

5.2. Background

5.2.1. Investigational Medicinal Product: FX006

FX006 is an extended-release formulation of triamcinolone acetonide (TA) for IA administration. It is approved in the US under the trade name ZILRETTA® (triamcinolone acetonide extended-release injectable suspension) for the management of pain of osteoarthritis of the knee. FX006 is intended to deliver TA to the synovial and peri-synovial tissues for a period of approximately 3 months 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% (weight by weight [w/w]) and is provided as a sterile white to off-white powder for reconstitution. The drug product is reconstituted with diluent containing an isotonic, sterile aqueous solution of sodium chloride (NaCl; 0.9% w/w), carboxymethylcellulose sodium (CMC; 0.5% w/w) and polysorbate-80 (0.1% w/w) to form a suspension prior to IA injection.

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

5.2.2. Rationale for FX006 in Hip Osteoarthritis

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

5.2.3. Non-Clinical Toxicology

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

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

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

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

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

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

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

In a Phase 2 PK/ PD study evaluating three dose levels of FX006 (10 mg, 40 mg, 60 mg) administered as a 3 mL injection, suppression of cortisol in the days following injection produced by the 10 and 40 mg dose of FX006 was less than that produced by injection of TAcs; the 60 mg dose of FX006 produced effects similar to 40 mg TAcs. Cortisol suppression subsequent to Day 1-2 associated with all doses of FX006 would not be expected to be of clinical consequence in adult patients without otherwise compromised hypothalamic-pituitary-adrenal (HPA) axis function. In a Phase 2 study in diabetic patients with knee OA, treatment with 32 mg FX006 resulted in a statistically significant ($p=0.0452$) reduction in blood glucose elevation relative to TAcs over a 72-hour period following IA injection. The time in glycemic target range (70-180 mg/dL) (American Diabetes Association, 2016) was greater for FX006 as compared to TAcs over the 48 hours post IA injection, providing another indication of the improvement in glycemic control.

Over the entire time course of the 15-day post injection glucose monitoring period, blood glucose levels associated with FX006 remained at levels similar to or lower than those produced by TAcs. This observation is consistent with PK studies demonstrating low systemic exposure to TA associated with FX006.

5.2.6. Efficacy in Patients with Osteoarthritis of the Knee

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

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

effect curve (AUE) analyses for Weeks 1 through 12 and Weeks 1 through 24. Results demonstrated that the analgesic effect of 32 mg FX006 is significant at Week 1, increases through Week 7, and is sustained through at least Week 16. Responder analyses further suggested that FX006 provides clinically relevant improvement from Weeks 1 through 16 relative to placebo.

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

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

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

The safety data from the 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 the Phase 3 study, qualitative assessments based on X-rays of the index knee at 24 weeks post injection included joint space narrowing (JSN), subchondral bone changes, osteonecrosis, and insufficiency fracture (Conaghan et al, 2018b).

- The overall rate of JSN worsening of at least 1-grade between Baseline and Week 24 was low and similar among treatment groups (5.0% [7/140], 4.1% [6/148], and 3.5% [5/145] of patients with both Baseline and Week 24 X-rays in the 32 mg FX006, 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 32 mg FX006 group and 1 in the placebo group, had a 1-grade increase in JSN. There were no reports of insufficiency fracture, subchondral bone changes, or osteonecrosis

5.2.8. Rationale for Protocol Amendment

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

Therefore, screening and enrollment for the FX006-2018-015 study was suspended by the Sponsor to allow for additional review of these cases of incomplete administration of FX006 and further investigation. Repeat administration of FX006 for qualifying patients in the OLE Phase was also suspended.

As part of the investigation to determine the root cause for these incomplete administrations, a laboratory model was developed to explore factors that could contribute to these events. The laboratory model identified two procedural factors potentially contributing to these incomplete administrations of FX006 into the hip joint. Specifically, if a syringe of resuspended FX006 was attached directly to a vertically placed spinal needle (as typically encountered during IA injection in the hip) and outflow from the needle was mildly restricted by the laboratory model simulating constrained joint space conditions, then blockage was observed at an appreciable rate. If the syringe was held horizontally or if the constrained joint space model was omitted (giving conditions similar to IA injection in the knee), such events did not occur.

Based on these findings, the FX006-2019-017 study was implemented to determine the feasibility of administering FX006 into the hip joint using a technique(s) based upon the laboratory findings.

Due to the duration of the enrollment and dosing hold, and the restriction that patients enrolled were not able to receive an open-label administration of FX006 per protocol, this amended protocol was created to separate this patient population impacted by the study hold (Part I). Per this amendment, patients enrolled up to that time were followed for at least 12 weeks or up to the time of this amendment. At the time that this amendment is implemented, patients are to be discontinued from the study without further assessments required.

The outcome of the FX006-2019-017 study will inform future modifications to this protocol.

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

Studies of FX006 were expanded to include studies in patients with symptomatic OA of the hip joint. Among approximately 12 patients administered 32 mg FX006 by IA into the hip (from Study FX006-2017-013), the incidence, nature, and intensity of treatment-emergent AEs was indistinguishable from that observed with IA injection into the knee. There were no treatment related SAEs.

5.2.10. Conclusion

FX006, an extended-release microsphere formulation of triamcinolone acetonide, demonstrated comparable safety profile to TAcs in animals after single or repeat IA administrations. Much lower peak plasma level and much longer duration than TAcs after IA injection in knee OA patients contributed to a better systemic safety profile, as evidenced by decreased duration and magnitude in hyperglycemia of diabetic patients. Furthermore, FX006 demonstrated comparable local joint safety as TAcs in patients with knee OA. Larger magnitude and longer duration of efficacy was observed with FX006 than TAcs as shown by WOMAC pain and function scores. Given the insufficient symptomatic management of hip OA patients and similar pathogenesis between knee and hip OA, it is anticipated that FX006 will provide improved benefit/risk profiles to hip OA patients. Thus, the sponsor is proposing continued clinical study of FX006 for hip OA.

6. STUDY OBJECTIVES

6.1. Primary Objective

6.1.1. Part I

Double-Blind Objectives

- To assess the treatment effect of FX006 on pain following an intra-articular (IA) injection in patients with hip osteoarthritis (OA)

6.1.2. Part II

Double-Blind Phase Objectives

- To assess the efficacy of FX006 on pain following an intra-articular (IA) injection in patients with hip osteoarthritis (OA)

6.2. Secondary Objectives

6.2.1. Part I

Double-Blind Objectives

- To assess the efficacy of FX006 on function, global impression of change, stiffness, quality of life, treatment satisfaction, sleep quality and consumption of rescue medication in patients with hip OA
- To assess the safety of FX006 in patients with hip OA

6.2.2. Part II

Double-Blind Phase Objectives

- To assess the effect of FX006 on function, global impression of change, stiffness, quality of life, treatment satisfaction, sleep quality and consumption of rescue medication in patients with hip OA
- To assess the safety of FX006 in patients with hip OA

6.3. Open Label Phase Objectives

6.3.1. Secondary Objective:

- To examine efficacy following a second injection of FX006 in patients with hip OA

6.3.2. Primary Objective:

- To assess the overall safety of a second injection of FX006 in patients with hip OA

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a two-part, multi-center, randomized, double-blind, placebo-controlled, parallel-group study in patients with hip OA. Approximately 70 patients will be enrolled in Part I and approximately 440 patients will be enrolled in Part II of the study. In each part, patients will be randomized to one of two treatment groups (1:1) and treated with a single IA injection of either 32 mg FX006 or normal saline.

Eligible patients will be randomized within strata defined by Baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) A (pain) (0-10 numeric ratings scale (NRS) average of Screening 2 and Day 1 with the following classifications: 5.0 to < 6.0, 6.0 to < 7.0, and ≥ 7.0 to 9.0 (see Section 9 for details).

FX006 or saline placebo will be administered as a single IA injection with a 12-week follow-up period in the double-blind phase.

Patients participating in Part I of the study will be treated with a single IA injection of either 32 mg FX006 or normal saline and will return for follow up visits at Weeks 12, 16, 20, and 24 or up until the time of this amendment. The patients will be discontinued at the time of notification by the Investigator.

Patients participating in Part II of the study will be treated with a single IA injection of either 32 mg FX006 or normal saline and will return for follow up visits at Weeks 12, 16, 20, and 24. Patients who are eligible for the second injection in the open-label phase at Week 12 will receive an open-label injection of FX006 at Week 12 and return for follow-up visits at Weeks 16, 20, and 24. These patients will complete the study at Week 24.

