STATISTICAL ANALYSIS PLAN

Protocol FX006-2017-014

An Open-Label Study to Evaluate the Effect of the Administration of FX006 on Synovial Inflammation in Patients with Osteoarthritis of the Knee

Protocol Number: (Version Date)	FX006-2017-014 Version 6.0 (12 July 2019)
Name of Test Drug:	FX006
Phase:	3b
Methodology:	Open-label, single group, one intra-articular injection study
Sponsor:	Flexion Therapeutics 10 Mall Road, Suite 301 Burlington, Massachusetts, USA Tel: 781-305-7777
Sponsor Representative:	Amy Cinar, PhD Director, Biostatistics
Document Date:	05 Nov 2019
Document Version:	Version 2.0

SIGNATURE PAGE

Protocol Title:	An Open-Label Study to Evaluate the Effect of the Administration of FX006 on Synovial Inflammation in Patients with Osteoarthritis of the Knee
Sponsor:	Flexion Therapeutics 10 Mall Road, Suite 301 Burlington, Massachusetts, USA Tel:781-305-7777
Protocol Number:	FX006-2017-014 Version 6.0 (12 July 2019)
Document Date / Version	05 November 2019 / Version 2.0
Cytel, Inc. Authors:	
Teresa Curto Associate Director, Biostatistics	Signature: _____ Date: 07-Nov-2019

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: 06 NOV 2019

Scott Kelley, MD
Chief Medical Officer

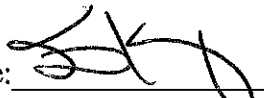
Signature: 
Date: 06 NOV 2019

TABLE OF CONTENTS

Section **Page**

Section **Page**

LIST OF IN-TEXT TABLES

Table **Page**

ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse Event
BMI	Body Mass Index
BP	Biomarker Population
CI	Confidence Interval
cm	Centimeter
CM	Concomitant Medications
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
EP	Efficacy Population
EULAR	European League Against Rheumatism
HIV	Human Immunodeficiency Virus
IA	Intra-articular
IL-1β	Interleukin 1 beta
IP	Imaging Population
IQ	Interquartile Range
IV	Intravenous
JSW	Joint Space Width
K-L	Kellgren-Lawrence
kg	Kilogram
KOOS	Knee injury and Osteoarthritis Outcome Score
LK	Likert
LSM	Least Square Mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Multiple Imputation
mL	Milliliter
m^2	Square meter
mm	Millimeter
mm^2	Square millimeter
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid (RNA)
n	Number of non-missing values
OA	Osteoarthritis

OARSI	Osteoarthritis Research Society International
PT	Preferred Term
QOL	Quality of Life
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIP	Synovitis Imaging Population
SP	Safety Population
TEAE	Treatment-emergent Adverse Event
TA[1]	Triamcinolone Acetonide
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

[1] Abbreviated in past protocols and documents as TCA

REVISION HISTORY

Version	Description of Change
1.0	Original Issue
2.0	• Section 4.9.1: Changed "baseline femur bone size" to baseline "femur bone volume (mm3)". • Section 4.9.2, 4.9.3: Changed "femur bone size" to "femur bone volume". • Section 4.9.4: Added "Femur bone volume". • Section 7.1: o Changed IL-1β mRNA Level units from "copy number" to "ΔΔct". o Changed "Imaging Population and Biomarker Population" to "Patients in the Imaging and Biomarker Populations". o Changed Listing 16.2.6.1.5 title from "Additional Imaging Variables" to "Femur Bone Volume". o Removed Listing 16.2.9.6 Index Knee X-ray Results since Listing 16.2.4.7 Screening Index Knee X-ray Results would present the same data. Renumbered subsequent outputs.

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 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. It is estimated 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 triamcinolone acetonide (TA) for IA administration. It is approved in the US under the trade name ZILRETTA® (triamcinolone acetonide extended-release injectable suspension) for the management of OA pain of the knee. FX006 is intended to deliver TA to the synovial and peri-synovial tissues for a period of approximately 3 months. (Bodick et al, 2013).

1.2. Objectives of Statistical Analysis

The primary objective of this study is to assess the effect of a single IA injection of FX006 32 milligrams (mg) to control inflammation as measured by a reduction in Magnetic Resonance Imaging (MRI) assessed synovial volume in patients with symptomatic OA of the knee and defined synovial volume at baseline.

Secondary objectives of the study include the following:

- To assess the effect of FX006 on pain, stiffness, function, and quality of life (QOL)
- To assess changes in bone area and cartilage thickness of the knee

Exploratory objectives of the study include the following:

- To assess structural changes in bone, cartilage and meniscus
- To assess changes in contrast enhancement of tissue other than synovial tissue

- To identify Responders and Non-Responders by assessing structural and contrast changes in bone, cartilage and other tissues
- Through assessment of blood Interleukin 1 beta (IL-1β) Messenger Ribonucleic Acid (mRNA) levels, to segment patients into inflammatory and non-inflammatory phenotypes, and to examine the response to therapy of these phenotypes

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 an open-label study assessing the effect of the administration of a single IA injection of FX006 32 mg on synovial volume in patients with OA of the knee. The study will be conducted in male and female patients who are ≥ 40 years of age.

