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APPLICATION NUMBER:

208845Orig1s000

CLINICAL REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: 208845

Submission Date(s): 12/8/16

Applicant: Flexion

Product: Zilretta

Reviewer: Pamela Horn, MD

Date of Review: 8/31/17

Covered Clinical Study (Name and/or Number): Applicant provided disclosure for studies 001, 002, 005, 006, 008, 009, 010

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: See table		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.¹ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. There were no disclosed interests.

Study Number	Number of Investigators	Number of Sub-investigators
FX006-2011-001	24	59
FX006-2011-002	2	6
FX006-2013-005	3	17
FX006-2014-006	51	275
FX006-2014-008	44	180
FX006-2015-009	4	16
FX006-2015-010	9	57

¹ See <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm119145.htm>.

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/s/

PAMELA J HORN
10/06/2017

ROBERT B SHIBUYA
10/06/2017

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208845
Priority or Standard	Standard

Submit Date(s)	12/8/16
Received Date(s)	12/8/16
PDUFA Goal Date	10/8/17
Division / Office	DAAAP

Reviewer Name(s)	Pamela Horn, MD
Review Completion Date	August 31, 2017

Established Name	Triamcinolone ER injectable suspension
(Proposed) Trade Name	Zilretta
Therapeutic Class	Synthetic corticosteroid
Applicant	Flexion

Formulation(s)	Microsphere extended release injectable suspension
Dosing Regimen	Single intra-articular injection
Indication(s)	Management of osteoarthritis pain of (b) (4)
Intended Population(s)	Osteoarthritis patients

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

At the time of finalization of this review, as noted in Section 4.1, there are unresolved Chemistry/Manufacturing/Controls issues. However, within the context of the clinical data, I recommend approval of the application. The Applicant has provided substantial evidence of effectiveness for management of osteoarthritis pain of the knee from one placebo-controlled clinical study in patients with osteoarthritis of the knee, and by way of referencing a previous Agency finding for Kenalog-40 (NDA 14901). This evidence is supported by a second smaller placebo-controlled clinical study in patients with osteoarthritis of the knee where the treatment effect was not statistically significantly different from placebo but numerically trended in favor of Zilretta. The risks of Zilretta did not exceed those of currently marketed immediate-release triamcinolone and are outweighed by the benefits in the proposed target population for the proposed use.

1.2 Risk Benefit Assessment

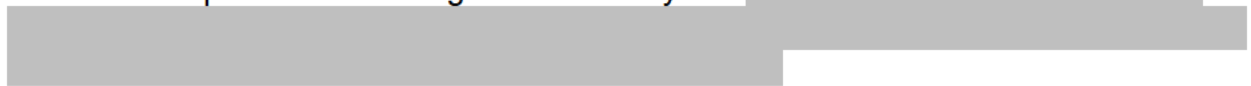
Zilretta is indicated for the management of osteoarthritis pain of the knee (b) (4). A single injection of the product has demonstrated effectiveness in decreasing pain in patients with knee osteoarthritis.

Osteoarthritis is a common, debilitating condition and the painful aspect of osteoarthritis affects patients' quality of life and ability to perform activities of daily living. An association between osteoarthritis, including knee osteoarthritis, and increased mortality due to cardiovascular and gastrointestinal causes in particular, has been observed. Treatment options include oral non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and duloxetine (a serotonin-norepinephrine reuptake inhibitor), topical NSAID, intra-articular (IA) injections of triamcinolone and methylprednisolone, and knee replacement surgery. Important risks exist for some of these treatment options: NSAIDs carry a risk of gastrointestinal adverse reactions, including serious gastrointestinal bleeding, and a risk of cardiovascular adverse reactions and there are significant risks associated with major surgeries like knee replacement surgery, especially for patients with osteoarthritis who have other medical problems.

Zilretta demonstrated a clinically meaningful and statistically significantly larger reduction in pain compared to placebo over a multi-week period. Zilretta provided a similar benefit to currently available immediate-release triamcinolone acetonide (TCA IR) both in magnitude and duration of effect.

