STATISTICAL ANALYSIS PLAN

Protocol FX006-2017-013

A Randomized, Open-label Study Comparing the Systemic Exposure to Triamcinolone Acetonide Following a Single Intra-articular Dose of Extended-release FX006 or Immediate-release TAcs (Triamcinolone Acetonide Suspension) in Patients with Osteoarthritis of the Shoulder (Glenohumeral Joint) or Hip

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SIGNATURE PAGE

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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatories:

Amy Cinar, PhD
Director, Biostatistics

Signature: _____

Date: 17 OCT 2018

Scott Kelley, MD
Chief Medical Officer

Signature: _____

Date: 17 OCT 2018

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ACR	American College of Rheumatology
AUC	Area Under the Plasma Concentration Curve
$AUC_{(0\text{-last})}$	Area Under the Plasma Curve from time 0 to the last quantifiable concentration (t).
$AUC_{(0\text{-inf})}$	Area Under the Plasma Concentration Curve from 0 extrapolated to infinity
$AUC_{(0\text{-t})}$	Area Under the Plasma Curve from time 0 to tau post-IA injection, where tau is defined for partial AUC parameters from 0 to 24, and 0-96 hours
BE	Bioequivalence
BLOQ	Below Limit of Quantification
BMI	Body Mass Index
CI	Confidence Interval
C_{last}	Last quantifiable plasma concentration
C_{max}	Maximum Plasma Concentration
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
EMA	European Medicines Agency
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GM	Geometric Mean
HbA1c	Hemoglobin A1C
HIV	Human Immunodeficiency Virus
IA	Intra-articular
ICH	International Conference on Harmonization
kg	Kilogram
LC/MS-MS	Liquid Chromatographic Method with Tandem Mass Spectrometry Detection
LSMD	Least Square Mean Difference
m	Meter
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
mg	Milligram
MRT	Mean Residence Time
NCA	Non-Compartmental pharmacokinetic analysis
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PDF	Portable Document Format
pg/mL	Picograms per Milliliter
PK	Pharmacokinetic
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
$t_{1/2}$	Terminal Half-Life
TA[1]	Triamcinolone Acetonide
TAcs[2]	Triamcinolone Acetonide Injectable Suspension, Immediate-Release (commercially available) (Reference Compound, Kenalog®-40)
t_{last}	Time of last quantifiable plasma concentration
t_{max}	Time from Dosing to Peak Exposure
TEAE	Treatment Emergent AE
US	United States
WHO	World Health Organization
λz	Terminal Elimination Rate Constant (aka: Lambda_z)

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

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

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 affects large weight-bearing joints like the knees and hips, but also occurs in the shoulders, hands, feet and spine. Patients with OA suffer from joint pain, tenderness, stiffness and limited movement. As the disease progresses, it becomes increasingly painful and debilitating, culminating, in many cases, in the need for total joint arthroplasty.

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

FX006 is an extended-release formulation of TA for IA administration. It is approved under the trade name ZILRETTA™ for the management of pain of osteoarthritis of the knee; however, shoulder and hip OA have not been studied and are investigational uses. 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)

1.2. Objectives of Statistical Analysis

Following a single IA injection of 32 milligram (mg) FX006 or 40 mg TAcs in patients with OA of either the glenohumeral (also referred to herein as shoulder) or hip joint, the primary objectives of this study are to:

- Compare the plasma pharmacokinetics (PK), including systemic exposure, of triamcinolone acetonide (TA) between extended-release (FX006) and immediate release (TAcs) formulations, and
- Assess the safety and general tolerability.

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial, as well as used for regulatory filings and manuscripts and presentations.

This SAP also will outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

2. STUDY DESIGN

2.1. Synopsis of Study Design

This is a randomized, open-label, single dose study that will be conducted in male and female patients ≥40 years of age with OA of either the shoulder or the hip.

