CLINICAL STUDY PROTOCOL

A Randomized, Open-label, Parallel Group Study in Patients with Bilateral Knee Osteoarthritis Comparing the Systemic Exposure of Triamcinolone Acetonide Following Administration into Both Knees of either Extended-release FX006 or Immediate-release TAcs (Triamcinolone Acetonide Suspension)

PROTOCOL NUMBER: FX006-2017-012

PHASE: 2a

STUDY MEDICATION(S): FX006

INDICATION: Osteoarthritis of the Knee

MEDICAL MONITOR: Robert D. Arbeit, MD

SPONSOR: Flexion Therapeutics

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SUPERCEDES: Version 1.0

SIGNATURE PAGE

Clinical Study Protocol Version 2.0 (dated 10Nov2017)

Sponsor Safety Officer Approval

Signature: _____ **Date:** _____

Name (print): Neil Bodick, MD, PhD

Title: Chief Scientific Officer

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

Signature: _____ **Date:** _____

Name (print): _____

TABLE OF CONTENTS

LIST OF TABLES

1. ABBREVIATIONS AND DEFINITION OF TERMS

ACR	American College of Rheumatology
ADL	Activities of Daily Living
ADP	Average Daily Pain
AE	Adverse Event
AUC	Area Under the Concentration-time Curve
AUE	Area Under the Effect Curve
BE	Bioequivalence
BMI	Body Mass Index
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CI	Confidence Interval
CMC	Carboxymethylcellulose Sodium
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EULAR	European League Against Rheumatism
FBR	Foreign Body Response
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HbA1c	Hemoglobin A1c
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-pituitary-adrenal
IA	Intra-articular
IB	Investigator's Brochure
IRB/EC	Institutional Review Board/Ethics Committee
IM	Intramuscular
IV	Intravenous
JSN	Joint Space Narrowing
Kg	Kilogram
K-L	Kellgren-Lawrence
KOOS	Knee injury and Osteoarthritis Outcome Score

LLOQ	Lower Limit of Quantification
LSM	Least Square Mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MRT	Mean Residence Time
msec	Millisecond
N	Number
NaCl	Sodium Chloride
NRS	Numeric Rating Scale
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PGIC	Patients' Global Impression of Change
PLGA	Poly[lactic-co-glycolic acid]
PK	Pharmacokinetic
PRP	Platelet Rich Plasma
QOL	Quality of Life
QTc	QT interval corrected for heart rate
RBC	Red Blood Cells
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent Adverse Event
TA[1]	Triamcinolone Acetonide
TAcs[2]	Triamcinolone Acetonide Injectable Suspension, Immediate-Release (commercially available)
US	United States
USP	United States Pharmacopeia
w/w	weight 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, Open-label, Parallel Group Study in Patients with Bilateral Knee Osteoarthritis Comparing the Systemic Exposure of Triamcinolone Acetonide Following Administration into Both Knees of either Extended-release FX006 or Immediate-release TAcs (Triamcinolone Acetonide Suspension)

Study Centers: Approximately 4

Study Phase: 2a

Objectives:

The objectives of this study are to:

- compare the plasma pharmacokinetics (PK), including systemic exposure, of triamcinolone acetonide (TA)
- assess the safety and general tolerability

when FX006 is administered as two 5 mL IA injections (one to each knee) for a total dose of 64 mg or TAcs is administered as two 1 mL injections (one to each knee) for a total dose of 80 mg in patients with bilateral knee OA.

Study Design and Methodology:

This randomized, open label, parallel group study will be conducted in male and female patients ≥ 40 years of age with bilateral knee OA.

Approximately 24 patients will be randomized to one of two treatment groups (1:1) and treated with IA injections to both knees of either:

- extended-release FX006 64 mg total dose (approximately 12 patients) or
- immediate-release TAcs 80 mg total dose (approximately 12 patients)

Each patient will be evaluated for a total of 6 weeks following the two IA injections. Following screening, pharmacokinetics (PK) and safety will be evaluated at 6 out-patient visits scheduled on Study Days 1 [calendar day of injection], 2, 8, 15, 29, and 43. The study is expected to enroll in approximately 1 month.

Number of Patients:

Approximately 24 patients with bilateral knee OA (approximately 12 per treatment arm) will be treated with two IA injections (one to each knee) of either FX006 or TAcs.

Test Product, Dose and Mode of Administration:

FX006 – extended release formulation of TA in 75:25 poly(lactic-co-glycolic) acid (PLGA) microspheres: Nominal 32 mg TA, IA injection, administered as a 5 mL injection: Total dose of 64 mg administered following an IA injection in each knee.

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

Commercially available TAcs (Kenalog®-40) injectable suspension, 40 mg/mL, IA, administered as a 1 mL injection. Total dose of 80 mg administered following an IA injection in each knee.

Duration of Dosing:

Two single IA injections (one to each knee)

Inclusion Criteria:

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

1. Written consent to participate in the study
2. Male or female ≥ 40 years of age
3. Symptoms consistent with OA in both knees for ≥ 6 months prior to Screening (patient reported is acceptable)
4. Currently meets ACR Criteria (clinical and radiological) for OA in both knees (Altman et al, 1986) as follows:
   - Knee pain
   - at least 1 of the following:
     - Age > 50 years
     - Stiffness < 30 minutes
     - Crepitus
   - Osteophytes
5. Knee pain in both knees for >15 days over the last month (as reported by the patient)
6. Body mass index (BMI) ≤ 40 kg/m^2
7. Morning serum cortisol result within normal range at Screening (5-23 mcg/dL or 138-635 nmol/dL)
8. Ambulatory and in good general health
9. Willing and able to comply with the study procedures and visit schedules and able to follow verbal and written instructions
10. Willing to abstain from use of the following protocol-restricted medications during the study:
    - Intravenous (IV), Intramuscular (IM), oral, inhaled, intranasal or topical corticosteroids
    - IA corticosteroids in any joint
    - IA viscosupplementation (hyaluronic acid) in either knee
    - Any investigational drug or device
    - Immunomodulators, immunosuppressives, or chemotherapeutic agents
    - Live or live attenuated vaccines
11. Sexually active males and females of child-bearing potential (defined as not surgically sterile or post-menopausal [defined as 12 consecutive months with no menses without an alternative medical cause] for at least 1 year as documented in medical history) agree to use one of the following 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 monogamous intercourse with a partner who is surgically sterile (post-vasectomy, post-hysterectomy, or tubal ligation.) Females must agree to use such contraceptive measures for at least 30 days after the administration of the study drug. Males must agree to use contraceptives for at least 90 days after administration of the study drug.