Patients participating in Part II of the study that are not clinically indicated for a second injection at Week 12 will return to the clinic at Weeks 16, 20, and 24 and will receive an open-label injection of FX006 at the first evaluation where the patient has been determined to meet all criteria. Patients will then return for follow-up visits every 4 weeks for 12 weeks post second injection and will complete the study 12 weeks post second injection (e.g., Week 24, 28, 32, or 36 depending on when the patient receives the open-label injection).

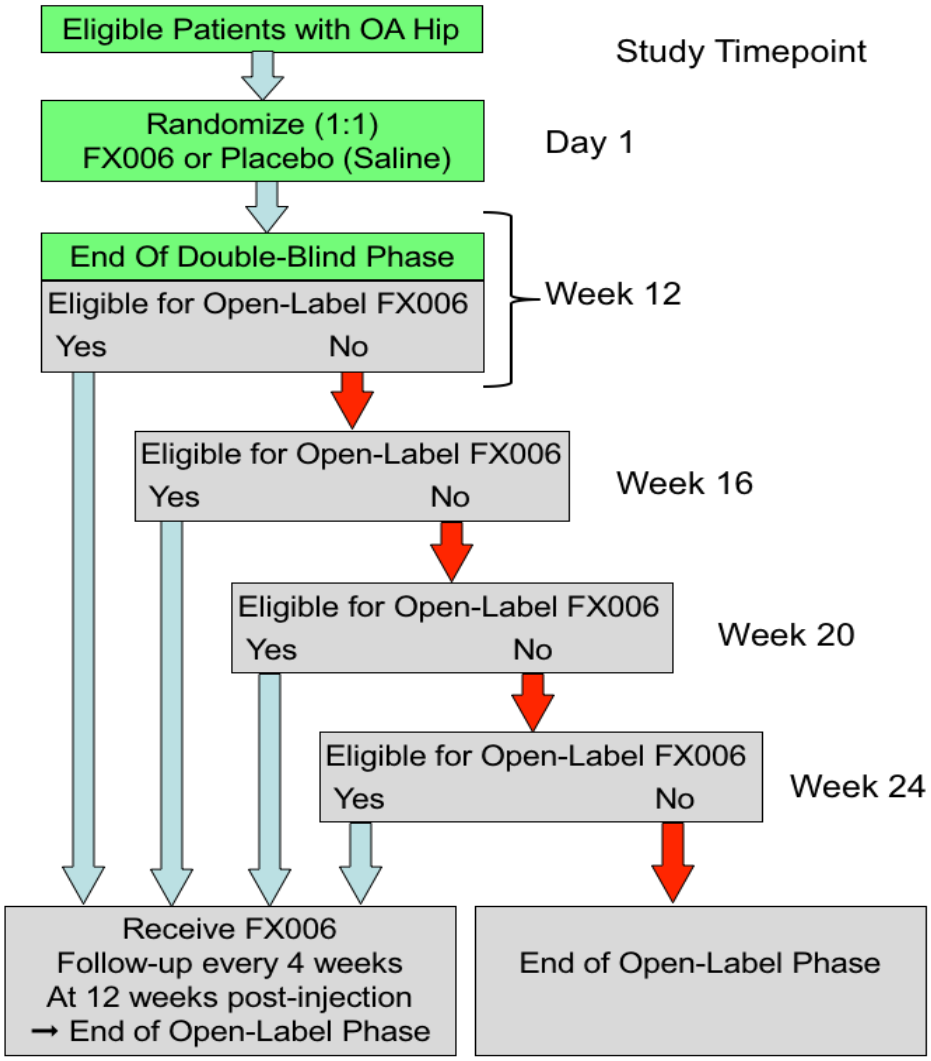
Patients participating in Part II of the study who are not eligible for a second injection after evaluation at Weeks 12, 16, 20, and 24 will complete the study at the Week 24 visit and complete the End of Study (EOS) assessments.

7.1.1. Flow of Study Participation

Patients participating in this study will complete visit schedules and procedures as detailed in the Study Flow Chart (Figure 1) and the Schedule of Study Assessments (Table 7-2 and Table 7-3).

The study will involve a Screening period (a minimum of 10 days, up to a maximum of 30 days), dosing at Day 1, and four additional outpatient visits at Weeks 1, 4, 8, and 12 during the double-blind phase.

Figure 1: Study Flow Chart (Part II Patients Only)



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 on the Clinical Site Responsibilities and Signature Log. The term 'Principal Investigator' is used throughout this protocol to refer to the actual Principal Investigator and/or his/her delegated team member(s) for the specific responsibility being described.

At a minimum, the study staff should consist of:

Unblinded 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
- Will not share treatment assignments with the blinded assessor, the patient and other blinded study personnel or Sponsor personnel/representatives and will make every effort to maintain the blind
- Will have no other contact with the patient throughout patient's participation in the study

Unblinded Injector

- Must be a Medical Doctor, Doctor of Osteopathy, or certified Physician Assistant with experience in administering IA injections of the hip using fluoroscopy guidance
- Is responsible for performing all IA injections of study medication using fluoroscopy guidance
- Will not share treatment assignments with the blinded assessor, the patient and other blinded study personnel or Sponsor personnel/representatives and will make every effort to maintain the blind
- Will have no other contact with the patient outside of treatment administration through patient's participation in the study other than obtaining informed consent at the Screening visit, if applicable

Blinded Assessor

- Must be a medical doctor, a physician's assistant, or nurse practitioner
- Must have relevant OA experience
- Is responsible for performing the physical examination and index hip assessments
- Is responsible for the overall safety of the patient, including assessing all adverse events for seriousness, severity, and relationship to study medication
- Must not be present during the administration of study medication, but should be available afterward to assess the patient for any adverse events that occurred during the procedure. (see Section 7.5.8 and Section 8.2 for details regarding handling of those events).

Delegation of responsibilities will be documented at each site and specified in each site's Blinding Plan. An individual that serves as an unblinded pharmacist/coordinator or an unblinded injector can only serve in the unblinded role for the duration of the study and must adhere to the roles as outlined above. It is permitted to have three (3) individuals delegated to each unblinded role defined above to ensure adequate back-up coverage if necessary; however, the Principal Investigator must not serve as an unblinded injector but will serve as one of the blinded assessors.

7.3. Discussion of Study Design

7.3.1. Rationale for Study Population

Most recently a few placebo-controlled randomized trials using conventional triamcinolone formulation at doses of 40 mg for hip OA have demonstrated acceptable safety profiles (Lambert et al, 2007; Qvistgaard et al, 2006; Atchia et al, 2011). This study will evaluate a similar patient population. In addition, the safety profile of FX006 has been demonstrated to be well-tolerated in over 600 patients with knee OA in clinical trials. Given the similar pathogenesis between knee and hip OA and demonstrated efficacy in knee OA, it is hypothesized that FX006 should be beneficial to hip OA patients, and thus supports FX006 evaluation in this patient population.

7.3.2. Rationale for Dose Selection

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

7.3.3. Rationale for Study Parameters

Pain, function and patient global impression of change are the three core efficacy measures that are accepted by regulatory agencies and various scientific committees for hip OA trials. Rescue medication use is commonly monitored in OA trials to further confirm symptomatic improvements. Sleep disturbance commonly occurs in hip OA patients, and as such, it is meaningful to reflect potential quality of life benefit. Patient satisfaction to therapeutics can assess overall satisfaction from various perspectives to the test article. Patient quality of life (e.g., EuroQol 5 Dimensions 5 Levels questionnaire (EQ-5D-5L) and Hip injury and Osteoarthritis Outcome Score quality of life (HOOS QOL)) are required measures per research committees (McAlindon et al, 2015). The clinical safety parameters to be assessed (physical examinations, index knee examinations, X-rays, vital signs, clinical laboratory evaluations and adverse events [AEs]) are standard safety and tolerability assessments.

7.3.4. Rationale for Control Type

Normal saline (NaCl; 0.9% w/w) has been selected as the placebo control for this study because it is the base component of the FX006 diluent. The other excipients of the FX006 diluent, sodium carboxymethylcellulose (NaCMC 0.5% w/w) and polysorbate-80 (0.1% w/w), have been accepted as standard inactive excipients by the FDA. These excipients are present in commercially available TCA IR (e.g., Kenalog-40®) which also utilizes sodium chloride for tonicity adjustment. Normal saline has been employed as a control in published studies of TCA and other corticosteroids (Gaffney et al, 1995).