Approximately 24 patients with OA of the shoulder and approximately 24 patients with OA of the hip will be randomized to one of two treatment groups (1:1) and treated with a single IA injection of either:

- 32 mg FX006 (approximately 12 patients per joint) or
- 40 mg TAcs (approximately 12 patients per joint)

Each patient will be screened to confirm the diagnosis of OA of either the shoulder or hip and eligibility based on the other inclusion/exclusion requirements and will be randomized to treatment on Day 1. Each patient will be evaluated for a total of 12 weeks following the IA injection. Following screening, sampling for PK and safety will be completed at 10 out-patient visits scheduled on Study Days 1 [calendar day of injection], 2, 3, 5, 8, 15, 22, 29, 57, and 85.

2.2. Randomization Methodology

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 stratified by joint cohort (hip or shoulder). This is an open-label study design and no patients or study personnel are blinded to treatment assignment.

2.3. Stopping Rules and Unblinding

Unblinding is not applicable to this study since this is an open label-study.

There will be no data review committee for this study.

Furthermore, discontinuation from treatment is not applicable to this study as each treated patient receives study medication at a single study visit as a single IA injection.

2.4. Study Procedures

Patients participating in this study will complete visit schedule as detailed in the Study Design, including the procedures indicated in the Schedule of Study Assessments. Those procedures include safety assessments, such as physical examinations, vital signs, blood collection for hematology and chemistry analyses, as well as adverse event (AE) monitoring and concomitant medication review.

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

See Schedule of Study Assessments for full details. The schedule of assessments, as outlined in the study protocol, is provided in Table 1.

Table 1 Schedule of Assessments

Procedures	Screening[1]	Day 1	Days 2, 3, 5	Day 8[2]	Days 15, 22[3] (Weeks 2,3)	Day 29[3] (Week 4)	Day 57[3] (Week 8)	Day 85[3] (Week 12) (End of Study)
Informed consent	X[4]							
Inclusion/Exclusion Review	X	X[5]						
Medical History/Update	X	X[5]						
OA Medical History	X	X[5]						
Prior Treatment & Medications[6]	X	X[5]						
Physical Examination	X	X[5]						X
Index Joint X-ray[7]	X							
Vital Signs	X	X[5]		X		X		X
12-Lead ECG	X							
Index Joint Assessments[8]	X	X[5]	X	X	X	X	X	X
Height	X							
Weight and BMI	X							X
Hematology & Chemistry[9]	X	X[5]				X		X
HIV, Hepatitis B/C, HbA1c[9]	X							
Pregnancy Test[10]	X	X[5]						X
Blood for Drug Concentrations		X[11]	X[12]	X	X	X	X	X
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

2 Visit should be conducted +/- 1 day from scheduled date.

3 Visits should be conducted +/- 2 days from scheduled date.

4 Consent must be obtained prior to performing any study-specific procedures

5 Complete assessment prior to dosing.

6 Record any medications received within 30 days prior to Screening.

7 Obtain new x-ray if >6 months since prior x-ray. Screening X-ray will be read locally for radiological findings of OA (S-P Classification for the shoulder and ACR criteria for the hip).

8 For all patients, the index joint (shoulder or hip) will be assessed for evidence of inflammation including tenderness, heat/ redness, swelling, and effusion. Clinically significant findings (new or worsening from baseline) should be recorded as AEs.

9 Via Central Laboratory.

10 Conduct for females of childbearing potential only. Serum pregnancy test to be performed via central laboratory at Screening and End-of-Study visit; urine pregnancy test to be performed locally on Day 1 and results available prior to dosing.

11 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 (±10 minutes).

12 On Day 2, blood for plasma drug concentration will be collected at 24 hours post-injection (+/- 2 hours).

13 To be performed under continuous ultrasound guidance.

14 AEs and Concomitant Medications will be captured from Day 1 (post-injection) to End of Study Visit.

2.5. Safety and Pharmacokinetic (PK) Variables

2.5.1. Safety Variables

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

2.5.2. 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 (±10 minutes) 1, 2, 3, 4, 5, 6, 8, 10, and 12 post-injection
- On Day 2, at 24 (±2) hours post-injection
- On Days 3, 5, 8, 15, 22, 29, 57, and 85 (time as convenient)

These represent a total of 19 samples from each patient, each sample representing 4 mL of blood for a maximum estimated total volume of 76 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.

