STATISTICAL ANALYSIS PLAN
Protocol FX006-2016-011

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

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Methodology:	Open-label, Repeat Dose Design
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SAP SIGNATURE PAGE

Protocol Title:	An Open-label Study to Assess the Safety of Repeat Administration of FX006 to Patients with Osteoarthritis of the Knee
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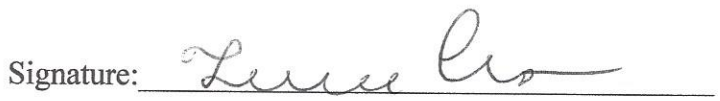
Cytel, Inc. Author: Teresa Curto Senior Biostatistician	Signature:  Date: 01-Aug-2018

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 guidance 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).

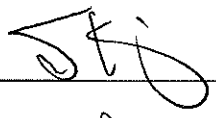
Sponsor Signatory:

Joelle Lufkin
Vice President – Clinical Development

Signature: 

Date: 01 AUG 2018

Scott Kelley, MD
Chief Medical Officer

Signature: 

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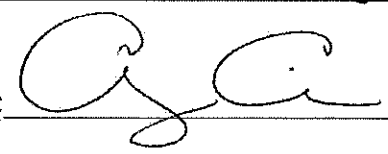
Signature: 

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ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	Adverse Event
ANCOVA	Analysis of Covariance
AUE	Area Under the Effect Curve
BMI	Body Mass Index
BP	Biomarker Population
CI	Confidence Interval
CM	Concomitant Medication
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
EULAR	European League against Rheumatism
FAS	Full Analysis Set
GPAQ	Global Physical Activity Questionnaire
HIV	Human Immunodeficiency Virus
IA	Intra-articular
ICH	International Conference on Harmonisation
iSAP	Interim Statistical Analysis Plan
JSN	Joint Space Narrowing
K-L	Kellgren-Lawrence
KOOS	Knee injury and Osteoarthritis Outcome Score
LSM	Least Square Means
MedDRA	Medical Dictionary for Regulatory Activities
MET	Metabolic Equivalent
mg	milligram
mmol	millimole
MMRM	Mixed Effects Model for Repeat Measures
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PDF	Portable Document Format
PPIP	Per Protocol Imaging Population
PT	Preferred Term
QOL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System

Abbreviation	Definition
SBC	Subchondral Bone Changes
SD	Standard Deviation
SE	Standard Error
SI	International System of Units
SOC	System Organ Class
SP	Safety Population
TA	Triamcinolone Acetonide
TAcs	Triamcinolone Acetonide Injectable Suspension, Immediate-Release (Commercially Available)
TEAE	Treatment Emergent AE
US	United States
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities

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 (ACR Subcommittee 2000; Hochberg et al, 2012; Jordan et al, 2003).

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

FX006 is an extended-release formulation of triamcinolone acetonide (TA) for IA administration that is being developed for the treatment of patients with pain attributed to OA of the knee. FX006 is intended to deliver TA to the synovial and peri-synovial tissues for a period of approximately 3 months depending on the dose administered (Bodick et al, 2013).

Available clinical and nonclinical data indicate that FX006 is likely to be safe and well tolerated and has the potential to provide pain relief that is meaningfully better and more persistent than that provided by immediate release triamcinolone acetonide (TAcs).

1.2. Objectives of Statistical Analysis

1.2.1. Primary Objective

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

1.2.2. Exploratory Objectives

Exploratory objectives of this study include the following:

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

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.

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

This SAP may be amended as study data are reviewed and interim analyses of these data are conducted.

2. STUDY DESIGN

2.1. Synopsis of Study Design

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

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

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

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

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

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

Refer to Appendix B for the study flow chart.

2.2. Randomization Methodology

No randomization technique is required to assign patients to treatment in this study.

2.3. Unblinding

Not applicable to the current study since this is an open-label study.

2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1.

Table 1 Schedule of Assessments

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

2.5. Study Variables

2.5.1. Safety Variables

Safety and tolerability will be evaluated on the basis of findings from the following assessments:

- Adverse events
- Physical examinations
- Index knee assessments
- Vital signs
- Clinical laboratory evaluations
- Index knee X-ray

2.5.2. Exploratory Efficacy Variables

The following exploratory efficacy endpoints will be analyzed as described in the SAP:

- Western Ontario and McMaster Universities (WOMAC®) A (pain subscale), B (stiffness subscale), C (function subscale), and total score at all time points.

- Knee injury and Osteoarthritis Outcome Score (KOOS) Quality of Life (QOL) Subscale at all time points.

- Daily activity measured as steps per day from Day 1 to Week 12.

- Global Physical Activity Questionnaire (GPAQ) domains (activity at work, travel to and from places and recreational activities) and total score at baseline/Day 1 and Week 12.

3. PATIENT POPULATIONS

3.1. Population Definitions

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

Safety Population (SP):

The Safety Population (SP) will include all patients who receive study treatment. The Safety Population will be used to assess safety and tolerability endpoints.

Full Analysis Set (FAS):

The Full Analysis Set (FAS) population will include all patients who receive study treatment and provide at least one post-baseline efficacy endpoint assessment. The FAS population will be used to examine exploratory efficacy endpoints.

Biomarker Population (BP)

The Biomarker Population (BP) will include all patients who receive study treatment and provide at least one synovial fluid sample for biomarker analysis. The BP will be used for future biomarker analyses.

Per Protocol Imaging Population (PPIP)

The Per Protocol Imaging Population (PPIP) will include all patients in the SP who have quantifiable x-ray imaging values at baseline and Week 52/End of Study except those patients who are terminated early or have major protocol deviations that could affect image results. These major protocol deviations will be identified by Flexion medical without regard to individual patient imaging data.

Additional study populations may be defined to meet interim analysis requirements. These population definitions will be fully specified and documented an interim SAP (iSAP) and in the final CSR.

