STATISTICAL ANALYSIS PLAN

Protocol FX006-2018-015
Part I

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

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Sponsor Approval

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

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

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

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ACR	American College of Rheumatology
ANCOVA	Analysis of Covariance
APR	Accurate Pain Reporting
AUE	Area Under the Effect Curve
BMI	Body Mass Index
CI	Confidence Interval
cm	Centimeter
CRF	Case Report Form
CSR	Clinical Study Report
EOS	End of Study
EQ	EuroQol
EQ-5D-5L	EQ 5 Dimensions 5 Levels questionnaire
EQ VAS	EQ Visual Analogue Scale
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
HIV	Human Immunodeficiency Virus
HOOS-QOL	Hip Injury and Osteoarthritis Outcome Score – Quality of Life Subscale
IA	Intra-articular
ICH	International Conference on Harmonization
JSN	Joint Space Narrowing
K-L	Kellgren-Lawrence
kg	Kilogram
LS	Least Squares
m	Meter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MMRM	Mixed Model for Repeated Measures
NRS	Numeric Rating Scale
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OLE	Open Label Extension
OMERACT	Outcome Measures in Rheumatology

Abbreviation	Definition
OR	Odds Ratio
PDF	Portable Document Format
PGIC	Patients' Global Impression of Change
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	Sleep Interference
SOC	System Organ Class
SP	Safety Population
TA[1]	Triamcinolone Acetonide
TEAE	Treatment Emergent AE
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

[1] Abbreviated in past protocols and documents as TCA

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 joints disease, affecting over 30 million Americans, with numbers expected to grow as a result of aging, obesity and sports injuries (Woolf, 2003; Cisternas, 2016; Martel-Pelletier, 2008; Michael, 2010). 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).

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

FX006 is an extended-release formulation of triamcinolone acetonide (TA) for IA administration. It is approved in the US under the trade name ZILRETTA® (triamcinolone acetonide extended-release injectable suspension) for the management of pain of OA 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). FX006 contains TA, United States Pharmacopeia (Ph. Eur/USP), formulated in 75:25 poly (lactic-co-glycolic acid) (PLGA) microspheres with a nominal drug load of 25% (weight by weight [w/w]) and is provided as a sterile white to off-white powder for reconstitution. The drug product is reconstituted with diluent containing an isotonic, sterile aqueous solution of sodium chloride (NaCl; 0.9% w/w), carboxymethylcellulose sodium (CMC; 0.5% w/w) and polysorbate-80 (0.1% w/w) to form a suspension prior to IA injection.

Similar as in knee OA, hip OA patients are confronted with insufficient management of their symptoms (Zhang et al, 2008). Conventional corticosteroids have demonstrated clinical benefits in patients with hip OA (Lambert et al, 2007; Qvistgaard et al, 2006; Atchia et al, 2011), but with short duration of effect (approximately 4-8 weeks) and side effects from burst release of steroids into systemic circulation (Habib et al, 2011). Due to its slow release formulation,

FX006 has the potential to offer longer duration of efficacy and minimized systemic exposure, thus, an improved benefits/risk profile for hip OA patients.

1.2. Objectives of Statistical Analysis

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

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

• To assess the safety of FX006 in patients with hip OA

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 Part I results sections of the clinical study report (CSR) for this trial, as well as used for regulatory filings and manuscripts and presentations.

This SAP will also 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 and Randomization Methodology

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

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

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

Patients participating in Part I of the study will be treated with a single IA injection of either 32 mg FX006 or normal saline and will return for follow up visits at Weeks 12, 16, 20, and 24 or up until implementation of Protocol Version 3.0. The patients will be discontinued at the time of notification by the Investigator.

2.2. Stopping Rules and Unblinding

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

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

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

There will be no data review committee for this study.

Furthermore, discontinuation from treatment is not applicable to this study as each randomized patient in the Part I and the Part II double blind phase of the study receives study medication at a single administration.

2.3. Study Procedures

Patients participating in this study will complete visit schedules and procedures as detailed in the Schedule of Study Assessments (Table 1).