Exclusion Criteria:

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

Disease-related criteria

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

Previous or concomitant treatment-related criteria

5. Presence of surgical hardware or other foreign body in either knee
6. Surgery or arthroscopy of either knee within 12 months of Screening
7. IA treatment of *any* joint with any of the following agents within six (6) months of Screening: any corticosteroid preparation (investigational or marketed, including FX006), any biologic agent (e.g., platelet rich plasma (PRP) injection, stem cells, prolotherapy, amniotic fluid injection; investigational or marketed)
8. IA treatment in either knee with hyaluronic acid (investigational or marketed) within 6 months of Screening
9. Parenteral or oral corticosteroids (investigational or marketed) within 3 months of Screening
10. Inhaled, intranasal, or topical corticosteroids (investigational or marketed) within 2 weeks of Screening

Patient-related criteria

11. Females who are pregnant or nursing or plan to become pregnant during the study; men who plan to conceive during the study
12. Known hypersensitivity to any form of triamcinolone
13. Skin breakdown at either knee where the injection would take place
14. 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) with positive test for HCV RNA
15. Currently using insulin and/or oral medication for the treatment of diabetes (Type I or Type II) or a hemoglobin A1c (HbA1c) of >7.5 %(>59 mmol/mol)
16. Any electrocardiogram (ECG) abnormality judged clinically significant by the Investigator
17. A medical history suggesting the patient will or is likely to require a course of systemic corticosteroids during the study period
18. History or evidence of active or latent systemic fungal or mycobacterial infection (including tuberculosis), or of ocular herpes simplex
19. History of sarcoidosis or amyloidosis
20. History of or active Cushing's syndrome
21. History of osteomyelitis of either leg at any time, or of other areas within 5 years
22. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents within 5 years of Screening
23. Active or history of malignancy within the last 5 years, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or effectively managed cervical carcinoma
24. Active substance abuse (drugs or alcohol) or history of substance abuse within the past 12 months
25. Has received a live or live attenuated vaccine within 3 months of Screening
26. Use of any other investigational drug, biologic or device within 3 months of Screening
27. Any bacterial or viral infection requiring IV antibiotics within 4 weeks of Screening or oral antibiotics within 2 weeks of Screening
28. Any other clinically significant acute or chronic medical conditions (e.g., bleeding disorder) that, in the judgment of the Investigator, would preclude the use of an IA corticosteroid or that could compromise patient safety, limit the patient's ability to complete the study, and/or compromise the objectives of the study

Procedures and Assessments:

Patients participating in this study will complete 7 scheduled visits for a total study duration of up to 8 weeks (including Screening period). The study will involve a Screening period (up to 14 days), a Baseline/Day 1 visit and 5 outpatient visits following Day 1. At each visit following Screening, subjects will provide plasma samples for pharmacokinetic analysis.

At specified times throughout the study, patients will undergo safety assessments such as physical examinations, vital signs, hematology and chemistry blood collection for analyses and adverse event and concomitant medication review.

Blood samples for drug concentration measurements will be obtained from all patients prior to administration of study medication on Day 1, and at hours 1, 2, 3, 4, 5, 6, 8, 10, and 12 (± 10 min) after the first knee injection, on Day 2 at 24 hours (± 2 hrs) after the first injection of study medication, and at each of the subsequent scheduled visits.

Blood samples for morning cortisol levels will be obtained between 7-9 am from all patients at Screening, prior to administration of the study medication on Day 1, and then at each of the subsequent scheduled visits.

See Schedule of Study Assessments for full details.

Blinding:

Not applicable, this is an open-label study

Study Drug Administration Procedure:

IA injections will be performed by the assigned injector. The injector may choose the position of the knees (e.g., extended or flexed), the approach for the injection (e.g., medial or lateral) and the numbing agent to be used based on standard of care. Sterile technique will be used.

Prior to injection, each knee should be thoroughly cleansed using a bactericidal solution. Each knee will be aspirated in all cases prior to administration of study medication. Following attempted aspiration, 5 mL of the reconstituted FX006 or 1 mL of TAcs will be injected into the synovial space. Refer to the Pharmacy Binder for detailed instructions on how to prepare FX006. The injection into the second knee should be given within 15 minutes of the injection in the first knee.

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

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

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

Concomitant Medications:

For the duration of the study, the following medications should not be prescribed by the investigator or taken by the patient from another source:

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

Criteria for Evaluation:

Extent and Duration of Exposure

- Drug concentration measurements in plasma (in ng/mL) and the following derived pharmacokinetic parameters
  - $C_{max:}$ Peak exposure, Maximum plasma concentration
  - $T_{max:}$ Time from dosing to peak exposure, time to maximum plasma concentration
  - $C_{last:}$ Last quantifiable plasma concentration (last value observed above assay BLOQ)
  - $T_{last:}$ Time of last quantifiable plasma concentration
  - $T_{1/2:}$ Terminal half-life
  - $AUC_{(0\text{-}last):}$ Exposure: Area Under the Plasma Curve from time 0 to the last quantifiable concentration (C_{last})
  - $AUC_{(0\text{-}24h)}$: Exposure: Area Under the Plasma Curve from time 0 to 24 hours post IA injection
  - $AUC_{(0\text{-}inf):}$ Exposure: Area Under the Plasma Curve from time 0 extrapolated to infinity.
  - MRT (Observed and Predicted): Mean residence time extrapolated to infinity
- Morning Serum Cortisol measurements

Safety

- AEs
- Physical examinations
- Bilateral knee examinations
- Vital signs
- Clinical laboratory evaluations

Sample Size Considerations:

In this study, it is expected that the systemic exposure in plasma of TA from extended-release FX006 should not exceed that of the immediate-release TAcs formulation for the key parameters of C_{max}, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}inf)}$.

In a previous pharmacokinetic study with knee OA patients (FX006-2015-009) the ratio of the mean exposure parameters for FX006 32 mg (N=60) and TAcs 40 mg (N=18) for C_{max} was 0.10 with the upper limit of its 90% CI being 0.15 and for $AUC_{(0\text{-}inf)}$ was 0.52 with the upper limit of its 90% CI being 0.86. The pooled coefficients of variation for the parameters was between 0.53 (C_{max}) and 0.68 ($AUC_{0\text{-}inf}$).