4. STATISTICAL METHODS

4.1. Sample Size Justification

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

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 Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

A list of tables, figures and listings to be generated, as well as mock shells, are provided in a separate document.

Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. Each table will present all patients combined, regardless of number of doses, unless otherwise specified.

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), confidence intervals (CI), minimum and maximum will be presented. Additional statistics may be presented for certain endpoints as described in the sections below.

Time to event data will be summarized using Kaplan-Meier Methodology using 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% confidence intervals, as well as percent of censored observations.

If performed, all statistical tests will be two-sided and a difference resulting in a p-value of less than or equal to 0.05 will be described as statistically significant and potentially informative.

All collected data will be presented in patient listings.

The sections below describe the intended analysis of the endpoints. Additional sensitivity analysis 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 statistical analyses will be performed using SAS® Software[1] (Version 9.4) or higher, unless otherwise noted. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 Concomitant medications will be coded using World Health Organization (WHO) Drug (March 2014 edition).

4.2.3. Methods of Pooling Data

Not applicable to the present study.

4.2.4. Adjustments for Covariates

The exploratory continuous endpoints will include baseline score and study site as covariates. Other covariates may be explored.

4.2.5. Multiple Comparisons/Multiplicity

Since these are exploratory analyses, there will be no adjustment for multiple endpoints.

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 in this study will receive an initial injection of FX006 and then be reevaluated starting at Week 12 for eligibility to receive a second injection. Therefore, discontinuation from treatment is not applicable. Whether or not patients receive the entire contents of study drug injection will be considered in the study drug exposure analyses.

Each patient may 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.

4.2.8. Missing, Unused, and Spurious Data

For WOMAC, the rules as described in the WOMAC user guide (Bellamy 2011) will be used. Specifically, if at least 2 pain, both stiffness, or at least 4 function items are missing, the patient's response will be regarded as invalid and the score for that given subscale as well as the total score will be left missing. If no more than 1 pain, 1 stiffness, and less than 4 function items are missing, the missing value in a given subscale will be imputed using the average of all items in the given subscale. Imputed WOMAC scores will be flagged in the data listings.

[1] Copyright 2015, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

For the KOOS QOL subscale, the rules as described in KOOS Scoring 2012 (http://www.koos.nu/) will be used. Specifically, the score is only calculated if at least 2 items are non-missing. Otherwise the score will be set to missing.

For calculating weekly mean steps per day using Fitbit data, patients need to have at least 3 of 7 daily values in a given week to provide a robust assessment of activity. The denominator used for calculating means will be the total number of days in which steps per day is non-missing.

To be included in the GPAQ analyses, there must be a valid response for at least one domain and no invalid responses for any domains.

Other than for the WOMAC and KOOS QOL, missing data will not be imputed and will be analyzed "as observed".

4.2.9. Visit Windows

All data listings that contain an evaluation date will contain a relative study day (Rel Day Dose 1). Pre-treatment and post-treatment study 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. Listings will also contain a study day (Rel Day Dose 2) relative to the second dose of study treatment, which is designated as Day 1. For patients that do not receive a second dose, Rel Day Dose 2 will be "NA". For Rel Day Dose 2, preceding days (e.g., Day -1, -2) will not be derived or presented. In other words, if the date is prior to Dose 2, only Rel Day Dose 1 will be presented. If the date is after Dose 2, then both Rel Day Dose 1 and Rel Day Dose 2 will be presented.

Steps per Day (Fitbit) data windowing:

The visit windows to be used for computing steps per day are provided in Table 2. Observations collected in these windows will be averaged and presented according to the nominal visit label for that window.

Table 2 Evaluation Intervals for the Data Points to be Included in the Table

Visit	Relative Day Interval for Analysis
Baseline	Day –7 to Day -1
Week 1	Day 1 to Day 7
Week 2	Day 8 to Day 14
Week 3	Day 15 to Day 21
Week 4	Day 22 to Day 28
Week 5	Day 29 to Day 35
Week 6	Day 36 to Day 42
Week 7	Day 43 to Day 49
Week 8	Day 50 to Day 56
Week 9	Day 57 to Day 63
Week 10	Day 64 to Day 70
Week 11	Day 71 to Day 77
Week 12	Day 78 to Day 84

Unscheduled visit windowing:

If a patient receives their second dose of study medication at an unscheduled visit that is not >3 weeks after Week 24, the dosing information and all other data collected at that visit will be mapped to the closest nominal visit, based on Rel Day Dose 1, even if data is already available in that visit. All data collected at the time of the second dose will be used for analysis. If data is available in the nominal visit, but was not collected at the unscheduled visit associated with the second dose, the data from the nominal visit will be used. If a patient receives their second dose at an unscheduled visit that is > 3 weeks past Week 24, data from that unscheduled visit will not be used for time to second dose analyses or exploratory efficacy analyses involving two-dose patients.

Data collected at unscheduled visits that are not associated with the second dose will be mapped to the closest scheduled visit, but only if that data is not already available in that visit. Otherwise data will be summarized and presented according to the nominal visit as recorded on the Case Report Form (CRF).

4.2.10. Baseline Definitions

Baseline for the first dose is the baseline/Day 1 assessment prior to administration of the first dose of study treatment. If the baseline result is missing, the last non-missing result prior to administration of study treatment may be used from the Screening period.

Baseline for the second dose of study treatment is defined as the last data collected prior to the second dose of study treatment administration. This is the same study visit, as long as the data are collected prior to the second dose.

Where noted in this SAP, change from baseline for efficacy analyses are also performed where baseline for the second dose is defined as the baseline/Day 1 assessment prior to administration of the first dose of study treatment.

Additional baselines may be defined to explore efficacy endpoints comparing the first dose and the second dose of study treatment administration. All new baseline definitions will be fully specified and documented an interim SAP (iSAP) and in the final CSR.