Zilretta had a similar adverse event profile in the double-blinded controlled studies to TCA IR. The most common adverse events were related to the index knee and did not have a notably higher incidence in the active treatment groups compared to the placebo saline injection group. Corticosteroids are known to have adverse systemic effects including reversible hypothalamic-pituitary-adrenal axis suppression and blood glucose elevation. Because there is some systemic exposure to IA triamcinolone, these effects were evaluated in pharmacodynamics studies. The results of the studies revealed no new or more serious risks than have been previously identified and did not alter the benefit-risk balance for the product compared to currently available intra-articular triamcinolone. The extended-release Zilretta formulation resulted in a longer duration of exposure in the synovial fluid compared to TCA IR. The safety data in the clinical studies did not reveal a difference in time-dependent adverse event incidence between Zilretta and TCA IR and there was no difference in joint imaging findings from one study of a single injection between Zilretta, placebo or TCA IR at 24 weeks. The effects of multiple injections of Zilretta were not evaluated in this clinical development program.

The benefits and risks of Zilretta have been adequately assessed in the development program and are not appreciably different than the currently marked TCA IR products. It has a similar role in managing osteoarthritis pain to the other corticosteroids available for IA injection within the existing armamentarium available for management of osteoarthritis pain. The labeling should convey that (b) (4)



1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategy is recommended for this product.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements are recommended for this product.

In order to comply with the Pediatric Research Equity Act of 2007, the Applicant submitted a Pediatric Plan and requested waiver of clinical studies in pediatric patients because OA does not occur in the pediatric population to an extent where it would be feasible to study. I concur with the pediatric plan and waiver request.

2 Introduction and Regulatory Background

2.1 Product Information

Zilretta (proposed trade name) is a microsphere extended-release injectable suspension of triamcinolone acetonide (TCA), a synthetic corticosteroid. Zilretta is a new dosage form of a previously approved molecular entity.

During development, the product was referred to as FX006. The clinical data submitted in the application is for a single intra-articular injection in the knee of adult patients with knee osteoarthritis. The efficacy data is primarily pain outcome measures and the safety data includes adverse events, knee joint imaging and pharmacodynamic data pertaining to blood glucose levels in patients with diabetes and measures of the HPA (hypothalamic-pituitary-adrenal) axis.

2.2 Tables of Currently Available Treatments for Proposed Indications

Triamcinolone acetonide and methylprednisolone acetate, both corticosteroids, are approved for adjunctive therapy for short-term intra-articular administration in osteoarthritis.

There are several NSAID products approved for the management of osteoarthritis pain: diclofenac topical gels and solutions and meloxicam oral capsules.

Products approved for the management of the signs and symptoms of osteoarthritis, which has historically been demonstrated by showing an improvement in pain, function, and patient global assessment, include: naproxen, celecoxib, ibuprofen, ketoprofen, fenoprofen, etodolac, piroxicam, sulindac, oxaprozin, indomethacin, nabumetone, duloxetine, and acetaminophen.

2.3 Availability of Proposed Active Ingredient in the United States

Triamcinolone acetonide (TA) is a synthetic corticosteroid and is a well-characterized USP drug substance. A search of labels.fda.gov on 7/31/17 yielded 363 human prescription drug products containing TA as an active ingredient.

2.4 Important Safety Issues With Consideration to Related Drugs

Important known risks of intra-articularly administered corticosteroids, both those related to intra-articular administration and to the systemic exposure to corticosteroids, include:

- Hypersensitivity and anaphylactic reactions
- Joint infection
- Joint tissue damage
- Increased risk of systemic infections

- HPA axis suppression
- Blood glucose elevation
- Gastrointestinal ulcers and bleeding
- Disruption of bone formation and increased bone resorption
- Mood and perceptual disturbances
- Increased intraocular pressure

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1 Presubmission Regulatory Activity

Date	OND Review Division	Milestone	Key Advice or Regulatory Action	Clinical study relevant to advice (if applicable)
June 15, 2011	DPARP	PIND meeting	Evaluation of the product's effects on the HPA axis for at least 6 weeks should be part of the clinical development program	Study 002
November 16, 2011	DPARP	IND submission	Full clinical hold for nonclinical toxicology findings	
November 14, 2012	DPARP	CRCH	Hold removed based on new nonclinical toxicology data	
September 24, 2013	DPARP	EOP2 meeting	Additional dose-ranging study should be performed to select dose for Phase 3 study	Study 006
			Additional information on how long FX006 is present in the joint should be collected	Study 005
			The primary endpoint of change from baseline to 12 weeks on mean pain score on 11-point NRS acceptable for OA pain indication	Study 008
			Primary efficacy analysis must compare FX006 to placebo	Study 008
			WOMAC pain and function subscales recommended as secondary endpoints	Study 008