In this study, it is expected that the ratio of exposure means (FX006/TAcs) will be less than 1.0 when administered to treat bilateral knees. A sample size of 12 in each treatment arm (24 in total) is estimated. The sample size of 24 achieves approximately 90% power, with a two-sided alpha 0.05, to detect a ratio less than 1.0 of the exposure PK parameter means (FX006 / TAcs), with a pooled coefficient of variation estimate of 0.68 (PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass). The sample size of 12 per treatment arm assumes a 10% noncompliance sampling rate (a drop-out rate) for providing complete blood samples for PK analysis, and is sufficient to characterize the comparative pharmacokinetic of FX006 and TAcs in this study. The total sample size is estimated to be 24 patients (12 in each treatment arm) for the study.

Statistical Methods:

Complete details of the statistical and PK analyses will be specified in the statistical analysis plan (SAP). Two analysis populations are planned for the study.

- The Safety Population will include all patients who receive at least one dose of study drug.
- The PK Population will include patients who receive two IA injections (one to each knee), complete scheduled sampling, and have sufficient plasma concentration data to allow calculation of PK parameters to be included in the PK population. Eligibility for inclusion into the PK Population will be determined by the pharmacokineticist for the study following review of plasma data.

Pharmacokinetic (PK) parameters will be derived for each patient from plasma concentrations of TA using model-independent non-compartmental analysis: (NCA) [Phoenix 7, WinNonlin® 7]. Individual elapsed sampling times (actual time) will be used in the PK calculations if significant deviations from the nominal sampling times are noted, otherwise nominal times will be used for analysis. Complete details on the calculation of PK parameters, and handling of concentration values below the Lower Limit of Quantification (LLOQ) will be fully specified in the SAP.

Descriptive summaries of the TA plasma concentration levels (ng/mL) observed at each nominal time point will be provided for FX006 and TAcs treatments. Descriptive summaries of the PK parameter estimates from each treatment group will also be completed. Summary statistics for continuous variables will include n, mean, standard deviation, coefficient of variation (CV%), median, minimum, and maximum, geometric mean and standard error of the geometric mean.

By patient plots (linear-linear, log-linear) of the plasma TA concentration data will be completed for each treatment group.

The PK parameters for C_{max}, T_{max}, AUC, and MRT PK parameters will be informative of the overall systemic exposure of TA from extended-release FX006 and immediate-release TAcs. A linear model will be used to compare the PK parameters from extended-release FX006 and immediate-release TAcs. Full details of the linear model will be specified in the SAP.

Bioequivalence (BE) ratios between extended-release FX006 (Test) and immediate-release TAcs (Reference) for C_{max} and AUC parameters will be explored. Bioequivalence between Test and Reference will be evaluated using the average BE method for the mean ratio between test and reference products (μT / μR) as described in FDA guidance. Full details on the analysis of BE will be included in the SAP.

Safety analyses will be performed on the Safety Population. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Incidences (number and percent) of treatment-emergent adverse events (TEAEs), those events that started after dosing or worsened after dosing, will be presented by treatment group. Incidences of TEAEs will also be presented by maximum severity and relationship to study medication.

Clinical laboratory data and vital sign information will be summarized by treatment group as summary statistics for value and change from baseline at each individual time point. Summary statistics will include n, mean, median, standard deviation, minimum, and maximum.

Details for the additional safety endpoints will be provided in the SAP.

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/EC 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 before his or her participation in the study. A copy of the informed consent document must be provided to the patient. 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 (US) and OA is the most common joint disease, affecting 27 million Americans, with numbers expected to grow as a result of aging, obesity and sports injuries. Recent data suggest that OA accounts for over $185 billion of annual healthcare expenditures in the US, which does not include loss of productivity costs. We estimate that by 2030, 45 million people will have OA. OA commonly affect large weight-bearing joints like the knees and hips, but also occurs in the shoulders, hands, feet and spine. Patients with OA suffer from joint pain, tenderness, stiffness and limited movement. As the disease progresses, it becomes increasingly painful and debilitating, culminating, in many cases, in the need for total joint arthroplasty.

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

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

5.2. Background

5.2.1. Investigational Medicinal Product: FX006

FX006 is an extended-release formulation of triamcinolone acetonide (TA) for IA administration. It is approved under the trade name ZILRETTA™ for the management of pain of osteoarthritis of the knee, however, injection in both knees has not been studied and is an investigational use. FX006 is intended to deliver TA to the synovial and peri-synovial tissues for a period of approximately 3 months depending on the dose administered. (Bodick et al, 2013)

FX006 contains TA, United States Pharmacopeia (Ph. Eur/USP), formulated in 75:25 poly(lactic-co-glycolic acid) (PLGA) microspheres with a nominal drug load of 25% (w/w) and is provided as a sterile white to off-white powder for reconstitution. The drug product is reconstituted with diluent containing an isotonic, sterile aqueous solution of sodium chloride (NaCl; 0.9% w/w), carboxymethylcellulose sodium (CMC; 0.5% w/w) and polysorbate-80 (0.1% w/w) to form a suspension prior to IA injection.

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

5.2.2. Rationale for FX006 in OA of the Knee

Available clinical and nonclinical data indicate that FX006 is safe and well tolerated when administered as a single injection into one knee and provides pain relief that is meaningfully better and more persistent than that provided by immediate release triamcinolone acetonide (TAcs). Nonclinical data and the literature suggest that this potential could extend to limiting structural progression in patients with inflammatory joint disorders. The near term clinical development program for FX006 focus on analgesics effects in patient with OA (bilateral knee, hip, and shoulder) as well as other shoulder maladies.

5.2.3. Toxicology

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

- 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 TAcs and the FX006 groups and were reversible. The single and repeat dose dog toxicity studies recapitulated known effects of TA that had been previously published in normal animal joints following prolonged exposure. These include decreased Safranin O staining and changes in structure and cellularity of articular cartilage.
- 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 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.

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 PK in Patients with Osteoarthritis of the Knee

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

PK 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. TA was absorbed systemically, with a plateau in plasma TA concentrations occurring in the first 24 hours post-dose, and slow elimination from the systemic circulation observed in the weeks thereafter.

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

5.2.5. Pharmacodynamics in Patients with Osteoarthritis of the Knee

In a Phase 2 PK/PD study, evaluating three dose levels of FX006 (10mg, 40mg, 60mg) administered as a 3mL 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 TAcs 40 mg. Cortisol suppression subsequent to Day 1-2 associated with all doses of FX006 would not be expected to be of clinical consequence in adult patients without otherwise comprised HPA axis function.