4.3. Interim Analyses

Interim analyses may be conducted evaluating safety and efficacy signals following administration of one or two doses of 32mg FX006. These interim analyses on exploratory endpoints may be completed for data review, regulatory updates, and/or publication (or presentation at congresses) for this open-label study. For any analyses completed not presently identified in this SAP an iSAP will be written and approved prior to interim analysis.. The iSAP will describe the purpose and analytical objectives of the interim analysis. Any changes made to the final analysis will be documented in an amendment to the SAP prior to final analysis. Final analyses will be conducted after completion of the study, when all patients have either discontinued the study early (prior to Week 52) or completed the study through Week 52.

4.4. Final Analysis

All final analyses will be completed following database lock. Final analyses specified in the protocol and SAP will be completed and reported in the CSR. Interim analyses conducted with exploratory endpoints to examine efficacy signals prior to database lock will also be reported in the final CSR. Post-hoc, or additional exploratory analyses, not defined in the SAP may be completed to further understanding and elucidation of the study results. Any post-hoc, exploratory, analyses completed will be clearly identified as such in the final CSR.

4.5. Patient Disposition

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

Patient disposition will be tabulated and include the total number of patients enrolled, treated, completed and early terminated, reason for early termination and the number in each patient population for analysis.

Subject completion will be presented overall and by the following categories:

1. At Week 12 (no clinical benefit)
2. At Week 24 (not clinically indicated to received second injection)
3. At Week 52

Early termination will be presented overall and by the following time periods:

1. Prior to Week 12, which is the first visit for second dose eligibility
2. On or after Week 12, but prior to receiving second dose
3. On or after second dose and prior to 12 Weeks after second dose
4. On or after receiving the second dose but prior to Week 52

The following by-patient data listings will be presented:

- Study completion information including the reason for premature study discontinuation, if applicable.
- Inclusion/exclusion criteria not met.
- Repeat dose inclusion/exclusion criteria not met for all patients. If a patient receives a repeat dose on a visit where repeat dose inclusion/exclusion criteria were not met, that visit will be flagged.
- Repeat dose eligibility at Weeks 12, 16, 20 and 24.
- Patient inclusion in each of the analysis populations (SP, FAS, BP and PPIP). Reasons for exclusion from the PPIP will be presented.

4.6. Protocol Deviations

The number and percentage of patients with at least one protocol deviation will be presented for the SP. Additionally, incidence by type of deviation will be presented; in these tabulations patients could be counted in more than one category if they have a deviation attributed to multiple categories. All protocol deviations will be presented in a data listing.

4.7. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized and presented for the SP for patients receiving only one dose, patients receiving two doses, and all patients combined. Age, height, weight, and body mass index (BMI) will be summarized using descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum). 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. The number and percentage of patients in each gender, ethnicity and race category will also be presented. Additionally, for two-dose patients only, demographic and baseline characteristic data will be presented separately based on the time at which the second dose was administered. These statistics will be presented for the following groups. Each group will be displayed as a different column in the same table, in this order:

1. Patients receiving the second dose at Week 12
2. Patients receiving the second dose at Week 16
3. Patients receiving the second dose at Week 20
4. Patients receiving the second dose at Week 24
5. Patients Receiving the Second Dose after Week 24

OA background characteristic data and index knee characteristic data as collected on the CRF will also be tabulated for the SP for all patients combined. Time from primary diagnosis of OA in the index knee to Day 1 of the study in years (dose date – date of diagnosis + 1)/365.25, will be computed and presented descriptively. Additionally, for two-dose patients only, OA background characteristic data and index knee characteristic data will be presented separately based on the time at which the second dose was administered. These statistics will be presented

for the following groups. Each group will be displayed as a different column in the same table, in this order:

1. Patients receiving the second dose at Week 12
2. Patients receiving the second dose at Week 16
3. Patients receiving the second dose at Week 20
4. Patients receiving the second dose at Week 24
5. Patients Receiving the Second Dose after Week 24

For all time to diagnosis calculations, 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 administration of study treatment minus year of diagnosis. If year is missing, time from diagnosis will not be computed.

All collected demographic, baseline characteristics, and medical history data will be provided in data listings, sorted by patient.

4.8. Study Drug Exposure

Details of study drug administration will be tabulated and presented for the SP by the following groups:

- First (and only) dose for patients receiving one dose
- First dose for patients receiving two doses
- Second dose for patients receiving two doses

The position of knee during injection, approach during injection, whether or not the entire contents of the syringe was injected, reason (if entire contents not injected), the numbing agent used, whether or not ultrasound guidance was used, volume of synovial fluid aspirated, and whether a 20 or 21-gauge needle was used will be presented.

Benefit from the initial dose of FX006 and patients with no major safety concerns during the initial dose period will be summarized for the Week 12 visit. In addition, patients clinically indicated to receive a second dose of FX006 and patients eligible for the second dose at Weeks 12, 16, 20 and 24 will be summarized, as well as the number of patients receiving the second dose at each of these visits. These data come from the “Repeat Dose Eligibility” CRF.

Patients receiving one dose and two doses and the visit at which the second dose was received will be summarized.

A summary of time to second dose will be displayed for patients receiving two doses. The median time to second dose will be estimated based on the 50th percentile of the Kaplan-Meier distribution. Additional summary statistics will be presented, including the 25th and 75th percentiles, and the corresponding 95% confidence intervals.

Additionally, repeat dose data will be presented separately by the following subgroups:

- K-L Grade 2, 3 and 4

- Prior IA steroid injection
- Unilateral/bilateral knee OA
- Prior index knee OA surgery or procedure

All study drug exposure data will be presented in a data listing.

4.9. Exploratory Efficacy Analyses

The examination of efficacy is exploratory in this study. All efficacy analyses will be conducted using the FAS.