Eligible patients who provide written consent and meet all entry criteria will undergo initial ultrasound examination and MRI with contrast of the index knee. For each MRI, a pretreatment synovial volume measurement will be derived by quantitative image analysis. Patients will then receive a single IA injection of FX006 administered to the index knee at Baseline/Day 1. Patients will return to the clinic at Weeks 6 and 24 for an MRI with contrast of the index knee and other assessments. Patients must also have a blood sample drawn for Estimated Glomerular Filtration Rate (eGFR) testing within 30 days prior to the scheduled MRIs. In addition, a patient questionnaire will be administered and adverse events (AEs) and concomitant medication (CM) updates will be collected via telephone at Weeks 12 and 18.

2.2. Randomization Methodology

This is a single arm, open-label study design. Participants are not randomized. Neither patients nor study personnel are blinded to treatment assignment.

2.3. Stopping Rules and Unblinding

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

There will be no data review committee for this study.

2.4. Study Procedures

The study will involve a Screening period (up to 28 days), a pretreatment day when an Ultrasound and MRI of the index knee will be performed, dosing at Baseline/Day 1 and two additional clinic visits at Weeks 6 and 24. In addition, patients must also have a blood sample drawn for eGFR testing within 30 days prior to the scheduled MRIs. Follow-up via telephone will occur at Weeks 12 and 18.

At specified times throughout the study, patients will undergo physical examinations, index knee assessments, imaging of the index knee (MRI with contrast), 12-lead Electrocardiogram (ECG); blood samples will be collected for laboratory safety tests and vital signs will be collected or measured. Information regarding AEs and CMs will be collected, and patient questionnaires (Western Ontario and McMaster Universities (WOMAC®) Osteoarthritis Index

Likert (LK) 3.1, the Knee injury and Osteoarthritis Outcome Score (KOOS) QOL Subscale, and a set of questions exploring pain and stiffness of the knee will be completed.

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

Table 1: Schedule of Study Assessments

Procedures	Screening[1]	Pre-Treatment[2]	Baseline / Day 1	Week 6[3]	Week 12[3,4]	Week 18[3,4]	Week 24 / End of Study[3]
Informed consent	X[5]						
Inclusion/Exclusion Review	X		X[6]				
Medical History/Update	X		X[6]				
OA Medical History/Update	X		X[6]				
Prior Treatment & Medications[7]	X		X[6]				
Physical Examination	X						X
Index Knee X-ray[8]	X						
Index Knee Assessment[9]	X		X[6]	X			X
Ultrasound examination of index knee[10]		X					
MRI with contrast of index knee[11]		X		X			X
12-Lead ECG	X						
Vital Signs	X		X[6]				X
Height	X						
Weight and BMI	X						X
Hematology & Chemistry[12]	X						X
HIV, Hepatitis B/C[12]	X						
IL-1β mRNA levels[12]			X[6]				
eGFR[12,13]	X			X			X
Serum Pregnancy Test[14]	X						
Urine Pregnancy Test [14]			X[6]				X
WOMAC[15]	X		X[6]	X	X	X	X
Supplemental pain and stiffness questionnaire[15]			X[6]	X			X
KOOS QOL[15]			X[6]	X			X
Index knee aspiration and collection of synovial fluid[6]			X[6]				
Treatment administration			X				
AEs & ConMeds [16]			----------X----------				
SAEs[17]	----------X----------						

[1] Screening may occur up to 28 days prior to Day 1.
[2] The Pre-Treatment visit must be within 10 days of Baseline/Day 1 and once eligibility is confirmed.
[3] Visit should be conducted within +/- 7 days from scheduled date.
[4] Via telephone.
[5] Consent must be obtained prior to performing any study-specific procedures.
[6] Complete assessment prior to dosing.
[7] Record any medications received within 30 days prior to the Screening visit
[8] Standing, fixed flexion PA view, weight bearing X-ray of the index knee will be taken using a standardized knee positioning device. The Screening X-ray will be read centrally for KL grade, the presence of osteophytes, and the measurement of joint space width.
[9] Index knee will be assessed for tenderness, heat/redness, swelling, effusion, and Baker's cyst. New clinically significant findings or findings that worsen from the patient's baseline condition should be recorded as AEs.
[10] Ultrasound must be performed within -10 days prior to Baseline/Day 1 and using a linear transducer and with the knee in a semi-flexed position. Synovial proliferation will be confirmed in a transverse view but measured in a longitudinal view only.
[11] MRI must be performed within -10 days prior to Baseline/Day 1 and +/- 7 days of Weeks 6 and 24 and only if eGFR results are ≥ 40 mL/min per the central laboratory. MRI images should follow the vendor specific knee sequences as detailed in MRI Acquisition Manual.
[12] Via Central Laboratory.
[13] Must be performed within 30 days prior to Week 6 and Week 24 MRI with contrast.
[14] Conduct for females of childbearing potential only. Serum pregnancy test to be performed via central laboratory at Screening; urine pregnancy test to be performed locally at Baseline/Day 1, and results available prior to dosing.
[15] Patient questionnaires to be completed prior to all other assessments.
[16] AEs and Concomitant Medications will be captured from Day 1 (from start of study drug administration) to Week 24/Final Visit.
[17] SAEs will be recorded from Informed Consent to the end of participation in the study or Week 24/Final Visit.

2.5. Safety, Imaging, Efficacy, and Biomarker Variables

2.5.1. Safety Variables

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

2.5.2. Imaging Variables

Synovial volume and structural changes in various tissues (bone, cartilage, meniscus) and change in contrast enhancement of tissues other than synovium will be evaluated on the basis of MRI by a central imaging vendor.

2.5.3. Efficacy Variables

Efficacy will be evaluated on the basis of the results of the WOMAC pain, stiffness and function domains independently and collectively (Bellamy et al, 1988), the KOOS QOL Subscale (http://www.koos.nu/) and a set of questions exploring pain and stiffness of the knee.