PK parameter endpoints are described in Section 4.7.4.

3. PATIENT POPULATIONS

3.1. Population Definitions

The following patient populations will be evaluated and used for presentation and analysis of the data:

Safety population:

All patients who received study drug. Patients will be analyzed according to the treatment they have received ("analyses as treated").

Pharmacokinetic Population:

All patients from safety population who receive a full dose of study drug, complete scheduled sampling, and have sufficient plasma concentration data to allow calculation of PK parameters will be included in the PK population. Review of the plasma drug concentration data and eligibility for inclusion into the PK population will be completed by the study Pharmacokineticist. The rationale for inclusion or exclusion in the PK population will be documented and listed. Patients will be analyzed according to the treatment they have received ("analyses as treated").

3.2. Protocol Deviations

All protocol deviations will be presented in the data listings.

4. STATISTICAL METHODS

4.1. Sample Size Justification

4.1.1. Sample Size Considerations

Sample size is based on the PK primary endpoint. 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 32 mg FX006 (N=60) and 40 mg TAcs (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}).

4.1.2. 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 either shoulder or hip OA. A sample size of 12 in each treatment arm (24 in total) is estimated for each joint cohort (hip and shoulder). Within each group 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 in each joint cohort 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 48 patients (hip: 12 in each treatment arm, shoulder: 12 in each treatment arm) for the study.

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

All output will be incorporated into Portable Document Format (PDF) or Word files, sorted and labeled according to the International Conference on Harmonization (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline and safety parameters. Summary tables will present data by joint cohort (hip and shoulder) and treatment arm.

For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented.

For continuous variables, the number of non-missing values (n), the mean, median, standard deviation (SD), minimum and maximum values will be presented. 95% Confidence Intervals (CI) may be provided. In addition, for concentration-based parameters, the coefficient of variation (CV %), the geometric mean (GM) and log-scale standard deviation will be provided. Additional statistics may be presented for certain endpoints as described below.

All collected data will be presented in by-patient listings sorted by joint cohort, treatment arm and patient number.

All data listings that contain an evaluation date will contain relative analysis day (Rel Day). Pre-treatment and post treatment analysis days are numbered relative to the day of the first dose of study treatment which is designated as Day 1. The preceding day is Day-1; the day before that is Day-2, etc.

For PK assessments, when several assessments are made on the same day, both relative study day and hour will be presented.

The sections below describe the intended analysis of the endpoints. Additional sensitivity analyses may be employed in the event of any unforeseen data anomalies or data issues not known at the time of writing this analysis plan.

4.2.2. Computing Environment

All descriptive statistical analyses will be performed using SAS® statistical software (Version 9.4 or higher), unless otherwise noted.

Non-compartmental PK analyses (NCA) will be conducted using Phoenix WinNonlin® Version 8 or higher (Certara Corporation).

AEs will be coding using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 (or higher).

Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary (DD) (Version B3 Mar 2014 or Higher).

4.2.3. Methods of Pooling Data

Not applicable to the present study.

4.2.4. Adjustments for Covariates

No formal statistical analysis that adjusts for possible covariate effects is planned.

4.2.5. Multiple Comparisons/Multiplicity

Not applicable.

4.2.6. Subpopulations

No pre-planned subpopulations are identified for this study. Subgroup tables and figures may be completed that are not identified in the list of planned tables and figures if needed to further explain results.

4.2.7. Discontinuations and Loss to Follow-up

Each treated patient from this study receives study medication as a single IA injection. Therefore, discontinuation from treatment is not applicable. Whether or not patients may receive the entire content of study drug injection will be considered in the study drug exposure analyses.

Each patient may only discontinue from the study for further assessments and study visits. Data collected from discontinued patients will be included in the CSR. Patients who discontinue from the study may be replaced at the discretion of the sponsor.

Data collected at unscheduled visits will be mapped to the closest scheduled visit, but only if that data is not already available in that visit. For assessments that are not collected at every visit, data will be mapped to the next scheduled visit where that assessment is to be performed (e.g., Hematology and Chemistry collected at Day 15 would be mapped to Week 4 since Hematology and Chemistry is not a planned assessment at Day 15).