4.9.1. WOMAC

The following WOMAC scales/questions will be analyzed:

- WOMAC A (pain subscale)
- WOMAC B (stiffness subscale)
- WOMAC C (function subscale)
- WOMAC (total)

For the WOMAC subscales, scores at each assessment time point (baseline, Week 4, Week 8, Week 12, etc.) will be calculated as the average of the responses to all questions in the subscale. Total score will be computed as the average of the average responses on each of the subscales (e.g. Average A + Average B + Average C divided by 3). This will provide a uniform scoring of 0 to 4 for each subscale and easier interpretation. Imputation rules are as presented in section 4.2.8.

Eligibility in this trial is based upon the WOMAC A total sum score at Screening and Day 1/baseline (maximum score of 20). This will be provided for all visits in a data listing.

4.9.1.1. Descriptive statistics, all patients

Descriptive statistics will be presented for the following groups. Each group will be displayed as a different column in the same table, in this order:

1. Patients receiving the second dose at Week 12
2. Patients receiving the second dose at Week 16
3. Patients receiving the second dose at Week 20
4. Patients receiving the second dose at Week 24
5. Patients receiving only one dose
6. All patients, first dose – all patients through patient discontinuation, study completion (through Week 12 or Week 24), or until the second dose is received (whichever happens sooner)

Descriptive statistics (number of observations, unadjusted mean, SD, median, minimum and maximum) will be presented for WOMAC A, WOMAC B, WOMAC C and WOMAC total by visit (baseline through Week 52). Change from baseline will also be presented. For the change from baseline calculation, baseline is the WOMAC result obtained on Day 1 prior to first dose.

The adjusted change from baseline will also be presented. This will be done using a longitudinal mixed effects model for repeat measures (MMRM) with fixed effects for study time point, study site and baseline score. Patient will be the random effect. The analysis will include all study visits of data. This model assumes that missing values are missing at random. This model will be run separately for each group and for WOMAC A, WOMAC B, WOMAC C and WOMAC total.

This model will be run using the SAS/STAT® PROC MIXED procedure with an unstructured correlation matrix to model the within-subject errors. If the unstructured covariance matrix does not converge when fitting the mixed model, further investigation into the most appropriate correlation matrix will be conducted. The final selection of the correlation matrix to be used in fitting the mixed model will be fully documented in the results section of the CSR.

This model will provide the baseline adjusted Least Square Means (LSM) at each visit with the corresponding standard error (SE) and associated 95% CI.

Sample SAS code that can be used to implement the mixed effects analysis is provided below:

```
proc mixed data=dsin1 method=reml;
  by group;
  class subjid group avisitn siteid;
  model chg= base group avisitn siteid;
  repeated avisitn /type=un subject=subjid;
  lsmeans group/diff=control (‘1’) cl;
run;
```

In the above code, "group" refers to the groups listed below. The model will be run for each group separately.

A line plot presenting LSM change from baseline in WOMAC score over time will be produced. Each group will be plotted on a separate line with SE bars. Jitter will be used as needed to distinguish overlapping data.

4.9.1.2. Change from baseline, patients receiving two doses

Change from Baseline to Week 12

A within patient analysis will be completed for patients who receive two doses of FX006. Change in WOMAC A, WOMAC B, WOMAC C and WOMAC total from first dose (Day 1) to Week 12 will be compared to change in WOMAC from second dose to 12 weeks after the second dose using a paired t-test.

The paired t-test will be completed by using the SAS/STAT® PROC MIXED procedure. Using the PROC MIXED procedure allows for multivariate modelling. Model covariates are study site, baseline WOMAC score, and potentially other covariates. Baseline WOMAC score for the first dose comes from the baseline visit. Baseline WOMAC score for the second dose comes from the second dose visit.

Descriptive statistics will include number of observations, unadjusted mean, standard deviation, median, minimum and maximum. Change from baseline LSM,SE and 95% CI from the mixed model will also be presented. The difference between the first dose (the control) and the second dose will be presented, and estimated via LSM from the analysis model along with 95% confidence intervals and associated 2-sided p-values. This model assumes that missing values are missing at random. Only patients that have data for both time points (i.e., change from Day 1 to Week 12 and change from the second dose to 12 weeks after the second dose) will be included in the model.

All patients who receive two doses of FX006 will be combined in the analysis and results will be displayed in the same table.

Sample SAS code that can be used to implement the analysis is provided below:

```
proc mixed data=<ADaM> method=type3;
   class subjid site arm;
   model chg = base site arm/ alpha=0.05 ddfm=kr outp=pred residual solution;
   random subjid;
   lsmeans arm / diff cl alpha=0.05;
   ods output diffs=diff1 lsmeans=lsml;
run;
quit;
```

In the above code, "arm" refers to the first or second dose administered (coded as a 1 or 2).

The analysis above will also be performed to compare the changes in WOMAC A, WOMAC B, WOMAC C and WOMAC total from first dose (Day 1) to Week 12 to the changes from first dose (Day 1) to 12 weeks after the second dose.

Change from Baseline to Week 4, 8 and 12

A second analysis will be completed for patients who receive two doses of FX006. Change in WOMAC A, WOMAC B, WOMAC C and WOMAC total from first dose (Day 1) to Week 4, Week 8 and Week 12 will be presented alongside change in WOMAC from second dose to 4, 8 and 12 weeks after the second dose.

This will be done using a longitudinal MMRM as described in section 4.9.1.1 with fixed effects for study time point (Week 4, Week 8 and Week 12), study site and baseline score. Patient will be the random effect. The analysis will include all study visits of data (Week 4, 8 and 12) through Week 12. This model assumes that missing values are missing at random. Separate models will be run for the first and second doses.

This model will be run using the SAS/STAT® PROC MIXED procedure with an unstructured correlation matrix to model the within-subject errors. If the unstructured covariance matrix does not converge when fitting the mixed model, further investigation into the most appropriate

correlation matrix will be conducted. The final selection of the correlation matrix to be used in fitting the mixed model will be fully documented in the results section of the clinical study report.