Table 1 Schedule of Study Assessments for Double Blind Phase

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

a. *The Double-Blind Phase* of the study ends at Week 12. Patients participating in Part I of the study will not receive a second injection but will return to the clinic at Weeks 12, 16, 20, and 24 or up until the time of this amendment. Patients participating in Part II of the study who are eligible for the second injection in the open-label phase at Week 12 will receive an open-label injection of FX006 at Week 12 and return for follow-up visits at Weeks 16, 20, and 24. These patients will complete the study at Week 24. Patients participating in Part II of the study who are not clinically indicated for a second injection at Week 12 will return to the clinic at Weeks 16, 20, and 24 and will receive an open-label injection of FX006 at the first evaluation where the patient has been determined to meet all criteria.
b. To be collected or assessed prior to injection of study medication
c. X-ray of weight-bearing anterior-posterior view for index hip will be taken for central reading.
d. After signing the ICF, patients must stop all restricted medications (other than rescue medication). The washout (at least 5 half-lives) must be completed at least 2 days prior to Screening 2 visit.
e. Rescue medication will be dispensed to the patient at the Screening visit, and a new bottle will be dispensed at each subsequent visit as needed. Drug accountability will be done at each visit
f. Pregnancy tests will be done in women of child bearing potential. *Serum Pregnancy Test* to be collected only at Screening visit. *Urine Pregnancy Test* to be collected prior to injection of study medication and at EOS (when it occurs)
g. Aspiration must be attempted prior to all injections. If effusion is detected by fluoroscopy guidance, withdraw to near dryness prior to injection
h. Via Central Laboratory
i. To be performed under fluoroscopy guidance
j. To be completed prior to questionnaires
k. To be completed after APR and PRR training but prior to any other assessments.

l. AEs and concomitant medications will be captured from Day 1 (post injection) to EOS visit.
m. Visit should be conducted within +/- 3 days from scheduled date.
n. Screening 1 and Screening 2 visits can be combined into one visit provided the patient does not have a washout from prohibited medications. If there is no washout, please perform APR/PRR first, then the questionnaires, with the WOMAC being completed after APR/PRR, then all subsequent questionnaires as they are listed for Screening 1.

2.4. Efficacy and Safety Endpoints

All endpoints will be exploratory in Part I of the study. The primary comparison for the primary endpoint will be FX006 32 mg versus placebo.

2.4.1. Primary Efficacy Endpoint

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

2.4.2. Key Secondary Efficacy Endpoints

- Change from Baseline on the WOMAC C (function) score at Week 12
- Patients' Global Impression of Change (PGIC) score at Week 12

2.4.2.1. Additional Secondary Efficacy Endpoints

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

- Change from Baseline on the EuroQol (EQ) 5 Dimensions 5 Levels questionnaire (EQ-5D-5L) at Weeks 1, 4, 8, and 12
- Change from Baseline on the Hip Injury and Osteoarthritis Outcome Score – Quality of Life Subscale (HOOS-QOL) at Weeks 1, 4, 8, and 12
- TSQM-9 at Week 12
- Change from Baseline on WOMAC A (pain), B (stiffness), C (function) and PGIC at Weeks 1, 4, 8, and 12 in patients with unilateral hip OA

3. PATIENT POPULATIONS

3.1. Population Definitions

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

- Full Analysis Set (FAS) Population: All patients who received a full dose of study drug. The FAS Population will be used to examine efficacy endpoints for the double-blind phase of the study. This population will be analyzed as randomized.
- Safety Population (SP): All subjects who received at least one dose (full or partial) of study drug. The Safety Population will be used to assess safety and tolerability. This population will be analyzed as treated.

One Part I patient received a second dose under a previous version of the protocol. This patient's data will be included in the SP in its entirety, but only data prior to the second dose will be used in the FAS.

4. STATISTICAL METHODS

4.1. Sample Size Justification

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

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

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

All outputs 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).

Tables will be presented as described in the sections below. Summary data will be presented by treatment group. For patient disposition, protocol deviations, demographic and baseline characteristics, OA medical history and study drug exposure, a total group that includes both treatment groups will also be presented. Any exceptions to this are described in the appropriate sections below.

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

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.

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

4.2.2. Computing Environment

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

AEs will be coding using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 (or higher).

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

4.2.3. Methods of Pooling Data

Not applicable to the present study.