4.2.8. Missing, Unused, and Spurious Data

Missing values will not be imputed and data will be analyzed “as observed”.

4.2.9. Visit Windows

Visit windows will be calculated based on the schedule of assessments.

All endpoints will be summarized and presented according to the nominal visit (and hour, if applicable) as recorded on the Case Report Form (CRF).

4.2.10. Baseline definitions

For all endpoints, for exposed patients, baseline is the Baseline/Day 1 assessment prior to study drug administration date and time. If baseline result is missing, the last non-missing result prior to study drug administration may be used from the Screening period. For randomized and not exposed patients the latest assessment during the screening period will be used.

4.3. Interim Analyses

An interim analysis is not planned for this study.

4.4. Patient Disposition

All patients who are enrolled will be accounted for in this study.

Patient disposition will be tabulated and include the number randomized, treated and completed; the number in each patient population for analysis; and the number who discontinued prior to completing the study and reason(s) for discontinuation.

Summary data will be presented by joint cohort (hip or shoulder). Each joint cohort will be presented by treatment arm and overall.

A by-patient data listing of study completion information including the reason for early study discontinuation, if applicable, will be presented.

A listing of patients by analysis population will also be provided, including reason for exclusion from an analysis population.

4.5. Protocol Deviations

All protocol deviations will be presented in a data listing.

4.6. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety Population and will be presented by joint cohort (hip or shoulder). Each joint cohort will be presented by treatment arm and overall.

No formal statistical comparisons will be performed.

All collected demographic, baseline characteristic, bilateral joint assessment and medical history data will be provided on the safety population.

All collected demographic, baseline characteristic, and medical history data will be provided in data listings.

4.6.1. Demographic characteristics

The following baseline parameters will be described:

- Age (year) at consent - Age will be calculated as the years between date of birth and date of informed consent, and will be rounded down to the nearest year.
- Weight (kilogram (kg));
- Height (cm);
- Gender (Male/Female);
- Body mass index (BMI) (kg/meter $(m)^2$);
- BMI category:
    - Underweight: <18.0 kg/m^2
    - Normal: 18.0 to <25.0 kg/m^2
    - Overweight: 25.0 to <30.0 kg/m^2
    - Obesity Class I: 30.0 to <35.0 kg/m^2
    - Obesity Class II: 35.0 to <40.0 kg/m^2
    - Obesity Class III: >=40.0 kg/m^2
- Ethnicity (Hispanic or Latino / Not Hispanic or Latino);
- Race (White, Asian / Black or African American / American Indian or Alaska Native / Native Hawaiian or Other Pacific Islander);

Age, height, weight, and BMI will be summarized using descriptive statistics (number of patients, mean, SD, median, minimum, and maximum). The number and percentage of patients in each gender, ethnicity, race and BMI category will also be presented.

4.6.2. OA Medical History

General OA and joint OA medical history data as collected on the CRF will be tabulated for the Safety Population.

General and joint OA medical history will be presented in separate tables (one for each joint cohort). Each table will be presented by treatment group and overall. Time from primary diagnosis of OA in the index joint to Day 1 of the study in days (first dose date – date of diagnosis + 1), will be computed and presented descriptively. If only month and year of initial diagnosis is available, day will be imputed as 1 for calculations. If month and day are missing, the time from primary diagnosis will be computed as year of first dose minus year of diagnosis. If year is missing, time from diagnosis will not be computed.

4.6.3. Prior medication

All prior medications will be presented in the concomitant medication data listing with a flag identifying which medications are prior medications (refer to Section 4.8.5 for details on defining prior and concomitant medications).

4.7. Study Drug Exposure and Pharmacokinetics Evaluation

4.7.1. Study Drug Exposure

Details of study drug administration will be tabulated and presented for the Safety Population and will be presented by joint cohort (hip or shoulder). Each joint cohort will be presented by treatment arm and overall.