This model will provide the adjusted LSM estimates at each visit with the corresponding standard error and associated 95% confidence interval.

In addition to change from baseline, descriptive statistics for the unadjusted observed WOMAC values will also be tabulated.

The same analysis that is described above for change from baseline will also be performed for percent change from baseline. Percent change from baseline will be calculated as follows:

Percent change from BL = (Value – BL value)/BL value * 100

Line plots presenting observed, LSM change and LSM percent change from baseline in WOMAC A, WOMAC B, WOMAC C and WOMAC total score over time will be produced. In these plots, Week 4, Week 8 and Week 12 as well as 4, 8 and 12 weeks after the second dose, will be presented. There will be a separate line for the first and second dose along with standard deviation bars for observed values and standard error bars for adjusted values. LSM change from baseline and percent change from baseline will come from separate mixed models as described above.

The analysis above will also be done where change in WOMAC A, WOMAC B, WOMAC C and WOMAC total from first dose (Day 1) to Week 4, Week 8 and Week 12 will be presented alongside change in WOMAC from first dose (Day 1) to dose to 4, 8 and 12 weeks after the second dose.

4.9.1.3. Responders

Responders are defined as patients who have ≥50% decrease in the WOMAC A score from baseline at a given visit. Descriptive statistics (number of evaluable patients and number and percent with ≥50% response) will be presented for Weeks 4 through 52 by the following groups. Each group will be displayed as a different column in the same table, in this order:

1. Patients receiving the second dose at Week 12
2. Patients receiving the second dose at Week 16
3. Patients receiving the second dose at Week 20
4. Patients receiving the second dose at Week 24
5. Patients receiving only one dose
6. All patients, first dose – all patients through patient discontinuation, study completion (through Week 12 or Week 24), or until the second dose is received (whichever happens sooner)

Response rate will be plotted by group with a bar chart.

Additionally, for Week 12, a continuous responder curve will display the cumulative proportion of responders on the y-axis versus the criteria/cut point used to define a responder on the x-axis;

in this figure, lines will display the proportion of patients responding under various % improvement cut points by group. Each group will be plotted on a separate line. Jitter will be used as needed to distinguish overlapping data.

4.9.1.4. Area Under the Effect Curve (AUE) for Change from Baseline in WOMAC over Time

The Area Under the Effect curve (AUE) for change from baseline in WOMAC A, B, C and total score over various time intervals will be examined.

AUE will be calculated from a linear trapezoidal rule using the following formula for change from baseline in WOMAC A, WOMAC B, WOMAC C and WOMAC total:

$$AUE_{t_i - t_{i+n}} = \sum_{t_i}^{t_{i+n}} ((WD_i + WD_{i+1})/2) * (t_{i+1} - t_i)$$

Where WD_i = WOMAC difference (change) from baseline in WOMAC score for time t_i, and WD_{i+1} = WOMAC difference (change) from baseline in WOMAC score for time t_{i+1}, over the time interval t_i to t_{i+1}. (Note that the difference for $t_{i+1} - t_i$ will be 4 week intervals). Only non-missing time intervals will be part of the sum for each AUE calculation (Farrar et al. 2000). Baseline for the first dose will be used for all WOMAC difference from baseline calculations.

Two within patient analyses will be completed for patients who receive two doses of FX006. In the first analysis, the AUE for the change from baseline for the first dose from Week 4 to Week 12 will be compared to the AUE for the change from baseline for the second dose from 4 to 12 weeks after the second dose for all patients. In the second analysis, the AUE for the change from baseline for the first dose from Week 4 to the second dose will be compared to the AUE for the change from baseline for the second dose from 4 weeks after the second dose to the comparable period after the second dose.

<u>Comparison of change from baseline to Week 12 for the first and second doses</u>

AUE for WOMAC A, WOMAC B, WOMAC C and WOMAC total change from baseline for the first dose from Week 4 Week 12 will be compared to AUE for WOMAC A, WOMAC B, WOMAC C and WOMAC total for the change from baseline for the second dose from 4 to 12 weeks after the second dose using a paired t-test. The examination of WOMAC A (Pain) will be an indication of the durability of the pain relief response, where WOMAC B (Stiffness) and WOMAC C (Function) will provide an indication of the durability of the responses for these two sub-scales over the course of two doses.

The paired t-test will be completed by using the SAS/STAT® PROC MIXED procedure. Model covariates are study site, baseline WOMAC score, and potentially other covariates. Baseline WOMAC score for the first dose comes from the first dose visit. Baseline WOMAC score for the second dose comes from the second dose visit. Sample SAS code provided in section 4.9.1.2 will be used.

Descriptive statistics will include the LSM and standard error, 95% confidence interval, LSM difference from control (first dose Week 4 to Week 12), and 2-sided p-value. This model assumes missing at random and only includes observed data; missing data are not imputed in

this model. Only patients that have data for both time points (i.e., first dose Week 4 to Week 12 and second dose Week 4 to Week 12) will be included in the model.

All patients who receive two doses of FX006 will be combined in the analysis and results will be displayed in the same column.

The analysis above will also be performed where baseline for the second dose is defined as the baseline/Day 1 assessment prior to administration of the first dose of study treatment.

Comparison of change from baseline to second dose and change from second dose to comparable period after second dose

AUE for WOMAC A, WOMAC B, WOMAC C and WOMAC total change from baseline for the first dose from Week 4 to the second dose will be compared to the AUE for WOMAC A, WOMAC B, WOMAC C and WOMAC total change from baseline for the second dose from 4 weeks after the second dose to the comparable period after the second dose using a paired t-test.

The paired t-test will be completed by using the SAS/STAT® PROC MIXED procedure. Model covariates are study site, baseline WOMAC score, and potentially other covariates. Baseline WOMAC score for the first dose comes from the baseline visit. Baseline WOMAC score for the second dose comes from the second dose visit. Sample SAS code provided in section 4.9.1.2will be used.