4.2.4. Adjustments for Covariates

The primary endpoint and secondary endpoints will be analyzed with a longitudinal mixed model for repeated measures (MMRM) with fixed effects for treatment group, study week, treatment-by-week interaction, Baseline score of the endpoint, Baseline WOMAC A score and study site. All models will include Baseline WOMAC A score as a covariate, regardless of the endpoint, since randomization was stratified by WOMAC A scores.

AUE will be calculated and comparisons of the AUE endpoints will be estimated from an Analysis of Covariance (ANCOVA) with model parameters for treatment group and covariates of Baseline score of the AUE endpoint, WOMAC A score and study site. All models will include Baseline WOMAC A score as a covariate, regardless of the AUE endpoint, since randomization was stratified by WOMAC A scores.

4.2.5. Multiple Comparisons/Multiplicity

As all analyses of the Part I data are exploratory in nature, there will be no controls for multiplicity.

4.2.6. Subpopulations

The analyses of WOMAC A, B and C change from Baseline and PGIC will be carried out for the subgroup of patients with WOMAC A (pain) average of Screening 2 and Day 1 scores of 5 to <6, 6 to <7, and ≥7 to 9, in order to assess any differences in treatment response in those groups, which were used as a stratification factor in randomization. These analyses will also be presented by unilateral/bilateral hip OA.

Other preplanned subgroups analyses (per aspiration status, Kellgren-Lawrence (K-L) grade, gender and the baseline pain score, etc.) will not be performed for Part I data. Other subgroups may be defined and explored after all pre-planned analyses have been completed to further elucidate study results.

4.2.7. Discontinuations and Loss to Follow-up

Each treated patient from this study receives study medication as a single IA injection. Therefore, discontinuation from treatment is not applicable.

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. Version 3.0 of the protocol separated the study into two parts as the study was put on-hold to new recruitment for an extended period to investigate six patients that did not receive complete study drug administration. All patients enrolled up to the time that the amendment was implemented at each site were followed for at least 12 weeks or up to the time of this amendment, when they were discontinued from the study.

4.2.8. Missing, Unused, and Spurious Data

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

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 HOOS-QOL subscale, the rules as described in HOOS Scoring 2013 (http://www.koos.nu/) will be used. Specifically, the score is only calculated if 50% items (2 out of 4) are non-missing. Otherwise the score will be set to missing.

4.2.9. Visit Windows

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. 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 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.

4.3. Interim Analyses

There will be no interim analyses for Part I of this study.

4.4. Final Analyses

The analyses of the Part I data will be performed in an unblinded manner when all Part I patients have completed, withdrawn or discontinued from the study. Only data from Part I of the

study will be presented. Final analyses specified in the protocol and SAP will be completed and reported in the CSR.

Post-hoc, exploratory analyses, may be completed to further understand and elucidate study results. Any post-hoc, exploratory, analyses completed will be clearly identified as such in the final CSR.

4.5. Patient Disposition

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

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

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.
- Patient inclusion in each of the analysis populations (FAS, SP).

4.6. Protocol Deviations

The number and percentage of patients with at least one protocol deviation will be summarized 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

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 provided in data listings.

4.7.1. Demographic Characteristics

The following Baseline parameters will be summarized for the SP:

- 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/meter $(m)^2$);
- BMI category:
    - Underweight: <18.5 kg/m^2
    - Normal: 18.5 to <25.0 kg/m^2
    - Overweight: 25.0 to <30.0 kg/m^2
    - Obesity Class I: 30.0 to <35.0 kg/m^2
    - Obesity Class II: 35.0 to <40.0 kg/m^2
    - Obesity Class III: >=40.0 kg/m^2
- Ethnicity (Hispanic or Latino / Not Hispanic or Latino);
- Race (White / Asian / Black or African American / American Indian or Alaska Native / Native Hawaiian or Other Pacific Islander);

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

WOMAC A (pain) average of Screening 2 and Day 1, which was used as a stratification factor in randomization, will be presented in the following classifications: 5 to < 6, 6 to < 7, and ≥ 7 to 9.

Patient questionnaires for Baseline PD-Q, PHQ-9, GAD-7, PCS, and ISI will be presented in data listings.