Index joint injected (left or right), injection approach, needle gauge and length, numbing agent used, whether or not the entire contents of the syringe were injected, total amount injected, and whether ultrasound guidance was used will be presented. Synovial fluid aspiration (yes/no and volume) will also be presented.

All dosing data will be presented in a data listing.

4.7.2. Plasma drug concentration analysis

Tabular summaries of mean TA plasma concentrations for each nominal sampling time will be presented for the PK population. Each joint cohort (hip and shoulder) will be presented separately by treatment arm.

Visit date and times are calculated relative to the Baseline/Day 1 visit. The reference time point is Day 1 time of study drug administration (Time 0). Of note, the pre-dose sample is only relevant if a quantifiable concentration of TA is present.

All data collected will be summarized and presented in individual plots. However, all data will be presented in data listings with those results falling outside of the visit window flagged. Both nominal (planned) and actual sampling time will be presented.

Descriptive statistics (n, mean, SD, geometric mean, log-scale SD, 95% CI, median, minimum, maximum) will be calculated by time point for plasma drug concentration levels. Frequencies of patients with values identified as below the limit of quantification (BLOQ) will be presented by time point.

4.7.3. Handling of Concentration Data below the Limit of Quantification

The bioanalytical assay sensitivity for TA will be noted in the table and listings. Values assayed below these limits will be identified as BLOQ. Concentrations that are not detected will be identified as "Not Detected" and recorded as BLOQ.

For the PK analysis and individual concentration vs. time plots, a concentration that is BLOQ is assigned a value of zero if it occurs in a profile before the first measurable concentration. If a BLOQ value occurs after a measurable concentration in a profile and is followed by a value above the lower limit of quantification, then the BLOQ is treated as missing data. If a BLOQ value occurs at the end of the collection interval (after the last quantifiable concentration) it is set to zero. If two BLOQ values occur in succession after Cmax, the profile is deemed to have terminated at the first BLOQ value and any subsequent concentrations are set to zero for PK calculations. If sufficient data are missing for a given subject, that subject may be considered non-evaluable for pharmacokinetic analysis and will not be included in the PK Population.

4.7.4. Pharmacokinetic analysis

PK analysis will be performed on the PK population. PK parameter estimates will be completed by the study pharmacokineticist and results provided for incorporation into study datasets.

PK parameters will be derived using model-independent methods (non-compartmental analysis (NCA)) as implemented in Phoenix WinNonlin® (version 8 or higher) and will be based on TA plasma concentrations from patients in the PK Population. Mean concentration profiles will be computed. Each joint cohort (hip and shoulder) will be presented separately by treatment arm.

Actual sampling times will be used for the estimation of the PK parameters if significant deviations from the nominal sampling time are noted in data review by the study pharmacokineticist. All descriptive summary tables and figures will be presented with the nominal (planned) sampling times.

The following pharmacokinetic parameters will be calculated for Plasma TA (Table 2).

Table 2 Plasma Pharmacokinetic Parameters

PK Parameter	Definition	Method of Determination
C_{max}	Peak exposure, Maximum plasma concentration observed.	Observed value
t_{max}	Time from dosing to peak exposure, time to maximum plasma concentration observed.	First occurrence of observed Cmax
C_{last}	Last quantifiable plasma concentration (last value observed above assay BLOQ)	Observed value
t_{last}	Time of last quantifiable plasma concentration	Observed value
λ_z	Terminal elimination rate constant	lambda_z
$t_{1/2}$	Apparent terminal elimination half-life	ln(2)/λz,
$AUC_{(0\text{-}last)}$	Area Under the Plasma Curve from time 0 to the last quantifiable concentration (t).	Will be calculated using the linear up/log down variant of the trapezoidal rule
$AUC_{(0\text{-}t)}$	Area Under the Plasma Curve from time 0 to tau post-IA injection, where tau is definedfor partial AUC parameters from 0 to 24, and 0-96 hours	Will be calculated using the linear up/log down variant of the trapezoidal rule
$AUC_{(0\text{-}\infty)}$	Area under concentration vs time curve from 0 to infinity after dosing.	Will be calculated using the linear up/log down variant of the trapezoidal rule using the following formula $AUC_{(0\text{-}last)}$ + Clast/λz
CL	Total Body Clearance	Dose/ $AUC_{(0\text{-}\infty)}$
MRT	Mean residence time extrapolated to infinity	$AUMC_{(0-\infty)}/AUC_{(0-\infty)}$

The AUC parameters will be calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations ('linear up, log down') calculation method option in WinNonlin.