			A safety database of 350 subjects may be acceptable depending of observed safety profile	
November 26, 2013	DAAAP	IND transferred from DPARP to DAAAP		
June 25, 2014	DAAAP	Type C meeting	Normal saline is appropriate control for pivotal studies X-rays of index knee at baseline and end of study required to be assessed by independent radiologist Assessment of local toxicity of FX006 must be clinically evaluated You may seek approval for single dose administration (b) (4) Repeat-dose safety data is not needed for single dose indication but monitoring period after single dose must be adequate	Study 008 Study 008
May 25, 2016	DAAAP	Pre-NDA prelim comments issued	Data from one positive AWC trial and reliance of previous finding of safety and efficacy from a suitable reference product acceptable to support filing of an NDA application Available safety database of 400 at to-be-marketed dose acceptable to support filing of NDA application (b) (4)	

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall organization and completeness of the clinical section was adequate.

3.2 Compliance with Good Clinical Practices

There were no site-specific issues or issues with compliance with good clinical practices evident from review of the clinical section of the application. Protocol deviations occurred in the pivotal efficacy study 008, but did not appear to affect the integrity of the data. Three deviations met the Applicant's criteria for being removed from the per-protocol population analyses. These were all in the TCA IR group and consisted of one subject receiving knee aspirations prior to the end of the 12-week efficacy ascertainment period, one subject receiving a depo-medrol injection prior to the end of the 12-week efficacy ascertainment period and one subject not meeting the inclusion criterion for Kellgren-Lawrence grade on screening x-ray. These deviations would not be expected to bias the study results in a clinically important way.

OSI completed inspection of two study sites for study 008. Site 33 in Anaheim, CA was chosen based on high enrollment and site 66 was chosen based on high enrollment and an observed treatment effect on the primary efficacy outcome that was larger than other sites. The findings of the inspections revealed no issues that raise concern about the integrity of the efficacy or safety data collected or revealed deficiencies in human subject protection.

3.3 Financial Disclosures

The Applicant has adequately disclosed financial arrangements with the clinical investigators and no concerns with the effect of these arrangements on data integrity have been identified. See the attached Clinical Investigator Financial Disclosure Review Template.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The following are preliminary findings from the review team.

It was noted in the course of the CMC review that due to residual volume of the suspension left in the vial, the drug product delivered to patients in the development program contained only 32 mg of FX006 rather than the 40 mg, which was the dose described throughout the application. Therefore, the review refers to the FX006 dose that was studied and that is being proposed for marketing as FX006 40 mg rather than FX006 32 mg, which is the dose that is recommended for product labeling.

The facilities inspection recommendation is for a withhold due to compliance issues at the inspection site. These findings preclude an approval recommendation.

The CMC review team also recommends that a dose-delivered test must be done prior to product approval due to the aforementioned observed variability in the residual volume of the suspension left in the vial.

4.2 Clinical Microbiology

In the preliminary findings of the review team, there are container-closure integrity and testing issues that have not been resolved.

4.3 Preclinical Pharmacology/Toxicology

The preliminary findings are that the excipients and impurities have been adequately justified, no safety concerns were identified in the review of the extractables and leachables and the general toxicology study findings are adequate to support a single use indication. The preliminary recommendation is for approval.

4.4 Clinical Pharmacology

The recommendation from the clinical pharmacology review team is for approval.

4.4.1 Mechanism of Action

The purported mechanism of action of synthetic glucocorticoid analogs like triamcinolone in the treatment of rheumatologic conditions is through anti-inflammatory effects.

4.4.2 Pharmacodynamics

The Applicant conducted two studies to evaluate pharmacodynamics effects of FX006: studies 002 and 010. The studies assessed the effect of FX006 vs. Kenalog-40/ TCA IR on cortisol and blood glucose levels, respectively.

Study 002

For a discussion of study 002, see Dr. Abraham's consult review. Dr. Abraham's main findings and conclusions are as follows (p. 1 of review):

"First, we note that the study is quite limited. The study, for example, lacks any clinical assessment of adrenal insufficiency, did not employ dynamic cortisol testing (i.e., the standard confirmatory diagnostic test), and lacked a standardized protocol for serum cortisol collection. These limitations hinder our ability to interpret the clinical meaningfulness of the PD changes.