2.5.4. Biomarker Variables

Whole blood samples will be taken from patients at Baseline/Day 1. Total RNA will be isolated from these samples for analysis of mRNA levels of the pro-inflammatory cytokine IL-1β. The expression of baseline IL-1β among patients will be compared to several other parameters, such as MRI images, with the goal of determining if baseline mRNA IL-1β expression contributes to the pathogenesis of OA and/or is associated with responsiveness to FX006 treatment.

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 (SP):

The SP will include all patients who receive any amount of study drug. The Safety Population will be used to assess safety and tolerability.

Synovitis Imaging Population (SIP):

The SIP will include all patients from the SP who have a pre-treatment synovial volume measurement of greater than 3000 mm^3 of gadolinium enhancement as determined by quantitative image analysis, as well as quality pre-treatment and Week 6 MRIs. In addition, the patients included in this population will have no major protocol deviations and/or imaging variations (i.e. change in coil, machine, or software) deemed to potentially impact the imaging analysis.

Imaging Population (IP):

The IP will include all patients from the SP who have quality MRI data available for pre-treatment and at least one post-baseline timepoint and with no major protocol deviations and/or imaging variations (i.e. change in coil, machine or software) deemed to potentially impact the imaging analysis.

Efficacy Population (EP):

The EP will include all patients from the SP, who have at least one post-Baseline/Day 1 WOMAC or KOOS assessment.

Biomarker Population (BP):

The BP will include all patients from the SP, who have a Baseline/Day 1 IL-1β result.

Patients must be included in both relevant study populations to be included in analyses comparing two parameters.

3.2. Protocol Deviations

All protocol deviations will be tabulated and presented in the data listings.

4. STATISTICAL METHODS

4.1. Sample Size Justification

Approximately 100 patients will be enrolled and treated with a single IA injection of 32 mg FX006 to ensure a minimum of 70 evaluable Synovitis Imaging patients, as defined by pre-treatment MRI synovial volume measurement of greater than 3000 mm^3 of gadolinium enhancement as determined by quantitative image analysis, with quality pre-treatment and Week 6 MRIs. Previous trials had similar sample sizes (Gait et al., 2016; O'Neill et al., 2016).

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

Once all enrolled patients have completed the Week 24 visit, all final analyses specified in the SAP will be completed following database lock and reported in the CSR. Post-hoc, exploratory analyses, may also be performed to further understand and elucidate study results; these analyses will be clearly identified as such in the CSR.

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).

All analyses will be done overall and stratified by baseline synovitis (yes/no). Stratified analyses will be descriptive in nature. There will be no statistical comparisons between baseline synovitis groups. Tables will be presented with one column for those with BL synovitis, one column for those without baseline synovitis and one columns for all patients. Figures will be presented stratified by baseline synovitis (yes/no) and for all patients.

Tabulations will be produced for appropriate demographic, baseline, safety, imaging, and efficacy parameters.

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, SD minimum and maximum values will be presented. 95% Confidence Intervals (CI) may be provided. Additional statistics may be presented for certain endpoints as described below.

All CIs, statistical tests, and resulting p-values will be reported as 2-sided. Significance will be assessed at $\alpha = 0.05$ level and the significance level will not be adjusted for the secondary endpoint analyses. P-values of less than or equal to 0.05 will be described as statistically significant and potentially informative.

All collected data will be presented in by-patient listings sorted by 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 (i.e., injection in the first knee), which is designated as Day 1. The preceding day is Day-1; the day before that is Day-2, etc.

The sections below describe the intended analysis of the endpoints. 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 descriptive statistical analyses will be performed using SAS/STAT® software (Version 9.4 or higher), unless otherwise noted.

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

CMs will be coded using World Health Organization (WHO) Drug Dictionary (DD) (Mar 2014 or higher).

4.2.3. Methods of Pooling Data

Not applicable to the present study.

4.2.4. Adjustments for Covariates

Continuous endpoints will include baseline score and study site as covariates. Covariates specific to particular endpoints are described in the sections below. Other covariates may be explored.

4.2.5. Multiple Comparisons/Multiplicity

Although confidence intervals and p-values will be calculated for change from baseline for primary, secondary and exploratory endpoints, only the primary endpoint is hypothesis driven. These measures are used for guidance regarding the strength of the association, informally.

4.2.6. Subpopulations

The following variables will be used for subgroup analyses:

1. Gender (Male/Female)
2. WOMAC A 30% and 50% responders at Week 6 as defined in Section 4.10.1.2. (Yes/No)
3. Prior IA steroid injection in index knee at Baseline (Yes/No)
4. Joint space width (JSW) at Screening (2-4 mm vs. >4 mm)

Details about whether particular subgroup analyses will be performed or not are described in the sections for each endpoint. Additional 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 drug as a single IA injection. Therefore, discontinuation from treatment is not applicable.

Each patient may only discontinue from the study for further assessments and study visits. 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 Week 6 would be mapped to Week 24 / End of Study (EOS) since Hematology and Chemistry is not a planned assessment at Week 6).

4.2.8. Missing, Unused, and Spurious Data

Unless noted below, missing values will not be imputed and data will be analyzed "as observed". Sensitivity analyses, such as multiple imputation (MI), may be performed to examine the effect of missing data where a particular variable is missing for >10% of a data point.

4.2.8.1. Safety data

Missing AE data will be imputed or otherwise handled as indicated in Section 4.8.1. Missing CM data will be handled as indicated in Section 4.8.7.