4.7.2. OA Medical History

OA history and index hip characteristics as collected on the CRF will be summarized for the SP.

Time from primary diagnosis of OA in the index hip to Day 1 of the study in days (first dose date – date of diagnosis + 1), will be computed and presented descriptively. If only month and year of initial diagnosis is available, day will be imputed as 1 for calculations. If month and day are missing, the time from primary diagnosis will be computed as year of first dose minus year of diagnosis. If year is missing, time from diagnosis will not be computed.

4.7.3. Prior medication

All prior medications will be presented in the concomitant medication data listing with a flag identifying which medications are prior medications (refer to Section 4.11.5 for details on defining prior and concomitant medications).

4.8. Patient Randomization

Patient Randomization information will be provided in a listing, with assigned treatment, patient ID, date of informed consent, randomization date, dose date, completed study, study completion date, reason for early termination.

4.9. Study Drug Exposure

Details of study drug administration will be summarized for the SP.

The position of hip during injection, approach during injection, the numbing agent used, whether or not fluoroscopy guidance was used, volume of synovial fluid aspirated, whether a 20 gauge, 3 1/2" or 6" needle, was used, whether entire contents of the syringe were injected, reason (if entire contents not injected), and volume remaining in syringe will be presented.

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

4.10. Efficacy Evaluation

All efficacy analyses will be conducted using the FAS.

In addition to the analyses described below, subgroup analyses will be performed as described in Section 4.2.6.

4.10.1. WOMAC

The following WOMAC scales/questions will be analyzed:

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

Since randomization is stratified by WOMAC A (pain) average of Screening 2 and Day 1 scores of 5 to <6, 6 to <7, and ≥7 to 9, this value will be provided in the data listing.

4.10.1.1. Change from Baseline

For the WOMAC subscales, scores at each assessment time point (Baseline, Week 1, 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 10 for each subscale and easier interpretation. Imputation rules are as presented in Section 4.2.8.

Each of the WOMAC subscales will be analyzed separately using a longitudinal MMRM with fixed effects for Baseline score for the endpoint, treatment group, study week, treatment-by-week interaction, study site, and Baseline WOMAC A score. The analysis will include all study weeks of data, and not be confined to only that at Baseline and Week 12. Subject will be the random effect. Treatment differences from placebo will be estimated via least squares (LS) means from the analysis model along with 95% CIs, and associated 2-sided p-values. This model assumes missing at random and includes only observed data.

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.

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

```
proc mixed data= dsin1 method=reml;
   class subjid armcd avisitn site;
   model chg = base armcd avisitn armcd*avisitn site base_womaca;
   repeated avisitn /type=un subject=subjid;
   lsmeans armcd/diff=control ('0') cl;
   /*[where 0 represents treatment=placebo]*/
   lsmeans armcd*avisitn /pdiff cl;
run;
```

Descriptive statistics will also be presented and will include number of observations, unadjusted mean, SD, median, minimum and maximum. 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 using results from the MMRM.

A line plot presenting LS means change from Baseline over time will be produced. Each treatment group will be plotted on a separate line with SE bars. Jitter will be used as needed to distinguish overlapping data.

4.10.1.2. AUE for Change from Baseline in WOMAC over Time

AUE for change from Baseline in WOMAC A and C over various time intervals will be examined.

AUE will be calculated for the subjects who have assessments in all available visits, from a linear trapezoidal rule using the following formula for change from Baseline in WOMAC A and WOMAC C:

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

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}. Only non-missing time intervals will be part of the sum for each AUE calculation (Farrar et al. 2000). If a patient does not have a value for the last visit in a time interval, that patient will be excluded from the AUE analysis for that time interval. For example, if a patient has missing data for Week 12, $AUE_{\text{Week 1 to Week 12}}$ will not be calculated.

The following AUE endpoints will be computed for each subject in the study over the sampling intervals:

- $AUE_{\text{Week 1 to Week 4}}$
- $AUE_{\text{Week 1 to Week 8}}$
- $AUE_{\text{Week 1to Week 12}}$

The comparisons the AUE endpoints will be estimated from an ANCOVA with model parameters for treatment and covariates of Baseline score of the AUE endpoint, WOMAC A score and study site. All models will include Baseline WOMAC A score as a covariate, regardless of the AUE endpoint, since randomization was stratified by WOMAC A scores.