7.3.5. Rationale for Blinding Approach

FX006 and normal saline will not be identical in appearance and administration differences may be apparent. As such, the blinded-assessor technique has been selected for this study.

7.4. Selection of Study Population

7.4.1. Number of Patients

Approximately 70 patients in Part I and approximately 440 patients in Part II will be randomized and treated in the double-blind phase of the study.

7.4.2. Inclusion Criteria

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

1. Written informed consent has been obtained prior to initiating any study specific procedures
2. Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions
3. Patients 40 to 80 years of age, inclusive, on the day of consent
4. Body Mass Index (BMI) ≤ 40 kg/m^2
5. Symptoms (including pain) associated with OA of the index hip for ≥ 3 months prior to Screening visit (patient self-report is acceptable).
6. Moderate to severe index hip pain due to OA for >15 days over the last month (as reported by the patient)
7. Currently meet the American College of Rheumatology (ACR) Criteria (clinical and radiological) for OA of the index hip (Altman et al, 1991):
    - Hip pain **and** radiographic femoral and/or acetabular osteophytes; ***OR***
    - Hip pain **and** erythrocyte sedimentation rate (ESR) < 20 mm/hour **and** radiographic axial joint space narrowing
8. Kellgren-Lawrence (KL) Grade 2 or 3 in the index hip as confirmed by X-ray during Screening visit (centrally read)
9. WOMAC A (pain) score in index hip ≥ 5.0 and ≤ 9.0 (0-10 NRS scale) at Screening 2 visit **and** Day 1
10. WOMAC C (function) score in index hip ≥ 4.0 (0-10 NRS scale) at Screening 2 visit **and** Day 1
11. Ambulatory and no change in use or addition of assistive devices within 3 months prior to screening
12. Agree to maintain the similar activity level and stable non-pharmacological therapies throughout the study
13. Willingness to abstain from use of protocol-specified restricted medications (See Section 7.6.2)

7.4.3. Exclusion Criteria

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

Disease-related criteria

1. Patients who cannot washout of prohibited medications (e.g., opioids or other analgesics) (Refer to Section 7.6.2)
2. Diagnosed as secondary OA in the index hip including but not limited to articular fracture, major dysplasia or congenital abnormality, osteochondritis dissecans, acromegaly, ochronosis, hemochromatosis, Wilson's disease, or primary osteochondromatosis, etc.
3. Current or any history of ipsilateral chronic knee pain (lasting ≥ 3 months)
4. Contralateral hip and/or knee pain ≥ 4.0 (0-10 NRS scale) within 1 month prior to Screening visit
5. Current or any history of chronic Sciatica (lasting ≥ 3 months)
6. Current or any historyof acetabular labrum tear in the study hip
7. Atrophic osteoarthritis, femoral head necrosis and/or collapse, or subchondral bone insufficiency fracture in the index hip joint determined via central reading
8. Current or history of infection in the index hip (e.g., osteomyelitis) or current skin infection at injection site
9. Concurrent chronic pain conditions with pain score ≥ 4.0 (0-10 NRS scale) within 1 month prior to Screening 1 visit, including but not limited to:
    - hip impingement syndrome, trochanteric bursalgia
    - peripheral or central neuropathy that may affect sensation of the index hip
    - non-radicular low back pain
    - peripheral nerve entrapment
    - diabetic neuropathy
    - post-herpetic neuralgia
    - post-stroke pain
    - fibromyalgia
10. Major surgery or clinically significant trauma (e.g., fracture) of lower limbs within 12 months prior to Screening visit or with ongoing sequelae.
11. painDETECT Questionnaire (PD-Q) score > 18 during Screening visit
12. History or current evidence of reactive arthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or arthritis associated with inflammatory bowel disease, systemic lupus erythematosus or other autoimmune diseases
13. Any planned surgeries in the lower limbs during the study period

Previous or concomitant treatment-related criteria

14. Presence of surgical hardware or other foreign body in the index hip
15. Planned/anticipated surgery that would require use of a restricted medication during the study period
16. IA corticosteroid of any joint within 3 months of Screening visit (investigational or marketed, including FX006)
17. IA treatment of index hip with any of the following agents within 6 months of Screening: any biologic agent (e.g., platelet rich plasma (PRP) injection, stem cells, prolotherapy, amniotic fluid injection) or hyaluronic acid (investigational or marketed)
18. Intravenous (IV) or Intramuscular (IM) corticosteroids (investigational or marketed) within 3 months of Screening
19. Oral corticosteroids (investigational or marketed) within 1 month of Screening
20. Inhaled, intranasal or topical corticosteroids (investigational or marketed) within 2 weeks of Screening visit
21. Changes to lifestyle with regard to physical activity, physical therapy, acupuncture, transcutaneous electrical nerve stimulation (TENS), or bracing within 1 month prior to Screening; or planned or expected changes during the study

Patient-related criteria

22. Patients with a total score of ≥ 15 or >0 on Question #9 on the Patient Health Questionnaire-9 (PHQ-9) at Screening visit
23. Patients with a score of ≥ 15 on the Generalized Anxiety Disorder (GAD-7) at Screening visit
24. Patients with Pain Catastrophizing Scale (PCS) score of ≥ 30 at Screening visit
25. Patients with Insomnia Severity Index (ISI) Questionnaire score ≥ 15 (moderate severity) at Screening visit
26. Known or suspected hypersensitivity to any form of triamcinolone or PLGA
27. Laboratory evidence of infection with human immunodeficiency virus (HIV), positive test for hepatitis B surface antigen (HBsAg) or positive serology for hepatitis C virus (HCV) antibody with positive test for HCV Ribonucleic acid (RNA)
28. A medical history suggesting the patient will or is likely to require a course of systemic corticosteroids during the study period
29. History or evidence of active or latent systemic fungal or mycobacterial infection (including tuberculosis), or of ocular herpes simplex
30. History of sarcoidosis or amyloidosis
31. History of or active Cushing's syndrome
32. Medical therapy for depression, including selective or non-selective serotonin reuptake inhibitors (SSRIs, NSRIs, SNRIs) and tricyclics, if dose/regimen has not been stable for ≥ 6 months prior to Screening
33. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents within 5 years of Screening

34. Active or history of malignancy within 5 years of Screening, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or effectively managed cervical carcinoma
35. Active substance abuse (drugs or alcohol) or history of substance abuse within the past 12 months of Screening
36. Has received a live (e.g., MMR vaccine, chicken pox vaccine, rotavirus vaccine) or live-attenuated vaccine (e.g., FluMist, Zostavax) within 3 months of Day 1
37. Use of any other investigational drug, biologic or device within 3 months of Screening visit
38. Any bacterial or viral infection requiring parenteral antibiotics within 4 weeks of Day 1 or oral antibiotics within 2 weeks of Day 1
39. Any other clinically significant acute or chronic medical conditions (e.g., uncontrolled diabetes) 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
40. Patients contraindicated to the use of acetaminophen/paracetamol (allowed rescue pain medicine) per National Product Labeling and/or Investigator's judgment
41. Patient is the Investigator or any Sub investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study
42. Women who are pregnant or nursing or plan to become pregnant during the study; men who plan to conceive during the study
43. 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)]

7.4.4. Second Injection Inclusion Criteria (Part II Patients Only)

To be eligible to receive the second injection during the open-label phase, patients must fulfill the following criteria:

1. Completed the double-blind phase of the study through Week 12
2. No major safety concerns during the initial dose period (including allergic reaction to initial dose of study medication) as assessed by the Investigator and patient
3. Clinically indicated to receive FX006, in the opinion of the Investigator and patient
4. WOMAC A (pain) score of ≥ 3 (0-10 NRS)
5. Compliant with study procedures and visit schedules up to the open-label injection with FX006 and the willingness and ability to continue to comply for additional 12 weeks after the second injection
6. Willingness to continue abstaining from use of protocol-restricted medications during the study (Refer to Section 7.6.2)

7.4.5. Second Injection Exclusion Criteria (Part II Patients Only)

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

1. Clinical signs and symptoms of active hip infection or crystal disease of the index hip
2. Received a non-protocol specified IA intervention (IA injection, IA aspiration, etc.) in index hip during study participation
3. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents during study participation
4. Received a live (e.g., MMR vaccine, chicken pox vaccine, rotavirus vaccine) or live-attenuated (e.g., FluMist, Zostavax) vaccine during study participation
5. Use of any other investigational drug, device or biologic during study participation
6. Any bacterial or viral infection requiring parenteral antibiotics within 4 weeks or oral antibiotics within 2 weeks of second injection
7. Skin breakdown at the hip where the injection would take place
8. Women who are pregnant or nursing or plan to become pregnant during the study; men who plan to conceive during the study
9. 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)]
10. 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

7.4.6. Removal of Patients from Therapy or Assessments

Each randomized and treated patient in Part I and the Part II double blind phase of the study receives study medication as a single administration. Therefore, discontinuation from treatment is not applicable. Patients may be discontinued from study follow-up as detailed below. Data collected from discontinued patients will be included in the clinical study report. Patients who discontinue the study may be replaced at the discretion of the Sponsor.