Overall, the data suggest systemic absorption of FX006 and some degree of acute Hypothalamic- Pituitary-Adrenal (HPA) axis suppression with all three doses of FX006 (i.e., 10 mg, 40 mg, and 60 mg). DMEP agrees with the Sponsor's conclusion that a single IA injection of FX006 results in a pattern of cortisol suppression that is dose and time-dependent with the lowest degree of suppression observed in the 10 mg group followed by higher degrees of suppression in the 40 mg and 60 mg groups, respectively.

The Sponsor seeks approval of the 40 mg dose of FX006, thus the effect on HPA axis of only 40 mg is discussed in further detail below.

Subjects who receive FX006 40 mg experience HPA axis suppression within the first 24 hours after dosing. HPA axis recovery seems to occur over 4-6 weeks following a single 40 mg dose. These data demonstrate that there is some level of HPA axis suppression and patients might be at risk for adrenal insufficiency once their systemic TCA level starts to decrease. However, accurate predictors are not available to distinguish between the patients that will become adrenally insufficient and those that will not. Previous clinical experience as documented in the literature and as recognized in the approved Kenalog-40 labeling identifies adrenal insufficiency as a risk associated with IA corticosteroid injections. The submitted data does not provide convincing evidence that clinically relevant HPA axis suppression that puts a patient at risk for development of adrenal insufficiency is not a risk associated with FX006 use. Therefore, we recommend including language in labeling to address these risks."

Study 010

For a discussion of study 010, see Dr. Archdeacon's consult review. Dr. Archdeacon's main findings and conclusions are as follows (Executive Summary of Dr. Archdeacon's review):

"Study FX006-2015-010 demonstrates a statistically significant difference exists between the impact of FX006 and TCA IR on certain metrics of glycemic control in patients with type 2 diabetes. However, the sponsor provides no justification for a margin for any of these metrics to support a conclusion that the differences observed are clinically meaningful. Moreover, even if FDA agreed that the FX006-2015-010 data are sufficient to establish that use of FX006 is less likely than TCA IR to cause adverse events related to hyperglycemia, (b) (4)

(b) (4)

4.4.3 Pharmacokinetics

Studies 001, 002, 005, and 009 included a pharmacokinetic component. Study 009 was the pivotal comparative bioavailability study used to establish a pharmacokinetic bridge between FX006 and the reference product, Kenalog-40. Studies 001, 002, and 005 also showed that FX006 40 mg caused lower TCA systemic exposure compared to Kenalog-40. These pharmacokinetic results support bridging to the systemic safety information of Kenalog-40.

A summary of the plasma PK data from study 009 recommended for labeling is as follows:

Table 2 Summary of Mean (SD) Plasma Pharmacokinetic Parameters for Triamcinolone Acetonide Following IA Administration of FX006 40 mg or 40 mg Immediate Release Triamcinolone Acetonide

Triamcinolone Acetonide PK Parameters ¹	ZILRETTA (N=60)	Triamcinolone Acetonide (N=18)
C _{max} (pg/mL)	1143.7 (611.06)	21062.2 (18466.79)
AUC _{0-24 hour} (pg•h/mL)	21219.2 (11325.62)	297545.3 (222402.77)
AUC _{0-inf} (pg•h/mL)	842149.2 (1062004.97) * (b) (4)	1567565.0 (1246330.95) † (b) (4)
t _{max} (h)	7 (1, 1008)	6 (2, 24)
t _{1/2} (h)	633.9 (893.0) * (b) (4)	146.9 (213.29) † (b) (4)
* (b) (4) 33 patients contributed to the analyses of these parameters † (b) (4) 14 patients contributed to the analyses of these parameters 1: Median (min, max) values for t _{max}		

The following tables are from Dr. Qui's review and summarize the local exposure findings from study 009.