Descriptive statistics will include the LS means and standard error, 95% CI, LS mean difference from placebo, and 2-sided p-value relative to placebo.

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

```
proc mixed data= dsin1;
   class armcd site;
   model aueval = base armcd site base_womaca;
   lsmeans armcd/diff=control ('0') cl;
   /*[where 0 represents treatment=placebo]*/
   ods output lsmeans = lsm diffs = diffs;
run;
```

All AUE data will be presented in a data listing.

4.10.1.3. WOMAC A (pain) Responder

Responders are defined as patients who have ≥20%, ≥30%, or ≥50% decrease in the WOMAC A score from Baseline at a given visit (Weeks 1, 4, 8, 12, etc.). All study visits will be analyzed and presented.

Percentages will only be based on those with non-missing data. The number of patients who have missing data at each visit will be presented.

At each weekly assessment, proportions of FX006 responders will be compared to those responding in the placebo group using logistic regression, displaying the p-value and odds ratio (OR) (with CI) for each comparison. Study site and Baseline WOMAC A score will be included as covariates in the model.

Bar charts displaying the percentage of responders in each treatment group at each weekly assessment will be presented. 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, by treatment group.

4.10.2. PGIC Score

4.10.2.1. Continuous

The continuous PGIC score will be analyzed similar the WOMAC A (pain) analysis described in Section 4.10.1.1. All available study visits will be analyzed and presented.

4.10.2.2. Categorical

In addition, the PGIC scores will be collapsed and categorized as follows:

PGIC Score	Category
1 = Very Much Improved	A = Improved
2 = Much Improved	A = Improved
3 = Minimally Improved	B = Minimal – No Change
4 = No Change	B = Minimal – No Change
5 = Minimally Worse	B = Minimal – No Change
6 = Much Worse	C = Worse
7 = Very Much Worse	C = Worse

The percent of "Improved" subjects (among those patients with available data) at each study visit will be compared between the FX006 treatment group and the placebo group using logistic regression, displaying the p-value and OR (with CI) for each comparison. Baseline score of the endpoint, Baseline WOMAC score and study site will be covariates in each model. Bar charts by visit and treatment will be presented for the collapsed categories of "Improved", "Minimal – No Change", and "Worse".

4.10.3. OMERACT-OARSI and Responder Status

The OMERACT-OARSI responder criteria will also be used to define response (Pham, 2004) using a combination of pain, function, and a patient assessment to form a composite endpoint. The WOMAC A pain subscale, WOMAC C function subscale, and PGIC will be used to derive the composite responder variable. While the OMERACT-OARSI defines patient assessment in terms of numeric changes from Baseline, this study only collects the PGIC which is a static assessment collected at post-Baseline visits asking how the patient feels relative to Baseline; thus, the responder criteria is being modified slightly for this context to consider PGIC responders as those reporting "Very Much Improved" or "Much Improved" status. Patients will be considered responders at a given weekly assessment if they show:

- At least a 50% improvement from Baseline in the WOMAC A pain subscale and an absolute improvement of at least 20 points or at least a 50% improvement from Baseline in the WOMAC C function subscale and an absolute improvement of at least 20 points; OR
- At least two of the following:

- At least a 20% improvement from Baseline in the WOMAC A pain subscale and an absolute improvement of at least 10 points
- At least a 20% improvement from Baseline in the WOMAC C function subscale and an absolute improvement of at least 10 points
- PGIC of "Very Much Improved" or "Much Improved"

It should be noted for the WOMAC Index that higher scores indicate worse function. Also, the absolute change in the responder criteria assumes the WOMAC is on a 100 point scale. To normalize the WOMAC A pain score, the sum of the 5 pain questions will be multiplied by 2. To normalize the WOMAC C function score, the sum of the 17 function questions will be multiplied by 0.59. Imputation of WOMAC A and C scores will follow the rules as displayed in Section 4.2.8. If WOMAC A or C scores cannot be imputed due to the amount of missing data or patients are missing PGIC at a given week, those patients will be counted as missing/not evaluable in the tabulations.