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

5.2.6. Efficacy in Patients with Osteoarthritis of the Knee

Efficacy data from three studies provide substantial evidence supporting the effectiveness of FX006 32 mg in the management of OA pain. (Bodick et al, 2015, Conaghan et al, 2017)

Results of the primary endpoint from the Phase 3, multi-center, adequate, and well-controlled trial, showed that patients treated with FX006 32 mg 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 FX006 32 mg was demonstrated.

Robustness of the primary outcome in the Phase 3 study was further supported by the internal consistency demonstrated in favor of FX006 32 mg 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 FX006 32 mg 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 (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. FX006 32 mg 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 FX006 32 mg is of potential important clinical consequence and adds a meaningful element to the overall effectiveness profile of FX006 32 mg. Collectively, these results provide substantial evidence to support FX006 32 mg 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 suggests 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.

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

5.2.8. Conclusion

These data provide bases for continued clinical study of FX006.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objectives of this study are (a) to compare the systemic exposure to triamcinolone acetonide from extended-release FX006 and immediate release TAcs and (b) to assess the safety and general tolerability, when FX006 is administered as two 5 mL IA injections (one to each knee) for a total dose of 64 mg or TAcs is administered as two 1 mL injections (one to each knee) for a total dose of 80 mg in patients with bilateral knee OA.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This randomized, parallel group study will be conducted in male and female patients ≥ 40 years of age with bilateral knee OA.

Approximately 24 patients will be randomized to one of two treatment groups (1:1) and treated with two IA injections of either:

- extended-release FX006 64 mg total dose (approximately 12 patients) or
- immediate-release TAcs 80 mg total dose (approximately 12 patients)

Each patient will be evaluated for a total of 6 weeks following the two IA injections. Following screening, PK and safety will be evaluated at 6 out-patient visits scheduled on Study Days 1 [calendar day of injection], 2, 8, 15, 29, and 43. The study is expected to enroll in approximately 1 month.

7.2. Site Staffing Requirements

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

Pharmacist/coordinator

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

Injector/Aspirator

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

Assessor

- must be a medical doctor, a physician's assistant, or nurse practitioner
- must have relevant OA experience
- responsible for performing the physical examination and knee assessments

- Assessing causality of an adverse event (AE) or SAE
  - Must be either the PI or physician sub-investigator

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

7.3. Discussion of Study Design

7.3.1. Rationale for Study Population

Patients with pain associated with OA of the knee as defined by clinical and radiologic criteria that are otherwise in good health or that have chronic conditions (for example, hypertension) that are well controlled are included. In general this population tolerates IA injections of commercially available corticosteroids (Habib 2009). In prior clinical studies of FX006 in this population, single injections of up to 60 mg of FX006 were well tolerated. It is expected that plasma levels will increase secondary to simultaneous injections in the knee. This study is to establish the safety with these increased levels.

7.3.2. Rationale for Dose Selection

The 32 mg dose of FX006 was selected for this study based on the safety and efficacy seen for this dose in the knee. In a Phase 2b study (FX006-2014-006) comparing 16 mg and 32 mg doses, both dose levels of FX006 achieved maximal analgesic effect based on the ADP intensity score using an NRS of similar magnitude at Week 5 post-injection. However, a dose effect was evident in the maintenance of maximal effect, which persisted through Week 9 with 16 mg FX006 and through Week 13 with 32 mg FX006. The durability of the treatment effect seen with the 32 mg dose was reproduced in the Phase 3 Study FX006-2014-008.

Thus, based on the collective clinical evidence (a) there is a dose response effect and (b) the 32 mg dose FX006 appears to be the most effective of those doses studied in OA of the knee. Further, across several trials, a single IA administration of 32 mg FX006 in the knee has been shown to be well-tolerated and in PK studies a single 5 mL IA injection of 32 mg FX006 resulted in substantial and sustained joint residency of TCA in adults with OA of the knee. The approved dose of FX006 is 32 mg, therefore this dose was selected for further study in investigational uses.

7.3.3. Rationale for Study Design

The current trial is design is substantially similar to PK studies previously conducted in OA of the knee. The randomized, open label, parallel group design applied in this protocol has proved reliable for comparing the plasma PK profiles for these two different formulations.

7.3.4. Rationale for Study Parameters

Plasma drug concentration measurements directly support the objective of the study to characterize the systemic PK and local extent and duration of exposure of TA from FX006 and TAcs.

The clinical safety parameters to be assessed (adverse events, physical examinations, knee examinations, vital signs, and clinical laboratory evaluations) are standard safety and tolerability assessments and support the clinical monitoring necessary based on the toxicology profile for FX006.

7.3.5. Rationale for Control Type

The active control (TAcs) Kenalog®-40 Injection is commonly used in treatment of OA of the knee, and differences in systemic exposure are informative to clinicians and may be extrapolated to other corticosteroids.

7.4. Selection and Withdrawal of Study Patients

7.4.1. Number of Patients

Approximately 24 patients with bilateral knee OA (up to 12 per treatment arm) will be treated with two IA injections (one to each knee) of FX006 or TAcs.

7.4.2. Inclusion Criteria

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

1. Written consent to participate in the study
2. Male or female ≥ 40 years of age
3. Symptoms consistent with OA in both knees for ≥ 6 months prior to Screening (patient reported is acceptable)
4. Currently meets ACR Criteria (clinical and radiological) for OA in both knees (Altman et al, 1986) as follows:
    - Knee pain
    - at least 1 of the following:
        - Age > 50 years
        - Stiffness < 30 minutes
        - Crepitus
    - Osteophytes
5. Knee pain in both knees for >15 days over the last month (as reported by the patient)
6. Body mass index (BMI) ≤ 40 kg/m2
7. Morning serum cortisol result within normal range at Screening (5-23 mcg/dL or 138-635 nmol/dL)
8. Ambulatory and in good general health
9. Willing and able to comply with the study procedures and visit schedules and able to follow verbal and written instructions.