Withdrawal of Consent

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

1. document in patient's source their withdrawal of consent and reason for withdrawing from the study,
2. assess the patient's clinical condition and take appropriate therapeutic measures if necessary,

3. attempt to complete the study assessments defined for the Final/Early Termination Visit, and
4. determine whether the patient is willing to be contacted on a monthly basis (via phone or in person) to follow ongoing or new AEs (including concomitant medication(s) associated with an AE) through the patient's scheduled final visit

Discontinuation of Follow-up by Investigator

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

Discontinuation of Follow-up by Sponsor

Patients participating in Part I of the study will return for follow up visits at Weeks 12, 16, 20, and 24 or up until the time of this amendment at which time they will be discontinued. The patients will be discontinued at the time of notification by the Investigator.

7.4.7. Screen Failures

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

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

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

7.5. Treatment Administered

7.5.1. Study Medication Treatment Arms

Investigational Medicinal Product Arm:

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

Reference Compound:

- Normal saline, sodium chloride (0.9% NaCl) solution, IA, administered as a 5 mL injection into the index hip OA joint under fluoroscopy guidance per injection procedure.

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. Identity of Reference Compound

Normal saline (0.9% sodium chloride injection, USP, supplied as a 10 mL vial) is a sterile, nonpyrogenic, isotonic solution of sodium chloride and water for injection. Each mL contains sodium chloride 9 mg.

7.5.4. Receipt, Preparation, Dispensing and Storage

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

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

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

7.5.5. Packaging and Labeling of Study Medication

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

7.5.6. Return of Study Medication

All study medications (packaged kits/used and unused vials) will be returned to the drug supply distribution center and will be documented within the Drug Tracking module. Return of study medications will be properly documented.

7.5.7. Method of Assigning Patients to Treatment Groups

Eligible patients will be randomized within strata defined by Baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) A (pain) (0-10 numeric ratings scale (NRS) average of Screening 2 and Day 1 as follows: 5.0 to < 6.0, 6.0 to < 7.0, and ≥ 7.0 to 9.0 (see Section 9 for details).

7.5.8. Blinding

The blinded-assessor technique will be used in this study in order to maintain double blind conditions. Key site staff roles are defined in Section 7.2 and a site specific blinding plan will be developed to ensure the blind is maintained throughout the duration of the study. Treatments will be prepared by an unblinded pharmacist/coordinator who has experience with the

preparation of study medication and who has been properly trained by the Sponsor or designee. IA injections will be performed by an unblinded injector.

Overall unblinded team responsibilities are as follows:

- Will have no other contact with the patient and will not have any blinded roles on the study (the only exception is that the unblinded injector may be delegated the role of obtaining informed consent at the Screening visit)
- Will not share treatment assignments with the blinded assessor, the patient and other blinded study personnel and Sponsor personnel/representatives
- Will make every effort to maintain the blind (e.g., preparation of both study agents will include similar tapping actions, so both "sound" the same).

Detailed responsibilities for the unblinded site staff are as follows:

- Unblinded Pharmacist/Coordinator:
  - Receives the randomization notification of the subject's study treatment
  - Dispenses the appropriate prepared study treatment and necessary materials for the injection
  - Completes the drug accountability logs
  - Transports assigned treatment to the location where injection will take place
  - Will remain with the patient and unblinded injector until the injection is completed
  - Ensures the blind is maintained by following the site specific blinding plan to ensure the patient is unaware of the treatment assignment prepared for injection
  - Performs the study drug reconstitution
  - Will ensure that the FX006 drug is re-suspended prior to injection
  - Will record details of study drug preparation, transport (if applicable) and administration.
  - Will, in collaboration with the Unblinded Injector as appropriate, record any product-related issues relating to reconstitution or administration of FX006 (e.g., inability to achieve an appropriate suspension, inability to administer the full dose due to clogging of the needle) and report the occurrence to the Unblinded Site Monitor, as detailed in the Pharmacy Binder.
  - Will, in collaboration with the Unblinded Injector, prepare a blinded written record of any clinical AE and report the event to the (blinded) Principal Investigator and the Blinded Study Coordinator who will enter the event in the EDC and assess, treat, and follow-up the patient as appropriate.
  - Will transport the used vials back to the drug storage location to be held until drug accountability is performed by the unblinded monitor.

Depending on site specific requirements, the unblinded pharmacist/coordinator may be split into two roles. Details will be specified in the site specific blinding plan

- Unblinded Injector
  - Performs the study drug reconstitution (if not completed by the unblinded pharmacist/coordinator)
  - Will ensure that the FX006 drug is re-suspended prior to injection
  - Performs the aspiration and injection of the index hip using fluoroscopy in accordance with both their experience and the protocol-specified procedure.
  - Will, in collaboration with the Unblinded Pharmacist/Coordinator, record any product-related issues relating to reconstitution or administration of FX006.
  - Will, if the patient experiences any clinical AE while in the procedure suite, provide prompt medical care, as appropriate, including requesting additional assistance. Patient safety is always paramount, but, if feasible, minor events should be handled without unblinding the blinded study team.
  - Will prepare a blinded written record of the AE and report it to the blinded assessor, who will assess, treat, and follow-up with the patient as clinically appropriate

All other site and Sponsor personnel/representatives involved in the study at the site will be blinded with regard to the study medication being administered with the following Sponsor/representative exceptions:

- Unblinded monitor(s):
  - Responsible for unblinded site monitoring.
  - Will perform study drug accountability (used and unused vials)
  - Is the primary point-of-contact for the Unblinded site personnel in the event of any "product complaint" (e.g., difficulty reconstituting study drug, inability to inject complete dose of study drug)
  - Will report all product-related issues within 24 hours to the designated unblinded personnel at the Sponsor.
- Unblinded clinical manager:
  - Responsible for oversight of unblinded site monitoring.
  - Will review unblinded monitoring visit reports and escalate unblinded site issues to unblinded Sponsor representative
- Unblinded Sponsor representative
  - Point of escalation for unblinded team
  - Will address any product related issues
  - Will escalate in a blinded manner to the blinded study team, if necessary
- Sponsor Regulatory and Pharmacovigilance personnel for safety assessment and reporting, if necessary

Information regarding the treatment assignments will be kept securely by Sponsor or designee, per its standard operating procedures.

7.5.9. Breaking The Blind

If there is a clinical adverse event that the Investigator judges requiring unblinding of study medication, they will promptly contact the Medical Monitor and review the situation. If the consensus is to unblind the subject's treatment, a trained and authorized site user will log into the Emergency Study Code Break Module and will be provided the patient's treatment assignment.

If there is a clinical adverse event that Pharmacovigilance or Regulatory judge requires unblinding of study medication, the Sponsor's internal procedure will be followed.

If any site team member is unblinded for any reason, the Investigator will notify the Sponsor that unblinding has occurred, without revealing the treatment, and document who was unblinded, the reason for doing so, and the date of unblinding in a note to file.

7.5.10. Investigational Medicinal Product Administration Procedure

IA Administration Into The Hip Joint

- IA injections will be performed by the assigned unblinded injector. The injector may choose the numbing agent to be used based on standard of care, if needed
- A 20 gauge or larger, 3.5 inch needle or longer is to be used for injection
- Sterile technique will be used
- Prior to injection, the injection site should be thoroughly cleansed using a bactericidal solution. The injection contents will not be visible to the patient.
- Aspiration must be attempted prior to all injections. If effusion is detected by fluoroscopy, withdraw to near dryness prior to injection
- Either 5 mL of the reconstituted FX006 or 5 mL of normal saline will be injected into the index hip joint. Refer to the Pharmacy Binder for detailed instructions on how to prepare FX006. Reconstitution process should not be visualized by any blinded study staff or by the patients
- Injection into the hip joint will be done with fluoroscopy guidance by the assigned injector (using contrast or air). The injector may choose the position of the hip (e.g., supine position with lower extremity internally rotated) and the approach for injection (e.g., anterior.)
- Patients will be observed per standard of care after the procedure

Refer to the Pharmacy Binder for detailed references on study drug preparation and IA administration.