Descriptive statistics will include the LSM and standard error, 95% confidence interval, LSM difference from control (first dose to second dose), and 2-sided p-value. This model assumes missing at random and only includes observed data; missing data are not imputed in this model. Only patients that have data for both time points will be included in the model.

Table 3 shows the AUE intervals that will be computed and compared:

Table 3 AUE Change from Baseline Comparisons

AUE	Patients receiving the second dose at Week 12	Patients receiving the second dose at Week 16	Patients receiving the second dose at Week 20	Patients receiving the second dose at Week 24
First Dose	Week 4 to Week 12	Week 4 to Week 16	Week 4 to Week 20	Week 4 to Week 24
Second Dose	Second Dose Week 4 to Week 12 (Week 16 to Week 24)	Second Dose Week 4 to Week 16 (Week 20 to Week 32)	Second Dose Week 4 to Week 20 (Week 24 to Week 40)	Second Dose Week 4 to Week 24 (Week 28 to Week 48)

Both within patient analyses will be presented in the same table. Each group will be displayed as a different column in the same table, in this order:

1. All patients receiving two doses
2. Patients receiving the second dose at Week 12

3. Patients receiving the second dose at Week 16
4. Patients receiving the second dose at Week 20
5. Patients receiving the second dose at Week 24

The analysis above will also be performed where baseline for the second dose is defined as the baseline/Day 1 assessment prior to administration of the first dose of study treatment.

All AUE data will be presented in a data listing. For patients receiving only one dose, the AUE for change from baseline for Week 4 to Week 12 will be presented.

4.9.2. KOOS

The KOOS QOL subscale (http://www.koos.nu/) has 4 questions, each of which is assigned a score from 0 to 4 (0=none, 1=mild, 2=moderate, 3=severe, 4=extreme). A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated using this formula: 100-AVERAGE(Q1-Q4)/4*100. Scores are calculated at each assessment time point (baseline, Week 4, Week 8, Week 12, etc.). Missing data rules are as presented in section 4.2.8.

The KOOS QOL subscale will be analyzed similarly to the WOMAC endpoints described in sections 4.9.1.1and 4.9.1.2. Change from baseline calculations will be based on the same time points that are described for WOMAC.

4.9.3. Daily activity measured as steps per day

Steps per day data are collected from baseline to Week 12, so analysis only applies to a single injection of FX006. Weekly mean steps per day from Fitbit data will be calculated for baseline through Week 12 using the visit windows presented in section 4.2.9. Values of <1000 will be set to missing since they were considered invalid upon review of the data. Handling of missing data is presented in section 4.2.8.

A cumulative activity score will be calculated for each patient, defined as the incremental sum of the weekly average between Weeks 1 and 12. Incremental sum of weekly mean steps per day will be calculated as follows:

- Incremental sum (Week 1) = Weekly mean steps per day (Week 1)
- Incremental sum (Week 2) = Incremental sum (Week 1) + Weekly mean steps per day (Week 2)
- Incremental sum (Week x) = Incremental sum (x-1) + Weekly mean steps per day (Week x)

Descriptive statistics will include number of observations, unadjusted mean, standard deviation, median, minimum and maximum values by week. Values presented will be actual weekly mean steps per day, change from baseline in weekly mean steps per day, and incremental sum of weekly mean steps per day. A line plot will present each of these values by week.

A responder analysis will be performed in the same way that is described in section 4.9.1.3. Steps per day (Fitbit) responders are defined as patients who have ≥10% increase in weekly mean steps per day from baseline at a given visit.

The correlation between change from baseline in steps per day and change from baseline in WOMAC A, B, C and total score and the KOOS QOL subscale at Week 4, Week 8 and Week 12 will be explored. Pearson correlation will be used if both parameters are normally distributed. Spearman correlation will be used if either parameter is not normally distributed. The mean and median values for each parameter and the correlation coefficient will be presented in a table. Change from baseline for WOMAC A, B, C and total score and the KOOS QOL subscale versus change from baseline for average steps per day at Week 4, Week 8 and Week 12 will be presented in scatter plots, which will also include a best fit line.

A data listing will present steps per day for each patient as well as number of days that contributed to each weekly average and the number that were missing.

4.9.4. GPAQ

GPAQ domains (activity at work, travel to and from places and recreational activities) and total will be presented descriptively at the two time points collected (baseline and Week 12). Average MET-minutes of moderate or vigorous physical activity per day will be calculated by domain and overall according to the GPAQ Analysis Guide. The change in average MET-minutes of physical activity per day from baseline to Week 12 will also be presented.

Missing data rules are presented in section 4.2.8. Descriptive statistics will include number of observations, unadjusted mean, standard deviation, median, minimum and maximum. These statistics will be presented for all patients combined.

The correlation between change from baseline in average MET-minutes per day from the total GPAQ (all domains combined) and change from baseline in average steps per day will be explored at baseline and Week 12 separately for all patients combined. Pearson correlation will be used if both parameters are normally distributed. Spearman correlation will be used if either parameter is not normally distributed. The mean and median values by visit for each parameter, and the correlation coefficient by visit will be presented in a table. Average MET-minutes per day versus average steps per day for each visit will be presented in scatter plots, which will also include a best fit line.

4.9.5. Sensitivity Analyses

Sensitivity analyses may be performed if required to better understand study results. Any sensitivity analyses will be identified as post-hoc in the clinical study report.

4.10. Safety Analyses

Safety analyses will be conducted using the SP. All change from baseline values will be calculated based on the pre-dose (screening) value.

4.10.1. Adverse Events

Adverse events will be coded using the MedDRA (version 19.1) coding system and displayed in tables and data 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.