10. Willing to abstain from use of the following protocol-restricted medications during the study:
    - Intravenous (IV), Intramuscular (IM), oral, inhaled, intranasal or topical corticosteroids
    - IA corticosteroids in any joint
    - IA viscosupplementation (hyaluronic acid) in either knee
    - Any investigational drug or device
    - Immunomodulators, immunosuppressives, or chemotherapeutic agents
    - Live or live attenuated vaccines
11. Sexually active males and females of child-bearing potential (defined as not surgically sterile or post-menopausal [defined as 12 consecutive months with no menses without an alternative medical cause] for at least 1 year as documented in medical history) agree to use one of the following 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 monogamous intercourse with a partner who is surgically sterile (post-vasectomy, post-hysterectomy, or tubal ligation.) Females must agree to use such contraceptive measures for at least 30 days after the administration of the study drug. Males must agree to use contraceptives for at least 90 days after administration of the study drug.

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

Previous or concomitant treatment-related criteria

5. Presence of surgical hardware or other foreign body in either knee
6. Surgery or arthroscopy of either knee within 12 months of Screening
7. IA treatment of *any* joint with any of the following agents within six (6) months of Screening: any corticosteroid preparation (investigational or marketed, including FX006),

any biologic agent (e.g., platelet rich plasma (PRP) injection, stem cells, prolotherapy, amniotic fluid injection; investigational or marketed).

8. IA treatment in either knee with hyaluronic acid (investigational or marketed) within 6 months of Screening
9. Parenteral or oral corticosteroids (investigational or marketed) within 3 months of Screening
10. Inhaled, intranasal or topical corticosteroids (investigational or marketed) within 2 weeks of Screening

Patient-related criteria

11. Females who are pregnant or nursing or plan to become pregnant during the study; men who plan to conceive during the study
12. Known hypersensitivity to any form of triamcinolone
13. Skin breakdown at either knee where the injection would take place
14. 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) with positive test for HCV RNA.
15. Currently using insulin and/or oral medication for the treatment of diabetes (Type I or Type II) or a hemoglobin A1c (HbA1c) of >7.5% (>59 mmol/mol)
16. Any electrocardiogram (ECG) abnormality judged clinically significant by the Investigator.
17. A medical history suggesting the patient will or is likely to require a course of systemic corticosteroids during the study period.
18. History or evidence of active or latent systemic fungal or mycobacterial infection (including tuberculosis), or of ocular herpes simplex
19. History of sarcoidosis or amyloidosis
20. History of or active Cushing's syndrome
21. History of osteomyelitis of either leg at any time, or of other areas within 5 years.
22. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents within 5 years of Screening
23. Active or history of malignancy within the last 5 years, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or effectively managed cervical carcinoma
24. Active substance abuse (drugs or alcohol) or history of substance abuse within the past 12 months
25. Has received a live or live attenuated vaccine within 3 months of Screening
26. Use of any other investigational drug, biologic or device within 3 months of Screening

27. Any bacterial or viral infection requiring IV antibiotics within 4 weeks of Screening or oral antibiotics within 2 weeks of Screening
28. Any other clinically significant acute or chronic medical conditions (e.g., bleeding disorder) that, in the judgment of the Investigator, would preclude the use of an IA corticosteroid or that could compromise patient safety, limit the patient's ability to complete the study, and/or compromise the objectives of the study.

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

7.5. Treatment Administered

7.5.1. Study Medication Treatment Arms

Investigation Medicinal Product Arm:

- FX006: an extended-release formulation of TA in 75:25 PLGA microspheres. Nominal 32 mg TA, administered as a single 5 mL IA injection to each knee for a total dose of 64 mg.

Reference Compound:

- Commercially available TAcs (Kenalog®-40) injectable suspension, 40 mg/mL, IA, administered as a 1 mL injection to each knee for a total dose of 80 mg.

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

TAcs (Kenalog®-40) is a synthetic glucocorticoid corticosteroid with anti-inflammatory action. Each mL of the sterile aqueous suspension provides 40 mg triamcinolone acetonide, with sodium chloride for isotonicity, carboxymethylcellulose sodium, and polysorbate 80. A preservative, benzyl alcohol may also be present. Sodium hydroxide or hydrochloric acid may be present to adjust pH to 5.0 to 7.5. At the time of manufacture, the air in the container is replaced by nitrogen.

7.5.4. Receipt, 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 on the drug accountability form in the Pharmacy Binder. Any temperature excursions should be documented and will require Sponsor assessment and authorization for continued use.

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

TAcs will be stored in a secure area at room temperature.

7.5.5. Packaging and Labeling of Study Medication

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

TAcs will be supplied as commercially available Kenalog®-40 Injection.

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. Return of study medications will be properly documented.

7.5.7. Method of Assigning Patients to Treatment Groups

Patients will be assigned to treatment groups by randomization using a central system accessed directly by the sites after the patient is assessed as eligible. Randomization will be continuous across the study (i.e., no stratification), using a block size of 4 (four). See Statistics Section 9 for further details.

7.5.8. Blinding

This is an open-label study.

7.5.9. Study Drug Administration Procedure

IA injections of study drug will be performed by the assigned injector. The injector may choose the position of the knee (e.g., extended or flexed), the approach for the injection (e.g., medial or lateral) and the numbing agent to be used based on standard of care. Sterile technique will be used.

Prior to injection, each knee should be thoroughly cleansed using a bactericidal solution. Each knee will be aspirated in all cases prior to administration of study medication. Following aspiration, 5 mL of the reconstituted FX006 or 1 mL of TAcs will be injected into the synovial space. Refer to the Pharmacy Binder for detailed instructions on how to prepare FX006. The injection into the second knee should be given within 15 minutes of the injection in the first knee.

The same needle used for fluid aspiration may also be used for IA injection of study medication, thereby allowing for a single injection with syringe replacement.

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

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

7.5.10. Treatment Compliance

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

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

7.5.11. Removal of Patients from Therapy or Assessments

Each treated patient in this study receives study medication as a single IA injection. Therefore, discontinuation from treatment is not applicable. Each patient may only discontinue from the study for further assessments and study visits.

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

1. Attempt to arrange for a formal Early Termination Visit and complete the study assessments specified for the End-of-Study Visit (Day 43).
2. Determine whether the patient is willing to be contacted to follow ongoing or new AEs through Day 43 (if reason for discontinuation is not "subject withdrew consent")
3. Document patient consent in the source document for continued follow-up.
4. Contact the patient as necessary (via phone or in-person) to follow ongoing or new AEs through Day 43 (concomitant medications associated with any AE will also be captured).

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

7.6. Prior and Concomitant Therapy

Prior therapy is defined as all medications taken by or administered to the patient prior to obtaining informed consent. Concomitant therapy is defined as all medications from obtaining consent to End of Study visit.