Post-Injection Care

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

7.5.11. Treatment Compliance

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

If for any reason the administration of study medication is stopped before the entire volume is injected, the injector should document the reason for stopping administration.

7.6. Prior and Concomitant Therapy

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

7.6.1. Allowable Medications/Non-Pharmacologic Therapies

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

- Any treatment for a pre-existing condition or for an AE, outside of the study indication, that is not listed as restricted
- Study-allocated rescue medication
- Aspirin for cardio protection at a maximum stable dose of 325 mg per day provided the dose has been stable over the 3 months prior to Screening
- Medical therapy for depression, including selective or non-selective serotonin reuptake inhibitors (SSRIs, NSRIs, SNRIs) and tricyclics *provided* the dose has been stable over the 6 months prior to Screening 1 (See Table 7-1)
- Stable lifestyle with regard to physical activity, physical therapy, acupuncture, TENS, or bracing during the 1 month prior to Screening and expected to remain stable throughout the duration of the study

Table 7-1 below lists the major classes of anti-depressants and examples of commonly prescribed agents by generic and brand name; it is not a complete listing. If a concomitant medication named by a patient being screened is not familiar, please check at https://www.pdr.net or post a query in the General Log.

Table 7-1: Commonly Prescribed Anti-depressants by Drug Class

Class	Class name	Generic name	Brand names
SSRIs	selective serotonin reuptake inhibitors	Citalopram	Celexa
		Escitalopram	Lexapro, Cipralex
		Fluoxetine	Prozac, Sarafem
		Fluvoxamine	Luvox
		Paroxetine	Paxil, Seroxat
		Sertraline	Zoloft
SNRIs	serotonin norepinephrine reuptake inhibitors	Tramadol	Ultram
		Venlafaxine	Effexor
TCAs	tricyclic antidepressants	Amitriptyline	Elavil
		Doxepin	Sinequan
		Imipramine	Tofranil
		Nortriptyline	Aventyl, Noritren, Pamelor
NDRI	norepinephrine-dopamine reuptake inhibitor	Bupropion	Wellbutrin, Zyban

7.6.2. Prohibited Medications/Non-Pharmacologic Therapies

The following medications should not be taken or used for the duration of the study, after the patient signs informed consent. The washout (at least 5 half-lives after the last dose) must be completed at least 2 days prior to Screening 2 visit.

- Oral non-steroidal anti-inflammatory drugs (NSAIDs)
- Aspirin (>325 mg per day)
- Centrally-acting pain medications (e.g., pregabalin, gabapentin)
- Opioids, Marijuana, Cannabidiol (CBD)
- Topical therapies (e.g., NSAIDs, capsaicin, lidocaine patches, other local treatments) applied to the index hip
- Anesthetic medications injected locally in the index hip (other than lidocaine if used for IA injection procedure)
- Muscle relaxants (e.g., cyclobenzaprine, tetrazepam, diazepam)
- IV, IM, oral, inhaled, intranasal or topical corticosteroids
- IA corticosteroids in any joint
- Any IA intervention in the index hip (e.g., IA viscosupplementation (hyaluronic acid))
- Initiation of or change in medical therapy for depression, including selective or non-selective serotonin reuptake inhibitors (SSRIs, SNRIs, NSRIs) and tricyclics; see Section 7.6.1 for examples of specific agents in each class
- Any investigational drug, device or biologic
- Immunomodulators, immunosuppressives, or chemotherapeutic agents

- Live (e.g., MMR vaccine, chicken pox vaccine, rotavirus vaccine) or live-attenuated (e.g., FluMist, Zostavax) vaccines
- Changes to lifestyle with regard to physical activity, physical therapy, acupuncture, TENS, or bracing throughout the duration of the study

7.6.3. Rescue Medication

To standardize pain-relief rescue medication across all patients, starting at screening, patients will discontinue all prohibited medications and follow procedures:

- The designated rescue medication is acetaminophen (paracetamol) 500 mg, one tablet every 4 to 6 hr to a maximum of 6 (six) tablets (3000 mg) per 24 hr period.
- Patients may not take any rescue medication during the 48 hr prior to a study visit.
- Starting at screening and at each study visit, patients will be provided with a sufficient quantity of rescue medication for the interval to the next scheduled visit.
- At each visit, patients will return the bottles provided at the previous visit for rescue medication accountability and be issued a new supply.

7.7. Study Variables

7.7.1. Safety Variables

- Adverse Events
- Physical examinations
- Index hip examinations
- Index hip X-rays
- Vital signs
- Clinical laboratory evaluations (hematology, chemistry)

7.7.2. Efficacy Variables

- WOMAC Osteoarthritis Index (0-10 NRS): pain, stiffness and function domains independently and collectively (Bellamy et al, 1988)
- PGIC: 7-point scale (Farrar et al, 2001; Guy, 1976; Dworkin et al, 2005)
- HOOS-QOL Subscale (http://www.koos.nu/)
- Sleep Interference (SI): Question 9F from the Brief Pain Inventory (Short Form)
- EQ-5D-5L: consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS) (https://euroqol.org)
- Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9)
- Responder status as defined by:

- Proportion of patients experiencing either ≥50%, ≥30% or ≥20% decrease (improvement) in pain) (substantial, at least moderate and minimum clinically important difference, respectively, as defined by (Dworkin et al, 2008)
- Outcome Measures in Rheumatology (OMERACT) - Osteoarthritis Research Society International (OARSI) criteria (Pham, 2004)

- Consumption of rescue medication

7.8. Schedule of Study Assessments

A summary of the schedule of assessments is provided in Table 7-2 and Table 7-3. Refer to Section 7.9 for details of each assessment.

Table 7-2: Schedule of Study Assessments for Double Blind Phase

List of Assessments	Screening 1[n] Day -30 to -1	Screening 2[n] Day -10 to -4	Day 1	Weeks 1, 4, 8[m]	Week 12 EOS for Double blind phase[a, m]
Informed consent	X				
Inclusion/Exclusion Review	X		X[b]		
Medical History/Update	X		X[b]		
Patient Demographics	X				
OA Medical History	X				
Prior Treatments and Medications	X		X[b]		
Physical examination	X				X
Index Hip Assessment	X		X[b]	X	X
Index Hip X-ray[c]	X				X
Vital signs	X		X[b]	X	X
Height	X				
Weight and BMI	X				X
Hematology, Chemistry[h]	X				X
ESR	X				
HIV, Hep B/C[h]	X				
Pregnancy Test[f]	X[h]		X[b]		X
Washout of restricted pain medication	X[d]				
PD-Q, PHQ-9, GAD-7, PCS, ISI	X				
Randomization			X[b]		
Second Injection Criteria					X
Index Hip Aspiration			X[b, g]		
IMP administration[i]			X		
Rescue Medication dispensing and accountability[e]	X		X	X	X
Accurate pain reporting and placebo response reduction training[j]		X	X[b]	X	X
WOMAC[k]		X	X[b]	X	X
PGIC[k]				X	X
TSQM-9[k]					X
SI, HOOS-QOL, EQ-5D-5L[k]			X[b]	X	X
AE/SAE & ConMeds[l]			----------X----------		