4.2.8.2. Efficacy 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.

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.

4.2.9. Visit Windows

No analysis visit windows are defined in this study. All parameters will be summarized and presented according to the nominal visit as recorded on the Electronic Case Report Form (eCRF), with the exception of unscheduled visits, which are mapped as detailed in Section 4.2.7.

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 enrolled patients who are not exposed to study drug, the latest assessment during the screening period will be used.

4.2.11. Baseline Synovitis Definition

The definition for baseline synovitis is the same definition that is used to determine the SIP population: pre-treatment synovial volume measurement of greater than 3000 mm^3 of gadolinium enhancement as determined by quantitative image analysis.

4.3. Interim Analyses

Once all enrolled patients in the SIP have completed the Week 6 visit, the mean standardized change from baseline at 6 weeks in synovial volume (the primary endpoint) and the mean absolute (non-standardized) change from baseline at 6 weeks in synovial volume will be analyzed. The descriptive statistics described in Section 4.9.1 will be presented for baseline and Week 6 only. The synovial volume analysis will also be performed by WOMAC A 30% and 50% responders at Week 6 subgroups, as defined in Section 4.2.6. No other subgroup analyses will be presented.

The following efficacy endpoints will also be presented for baseline and Week 6 only, as described in the sections below:

- WOMAC A, B, C and Total
- WOMAC A 30% and 50% responders
- KOOS QOL

In addition, patient disposition, demographic and baseline characteristics, OA medical history, study drug exposure and adverse events will be presented as described in the sections below.

Full results of this interim analysis will be presented to the Sponsor.

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 enrolled, 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.

Data listings will be provided for the following:

- Study completion information, including the reason for early study discontinuation, if applicable.
- Analysis populations, including reason for exclusion from an analysis population.
- Inclusion and exclusion criteria not met.

4.5. 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.

4.6. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the SP.

No formal statistical comparisons will be performed.

All collected demographic, baseline characteristic and medical history data will be tabulated and 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 (centimeter (cm));
- Gender (Male/Female);
- Body mass index (BMI) (kg/m^2);
- BMI category:
    - Underweight: <18.0 kg/square meter (m^2)

- Normal: 18.0 to <25.0 kg/m²
- 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);

4.6.2. OA Medical History

General OA and knee OA medical history data as collected on the CRF will be tabulated for the SP.

Years since primary diagnosis of OA in the index knee to Day 1 of the study in days (dose date – date of diagnosis + 1)/365.25, 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 CM data listing with a flag identifying which medications are prior medications (refer to Section 4.8.7 for details on defining prior and concomitant medications).

4.7. Study Drug Exposure

Details of study drug administration will be tabulated and presented for the SP. Specifically, the position of the knee during injection, the approach during injection, the numbing agent used, whether or not the entire contents of the syringe were injected, needle size used and synovial fluid volume aspirated will be presented.

All dosing data will be presented in a data listing.

4.8. Safety Analyses

Safety analyses will be conducted using the SP.

4.8.1. Adverse Events

AEs will be coded using the 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 EOS.

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 (mild/moderate/severe)
- 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 (mild/moderate/severe)
- 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 TEAEs by PT (decreasing frequency)
- All SAEs by SOC and PT

- All TEAEs related to study drug 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

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 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, as applicable.

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. For hematology and chemistry, in the event of repeat values, the last non-missing value prior to the visit will be used.

All laboratory data will be provided in data listings.

4.8.3. Vital Signs, Physical Examinations and Index Knee Assessment

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

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

The incidence of inflammation, as determined from the index knee 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 knee assessment at a given visit. Index knee assessment as well as knee aspiration data will be presented in a data listing.

4.8.4. Ultrasound

Ultrasound data will be provided in patient data listing.

4.8.5. Electrocardiogram

ECG data will be provided in patient data listing.

4.8.6. Index Knee X-Ray

Kellgren-Lawrence (K-L) grade, presence of osteophytes (Yes/No) and JSW data at Screening will be summarized and presented with the OA history and index knee characteristics data. X-ray data for each patient will also be provided in a data listing.

4.8.7. Concomitant Medications

CMs will be defined as those medications that were initiated after first dose of treatment or those that were ongoing at the time of first 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 the first dose, the medication will be assumed concomitant. If the start date occurs prior to the first dose date but the end date is on or after the first dose 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 (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 (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 first dose or completely missing, the medication will be assumed to be a prior medication.

All prior and concomitant medications 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, restrictive or per-protocol) and whether the CM was used for treatment of an AE.

4.8.8. Surgical Procedures

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

4.9. Imaging Analyses

All imaging analyses will be conducted using the IP. The following MRI collection data will be presented in a listing:

- Was the eGFR performed within 30 days prior to the MRI assessment with result ≥ 40 mL/min per central laboratory?
- Was the MRI with contrast of index knee performed?

- Use of MRI contrast?
- Date performed

Analyses of imaging data are presented below.

4.9.1. Synovial Volume Change from Baseline

The primary efficacy endpoint is the mean standardized change from baseline at 6 weeks in synovial volume. Secondary efficacy endpoints are mean absolute change from baseline at 6 weeks in synovial volume as well as mean standardized and absolute change from baseline in synovial volume at Week 24.

Descriptive statistics (number of observations, unadjusted mean, SD, median, 25^{th} and 75^{th} percentiles, minimum and maximum) will be presented for synovial volume by visit (baseline, Week 6 and Week 24/EOS). Change from baseline will also be presented. For the change from baseline calculation, baseline is the synovial volume result obtained at baseline (pretreatment).