Onset of the apparent terminal log-linear phase used in the calculation of λz will be determined using WinNonlin Auto Selection and will be reviewed by the pharmacokineticist for reasonableness. No values for $AUC_{(0\text{-}\infty)}$ or Apparent Terminal $t_{1/2}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

In determining the individual Apparent Terminal $t_{1/2}$ and $AUC_{(0\text{-}\infty)}$ values, the parameters "Rsq_adjusted" (adjusted R2), $AUC_{(0\text{-}last)}$, and "AUC%extrap_predicted" (predicted percent extrapolated $AUC_{(0\text{-}\infty)}$) will be used. However, these values will only be referenced in the CSR

in cases where the extrapolated $AUC_{(0-\infty)}$ is ≥ 25% of predicted, when it will be starred with added footnote in the text with justification for inclusion/exclusion and percent extrapolated.

Descriptive summaries of the individual patient PK parameters and population summaries over all patients will be presented. Individual linear-linear and log-linear concentration profiles will be completed for each patient. Graphical display (plasma drug concentration curves) will be used to present mean with SE and geometric mean with 95% CIs for plasma drug concentrations (linear-linear and log-linear plots) for each treatment arm. The distribution of plasma drug concentrations by time point will be displayed using box plots.

All PK parameters and data will be presented in a data listing. Results from the PK analysis will be included in the CSR. Along with the bioanalytical report from the assay laboratory, model output from the NCA analysis will be provided in a separate document.

Hip patients in the TAcs group received an injection volume of 1.0 mL or 5.0 mL depending on which version of the protocol was in use at the time of injection. If different PK profiles are observed within the hip cohort for subjects receiving TAcs, either due to differences in volume or due to other reasons, exploratory analyses may be performed to investigate potential sources of the difference.

4.7.5. Exploration of Bioequivalence between FX006 and TAcs

Bioequivalence (BE) ratios between extended-release FX006 (Test) and immediate-release TAcs (Reference) for C_{max} and AUC parameters will be explored. BE 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 for the assessment of bioequivalence (FDA, 2013). Each joint cohort (hip and shoulder) will be tested for BE separately.

The FDA Guidance on the assessment of Bioequivalence recommends that bioequivalence measures of AUC and C_{max} be log-transformed. In this study, the natural log will be used to transform the values for the model, and the C_{max}, $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$. PK parameters will be exponentiated from a mixed effects model to examine bioequivalence.

In this study bioequivalence is not expected for the ratio of FX006 / TAcs. The properties of FX006 suggest that a reduced C_{max} (reduced maximum exposure) is evident due to slower release of TA into systemic circulation. The potential shift in T_{max} and potential decay in C_{max}, both of which would be associated with corresponding differences in AUC will be explored.

A linear mixed effects model may be used for this study to average bioequivalence with PK parameters of log-transformed $AUC_{(0-24)}$, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and C_{max}. In the initial model fixed effects for treatment and site will be included, with a random effect for patient.

GM with 95% CIs will be presented for each treatment group. BE ratio with standard error (SE) and 90% CIs will be presented for C_{max}, $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$.

4.8. Safety Analyses

Safety analyses will be conducted using the Safety Population by joint cohort (hip and shoulder). Each joint cohort will be presented by treatment arm, according to the treatment that was received.

4.8.1. Adverse Events

AEs will be coded using MedDRA and displayed in tables and listings using System Organ Class (SOC) and Preferred Term (PT).

Analyses of AEs will be performed for those events that are considered treatment emergent, where treatment emergent is defined as any AE with onset after the administration of study treatment, or any event that was present at baseline but worsened in intensity through the end of the study.