a. *The Double-Blind Phase* of the study ends at Week 12. Patients participating in Part I of the study will not receive a second injection but will return to the clinic at Weeks 12, 16, 20, and 24 or up until the time of this amendment. Patients participating in Part II of the study who are eligible for the second injection in the open-label phase at Week 12 will receive an open-label injection of FX006 at Week 12 and return for follow-up visits at Weeks 16, 20, and 24. These patients will complete the study at Week 24. Patients participating in Part II of the study who are not clinically indicated for a second injection at Week 12 will return to the clinic at Weeks 16, 20, and 24 and will receive an open-label injection of FX006 at the first evaluation where the patient has been determined to meet all criteria.
b. To be collected or assessed prior to injection of study medication
c. X-ray of weight-bearing anterior-posterior view for index hip will be taken for central reading.
d. After signing the ICF, patients must stop all restricted medications (other than rescue medication). The washout (at least 5 half-lives) must be completed at least 2 days prior to Screening 2 visit.
e. Rescue medication will be dispensed to the patient at the Screening visit, and a new bottle will be dispensed at each subsequent visit as needed. Drug accountability will be done at each visit
f. Pregnancy tests will be done in women of child bearing potential. *Serum Pregnancy Test* to be collected only at Screening visit. *Urine Pregnancy Test* to be collected prior to injection of study medication and at EOS (when it occurs)
g. Aspiration must be attempted prior to all injections. If effusion is detected by fluoroscopy guidance, withdraw to near dryness prior to injection
h. Via Central Laboratory
i. To be performed under fluoroscopy guidance
j. To be completed prior to questionnaires
k. To be completed after APR and PRR training but prior to any other assessments following the sequence in Table 7-5.
l. AEs and concomitant medications will be captured from Day 1 (post injection) to EOS visit.
m. Visit should be conducted within +/- 3 days from scheduled date.
n. Screening 1 and Screening 2 visits can be combined into one visit provided the patient does not have a washout from prohibited medications. If there is no washout, please perform APR/PRR first, then the questionnaires in order they are shown on Table 7-6 , with the WOMAC being completed after APR/PRR, then all subsequent questionnaires as they are listed for Screening 1.

Table 7-3: Schedule of Study Assessments for Open Label Extension (OLE) Phase

List of Assessments	Second Injection OLE (Week 12[i], 16, 20, 24) [c,n]	Follow-up (every 4 weeks post 2nd injection) [g,n,o]	EOS for OLE [e, g, n, p]
Second Injection Criteria	X		
Physical examination			X
Index Hip Assessment	X	X	X
Index Hip X-ray[b]			X
Vital signs	X[a]	X	X
Weight and BMI			X
Hematology, Chemistry[j]			X
Pregnancy Test[h]	X[a, o]		X
Index Hip Aspiration	X[a, f, o]		
IMP administration[c, k]	X[a, o]		
Rescue Medication dispensing and accountability[d]	X	X	X
Accurate pain reporting and placebo response reduction training[l]	X	X	X
WOMAC[m]	X	X	X
PGIC[m]	X	X	X
SI, HOOS-QOL, EQ-5D-5L[m]	X	X	X
AE/SAE & ConMeds	*To be collected at every visit and whenever applicable*		

a. To be collected or assessed prior to 2nd injection of study medication only if patient is receiving an open label injection of FX006.
b. X-ray of weight-bearing anterior-posterior view for index hip will be taken for central reading
c. Open-label injection of FX006 may occur at either Week 12, 16, 20, or 24 depending on when the patient is clinically indicted to receive a second injection
d. Rescue medication will be dispensed to the patient at each visit as needed. Drug accountability will be done at each visit
e. To be performed at Week 24, 28, 32, or 36, depending on timing of second injection
f. Aspiration must be attempted prior to all injections. If effusion is detected by fluoroscopy guidance, withdraw to near dryness prior to injection
g. If second injection occurs at Week 12, FU visits occur at Weeks 16, 20, and EOS occurs at Week 24. If second injection occurs at Week 16, FU visits occur at Week 20, 24, and EOS occurs at Week 28, and so on in sequence
h. Pregnancy test will be done in women of child bearing potential. *Urine Pregnancy Test* to be collected prior to injection of study medication and at EOS (when it occurs)
i. If patient receives the open-label injection at Week 12, assessments for this visit do not need to be duplicated as per the Week 12 double - blind period.
j. Via Central Laboratory
k. To be performed under fluoroscopy guidance
l. To be completed prior to questionnaires
m. To be completed after APR and PRR training but prior to any other assessments following the sequence in Table 7-6.
n. Visit should be conducted within +/- 3 days from scheduled date.
o. Not performed on Part I patients
p. Not required for Part I patients discontinued upon implementation of this amendment (Protocol V 3.0; Amendment 2.0)

7.9. Study Procedures

7.9.1. 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. Randomization

At Day 1, after confirmation of eligibility and completion of all required assessments per Table 7-2, blinded site personnel will randomize eligible patients within the randomization module in a 1:1 ratio.

7.9.3. 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 at Day 1 per the schedule noted in Table 7-2.

OA medical history includes ACR diagnosis details, OA diagnosis date (if available), number of days with index hip pain in the last month, previous IA steroid, PRP or hyaluronic injections, presence of OA in other joints, prior procedures or surgeries for index hip OA.

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

7.9.4. Physical Examination

The physical exam will assess the following body systems:

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

Physical exams are to be conducted at the days indicated in Table 7-2 and Table 7-3.

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.

7.9.5. Index Hip Assessment

The index hip assessment will be performed by the blinded assessor at the days indicated in the Table 7-2 and Table 7-3. The index hip will be assessed for tenderness, warmth, redness, swelling, and effusion, limitation on range of motion (directions: flexion, extension, abduction, adduction, internal rotation or external rotation; severity: mild, moderate or severe). If there is a clinically significant finding at the Screening or Day 1 Visit (pre-injection), add to the Medical History. At time points post-injection, if there are new clinically significant findings or findings that worsen for the patient's baseline condition, record as AEs.

7.9.6. Index Hip X-ray

A diagnostic quality X-ray of the index hip is required (weight-bearing anterior-posterior pelvic view with the lower limbs in 10 degree internal rotation with a size ratio of 1:1) at Screening, Week 12 and End of Study Visit (for patients who receive an open-label injection of FX006) (see Table 7-2 and Table 7-3).

The Screening X-ray will be read centrally for K-L grading and potential risk signs of rapidly progressive OA (e.g., atrophic osteoarthritis, femoral head necrosis and/or collapse, subchondral bone insufficiency fracture, etc.). In addition to the Screening X-ray, the Week 12 and End of Study X-rays will be read centrally. An image acquisition protocol will be distributed to sites with instructions for radio-anatomic positioning for reliable grading.

Kellgren-Lawrence grading is a global scoring method that considers osteophytes, JSN, subchondral bone sclerosis and/or bone attrition. Grading criteria for the hip are (Rheumatology 2005;44 Suppl 4:54):

Grade 0: Normal appearance.

Grade 1: Possible osteophytes, possible JSN medially.

Grade 2: Definite osteophytes, definite JSN, slight sclerosis.

Grade 3: Mild osteophytes, marked JSN, moderate sclerosis, cysts and deformity

Grade 4: Large osteophytes, severe JSN, cysts sclerosis and deformity

Subjects will be considered radiographically eligible for enrollment in the study if the (index) hip is Kellgren-Lawrence Grade 2 or 3.

7.9.7. Vital Signs

Vital signs are to be taken at the days indicated in Table 7-2 and Table 7-3.

The following measurements will be taken: sitting blood pressure, heart rate, respiration rate, and oral temperature.

7.9.8. Height, Weight and BMI Determination

Height and weight are to be taken at the days indicated in Table 7-2 and Table 7-3. Height will be measured in centimeters or inches. Weight will be measured in kilograms or pounds. BMI will be calculated using the following formulas (reference: www.cdc.gov):

Table 7-4: Height, Weight and BMI Determination

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 as follows at the days indicated Table 7-2 and Table 7-3. The specific laboratory panels to be run can be found in the table below. Follow the Central Laboratory Manual for detailed sample collection, handling, storage, and shipping instructions. Please see Table 7-5 below.

Table 7-5: Clinical Laboratory Panel

CLINICAL LABORATORY PANELS	
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
	Glucose
INFECTIOUS DISEASES	Total protein
Hepatitis B Surface Antigen	Albumin
Hepatitis C Antibody1	
HIV2	ESR: test provided by Central Laboratory but performed and read at the site
PREGNANCY TESTS (WOMEN OF CHILD BEARING POTENTIAL ONLY) • Serum: submitted to and performed by Central Laboratory • Urine: test provided by Central Laboratory but performed and read at the site	

1. Patients positive for HCV Antibody will have reflex testing for circulating HCV RNA.
2. HIV screening will use a current 4th generation test for both antibody and viral antigen.

7.9.10. Index Hip Aspiration

Aspiration must be attempted prior to injection of study medication at Day 1 and prior to second injection of study medication. If effusion is detected by fluoroscopy guidance, withdraw to near dryness prior to injection.