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

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

- Any TEAE
- Any Serious Adverse Event (SAE)
- Any TEAE leading to study discontinuation
- Any TEAE by severity (grade 1-5)
- Any TEAE by relationship
- Any index-knee related TEAE
- Any index-knee related SAE
- Any index-knee related TEAE leading to study discontinuation

- Any index-knee related TEAE by severity (grade 1-5)
- Any index-knee 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-knee related TEAEs by SOC and PT
- All index-knee related TEAEs related to study drug by SOC and PT
- All index-knee related TEAEs by maximum severity by SOC and PT

Summary tables and the tabulation of All TEAEs by SOC and PT will be presented for the following patient groups and time periods, with a separate table for each patient group:

1. Patients receiving only one dose
    a. First dose to Week 12
    b. First dose to Week 24 (end of study)
2. Patients receiving the second dose at Week 12
    a. First dose to Week 12
    b. Week 12 to Week 24
    c. Week 12 to Week 52
3. Patients receiving the second dose at Week 16
    a. First dose to Week 16
    b. Week 16 to Week 32
    c. Week 16 to Week 52
4. Patients receiving the second dose at Week 20
    a. First dose to Week 20
    b. Week 20 to Week 40
    c. Week 20 to Week 52
5. Patients receiving the second dose at Week 24
    a. First dose to Week 24
    b. Week 24 to Week 48
    c. Week 24 to Week 52

Summary tables and all tabulations will be presented for the following time periods for patients receiving two doses only (same table):

1. Baseline to Week 52
2. Baseline to Week 12
3. Second dose to 12 weeks after second dose

Date and time of onset of TEAE will be used to assign the time periods.

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.

If an event has a TEAE start date that, after imputation rules are applied, is not complete enough to determine the time period in which the TEAE occurred, that event will not be included in the tabulations by study day.

Formal hypothesis-testing of AE incidence rates will not be performed.

By-patient listings will be provided for the following, for all patients: patient deaths, SAEs and AEs leading to discontinuation.

4.10.2. Laboratory Data

Clinical laboratory values will be expressed in the international system of units (SI).

The following values will be summarized for each hematology and clinical chemistry laboratory parameter for all patients combined:

1. Baseline (Screening) - Observed
2. Second dose visit (two-dose group only) - Observed and change from baseline
3. Final study visit - Observed and change from baseline

In the event of repeat values, the last non-missing value per study visit will be used.

All laboratory data, including Common Terminology Criteria for Adverse Events (CTCAE) 4.03 grade, will be provided in data listings. See Appendix A for CTCAE grade definitions.

4.10.3. Vital Signs, Physical Examination, and Index Knee Assessment

The following values will be summarized for each vital sign parameter for all patients combined:

1. Baseline - Observed
2. Second dose visit (two-dose group only) - Observed and change from baseline
3. Final study visit - Observed and change from baseline

In the event of repeat values, the last non-missing value per study visit will be used.

Vital sign measurements will be presented for each patient in a data listing.

All clinically significant abnormalities noted in the physical examination will be presented in a data listing.

The following values will be summarized for incidence of inflammation, as determined from the index knee assessment, for all patient combined:

1. Baseline - Observed
2. Second dose visit (two-dose group only) - Observed
3. Final study visit - Observed

For those patients experiencing inflammation, the details of the inflammation (tenderness, swelling, effusion, heat/redness, Baker's cyst) will also be presented. In these tabulations, percentages will be based on those patients who have a non-missing index knee assessment at a given visit.

Index knee assessment as well as index knee aspiration data will be presented in a data listing.

4.10.4. Electrocardiogram

Electrocardiogram (ECG) data for each patient will be provided in a data listing.

4.10.5. Index Knee X-ray

Index knee X-rays are performed at Screening for all patients, and at Week 52/End of Study for patients that receive a second injection. The X-rays are read at a central imaging laboratory and are evaluated for joint space narrowing (JSN), subchondral bone changes (SBC), osteonecrosis, and insufficiency fracture at baseline and the end of study. Two independent radiologists will initially read and score each X-ray.

<u>JSN</u>

Joint space narrowing will be scored in two locations (medial and lateral tibiofemoral compartments) according to the following 4-point ordinal scale of 0 to 3 scale:

0. None: Normal appearance.
1. Mild: Presence of mild narrowing.
2. Moderate: Presence of moderate narrowing.
3. Severe: Presence of severe narrowing

Joint space narrowing for each location will be defined as follows:

- If Reader 1 and Reader 2 agree (are concordant) on the JSN score, then that score will be used in the analysis.
- If Reader 1 and Reader 2 do not agree (are discordant) then the average score of Reader 1 and Reader 2 will be obtained and used in the analysis.

At each visit, the maximum score of the two locations as defined above will be used as the analysis value.

SBC

SBC will be derived by determining the presence/absence (0=absent, 1=present) of sclerosis and/or bone attrition in each of four locations (medial femur, lateral femur, medial tibia and lateral tibia). SBC will be presented overall, rather than by category or location and will be derived as follows:

- For each of the 8 possible categories/locations, (sclerosis and bone attrition at each of four locations):
    - If Reader 1 and Reader 2 agree (are concordant) on the SBC score, then that score will be used in the analysis.
    - If Reader 1 and Reader 2 do not agree (are concordant) on the SBC score, then a score of 0 (absent) will be used in the analysis.

  If any of the 8 categories/locations are 1 (present), then the SBC will be considered present. It will be considered 0 (absent) only if all of the parameters are 0 (absent).

Osteonecrosis and Insufficiency Fracture

Osteonecrosis and insufficiency fracture are each measured on a binary scale as absent or present (0=absent, 1=present) and will be adjudicated as follows:

- If Reader 1 and Reader 2 agree (are concordant) on the score of absent or present, then that score is used in the analysis.
- If Reader 1 and Reader 2 do not agree (are discordant) on the score of absent or present, then the X-ray will be read by a third independent radiologist and scored as absent or present. The adjudicated score will agree with either Reader 1 or Reader 2 and that score will be used in the analysis.