If the start date/time of an AE is partially or completely missing, the date/time will be compared as far as possible with the date/time of the start of administration of study drug. The AE will be assumed to be treatment emergent if it cannot be definitively shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach). The following general rules will be used:

- If the start time of an AE is missing but the start date is complete, an AE will only be excluded as being treatment emergent if the start date is before the date of study drug administration or if the stop date/time is before study drug administration.
- If the start time and day are missing but the start month and year are complete, an AE will only be excluded as being treatment emergent if the start month/year is before the month/year of study drug administration or if the stop date/time is before study drug administration.
- If the start day and month are missing but the start year is complete, an AE will only be excluded as being treatment emergent if start year is before the year of study drug administration or if the stop date/time is before study drug administration.
- If the start date is completely missing, an AE will be considered treatment-emergent unless the stop date/time is before study drug administration.

AEs will be summarized by patient incidence rates; therefore, in any tabulation, a patient contributes only once to the count for a given SOC or PT.

Summary tables will display the number and percentage of patients who experienced at least one treatment emergent AE (TEAE) in each of the following categories:

- Any TEAE
- Any Serious AE (SAE)
- Any TEAE leading to study discontinuation

- Any TEAE by severity (grade 1-5)
- Any TEAE by relationship
- Any index-joint related TEAE
- Any index- joint related SAE
- Any index- joint related TEAE leading to study discontinuation
- Any index- joint related TEAE by severity (grade 1-5)
- Any index- joint related TEAE by relationship
- Any TEAE related to injection procedure

Separate tabulations will be produced for each of following categories:

- All TEAEs by SOC and PT
- All SAEs by SOC and PT
- All TEAEs related to study drug by SOC and PT
- All TEAEs related to injection procedure by SOC and PT
- All TEAEs by maximum severity by SOC and PT
- All TEAEs leading to study discontinuation
- All TEAEs leading to death
- All index-joint related TEAEs by SOC and PT
- All index-joint related TEAEs related to study drug by SOC and PT
- All index-joint related TEAEs by maximum severity by SOC and PT

In the summary table for "Any TEAE by SOC and PT", an additional row with the number of events observed will be presented. A patient will be counted once for the number of patients if they have multiple events. The total number of events will be the absolute number of events observed, and a patient will be counted more than once for the event totals if they have multiple events.

In these tabulations, related is defined as any TEAE deemed possibly, probably or definitely related to study drug by the investigator. If relationship is missing, it will be imputed as related and flagged in the listings.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

By-patient listings of all AEs occurring on-study will be provided as well as for the following, for all patients: patient deaths, SAEs and AEs leading to discontinuation.

4.8.2. Laboratory Data

Clinical laboratory values will be expressed in SI units.

The actual value and change from baseline (Day 1 or Screening if Day 1 is missing) will be summarized for each hematology and clinical chemistry laboratory parameter. In the event of repeat values, the last non-missing value per study day/time will be used.

All laboratory data will be provided in data listings.

4.8.3. Vital Signs and Physical Examinations and Index Joint Assessment

The actual value and change from baseline (Day 1) at each time point will be summarized. Vital sign measurements will be presented for each patient in a data listing.

All physical examination abnormalities will be presented in a data listing.

The incidence of inflammation, as determined from the index joint assessment, will be tabulated for each visit. For those patients experiencing inflammation, the details of the inflammation will also be tabulated. In these tabulations, percentages will be based on those patients who have a non-missing index joint assessment at a given visit. Index joint assessment as well as index joint aspiration data will be presented in data listings.

4.8.4. Electrocardiogram

ECG data will be provided in patient data listing.

4.8.5. Concomitant Medications

Concomitant medications will be defined as those medications that were initiated after study drug administration or those that were ongoing at the time of study drug administration. If the start date or stop date of a medication is partially missing, the date will be compared as far as possible with the date of the start of administration of study drug. The medication will be assumed to be prior medication if it cannot be definitively shown that the medication did not start or continue during the treatment period. The following approach will be taken:

- If the start date of medication is complete and occurs on or after the day of administration of study treatment, the medication will be assumed concomitant. If the start date occurs prior to administration of study treatment but the end date is on or after the administration of study treatment date or the medication is recorded as ongoing, the medication will be considered concomitant.
- If the start day is missing but the start month and year are complete, a medication will only be excluded as being concomitant if the start month/year is before the month/year of study drug administration and if the stop date (either full date, month and year if missing day, or year if missing month and day) is before study drug administration.