Table 5 Synovial Fluid TCA Concentration (pg/mL) Following A Single IA Injection of FX006 40 mg

Treatment Time	Number Below LLOQ						Statistic		
	N ¹	N	Mean	SD	Geometric Mean	Log-Scale SD	95 % CI	Median	Min, Max
Baseline (pre-treatment)	16	17	0.0	0.00	1.0	NA	1.00, 1.00	0.0	0, 0
Week 1	0	8	391063.4	221546.30	231328.9	1.69	56460.40, 947798.36	469104.8	4087, 670393
Week 6	1	6	45944.6	57251.92	3590.0	2.21	32.89, 391914.74	22928.0	0, 139494
Week 12	2	9	8258.6	19230.28	290.6	2.34	15.67, 5390.53	499.1	0, 58928
Week 16	2	2	0.0	0.00	1.0	NA	1.00, 1.00	0.0	0, 0
Week 20	4	4	0.0	0.00	1.0	NA	1.00, 1.00	0.0	0, 0

Note: All baseline (pre-treatment) values and all post-baseline values that are recorded as below LLOQ were set to zero. Geometric mean summary statistics were computed on adjusted concentration values. One (1) was added to each concentration value observed. BLQ values for the computation of geometric mean are included in the summary with a value of 1 (0+1). No adjustment was applied for the computation of the arithmetic mean.

¹ LLOQ = Lower Limit of Quantification (<50 pg/mL).

Source: Table 23 of study report for protocol FX006-2015-009.

Table 6 Synovial Fluid TCA Concentration (pg/mL) Following A Single IA Injection of Kenalog-40

Treatment Time	Number Below LLOQ		Statistic						
	N ¹	N	Mean	SD	Geometric Mean	Log-Scale SD	95 % CI	Median	Min, Max
Baseline (pre-treatment)	3	5	0.0	0.00	1.0	NA	1.00, 1.00	0.0	0, 0
Week 6	6	8	1704.9	4439.15	7.7	1.81	0.31, 191.34	0.0	0, 12658

Note: All baseline (pre-treatment) values and all post-baseline values that are recorded as below LLOQ were set to zero. Geometric mean summary statistics were computed on adjusted concentration values. One (1) was added to each concentration value observed. BLQ values for the computation of geometric mean are included in the summary with a value of 1 (0+1). No adjustment was applied for the computation of the arithmetic mean.

¹ LLOQ = Lower Limit of Quantification (<50 pg/mL).

Source: Table 23 of study report for protocol FX006-2015-009.

While the local synovial fluid concentrations at week 12 in study 009 and 005 were greater in the FX006 40 mg cohort than the TCA IR 40 mg cohort, these differences did not correlate with differences in the efficacy or safety data and do not appear to be clinically relevant.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3 Clinical Studies

Study Number	Type of Study	Treatment Arms in Study				
		FX006 10 or 20 mg	FX006 40 mg	FX006 60 mg	placebo	TCA IR 40 mg
008	Efficacy		X		X	X
006	Efficacy	X	X		X	
001	Efficacy	X	X	X		X
002	PK and PD	X	X	X		X
005	PK	X	X			X
009	PK		X			
010	PK and PD		X			X

5.2 Review Strategy

Studies 008 and 006 were randomized, double-blinded, placebo-controlled studies and are reviewed individually in section 5.3. Study 001 was active-controlled without a placebo control. It therefore lacks assay sensitivity and is not reviewed in detail for its contribution to the evidence of efficacy for the product. Study 001 is discussed for its contribution to supporting the dosing recommendations and dose selection for the pivotal phase 3 study 008 in 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.

The efficacy analysis results presented in this review are from the Applicant. The analyses conducted by the biostatistical reviewer are not reproduced in this review. The preliminary findings of the biostatistical reviewer do not differ substantively from the Applicant's results and support the conclusions and recommendations for regulatory action made in the efficacy section of this review.

Studies 002 and 010 evaluated pharmacodynamic effects of FX006 and TCA IR and the pharmacodynamic portion of the studies are discussed in 4.4.2

Pharmacodynamics. Studies 005 and 009 have been reviewed in the clinical pharmacology review. For a summary of studies that contributed to the safety review, see the table in 7.1.1 Studies/Clinical Trials Used to Evaluate Safety.

5.3 Discussion of Individual Studies/Clinical Trials

Study 008

FX006-2014-008: A Double-blind, randomized, single-dose study to assess the safety and efficacy of FX006 for the treatment of pain in patients with osteoarthritis of the knee.

There was only one version of the protocol dated November 14, 2014, with no subsequent revisions or amendments.