The adjusted change from baseline will also be presented. This will be done using a mixed effects model for repeat measures (MMRM) with fixed effects for study time point, study site, baseline score and baseline femur bone volume (mm^3). Baseline femur bone volume will be included because synovial volume is related to patient size. Change from baseline is the outcome. 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 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 presented in the table output and fully documented in the results section of the CSR.

This model will provide the change from baseline estimated at each visit with the corresponding standard error (SE), 95% CI and 2-sided p-value. The standardized change from baseline and corresponding 95% CIs will also be presented. These values will be calculated by dividing the model-derived LSM and 95% CIs by the adjusted SD.

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

```
proc mixed data=dsin1 method=reml;
  class subjid avisitn siteid;
  model chg= base avisitn siteid femursize;
  repeated avisitn/type=un subject = subjid;
  lsmeans avisitn /pdiff cl;
run;
```

Line plots presenting observed mean and LSM change from baseline in synovial volume over time will be produced for absolute values. Line plots presenting standardized LSM change from baseline in synovial volume over time will be produced as well. In these plots, all visits will be presented. There will be standard deviation bars for observed values and standard error bars for adjusted values. LSM change from baseline will come from a mixed model as described above.

In addition, by-patient spaghetti plots will be presented using unadjusted absolute patient values. The population mean will also be presented on these plots.

The synovial volume analysis will also be performed by the following subgroups, as defined in Section 4.2.6: gender, WOMAC A 30% and 50% responders at Week 6, prior IA steroid injection in index knee at baseline, and JSW at Screening.

4.9.2. Change in Bone Area and Cartilage Thickness

The following parameters will be analyzed:

- Bone area of the medial femur (square millimeters [mm^2])
- Cartilage thickness of the central medial femur (millimeters [mm])

Descriptive statistics (number of observations, unadjusted mean, SD, median, minimum and maximum) will be presented for bone area and cartilage thickness by visit (baseline, Week 6 and Week 24/EOS). Change from baseline will be presented as well.

The adjusted change from baseline will also be presented. This will be performed similarly to synovial volume as described in Section 4.9.1. Models for change in bone area will include baseline femur bone volume as a covariate, but models for change in cartilage thickness will not. Line plots will also be presented as described in Section 4.9.1. Analyses will not be performed for subgroups and standardized change from baseline will not be presented.

4.9.3. Structural Changes in Femur Bone Shape Score (B-score)

Femur bone shape score (B-score) measures bone age, with lower scores indicating a healthier knee.

Descriptive statistics (number of observations, unadjusted mean, SD, median, minimum and maximum) will be presented for femur bone shape by visit (baseline, Week 6 and Week 24/EOS). Change from baseline will be presented as well.

Femur bone shape will be analyzed similarly to synovial volume as described in Section 4.9.1. Models for change in B-score will not include femur bone volume as a covariate, since this endpoint is already normalized for the size of the individual knee. Analyses will not be performed for subgroups and standardized change from baseline will not be presented.

4.9.4. Other Imaging Variables

Additional imaging variables, including the following, will also be available and will be presented in data listings:

- Femur bone volume
- Bone area for lateral/medial femur, tibia and patella
- Cartilage thickness for central lateral femur, medial/lateral tibia/patella
- Tibia/patella bone shape.

4.9.5. Contrast Enhancement and Responders/Non-Responders

Changes in contrast enhancement of tissue other than synovial tissue and the dichotomization of patients into responders/non-responders based on changes in synovial volume and/or pain are exploratory in nature, and will be detailed in a separate SAP.

4.10. Efficacy Analyses

All efficacy analyses will be conducted using the EP.

4.10.1. WOMAC

The following WOMAC scales/questionnaires 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 6, Week 12, Week 18 and Week 24/EOS) 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.

4.10.1.1. Change from Baseline

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 24/EOS) for the EP. 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.

WOMAC change from baseline will be analyzed similarly to synovial volume change from baseline, as described in Section 4.9.1. Fixed effects will be study time point, study site and baseline score. This model will be run separately for WOMAC A, WOMAC B, WOMAC C and WOMAC total.

Line plots presenting observed mean and LSM change from baseline in WOMAC A, WOMAC B, WOMAC C and WOMAC total score over time will be produced. In these plots, all visits will be presented. There will standard deviation bars for observed values and standard error bars for adjusted values. LSM change from baseline will come from separate mixed models as described above.

4.10.1.2. 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 6 through Week 24/EOS.

Response rate will be plotted with a bar chart.

Additionally, for Week 12, a continuous responder curve will display the cumulative proportion of responders on the y-axis versus percentage of improvement from baseline on the x-axis.

The same descriptive analyses will be done where responders are defined as patients who have ≥30% decrease in the WOMAC A score from baseline at a given visit.

4.10.2. KOOS QOL

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 6 and Week 24/EOS). Missing data rules are as presented in Section 4.2.8.

The KOOS QOL subscale will be analyzed similarly to the WOMAC Change from Baseline, as described in Section 4.10.1.1.

4.10.3. Pain/Stiffness Questionnaire

The supplemental pain and stiffness questionnaire has 10 questions that ask about the patient's pain in the last 7 days. Descriptive statistics (number of evaluable patients and number and percent with each possible response) will be presented for each question by visit (Baseline, Week 6 and Week 24/EOS) for the EP.