7.9.11. Second Injection Criteria

Second Injection Inclusion and Exclusion Criteria must be assessed prior to administration of second injection of study medication. Please reference Section 7.4.4 and Section 7.4.5 for Second Injection Inclusion/Exclusion criteria listing. Please also reference Table 7-3.

7.9.12. Rescue Medication Dispensing and Accountability

Rescue medication (500 mg tablets of acetaminophen or paracetamol) will be dispensed to patients at the Screening visit. At each subsequent visit, at any time during the visit, rescue medication accountability will be performed. Additional rescue medication will be returned/dispensed as needed. Refer to Section 7.6.3 for further information regarding rescue medication.

7.9.13. Accurate Pain Reporting and Placebo Response Reduction Training

Placebo Response Reduction (PRR) Training

This training ("Participating in a Research Study, What you need to know," Analgesic Solutions, Wayland, MA) consists of a set of patient and staff educational materials for training on appropriate expectations of personal benefit while participating in a clinical trial. The purpose is to provide patients truthful information that will neutralize the potentially excessive expectations that drive high placebo responses in clinical trials. Patients will receive training at each study visit indicated in Table 7-2 and Table 7-3. The training video takes approximately 5 minutes to complete, and should be completed prior to any patient questionnaires.

All staff that have contact with patients must also complete the staff assigned PRR portion of the training prior to injection/dosing of patient.

Accurate Pain Reporting (APR) Training

The Accurate Pain Reporting Program ("Reporting Your Pain," Analgesic Solutions, Wayland, MA) consists of a set of patient and staff educational materials and instructions on how to accurately and reliably report pain scores, and on the proper use of pain intensity scales, with the aim of increasing patients' pain reporting accuracy. Staff training is conducted prior to the first subject visit. Patients will receive training at each study visit indicated in Table 7-2 and Table 7-3. The training video takes approximately 5 minutes to complete, and should be completed prior to any patient questionnaires.

All staff that have contact with patients must also complete the staff assigned APR portion of the training prior to injection/dosing of patient.

7.9.14. Patient Questionnaires

Questionnaires will be completed by the patient at each visit as scheduled (see Table 7-2 and Table 7-3). APR and PRR training will be completed first and then the patient will complete the

questionnaires based on the sequence listed below in Table 7-6 and Table 7-7. All other assessments or procedures will occur after completion of the questionnaires.

Note: If Screening 1 and Screening 2 are combined into one visit (provided the patient does not have a washout from prohibited medications), please perform APR/PRR first, then the questionnaires in order they are shown below on Table 7-7, with the WOMAC being completed after APR/PRR, then all subsequent questionnaires completed as they are listed for Screening 1.

Table 7-6: Patient Questionnaires

Sequence at Visit	Screening 1	Screening 2	Day 1	Weeks 1, 4, 8	Week 12	Every 4 weeks during the OLE
1	PD-Q	WOMAC	WOMAC	WOMAC	WOMAC	WOMAC
2	PHQ-9			PGIC	PGIC	PGIC
3	GAD-7		SI	SI	SI	SI
4	PCS		HOOS-QOL	HOOS-QOL	HOOS-QOL	HOOS-QOL
5	ISI		EQ-5D-5L	EQ-5D-5L	EQ-5D-5L	EQ-5D-5L
6					TSQM-9	

Table 7-7: Patient Questionnaire Sequence if Screening 1 and Screening 2 Visits are Combined

Sequence at Visit	Screening 1 & Screening 2 (combined)
1	APR/PRR Training
2	WOMAC
3	PD-Q
4	PHQ-9
5	GAD-7
6	PCS
7	ISI

7.9.15. Review of Adverse Events and Concomitant Medications

After receiving assigned study medication and at all visits, the patient should be monitored for any AEs by the blinded assessor. Review of any Concomitant Medications should also be performed and documented in source documentation. Refer to Section 8.4.1 for further information in regard to reporting of AEs. Refer to Section 7.6 for further information in regard to allowed and restricted concomitant medication.

8. ADVERSE EVENTS

Subjects will be monitored for adverse events from first dose of study medication through the end of their participation in the study.

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

8.1. Definitions

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

An AE can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product
- Any clinically significant abnormality found on an ECG, laboratory test, or physical examination
- Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition, which is temporally associated with the use of the medicinal (investigational) product

Pregnancy is not an AE; however, if a female patient or the female partner of a male patient who has received at least one dose of study medication becomes pregnant during the conduct of the study, the Investigator must notify the Sponsor according to the procedures in Section 8.4.1.

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

- Results in death
- Is life-threatening
    - "Life-threatening" refers to an event in which the patient was at substantial risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization,
    - Note: Adverse events requiring hospitalizations that are less than 24 hours in duration do not meet this criterion. A planned hospitalization for an elective procedure or a pre-existing condition that has not worsened during participation in the study does not meet this criterion
- Results in permanent or significant disability/incapacity; a substantial disruption of the patient's ability to carry out normal life functions
- Is a congenital anomaly/birth defect

- Is an important medical event: event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above

Planned Hospitalization:

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

8.2. Monitoring of Adverse Events

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

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

Results of study efficacy assessments and patient reported outcome surveys should not be reported as adverse events unless they indicate a significant worsening from baseline.

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

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

8.2.1. Monitoring of Laboratory Assessments and Other Diagnostic Tests

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

8.2.2. Adverse Events That Occur During the Injection Procedure

If an adverse event occurs during the injection procedure, the Unblinded Injector will record the details of the AE in the patient's chart and provide a full report of the event to the Blinded Assessor in a blinded manner. Any difficulties with the study drug administration should not be reported to the Blinded Assessor unless it is a direct cause of an AE. For any difficulties with the study drug, the Unblinded Injector should refer to the Pharmacy Binder.

8.2.3. Reporting Arthralgia in the Index Hip

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

8.3. Assessment of Adverse Events

8.3.1. Assessment of Seriousness

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

8.3.2. Assessment of Severity

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

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

8.3.3. Assessment of Relationship to Study Medication

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, as **related** or **not related**, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors
- The temporal association between drug exposure and onset of the AE
- Whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product

The causal relationship between the study medication and the AE will be assessed using one of the following categories:

Not Related: An AE is not associated with study medication if:

- Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the study medication); ***or***
- Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant treatments)

Related: An AE is attributed to the study medication if:

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

8.4. Recording of Adverse Events

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

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

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

8.4.1. Reporting of Serious Adverse Events

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

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

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

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

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

8.4.2. Unblinding Treatment for a Patient during the Trial

Requirements for emergency unblinding by the Investigator are detailed in Section 7.5.9. To assess an occurrence of a serious adverse event for regulatory reporting purposes, Flexion Pharmacovigilance or Regulatory Operations may unblind the treatment of any subject.

8.5. Safety Monitoring Roles

The site personnel will carefully monitor each patient throughout the study for possible AEs. All AEs will be reviewed and assessed by the Blinded Assessor. All AEs will be documented on the eCRF and will be followed until either completely resolved or until a stable chronic outcome is determined by the Principal Investigator. SAEs will be reported in accordance with Section 8.4.1. The Medical Monitor must promptly review all information relevant to the safety of an investigational new product received from any source. The Medical Monitor 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 blinded AE 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.

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

8.6. Clinical Management of Index Hip-Related Events

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

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

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

8.7. Pregnancy

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical and Analytical Plans

A comprehensive statistical analysis plan (SAP) will be written and approved for Part I and Part II prior to database lock for each part of the study. If, after the study has been completed, changes are made to the SAP referenced below, these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report (CSR). The key aspects of the proposed analyses are summarized below. Parts I and II of the study will enroll separate patients, and as such all analyses will be performed independently of one another. Analyses for Parts I and II of the study will be performed in the same manner, as detailed below. The analyses of the Part I data will be performed in an unblinded manner and results may be used to inform the conduct of Part II; as the analyses of Part I will be completed prior to the enrollment of any patients in Part II, this will have no impact on maintaining the blind for Part II.

9.1.1. Planned Analyses

Part I Analysis

An unblinded analysis will be conducted when all Part I patients have completed the study. All data collected on Part I patients will be analyzed. All analyses of the Part I data are exploratory in nature.

Part II Interim Analysis

An unblinded interim analysis will be conducted when all Part II patients have completed the double-blind phase of the study.

Final Analysis

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

9.2. General Considerations and Methods

Data collected in this study will be presented using summary tables, figures, and subject 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 mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages. Confidence intervals may also be provided. 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, should one occur.