7.6.1. Allowable Medications

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

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

7.6.2. Restricted Medications

Per the exclusion criteria, a patient is not eligible for this study if he/she has received any of the indicated treatments within the specified windows detailed in the Exclusion criteria (Section 7.4.3)

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

- IV, IM, oral, inhaled, intranasal, or topical corticosteroids
- IA corticosteroids in any joint
- Any IA intervention either knee including aspiration or the injection of any approved or investigational agent, including viscosupplementation (hyaluronic acid)
- Any investigational drug, device or biologic
- Immunomodulators, immunosuppressives, or chemotherapeutic agents
- Live or live attenuated vaccines

7.7. Study Variables

7.7.1. Safety Variables

Safety and tolerability will be evaluated on the basis of AEs spontaneously reported by the patient or discovered by the Investigator and findings from the following assessments: physical examinations, knee assessments, vital signs, and clinical laboratory evaluations.

7.7.2. Pharmacokinetic Variables

Blood samples (4 mL per sample) for drug concentration measurements will be obtained from all patients at the following times:

- On Day 1, within 1 hour prior to administration of study medication
- On Day 1, at Hours 1, 2, 3, 4, 5, 6, 8, 10, and 12 after injection of the first knee
- On Day 2, at 24 (± 2) hours after the first injection of study drug
- On Days 8, 15, 29, and 43 (time as convenient)

These represent a total of 15 samples from each patient, each sample representing 4 mL of blood, for a maximum estimated total volume of 60 mL of blood collected from each patient for drug concentration measurement.

Procedures for sample collection, handling, storage and shipment will be described in the Laboratory Manual. Plasma TA concentrations will be measured using an established validated LC-MS/MS method.

7.7.3. Pharmacodynamic Variables

Blood samples for morning serum cortisol levels will be collected between 7 am and 9 am at Screening and on Study Days 1, 2, 8, 15, 29, 43. Levels observed in the two treatment arms will be compared using descriptive statistics. There is no statistical hypothesis or objective for this parameter.

Synovial fluid samples will be preserved for a maximum of 5 years for potential future analyses of biomarkers that may contribute to the pathogenesis of OA and/or be associated with responsiveness to FX006 treatment. No genomic analyses (gene sequencing studies) will be performed using these samples. Patients will be able to withdraw consent throughout the duration of storage. Once analysis has begun, consent will no longer be able to be withdrawn.

7.8. Schedule of Study Assessments

A summary of the schedule of study assessments is provided in **Table 1**. All visits will be conducted on an out-patient basis.

Refer to Section 7.9 for details of each assessment.

Table 1: Schedule of Study Assessments

Procedures	Screening[1]	Day 1	Day 2	Day 8[2]	Day 15[2]	Day 29[2]	Day 43[2] (End of Study)
Informed consent	X[3]						
Inclusion/Exclusion Review	X	X[4]					
Medical History/Update	X	X[4]					
OA Medical History	X						
Prior Treatment & Meds[5]	X	X[4]					
Physical Examination	X	X[4]					X
Bilateral Knee X-rays	X[6]						
Bilateral Knee Assessments[7]	X	X[4]					X
12-Lead ECG	X						
Vital Signs	X	X[4]	X	X	X	X	X
Height	X						
Weight and BMI	X						X
Hematology & Chemistry[8]	X	X[4]					X
HIV, Hepatitis B/C, HbA1c[8]	X						
Pregnancy Test[9]	X	X[4]					X
Blood for Drug Conc.		X[10]	X[11]	X	X	X	X
Blood for Morning Serum Cortisol[12]	X	X[4]	X	X	X	X	X
Knee Aspiration and Collection of Synovial Fluid		X[4]					
Treatment Administration[13]		X					
Adverse Event Monitoring[14]		---------- X----------					
Concomitant Medications[14]		---------- X----------					

[1] Screening may occur up to 14 days prior to Day 1 (calendar day of dosing).
[2] Visit should be conducted +/- 2 days from scheduled date
[3] Consent must be obtained prior to performing any study-specific procedures.
[4] Complete assessment prior to dosing.
[5] Record any medications received within 30 days prior to Screening.
[6] Obtain new x-rays if >6 months since prior x-ray.
[7] Both knees will be assessed for tenderness, heat/redness, swelling, effusion, and Baker's cyst. Clinically significant findings (new or worsening from baseline) should be recorded as AEs.
[8] Via Central Laboratory
[9] Conduct for female of childbearing potential only. Serum pregnancy test to be performed via central laboratory at Screening and End-of-Study visits (scheduled for Day 43); urine pregnancy test to be performed locally on Day 1 and results available prior to dosing.
[10] On Day 1, blood for plasma drug concentration measurements will be collected at Time 0 (prior to administration) and at Hours 1, 2, 3, 4, 5, 6, 8, 10, and 12 post-injection of the first knee (±10 minutes).
[11] On Day 2, blood for plasma drug concentration measurements will be collected at 24 hours post-injection of the first knee (± 2 hours), and on subsequent visits as convenient.
[12] Blood for morning cortisol measurements will be collected between 7 and 9 am.
[13] The injection of the second knee should take place within 15 minutes of the first knee injection.
[14] AEs and Concomitant Medications will be captured from Day 1 (post-injection) to End of Study Visit.

7.9. Study Procedures

7.9.1. Informed Consent

Prior to initiation of any study related procedures, patients will be informed about the nature and purpose of the study, participation and termination conditions, and risks and benefits. Patients will be given the opportunity to ask questions of site personnel and to discuss with family or friends if they wish. After a patient has had ample opportunity to consider the information provide, they will be asked to sign the study's informed consent form in order to participate in the study.

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

Eligibility criteria (inclusion and exclusion criteria), medical history (including OA history), and prior treatment and medications are reviewed during screening and again pre-dosing on Day 1.

OA medical history includes ACR diagnosis details, OA diagnosis date (if available), number of days with pain in both knees in the last month, and previous IA steroid or hyaluronic injections.

7.9.3. Physical Examination

The physical exam will assess the following body systems:

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

Any clinically significant findings, outside of the typical disease state, 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 pre-dosing on Day 1 to any time point post-dosing to final study visit.

7.9.4. Knee X-rays

An X-ray is required for each knee within 6 months prior to Screening or during the Screening period. It is recommended that the anterior-posterior view, weight bearing and extended be used. If possible, the X-ray will be read locally for K-L grading at Screening.