Change from baseline to end of study in JSN score will be presented for two-dose patients by patient group (timing of second dose) and for all two-dose patients combined. Any patients whose serial x-rays demonstrate a $\geq$ 2-point grade increase in JSN will be categorized as indicating Chondrolysis. The frequency and percentage of Chondrolysis will be presented in a summary table for the PPIP and SP separately.

Shift tables of joint space narrowing, subchondral bone changes, osteonecrosis and insufficiency fracture will be presented for two-dose patients, showing shifts from baseline to the end of study by patient group (timing of second dose) and for all two-dose patients combined. These tables will be presented for the PPIP and SP separately.

These X-ray data for all patients, including results for each reader, will be presented in a by patient listing. A separate listing will present baseline Kellgren-Lawrence (K-L) Grade.

After review of X-ray results additional sensitivity analyses may be performed to better understand imaging results.

4.10.6. 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 concomitant or pain/restrictive) and whether the CM was used for treatment of an AE.

4.10.7. Surgical Procedures

Surgical procedures that occurred during the study will be provided in a data listing.

5. CHANGES TO PLANNED ANALYSES

In the original protocol the intended analysis was to compare the responses for those patients who received only a single dose to those patients who received two doses of FX006. During the study >90% of the patients enrolled have received a second dose, with approximately 10 patients only receiving one dose. This limited enrollment in a single dose does not adequately support making the protocol specified one-dose to two-dose comparisons for safety and exploratory efficacy meaningful. These comparisons have been eliminated from planned analyses.

According to the protocol, time to maximal pain relief response with WOMAC A (pain) following the first and second doses of FX006 would be examined using a Kaplan-Meier procedure. Instead, the time to second dose was examined using the Kaplan-Meier procedure as this provides a better indication of durability of first-dose response.

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APPENDIX A. LABORATORY GRADE DEFINITIONS - CTCAE 4.03

Lab Parameter	Hypo/Hyper	CTCAE Definition	SI Unit	Grade 1	Grade 2	Grade 3	Grade 4
Alanine Aminotransferase	Hyper	Alanine Aminotransferase increased	IU/L	>ULN-3xULN	>3-5xULN	>5-20xULN	>20xULN
Albumin	Hypo	Hypoalbuminemia	g/L	<LLN-30	<30-20	<20	-
Alkaline Phosphatase	Hyper	Alkaline Phosphatase increased	IU/L	>ULN-2.5xULN	>2.5-5xULN	>5-20xULN	>20xULN
Aspartate Aminotransferase	Hyper	Aspartate Aminotransferase increased	IU/L	>ULN-3xULN	>3-5xULN	>5-20xULN	>20xULN
Bilirubin	Hyper	Blood bilirubin increased	umol/L	>ULN-1.5xULN	>1.5-3xULN	>3-10xULN	>10xULN
Calcium	Hypo	Hypocalcemia	mmol/L	<LLN-2	<2-1.75	<1.75-1.5	<1.5
Calcium	Hyper	Hypercalcemia	mmol/L	>ULN-2.9	>2.9-3.1	>3.1-3.4	>3.4
Creatinine	Hyper	Creatinine increased	umol/L	>1-1.5x baseline; >ULN-1.5xULN	>1.5-3x baseline; >1.5-3x ULN	>3x baseline; >3-6xULN	>6xULN
Glucose	Hyper	Hyperglycemia	mmol/L	>ULN-8.9	>8.9-13.9	>13.9-27.8	>27.8
Potassium	Hypo	Hypokalemia	mmol/L	<LLN-3	<LLN-3	<3-2.5	<2.5

Lab Parameter	Hypo/Hyper	CTCAE Definition	SI Unit	Grade 1	Grade 2	Grade 3	Grade 4
Potassium	Hyper	Hyperkalemia	mmol/L	>ULN-5.5	>5.5-6	>6-7	>7
Sodium	Hypo	Hyponatremia	mmol/L	<LLN-130	-	<130-120	<120
Sodium	Hyper	Hypernatremia	mmol/L	ULN-150	>150-155	>155-160	>160
Hemoglobin	Hypo	Anemia	g/L	<LLN-100	<100-80	<80	-
Hemoglobin	Hyper	Hemoglobin increased	g/L	Increase in>0-20 above ULN or above baseline if baseline is above ULN	Increase in >20-40 above ULN or above baseline if baseline is above ULN	Increase in >40 above ULN or above baseline if baseline is above ULN	-
Leukocytes	Hypo	White blood cells decreased	10^9/L	<LLN-3.0	<3.0-2.0	<2.0-1.0	<1.0
Leukocytes	Hyper	Leukocytosis	10^9/L	-	-	>100	-
Lymphocytes	Hypo	Lymphocyte count decreased	10^9/L	<LLN-0.8	<0.8-0.5	<0.5-0.2	<0.2
Lymphocytes	Hyper	Lymphocyte count increased	10^9/L	-	>4-20	>20	-
Neutrophils	Hypo	Neutrophils count decreased	10^9/L	<LLN-1.5	<1.5-1	<1-0.5	<0.5

Lab Parameter	Hypo/Hyper	CTCAE Definition	SI Unit	Grade 1	Grade 2	Grade 3	Grade 4
Platelets	Hypo	Platelet count decreased	10^9/L	<LLN-75	<75-50	<50-25	<25

The following hematology and chemistry parameters collected in the study are not gradable with CTCAE v4.03:

- Bicarbonate (removed from version 4.x; it was available in version 3)
- Blood urea nitrogen
- Chloride
- Basophils
- Eosinophils
- Erythrocyte count (RBC)
- Hematocrit
- Mean cell volume
- Monocytes
- Total protein
- Uric acid

APPENDIX B. STUDY VISIT FLOW CHART