4.11. Biomarker Analyses

4.11.1. IL-1β mRNA

Pro-inflammatory cytokine interleukin 1 beta (IL-1β) mRNA analyses will be done using patients that are in both the IP and BP. Whole blood samples will be taken from patients at Baseline/Day 1. Total Ribonucleic Acid (RNA) will be isolated from these samples for analysis of messenger RNA (mRNA) levels of the pro-inflammatory cytokine interleukin 1 beta (IL-1β). The expression of baseline IL-1β mRNA among patients will be compared to several other parameters, with the goal of determining if baseline IL-1β mRNA expression contributes to the pathogenesis of OA and/or is associated with responsiveness to FX006 treatment. These parameters will include:

- Change from Baseline in imaging endpoints as defined in Section 4.9
    - Synovial Volume Change
    - Bone Area and Cartilage Thickness
    - Femur Bone Shape Score (B-score)

The correlation between baseline IL-1β mRNA expression and change from baseline for each of the imaging variables and time points 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. Each of the imaging variables versus baseline IL-1β mRNA will be presented in scatter plots, which will also include regression lines.

Per the protocol, patients were to be segmented into inflammatory and non-inflammatory phenotypes through assessment of blood IL-1β mRNA levels, and to examine the response to therapy of these phenotypes. However, given that there is no prior evidence for such a cut-point,

the baseline IL-1β mRNA levels will instead be summarized using descriptive statistics. If the graphical summaries demonstrate that a reasonable cut-point to define an inflammatory phenotype group exists then the response to therapy within the phenotypes may be further explored.

5. CHANGES TO PLANNED ANALYSES

There are no major changes to the planned analyses.

The following minor changes were made:

1. The biomarker population definition was added to support the planned biomarker analysis (Section 3.1).
2. Changes in contrast enhancement of tissue other than synovial tissue and the responder/non-responder analysis will be performed separately and detailed in a separate document (Section 4.9.5).
3. The analyses of inflammatory and non-inflammatory phenotypes defined by the IL-1β levels will only be performed in the case that a clear cut-point exists (Section 4.11.1).
4. The correlative analyses of IL-1β levels is intended to determine if IL-1β levels contribute to the pathogenesis of OA. The protocol stated that correlations between the IL-1β levels and the x-ray and MRI imaging endpoints would be examined. However, as x-ray is only performed at baseline, such an analysis would not provide any information as to the pathogenesis of OA and has been removed (Section 4.11.1).

6. REFERENCES

Ayral X, Pickering EH, Woodworth TG, Mackillop N, Dougados M. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis -- results of a 1 year longitudinal arthroscopic study in 422 patients. Osteoarthritis Cartilage. 2005 May;13(5):361-7.

Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15(12):1833-1840.

Benito MJ, Veale DJ, FitzGerald O, van den Berg WB, Bresnihan B. Synovial tissue inflammation in early and late osteoarthritis. Ann Rheum Dis. 2005 Sep;64(9):1263-7.

Bodick N, Lufkin J, Willwerth C, Blanks R, Inderjeeth C, Kumar A, Clayman M. FX006 prolongs the residency of triamcinolone acetonide in the synovial tissues of patients with knee osteoarthritis. Osteoarthritis Cartilage. 2013;21:(Suppl); S144-5.

Creamer P, Hochberg MC. Osteoarthritis. Lancet 1997;350(906):503–508.

Gait AD, Hodgson R, Parkes MJ, Hutchinson CE, O'Neill TW, Maricar N, et al. Synovial volume vs synovial measurements from dynamic contract enhanced MRI as measures of response in osteoarthritis. Osteoarthritis and Cartilage 2016;24: 1392-1398.

Goldring SR and Goldring MB. Clinical aspects, pathology and pathophysiology of osteoarthritis. J Musculoskelet Neuronal Interact 2006;6(4):376–378.

Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken) 2012; 64(4):465-474.

Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003;62(12):1145–1155.

Menge TJ, Boykin RE, Byram IR, Bushnell BD. A Comprehensive Approach to Glenohumeral Arthritis. South Med J. 2014;107(9):567-573.

Sellam J and Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol. 2010 Nov;6(11):625-35.

Wenham CY and Conaghan PG. The role of synovitis in osteoarthritis. Ther Adv Musculoskelet Dis. 2010 Dec;2(6):349-59.