- If the start day and month are missing but the start year is complete, a medication will only be excluded as concomitant if the start year is before the year of study drug administration and if the stop date (either full date, month and year if missing day, or year if missing month and day) is before study drug administration.
- If the start date is completely missing and the stop date is prior to administration of study treatment or completely missing, the medication will be assumed to be a prior medication.

All prior and concomitant medications (CM) will be presented in a data listing with flags indicating whether each medication was prior and/or concomitant. The listings will include type of medication (general or restrictive) and whether the CM was used for treatment of an AE.

5. CHANGES TO PLANNED ANALYSES

Although the protocol states that listings will be provided by joint cohort, treatment, study site and patient, per this SAP, by-patient listings will be sorted by joint cohort, treatment arm and then patient number.

The protocol states that a linear model will be used to compare the PK parameters from extended-release FX006 and immediate-release TAcs. This analysis will not be performed, since comparison of the PK parameters will be accomplished via the BE testing.

6. REFERENCES

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7. CLINICAL STUDY REPORT APPENDICES

7.1. Statistical Tables to be Generated

Table 14.1.1	Patient Enrollment and Disposition
Table 14.1.2	Demographic and Baseline Characteristics (Safety Population)
Table 14.1.3.1	Osteoarthritis Medical History and Index Joint Characteristics of the Shoulder (Safety Population)
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Table 14.1.5	Study Drug Exposure Summary (Safety Population)
Table 14.1.6	Plasma Drug Concentrations (pg/mL) by Time Point (PK Population)
Table 14.2.1	Plasma Pharmacokinetic Parameters (PK Population)
Table 14.2.2	Summary of Bioequivalence Geometric Mean Ratios (PK Population)
Table 14.3.1.1	Summary of Treatment-Emergent Adverse Events (Safety Population)
Table 14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.3	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Related to Study Drug (Safety Population)
Table 14.3.1.4	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Maximum Severity (Safety Population)
Table 14.3.1.5	Index-Joint-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.6	Index-Joint-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term- Related to Study Drug (Safety Population)
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Table 14.3.2.1	Patient Listing of Deaths
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Table 14.3.2.3	Patient Listing of Discontinuations Due to Adverse Events
Table 14.4.1.1	Summary and Change from Baseline for Hematology Parameters by Visit (Safety Population)
Table 14.4.1.2	Summary and Change from Baseline for Chemistry Parameters by Visit (Safety Population)
Table 14.4.2	Summary and Change from Baseline for Vital Signs by Visit (Safety Population)
Table 14.4.3	Summary of Index Joint Assessments (Safety Population)

7.2. Statistical Figures to be Generated

Figure 14.1.6.1	Distribution of Plasma Drug Concentrations (pg/mL) by Time Point (PK Population)
Figure 14.1.6.2	Mean and GM for Plasma Drug Concentration Curve (Plasma Drug Concentration)
Figure 14.2.1	Individual Patient Linear-Linear and Log-Linear Plasma Drug Concentration Profiles (PK Population)

7.3. Data Listings to be Generated

Listing 16.2.1	Patient Disposition
Listing 16.2.2.1	Inclusion/Exclusion Criteria Not Met
Listing 16.2.2.2	Protocol Deviations
Listing 16.2.3	Analysis Populations
Listing 16.2.4.1	Demographics and Baseline Characteristics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3.1	Medical History - Shoulder Osteoarthritis
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Listing 16.2.7.3	Adverse Events – Glossary by MedDRA SOC, Preferred Term and Verbatim
Listing 16.2.8.1	Laboratory Assessment – Hematology
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Listing 16.2.9.5	Index Joint Aspiration
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