The OMERACT analysis will be conducted in the same way as the WOMAC A (pain) Responder analysis as described in Section 4.10.1.3. All available study visits will be analyzed and presented.

4.10.4. Consumption of Rescue Medications

A descriptive summary of the average rescue medications taken per patient each day will be presented by visit and overall.

Use of rescue medication is recorded on the Rescue Medication Accountability CRF. Each tablet of rescue medication contains 500mg of acetaminophen (paracetamol). The mean number of rescue medication tablets used per day will be computed for each patient according to the following algorithm:

1. At each visit, the number of pills taken will be determined by subtracting the number returned at the current visit by the number dispensed at the previous visit.

2. The number of days between the current and previous visits will be calculated by using the dates of each visit.

3. The average number of pills taken per day will be calculated by dividing the total number of pills used between visits by the total days between visits.

The value for each visit indicates the daily average for the period from the previous visit to the current visit. For example, the value for the Week 8 visit represents the daily average over the time period from Week 4 to Week 8.

Patients who do not report use of rescue medications at a given visit will be counted as having used 0 tablets when calculating the mean number of tablets used, and patients will only be analyzed through the time of study discontinuation or study completion.

Rescue medication consumption will be analyzed similar the WOMAC A (pain) analysis described in Section 4.10.1.1. All available study visits will be analyzed and presented.

Rescue medication usage and accountability data will be provided in by-patient listings.

4.10.5. Sleep Interference (SI)

SI is a single-item measure that was developed specifically to quantify sleep interference due to pain. SI has an 11-point response scale (ranging from 0 'did not interfere with sleep' to 10 'completely interfered with sleep – unable to sleep due to pain') and asks patients to select the number that best describes how much their pain has interfered with their sleep over a period of 24 hours.

SI change from Baseline will be analyzed similar the WOMAC A (pain) analysis described in Section 4.10.1.1. All available study visits will be analyzed and presented.

4.10.6. EQ-5D-5L

For the EQ-5D-5L, the scoring information that is described in the EQ-5D-5L User Guide (https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf) will be used. The EQ-5D-5L has 2 parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D has five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is scored from 1 to 5 (best to worst). The EQ VAS is a single question with the subject's self-rated health, which is recorded on a vertical, visual analogue scale. The available responses range from "Worst imaginable health state" (0) to "Best imaginable health state" (100). In addition, an index score will be derived using the US value set, as described in the EQ-5D-5L User Guide.

Each dimension of the EQ-5D, the EQ VAS and the index score changes from Baseline will be analyzed similar to the WOMAC A (pain) analysis described in Section 4.10.1.1. All available study visits will be analyzed and presented.

4.10.7. HOOS-QOL subscale

The HOOS-QOL subscale (http://www.koos.nu/) has 4 questions, each of which is assigned a score from 0 to 4. The first questions, "How often are you aware of your hip problem?" is coded as follows: 0=never, 1=monthly, 2=weekly, 3=daily, 4=constantly). The remaining questions are coded as follows: 0=not at all, 1=mildly, 2=moderately, 3=severely, 4=totally. 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. Imputation rules are as presented in Section 4.2.8.

HOOS-QOL change from Baseline will be analyzed similar the WOMAC A (pain) analysis described in Section 4.10.1.1. All available study visits will be analyzed and presented.

4.10.8. TSQM-9

The Treatment Satisfaction Questionnaire for Medication (TSQM-9) consists of 9 items with a 5 to 7 point scale for each item. There are 3 domains: global satisfaction, effectiveness and convenience. Each domain will be scored as described in the TSQM-9 User Manual (Version 1.1, October 2018). Instructions for Version 1.4 of the TSQM-9 will be used. The TSQM-9 score at Week 12 for each domain will be analyzed using ANCOVA in the same way as the WOMAC AUE analysis as described in Section 4.10.1.2 except that Baseline TSQM-9 score at Baseline will not be a covariate in the model since TSQM-9 was not administered at Baseline. In addition, a figure will not be produced since there is only one visit.

4.10.9. Sensitivity Analyses

Additional sensitivity analyses may be performed to examine the effect of missing data, as well as the effect of Baseline imbalance, should one occur.

4.11. Safety Analyses

Safety analyses will be conducted using the SP.