7. CLINICAL STUDY REPORT APPENDICES

7.1. Statistical Tables and Figures 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	Osteoarthritis History and Index Knee Characteristics (Safety Population)
Table 14.1.4	Summary of Protocol Deviations (Safety Population)
Table 14.1.5	Study Drug Exposure Summary (Safety Population)
Table 14.2.1.1	Summary of Synovial Volume (mm^3) (Imaging Population)
Figure 14.2.1.1.1	Mean (+/- SD) Synovial Volume (mm^3) over Time (Imaging Population)
Figure 14.2.1.1.2	LS Mean Change from Baseline (+/- SE) in Synovial Volume (mm^3) over Time (Imaging Population)
Figure 14.2.1.1.3	Individual Patient Plots of Synovial Volume (mm^3) over Time (Imaging Population)
Table 14.2.1.2.1	Summary of Synovial Volume (mm^3), Males (Imaging Population)
Table 14.2.1.2.2	Summary of Synovial Volume (mm^3), Females (Imaging Population)
Figure 14.2.1.2.1.1	Mean (+/- SD) Synovial Volume (mm^3) over Time, by Gender (Imaging Population)
Figure 14.2.1.2.1.2	LS Mean Change from Baseline (+/- SE) in Synovial Volume (mm^3) over Time, by Gender (Imaging Population)
Table 14.2.1.3.1	Summary of Synovial Volume (mm^3), WOMAC A 30% Responders (Imaging Population)
Table 14.2.1.3.2	Summary of Synovial Volume (mm^3), WOMAC A 30% Non-Responders (Imaging Population)
Figure 14.2.1.3.1.1	Mean (+/- SD) Synovial Volume (mm^3) over Time, by WOMAC A 30% Responder (Yes/No) (Imaging Population)
Figure 14.2.1.3.1.2	LS Mean Change from Baseline (+/- SE) in Synovial Volume (mm^3) over Time, by WOMAC A 30% Responder (Yes/No) (Imaging Population)
Table 14.2.1.4.1	Summary of Synovial Volume (mm^3), WOMAC A 50% Responders (Imaging Population)
Table 14.2.1.4.2	Summary of Synovial Volume (mm^3), WOMAC A 50% Non-Responders (Imaging Population)
Figure 14.2.1.4.1.1	Mean (+/- SD) Synovial Volume (mm^3) over Time, by WOMAC A 50% Responder (Yes/No) (Imaging Population)
Figure 14.2.1.4.1.2	LS Mean Change from Baseline (+/- SE) in Synovial Volume (mm^3) over Time, by WOMAC A 50% Responder (Yes/No) (Imaging Population)
Table 14.2.1.5.1	Summary of Synovial Volume (mm^3), Patients with Previous Intra-Articular Steroid Injection in Index Knee (Imaging Population)

Table 14.2.1.5.2	Summary of Synovial Volume (mm^3), Patients without Previous Intra-Articular Steroid Injection in Index Knee (Imaging Population)
Figure 14.2.1.5.1.1	Mean (+/- SD) Synovial Volume (mm^3) over Time, by Previous Intra-Articular Steroid Injection in Index Knee (Yes/No) (Imaging Population)
Figure 14.2.1.5.1.2	LS Mean Change from Baseline (+/- SE) in Synovial Volume (mm^3) over Time, by Previous Intra-Articular Steroid Injection in Index Knee (Yes/No) (Imaging Population)
Table 14.2.1.6.1	Summary of Synovial Volume (mm^3), Patients with Screening Joint Space Width 2-4 mm (Imaging Population)
Table 14.2.1.6.2	Summary of Synovial Volume (mm^3), Patients with Screening Joint Space Width >4 mm (Imaging Population)
Figure 14.2.1.6.1.1	Mean (+/- SD) Synovial Volume (mm^3) over Time, by Screening Joint Space Width (2-4 mm vs. >4 mm) (Imaging Population)
Figure 14.2.1.6.1.2	LS Mean Change from Baseline (+/- SE) in Synovial Volume (mm^3) over Time, by Screening Joint Space Width (2-4 mm vs. >4 mm) (Imaging Population)
Table 14.2.2	Summary of Bone Area (mm^2) (Imaging Population)
Figure 14.2.2.1	Mean (+/- SD) Bone Area (mm^2) over Time (Imaging Population)
Figure 14.2.2.2	LS Mean Change from Baseline (+/- SE) in Bone Area (mm^2) over Time (Imaging Population)
Table 14.2.3.1	Summary of Cartilage Thickness (mm) (Imaging Population)
Figure 14.2.3.1.1	Mean (+/- SD) Cartilage Thickness (mm) over Time (Imaging Population)
Figure 14.2.3.1.2	LS Mean Change from Baseline (+/- SE) in Cartilage Thickness (mm) over Time (Imaging Population)
Table 14.2.4	Summary of Femur Bone Shape Score (Vector Units) (Imaging Population)
Figure 14.2.4.1	Mean (+/- SD) Femur Bone Shape Score (Vector Units) over Time (Imaging Population)
Figure 14.2.4.2	LS Mean Change from Baseline (+/- SE) in Femur Bone Shape Score (Vector Units) over Time (Imaging Population)
Table 14.2.5.1	Summary of WOMAC A Pain Subscale (Efficacy Population)
Figure 14.2.5.1.1	Mean (+/- SD) WOMAC A Pain Subscale over Time (Efficacy Population)
Figure 14.2.5.1.2	LS Mean Change from Baseline (+/- SE) in WOMAC A Pain Subscale over Time (Efficacy Population)
Table 14.2.5.2	Summary of WOMAC B Stiffness Subscale (Efficacy Population)
Figure 14.2.5.2.1	Mean (+/- SD) WOMAC B Stiffness Subscale over Time (Efficacy Population)
Figure 14.2.5.2.2	LS Mean Change from Baseline (+/- SE) in WOMAC B Stiffness Subscale over Time (Efficacy Population)