7.9.5. Knee Assessment

The knee assessment will be performed on both knees by the designated assessor at the days indicated in the Schedule of Study Assessments. The knee will be assessed for tenderness,

heat/redness, swelling, effusion, and Baker's cyst. If there is a clinically significant finding outside of the patient's typical disease state at the Screening or Baseline Visit, add to the Medical History. At time points post-injection, if there are new clinically significant findings outside of the patient's typical disease state or findings that worsen from the patient's baseline condition, record as AEs.

7.9.6. 12-lead ECG

At Screening, a 12-lead ECG will be obtained in the supine position. Measures of heart rate, PR interval, RR interval, QT interval, QTc (corrected for Bazett's or Fridericia's) interval and QRS duration will be obtained. If QTc > 450 msec for male patients or > 470 msec for female patients on the first 10-second 12-lead ECG recording, two additional 10-second 12-lead ECG recordings must be collected 1 to 2 minutes apart. ECGs will be locally read and a copy of each recording will be kept with the patient's source documentation.

7.9.7. Vital Signs

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

7.9.8. Height, Weight, and BMI Determination

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

Table 2: BMI Calculations

Measurement Units	Formula and Calculation
Kilograms and meters (or centimeters)	**Formula: weight (kg) / [height (m)]^2** With the metric system, the formula for BMI is weight in kilograms divided by height in meters squared. If, as common, height is 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: $68 \div (1.65)^2 = 24.98$
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: $[150 \div (65)^2] \times 703 = 24.96$

7.9.9. Pharmacokinetic Evaluations

Blood samples will be taken at the time points indicated in the Schedule of Study Assessments. Follow the Central Laboratory Manual for detailed sample collection, handling, storage, and shipping instructions.

7.9.10. Central Clinical Laboratory Evaluations

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

Table 3: Clinical Laboratory Panel

Hematology	**Clinical Chemistry**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Leukocytes (WBC)	Calcium
Absolute counts of:	Total bilirubin
• Neutrophils	Alkaline phosphatase
• Lymphocytes	Alanine aminotransferase
• Monocytes	Aspartate aminotransferase
• Eosinophils	Blood urea nitrogen
• Basophils	Creatinine
• Platelets	Uric acid
	Glucose
Infectious diseases	Total protein
Hepatitis B Surface Antigen	Albumin
Hepatitis C Antibody[1]	Total cholesterol
HIV[2]	Triglycerides
Other	
HbA1c	
Morning Serum Cortisol	
Pregnancy tests (females 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 fourth generation test for both antibody and viral antigen.

7.9.11. Synovial Fluid Aspiration

Synovial fluid samples for potential future biomarker evaluation will be obtained from all patients via aspiration on Day 1 prior to study medication administration. The injector/aspirator will attempt to aspirate synovial fluid from the knee using sterile technique. The volume of the synovial fluid obtained will be recorded in the eCRF. If no synovial fluid is obtained then 0 mLs should be recorded. Procedures for sample collection, handling, storage and shipment will be described in the Laboratory Manual. The synovial fluid samples will be preserved for potential future analyses of biomarkers that may contribute to the pathogenesis of OA and/or be associated with responsiveness to FX006 treatment.

7.9.12. Treatment Administration

On Day 1, after completing all the required assessments, the following will occur:

- Study medication will be prepared by the pharmacist/coordinator. (refer to the Pharmacy Binder for FX006 dose preparation instructions.)
- Synovial fluid will be aspirated from each knee just prior to administration of study medication (refer to Section 7.9.10 for more details of the synovial fluid aspiration).
- The injector/aspirator will perform the IA injection of the study medication (refer to Section 7.5.9 for instructions).

7.9.13. Review of Adverse Events and Concomitant Medications

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

8. CLINICAL SAFETY ASSESSMENTS

Safety evaluations will be based on the assessment of AEs occurring after the administration of study medication on Day 1 through the Final Visit (scheduled for Day 43). Results of clinical safety assessments are to be recorded in the patient's medical records and transcribed to the appropriate eCRF, including the AE eCRF for clinically significant findings.

8.1. Adverse Events

8.1.1. Definitions

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

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

- Results in death,
- Is life-threatening,
    - This serious criterion refers to an event in which the patient was at substantial risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization,
    - This serious criterion applies if the reported AE requires at least a 24-hour inpatient hospitalization or, if in the opinion of the Principal Investigator, prolongs an existing hospitalization. A hospitalization for an elective procedure or a routinely scheduled treatment is not an SAE by this criterion because a "procedure" or a "treatment" is not an untoward medical occurrence.
- Results in permanent or significant disability/incapacity, or
    - This serious criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the patient's ability to carry out normal life functions.

- Is a congenital anomaly/birth defect.
    - This serious criterion applies if a patient exposed to a medicinal (investigational) product gives birth to a child with congenital anomaly or birth defect.
- Is, in the judgement of the PI, an important medical event. Medical and scientific judgment should be exercised in deciding that a medical event, although not immediately life-threatening, resulting in hospitalization, or in death is, nevertheless, clinically important and serious based on because the patient was in jeopardy of or require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.1.2. Evaluating and Recording of Adverse Events

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

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

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

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

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

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

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

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

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

improvement on stopping or reducing the dosage of the study medication, and reappearance of the reaction on repeated exposure.

If discernible at the time of completing an AE eCRF, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the appropriate AE eCRF. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the appropriate AE eCRF.

8.1.3. Reporting of Serious Adverse Events

When an SAE occurs, the Investigator or designee, must log into the electronic data capture (EDC) system and complete the SAE report form within 24 hours of first becoming aware of the SAE. The SAE will automatically be reported to the Medical Monitor, or designee, electronically.

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

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

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

8.1.4. Safety Monitoring Roles

The site personnel will carefully monitor each patient throughout the study for possible AEs. All AEs will be documented on the eCRF designed specifically for this purpose, and will be followed until either completely resolved or until a stable chronic outcome is determined by the Principal Investigator. SAEs will be reported in accordance with Section 8.1.3.

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

8.1.5. Clinical Management of Knee-related Events

In the event that the patient has an immediate reaction following administration of study medication or returns to the clinic with an acute exacerbation (e.g., tenderness, increased pain,

swelling, effusion, decreased mobility of the knee), the patient should be treated according to local clinical guidelines and physician experience.

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

Any event that is a change from the patient's baseline status (new or worsening case) should be reported as an AE and those meeting the definition of serious must be reported in accordance with Section 8.1.3.