4.11.1. Adverse Events

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

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

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

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

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

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

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

- Any TEAE
- Any Serious AE (SAE)
- Any TEAE leading to study discontinuation
- Any TEAE by severity (Mild/Moderate/Severe)
- Any TEAE by relationship
- Any index-hip related TEAE
- Any index-hip related SAE
- Any index-hip related TEAE leading to study discontinuation
- Any index-hip related TEAE by severity (Mild/Moderate/Severe)
- Any index-hip 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 of FX006 group)
- 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-hip related TEAEs by SOC and PT
- All index-hip related TEAEs related to study drug by SOC and PT
- All index-hip related TEAEs by maximum severity by SOC and PT

Summaries will be presented by treatment group. Within each treatment group, AEs will be presented by the following time periods:

1. Baseline to Week 12
2. Week 12 to Last Visit

Date and time of onset of TEAE will be used to assign the time periods. TEAEs that occurred on the same day as the Week 12 visit will be counted in the "Baseline to Week 12" time period.

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.

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

4.11.2. Laboratory Data

The following values will be summarized for each hematology and clinical chemistry laboratory parameter by treatment group:

1. Baseline (Screening) - Observed
2. Week 12 - Observed and change from Baseline
3. EOS - 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 Section 7.3 for CTCAE grade definitions.

4.11.3. Vital Signs and Physical Examinations and Index Hip Assessment

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

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

The incidence of inflammation, as determined from the index hip assessment, will be tabulated for each visit by treatment group. 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 hip assessment at a given visit. Index hip assessment as well as index hip aspiration data will be presented in data listings.

4.11.4. Index Hip X-Ray

Index hip X-rays are performed at Screening and Week 12 for all patients and EOS for all some patients depending on the timing of the EOS visit. All X-rays will be read centrally. At Screening, each patient will have at least one X-ray reading. If the patient is found ineligible by the first reader, they will receive a second eligibility reading. Follow-up visits will have two independent safety readings and findings for osteonecrosis and subchondral insufficiency fracture will be adjudicated by a third reader.

The Screening X-ray will include the following variables:

- K-L grade (0-4)
- Osteonecrosis (absent/present)
- Subchondral insufficiency fracture (absent/present)
- Joint Space Narrowing (JSN) (0-3)
- Sclerosis (absent/present)
- Attrition (absent/present)

The Week 12 and EOS X-rays will include the following variables:

- Osteonecrosis (absent/present)
- Subchondral insufficiency fracture (absent/present)
- Joint Space Narrowing (JSN) (0-3)
- Sclerosis (absent/present)
- Attrition (absent/present)

The variables will be analyzed and presented as follows:

K-L Grade

K-L grade at Screening will be summarized and presented with the OA history and index hip characteristics data. If there is more than one eligibility reading, the second will be used for analysis.

Osteonecrosis and Subchondral Insufficiency Fracture

Osteonecrosis and subchondral insufficiency fracture will each be measured on a binary scale as absent or present (0=absent, 1=present). For the Screening X-ray, if there is more than one eligibility reading, the second will be used for analysis. Follow-up X-rays 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.

JSN

JSN will be scored 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.

JSN 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.

Sclerosis and Attrition

Sclerosis and attrition will each be measured on a binary scale as absent or present (0=absent, 1=present) by each reader.

Sclerosis and attrition will each be defined as follows:

- If Reader 1 and Reader 2 agree (are concordant), then that score will be used in the analysis.
- If Reader 1 and Reader 2 do not agree (are discordant) a score of 0 (absent) will be used in the analysis.

Change from Baseline to Week 12 and change from baseline to EOS (where available) in JSN score will be presented by treatment group. Any patients whose serial X-rays demonstrate a ≥ 1-point grade increase in JSN will be categorized as indicating Chondrolysis. The frequency and percentage of Chondrolysis will be presented in a summary table.

Shift tables of osteonecrosis, subchondral insufficiency fracture, JSN, sclerosis and attrition will be presented by treatment group.

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 K-L grade.

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

4.11.5. Concomitant Medications

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

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

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

4.11.6. Surgical Procedures

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

5. CHANGES TO PLANNED ANALYSES

There are no major changes to the planned analyses.