Table 14.2.5.3	Summary of WOMAC C Function Subscale (Efficacy Population)
Figure 14.2.5.3.1	Mean (+/- SD) WOMAC C Function Subscale over Time (Efficacy Population)
Figure 14.2.5.3.2	LS Mean Change from Baseline (+/- SE) in WOMAC C Function Subscale over Time (Efficacy Population)
Table 14.2.5.4	Summary of WOMAC Total (Efficacy Population)
Figure 14.2.5.4.1	Mean (+/- SD) WOMAC Total over Time (Efficacy Population)
Figure 14.2.5.4.2	LS Mean Change from Baseline (+/- SE) in WOMAC Total over Time (Efficacy Population)
Table 14.2.5.6	Analysis of WOMAC A 30% Responders (Full Analysis Set)
Figure 14.2.5.6.1	Proportion of WOMAC A 30% Responders (Full Analysis Set)
Figure 14.2.5.6.2	Continuous WOMAC A 30% Responder Curve at Week 12 (Full Analysis Set)
Table 14.2.5.7	Analysis of WOMAC A 50% Responders (Full Analysis Set)
Figure 14.2.5.7.1	Proportion of WOMAC A 50% Responders (Full Analysis Set)
Figure 14.2.5.7.2	Continuous WOMAC A 50% Responder Curve at Week 12 (Full Analysis Set)
Table 14.2.6.1	Summary of KOOS QOL Subscale (Efficacy Population)
Figure 14.2.6.1.1	Mean (+/- SD) KOOS QOL Subscale over Time (Efficacy Population)
Figure 14.2.6.1.2	LS Mean Change from Baseline (+/- SE) in KOOS QOL Subscale over Time (Efficacy Population)
Table 14.2.7	Summary of Pain/Stiffness (Efficacy Population)
Table 14.2.8	Correlation between Baseline IL-1β mRNA Level (ΔΔct) and Imaging Endpoints Change from Baseline (Patients in the Imaging and Biomarker Populations)
Figure 14.2.8.1	Scatter Plots of Baseline IL-1β mRNA Level (ΔΔct) and Synovial Volume (mm^3) Change from Baseline at Week 6 and Week 24 (Patients in the Imaging and Biomarker Populations)
Figure 14.2.8.2	Scatter Plots of Baseline IL-1β mRNA Level (ΔΔct) and Bone Area (mm^2) Change from Baseline at Week 6 and Week 24 (Patients in the Imaging and Biomarker Populations)
Figure 14.2.8.3	Scatter Plots of Baseline IL-1β mRNA Level (ΔΔct) and Cartilage Thickness Change (mm) from Baseline at Week 6 and Week 24 (Patients in the Imaging and Biomarker Populations)
Figure 14.2.8.4	Scatter Plots of Baseline IL-1β mRNA Level (ΔΔct) and Femur Bone Shape Score (Vector Units) Change from Baseline at Week 6 and Week 24 (Patients in the Imaging and Biomarker Populations)
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 Preferred Term (Safety Population)
Table 14.3.1.4	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Related to Study Drug (Safety Population)
Table 14.3.1.5	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Related to Injection Procedure (Safety Population)
Table 14.3.1.6	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Maximum Severity (Safety Population)
Table 14.3.1.7	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Leading to Study Discontinuation (Safety Population)
Table 14.3.1.8	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Leading to Death (Safety Population)
Table 14.3.1.9	Index Knee-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.10	Index Knee Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term- Related to Study Drug (Safety Population)
Table 14.3.1.11	Index Knee Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Maximum Severity (Safety Population)
Table 14.3.1.12	Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)
Table 14.3.2.1	Patient Listing of Deaths
Table 14.3.2.2	Patient Listing of Serious Adverse Events
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 Knee Assessments (Safety Population)

7.1. Data Listings to be Generated

Listing 16.2.1.1	Patient Disposition
Listing 16.2.1.2	Inclusion/Exclusion Criteria Not Met

Listing 16.2.2	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	Medical History – Index Knee Osteoarthritis
Listing 16.2.4.4	Medical History - Prior Treatment of Knee Osteoarthritis
Listing 16.2.4.5	Medical History - Other Osteoarthritis
Listing 16.2.4.6	Medical History - Other Osteoarthritis Procedures or Surgeries
Listing 16.2.4.7	Screening Index Knee X-ray Results
Listing 16.2.5	Study Drug Exposure
Listing 16.2.6.1.1	MRI Collection Data
Listing 16.2.6.1.2	Synovial Volume
Listing 16.2.6.1.3	Bone Area and Cartilage Thickness
Listing 16.2.6.1.4	Bone Shape
Listing 16.2.6.1.5	Femur Bone Volume
Listing 16.2.6.2.1	WOMAC Questionnaire – List of Questions by Section
Listing 16.2.6.2.2	WOMAC A Pain Subscale
Listing 16.2.6.2.3	WOMAC B Stiffness Subscale
Listing 16.2.6.2.4	WOMAC C Function Subscale
Listing 16.2.6.2.5	WOMAC Total (Subscale Means and Total Score)
Listing 16.2.6.3.1	KOOS QOL Subscale - List of Questions
Listing 16.2.6.3.2	KOOS QOL Subscale
Listing 16.2.6.4.1	Pain and stiffness – List of Questions
Listing 16.2.6.4.2	Pain and stiffness
Listing 16.2.6.5.1	Biomarker Assessments - IL-1β
Listing 16.2.7.1	Adverse Events – Sorted By Patient and Onset Date
Listing 16.2.7.2	Adverse Events – Sorted by System Organ Class, Preferred Term, Treatment, Patient, and Onset Date
Listing 16.2.7.3	Adverse Events – Glossary by MedDRA SOC, Preferred Term and Verbatim
Listing 16.2.8.1	Laboratory Assessments – Hematology
Listing 16.2.8.2	Laboratory Assessments – Chemistry
Listing 16.2.8.3	Laboratory Assessments – eGFR
Listing 16.2.8.4	Screening Laboratory Assessments and Urine/Serum Pregnancy Test Results
Listing 16.2.9.1	Vital Signs
Listing 16.2.9.2	Physical Examination Findings
Listing 16.2.9.3	Index Knee Assessments
Listing 16.2.9.4	Ultrasound Results

Listing 16.2.9.5	Electrocardiogram Results
Listing 16.2.9.6	Prior and Concomitant Medications
Listing 16.2.9.7	Index Knee Aspiration
Listing 16.2.9.8	Surgical Procedures