8.1.6. Pregnancy

All pregnancies occurring during the study will be reported in the same timeframe as SAEs. All reports of pregnancy, including male patients who conceive, must be followed for information regarding the course of the pregnancy and delivery, as well as the condition of the newborn. Follow-up information concerning the outcome of the pregnancy should be provided to the Sponsor in a timely manner. Additional follow-up is not needed when a newborn baby is healthy.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical and Analytical Plans

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

9.1.1. Final Analyses

All final analyses specified in the SAP will be completed following database lock and reported in the trial CSR. Post-hoc, exploratory analyses, may also be performed to further understand and elucidate study results; there analyses will be clearly identified as such in the CSR.

9.2. General Considerations and Methods

Data collected in this study will be presented using summary tables, figures, and patent 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, including 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.

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

9.2.1. Analysis Populations

Complete details of the statistical and PK analyses will be specified in the statistical analysis plan (SAP). Two analysis populations are planned for this study as follows:

- The Safety Population will include all subjects who received at least one dose of study drug. The Safety Population will be used to assess safety and tolerability.
- The PK Population will include subjects who receive two IA injections (one to each knee), complete scheduled sampling, and have sufficient plasma concentration data to allow calculation of PK parameters to be included in the PK population. Eligibility for inclusion into the PK Population will be determined by the Pharmacokineticist for the study following review of plasma data.

9.2.2. Study Data

Study data identified in this protocol are collected, and source verified, on electronic Case Record 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.

9.2.3. Study Variables for Assessment

Please refer to Section 7.7 for study variables.

9.2.4. Sub-Groups and Covariates

No pre-planned sub-groups are identified for this study. Sub-groups may be defined and explored after all pre-planned analyses have been completed to further elucidate study results.

9.3. Determination of Sample Size

9.3.1. Sample Size Considerations

In this study, it is expected that the systemic exposure in plasma of TA from extended-release FX006 should not exceed that of the immediate-release TAcs formulation for the key parameters of C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$.

In a previous pharmacokinetic study with knee OA patients (FX006-2015-009) the ratio of the mean exposure parameters for FX006 32 mg (N=60) and TAcs 40 mg (N=18) for C_{max} was 0.10 with the upper limit of its 90% CI being 0.15 and for $AUC_{(0-inf)}$ was 0.52 with the upper limit of its 90% CI being 0.86. The pooled coefficients of variation for the parameters was between 0.53 (C_{max}) and 0.68 (AUC_{0-inf}).

9.3.2. Sample Size Estimate:

In this study, it is expected that the ratio of exposure means (FX006/TAcs) will be less than 1.0 when administered to treat bilateral knee OA. A sample size of 12 in each treatment arm (24 in total) is estimated. The sample size of 24 achieves approximately 90% power, with a two-sided alpha 0.05, to detect a ratio less than 1.0 of the exposure PK parameter means (FX006 / TAcs), with a pooled coefficient of variation estimate of 0.68 (PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass). The sample size of 12 per treatment arm assumes a 10% noncompliance sampling rate (a drop-out rate) for providing complete blood samples for PK analysis, and is sufficient to characterize the comparative pharmacokinetic of FX006 and TAcs in this study. The total sample size is estimated to be 24 patients (12 in each treatment arm) for the study.

9.4. General Statistical Methods

9.4.1. Demographics and Baseline Characteristics

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

9.4.2. Exposure

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

9.4.3. Efficacy Analyses

Not applicable.

9.4.4. Safety Analyses

9.4.4.1. Analysis of Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Incidences (number and percent) of treatment-emergent adverse events (TEAEs), those events that started after dosing or worsened after dosing, will be presented by treatment group. Incidences of TEAEs will also be presented by maximum severity and relationship to study medication. Similar presentations will be provided for serious AEs, AEs leading to withdrawal from the study, or AEs leading to death. Analysis of AE data will include examination of the incidence rates of TEAEs and index knee related TEAEs.

9.4.4.2. Other Safety Analyses

Clinical laboratory data and vital sign information will be summarized by treatment group as summary statistics for value and change from pre-dose at each individual time point. Summary statistics will include n, mean, median, standard deviation, minimum, and maximum.

9.4.5. Pharmacokinetic Analysis

Pharmacokinetic (PK) parameters will be derived for each patient from plasma concentrations of TA using model-independent non-compartmental analysis: (NCA) [Phoenix 7, WinNonlin® 7]. Individual elapsed sampling times (actual time) will be used in the PK calculations if significant deviations from the nominal sampling times are noted, otherwise nominal times will be used for analysis. Complete details on the calculation of PK parameters, and handling of concentration values below the LLOQ will be fully specified in the SAP.

Descriptive summaries of the TA plasma concentration levels (ng/mL) observed at each nominal time point will be provided for FX006 and TAcs treatments. Descriptive summaries of the PK parameter estimates from each treatment group will also be completed. Summary statistics for continuous variables will include n, mean, standard deviation, coefficient of variation (CV%), median, minimum, and maximum, geometric mean and standard error of the geometric mean.

By patient plots (linear-linear, log-linear) of the plasma TA concentration data will be completed for each treatment group.

The PK parameters for C_{max}, T_{max}, AUC, and MRT PK parameters will be informative of the overall systemic exposure of TA from extended-release FX006 and immediate-release TAcs. A linear model will be used to compare the PK parameters from extended-release FX006 and immediate-release TAcs. Full details of the linear model will be specified in the SAP.

Bioequivalence (BE) ratios between extended-release FX006 (Test) and immediate-release TAcs (Reference) for C_{max} and AUC parameters will be explored. Bioequivalence between Test and Reference will be evaluated using the average BE method for the mean ratio between test and reference products ($\mu T / \mu R$) as described in FDA guidance. Full details on the analysis of BE will be included in the SAP.

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. 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 per instructions in the Pharmacy Binder.

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

In the event of a product complaint, complete the Product Complaint Form located in the Pharmacy Binder and send to the assigned monitor or clinical manager who will coordinate with the Sponsor for further guidance.

11.3. Confidentiality of Data

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

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

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

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

11.4. Retention of Records

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

representative will notify the Principal Investigator of these events. In the event that local regulations are more stringent than that specified above, the local regulations will be adhered to.

11.5. Protocol Adherence

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

12. PUBLICATION POLICY

12.1. Sponsor's Publication Policy

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

12.2. Site Publication

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

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