The following minor changes were made:

1. As a result of the six patients who were unable to receive complete study drug administration, the analysis populations were updated as follows:
    a. The FAS was updated to clarify that this includes only patients who received a full dose of study drug (Section 3.1).
    b. The SP was updated to clarify that this includes all patients who received at least one dose (full or partial) of study drug (Section 3.1).
2. Study site was added as a covariate, since it was determined in previous studies to be an important covariate (Section 4.2.4).
3. The protocol indicates that categorical end points will be compared via chi-square or exact tests. Instead, logistic regression will be used to analyze the WOMAC A pain (Section 4.10.1.3), PGIC categorical (Section 4.10.2.2) and OMERACT responder (Section 4.10.3) outcomes. This allows us to control for covariates in the models.

6. REFERENCES

Atchia I, Kane D, Reed MR, Isaacs JD, Birrell F. Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis. Ann Rheum Dis. 2011 Jan;70(1):110-6.

Bellamy N. WOMAC Osteoarthritis Index User Guide. Version X. Brisbane, Australia 2011.

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.

Cisternas MG, Murphy L, Sacks JJ, Solomon DH, Pasta DJ, Helmick CG. Alternative Methods for Defining Osteoarthritis and the Impact on Estimating Prevalence in a US Population-Based Survey. Arthritis Care Res (Hoboken). 2016;68(5):574–80.

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

Farrar JT, Portenoy RK, Berlin, JA, Kinman JL, and Strom BL. Defining the clinically important difference in pain outcome measures. Pain 2000; 88:287-294.

Habib GS and Miari W. The effect of intra-articular triamcinolone preparations on blood glucose levels in diabetic patients: a controlled study. J Clin Rheumatol 2011;17:302-305.

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.

Lambert RG, Hutchings EJ, Grace MG, Jhangri GS, Conner-Spady B, Maksymowych WP. Steroid injection for osteoarthritis of the hip: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2007 Jul;56(7):2278-87.

Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58:26-35.

Martel-Pelletier J, Boileau C, Pelletier JP, Roughley PJ. Cartilage in normal and osteoarthritis conditions. Best Pract Res Clin Rheumatol. 2008;22(2):351–84.

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

Michael JW, Schlüter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. Dtsch Arztebl Int. 2010;107(9):152–62.

Murphy L, Helmick CG. The impact of osteoarthritis in the United States: a population-health perspective: A population-based review of the fourth most common cause of hospitalization in U.S. adults. Orthop Nurs 2012;31:85-91.

Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, Simon L, Strand V, Woodworth T, Dougados M. OMERACT–OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage 2004;12:389–99.

Qvistgaard E, Christensen R, Torp-Pedersen S, Bliddal H. Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. Osteoarthritis Cartilage. 2006 Feb;14(2):163-70.

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.

Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ. 2003;81(9):646–56.

Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16:137-162.

7. CLINICAL STUDY REPORT APPENDICES

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7.3. 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
Cholesterol	Hyper	Hypercholestremia	mmol/L	>ULN-7.75	>7.75-10.34	>10.34-12.92	>12.92
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

Lab Parameter	Hypo/Hyper	CTCAE Definition	SI Unit	Grade 1	Grade 2	Grade 3	Grade 4
Glucose	Hyper	Hyperglycemia	mmol/L	>ULN-8.9	>8.9-13.9	>13.9-27.8	>27.8
Phosphate	Hypo	Hypophosphatemia	mmol/L	<LLN-0.8	<0.8-0.6	<0.6-0.3	<0.3
Potassium	Hypo	Hypokalemia	mmol/L	<LLN-3	<LLN-3	<3-2.5	<2.5
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
Triglycerides	Hyper	Hypertriglyceridemia	mg/dL	150-300	>300-500	>500-1000	>1000
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	-

Lab Parameter	Hypo/Hyper	CTCAE Definition	SI Unit	Grade 1	Grade 2	Grade 3	Grade 4
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
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:

- Blood Urea Nitrogen
- Bicarbonate (removed from version 4.x; it was available in version 3)
- Chloride
- Erythrocyte Mean Corpuscular Volume
- HDL Cholesterol
- LDL Cholesterol
- Urate
- Basophils
- Eosinophils
- Erythrocytes
- Hematocrit
- Monocytes