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.

9.2.1. Analysis Populations

The following analysis populations are planned for each part of this study as follows:

- Full Analysis Set (FAS) Population: All patients who received study drug. The FAS population will be used to examine efficacy endpoints for the double-blind phase of the study
- Safety Population: All subjects who received at least one dose of study drug. The Safety Population will be used to assess safety and tolerability
- Second Injection Population (Part II only): All patients who received a second injection. The Second Injection Population will be used to examine efficacy endpoints in the open-label extension phase of the study
- Per Protocol Population (Part II Only): All patients in the FAS population who completed the Week 12 visit with no major protocol deviations that may impact the evaluation of the primary efficacy endpoint based on blinded data prior to unblinding of the double-blind phase data.

9.2.2. Study Data

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

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

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

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

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

9.2.3. Study Endpoints for Assessment

The same endpoints for Part I and the double-blind phase of Part II of the study will be used. However, all endpoints will be exploratory in Part I of the study.

9.2.3.1. Key Primary Efficacy Endpoint

- Change from Baseline on the WOMAC A (pain) score at Week 12

9.2.3.2. Key Secondary Efficacy Endpoints

- Change from Baseline on the WOMAC C (function) score at Week 12
- PGIC score at Week 12

9.2.3.3. Additional Secondary Efficacy Endpoints:

- Area Under the Effect curve (AUE) of change from Baseline on the WOMAC A (pain) subscale over the time intervals (e.g., Weeks 1 to 4, Weeks 1 to 8, and Weeks 1 to 12)
- AUE of change from Baseline on the WOMAC C (function) score over the time intervals (e.g., Weeks 1 to 4, Weeks 1 to 8, and Weeks 1 to 12)
- PGIC at Weeks 1, 4, and 8
- Change from Baseline on the WOMAC A (pain) score at Weeks 1, 4, and 8
- Change from Baseline on the WOMAC C (function) score at Weeks 1, 4, and 8
- Change from Baseline on the WOMAC B (stiffness) score at Weeks 1, 4, 8, and 12
- Change from Baseline on the WOMAC total score at Weeks 1, 4, 8, and 12
- Percent of responders (defined as patients with high improvement in pain or function) according to OMERACT-OARSI criteria at Weeks 1, 4, 8, and 12
- Proportion of patients experiencing a ≥20%, ≥30%, or ≥50% decrease in WOMAC A (pain) at Weeks 1, 4, 8, and 12
- Rescue medication use at Weeks 1, 4, 8, 12 and total consumption
- Change from Baseline on the SI at Weeks 1, 4, 8, and 12
- Change from Baseline on the EQ-5D-5L at Weeks 1, 4, 8, and 12
- Change from Baseline on the HOOS-QOL at Weeks 1, 4, 8, and 12
- TSQM-9 at Week 12
- Change from Baseline on WOMAC A (pain), B (stiffness), C (function) and PGIC at Weeks 1, 4, 8, and 12 in patients with unilateral hip OA

The same endpoints as above will be examined post Week 12 during the OLE phase of Part II with the addition of the following:

- Time to second injection for patients who receive a second injection of FX006

9.2.4. Sub-Groups and Covariates

Other pre-planned sub-groups analyses per aspiration status, KL grade, gender and the baseline pain score, etc. will be detailed in the SAP. Sub-groups (e.g., second dose cohorts (Week 12, 16, 20, or 24)) may be defined and explored after all pre-planned analyses have been completed to further elucidate study results.

Covariates for efficacy analyses will include baseline WOMAC A score, baseline score for the endpoint and study site. Other covariates may be explored and will be fully defined in the SAP.

9.3. Determination of Sample Size

9.3.1. Sample Size Considerations

Approximately 70 patients will be randomized in Part I and approximately 440 patients will be randomized in Part II in this study (an estimated 35 and 220 per treatment group respectively.)

For Part I, a sample size of approximately 35 per arm will provide information regarding the treatment effect. For Part II of the study, the expected sample size was determined based on the primary endpoint as follows. A minimum sample size of N=212 per arm for the placebo and the FX006 group has 90% power to yield a statistically significant difference (alpha=0.05, 2-sided) if the true underlying difference at Week 12 is 0.65 and with an assumption of 2.0 for the SD. For the first key secondary endpoint, the sample size of N=220 per treatment group has 90% power to yield a statistically significant difference between FX006 and placebo if the true underlying difference is 0.68 at Week 12, assuming a SD of 2.125. An early discontinuation rate of 6% was assumed. The data from Part I may be used to inform if the above assumptions were appropriate and the planned sample size for Part II should remain at 440, or whether a smaller sample size would be feasible.

9.4. General Statistical Methods

Complete details of the statistical analysis will be specified in the SAP. A separate SAP will be prepared for Part I and Part II of the study prior to database lock for each part of the study. Parts I and II of the study will enroll separate patients, and as such all analyses will be performed independently of one another. Analyses for Parts I and II of the study will be performed in the same manner, as detailed below. The analyses of the Part I data will be performed in an unblinded manner and results may be used to inform the conduct of Part II; as the analyses of Part I will be completed prior to the enrollment of any patients in Part II, this will have no impact on maintaining the blind for Part II. All analyses of Part I data are exploratory in nature.

9.4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be listed by study site and subject, 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 subject, and will be summarized by treatment and dose. The number of doses administered as well as total exposure will be summarized. Time between first and second injections will also be summarized.

9.4.3. Efficacy Analyses

Primary Efficacy Analysis

The primary endpoint will be analyzed with a longitudinal mixed model for repeated measures (MMRM) with fixed effects for treatment group, study week, treatment-by-week interaction and Baseline score. Subject will be the random effect. Treatment differences from control will be estimated via least square means from the analysis model along with 95% confidence intervals, and associated 2-sided p-values. This model assumes missing at random and includes only observed data.

Secondary Efficacy Analyses

Key secondary endpoints will be assessed similarly to the primary endpoint. Multiplicity will be addressed by analyzing the key secondary endpoints sequentially in the order presented in the protocol, testing each endpoint at the nominal alpha=0.05, 2-sided level to ensure overall type I error control at the 2-sided 0.05 level.

Additional continuous secondary efficacy endpoints will also be assessed similarly to the primary endpoint, but are not part of the sequential testing approach. Categorical end points will be compared via chi-square or exact tests depending on incidence rates.

AUE will be calculated and comparisons of the AUE endpoints will be estimated from an Analysis of Covariance (ANCOVA) with model parameters for treatment and covariates of Baseline WOMAC A score and study site. Full details of the AUE analyses will be detailed in the SAP.

Efficacy Analyses For The Open-Label Extension Phase (Part II)

Exploratory efficacy endpoints for the open-label extension phase will be analyzed similarly to the primary and secondary endpoints, but separately for the time period prior to the second injection and the time period post the second injection. Time-to-event endpoints will be assessed via log-rank tests and results will be presented in Kaplan-Meier plots.

9.4.4. Safety Analyses

Analysis of Adverse Events

Safety analyses will be performed on the Safety Population. AEs will be coded using MedDRA. Incidences (number and percent) of TEAEs, those events that start after dosing or worsened in severity after 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 hip TEAEs following the first dose and second dose, as well as the cumulative incidence of TEAEs after all doses of FX006.

Other Safety Analyses

Laboratory data, vital sign information and X-ray data will be presented as descriptive summary statistics for value and change from Baseline at each individual time point. Categorical variables will be summarized by frequencies and percentages.

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 product complaint, complete the Complaint Notification Form located in the Pharmacy binder.

11.3. Rescue Medication Accountability

Each patient will be provided with a sufficient quantity of acetaminophen/paracetamol 500 mg tablets at each scheduled clinic visit starting at Screening.

Patients will bring back the used and unused bottles at the next visit to allow for medication accountability.

11.4. 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.

11.5. Retention of Records

In accordance with US federal regulations (21 CFR 312.62[c]), the Sponsor requires that records and documents pertaining to the conduct of this study and the distribution of study medications, including eCRFs, consent forms, laboratory test results, source data, and medical inventory

records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the regulatory authorities are notified. The Sponsor or their representative will notify the Principal Investigator of these events. In the event that local regulations are more stringent than that specified above, the local regulations will be adhered to. If local records retention regulations are more stringent than that specified above, the local regulations will prevail.

11.6. 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.

13. REFERENCES

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