Primary Objective: assess magnitude and duration of pain relief of single extended-release formulation injection of TCA (FX006) compared to a normal saline placebo control

Secondary Objectives:

- assess magnitude and duration of pain relief of FX006 compared to injection of commercially available immediate-release (IR) TCA,
- assess effect of FX006 on function, global impression of change, stiffness, and consumption of rescue medication compared to control conditions,
- assess safety and tolerability of FX006 compared to controls

Study Design

N=450 randomized 1:1:1 in double-blind fashion to:

40 mg FX006

Normal saline placebo or

40 mg TCA IR

Normal saline is the base component of the FX006 diluent and was thought to be a suitable placebo control.

Reviewer comment: to maintain patient blinding and allow separation of the effects of FX006 from the effects of the injection procedure, a normal saline injection appears to be a suitable placebo control.

A blinded assessor was used because the study personnel who administered the injection could have differentiated the product administered by appearance.

Inclusion Criteria

Subjects were to meet the following criteria to be eligible for enrollment:

1. Provided written consent to participate in the study.
2. Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions.
3. Male or female ≥ 40 years of age.

4. Symptoms associated with OA of the knee for ≥ 6 months prior to Screening (patient reported was acceptable).
5. Currently met ACR Criteria (clinical and radiological) for OA (Altman *et al*, 1986) as follows:
 - a. Knee pain.
 - b. at least 1 of the following:
 - i. Age > 50 years.
 - ii. Stiffness < 30 minutes.
 - iii. Crepitus.
 - c. Osteophytes.
6. Kellgren-Lawrence (K-L) Grade 2 or 3 in the index knee based on X-ray performed during Screening (locally read):
 - a. Grade 2: definite osteophytes and possible narrowing of joint space.
 - b. Grade 3: moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends.
7. Index knee pain for > 15 days over the previous month (as reported by the patient).
8. Mean score of ≥ 5 and ≤ 9 on the 24-hour average pain score (0-10 NRS) using the average daily ratings for at least 5 of the 7 days prior to Day 1.
9. No more than one 24-hour average pain score (0-10 NRS) reported as "10" during the 7 days prior to Day 1.
10. If bilateral OA existed, pain in the contralateral knee was less than pain in the index knee, as reported by the patient.
11. Body mass index (BMI) ≤ 40 kg/m².
12. Ambulatory and in good general health.
13. Willingness to abstain from use of protocol-specified restricted medications and nonpharmacological therapies during the study.

Reviewer Comment: The study population was required to meet clinical and radiologic criteria for knee osteoarthritis and to have an average pain score of at least 5 during a 7 day baseline period. These are reasonable criteria to identify a suitable study population. A minimum age of 40 was unlikely to exclude many OA patients and is likely to be acceptable in terms of generalizability of the study results. The limitation on BMI to a maximum value of 40 excludes patients with extreme obesity but allows enrollment of subjects with overweight or obesity based on BMI. The most recent NIDDKD data from a 2009-10 survey showed that 6.3% of adults in the U.S. had extreme obesity. This exclusion somewhat limits the generalizability of the study results. In a response to information request on 4/14/17, the Applicant clarified that the rationale for excluding subjects with extreme obesity was because of the high association with significant comorbidities and exceptionally high rates of multiple painful lower extremity orthopedic problems that would make it difficult to isolate the effects of therapy treating a single joint.

Exclusion Criteria

Subjects were to be excluded for meeting any of the following criteria:

Disease-related criteria

1. Any condition that could possibly confound the patient's assessment of index knee pain in judgment of the investigator (i.e., ipsilateral hip OA, gout, radicular low back pain and hip pain that is referred to the knee that could cause misclassification, pain in any other area of the lower extremities or back that is equal to or greater than the index knee pain)
2. Fibromyalgia, Reiter's syndrome, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or arthritis associated with inflammatory bowel disease
3. History of infection in the index knee
4. Clinical signs and symptoms of active knee infection or crystal disease of the index knee within 1 month of Screening
5. Unstable joint (such as a torn anterior cruciate ligament) within 12 months of Screening

Previous or concomitant OA treatment-related criteria

6. IA corticosteroid (investigational or marketed) in any joint within 3 months of Screening
7. IA hyaluronic acid (investigational or marketed) in the index knee within 6 months of Screening
8. Intramuscular (IM) or oral corticosteroids (investigational or marketed) within 1 month of Screening
9. Any other IA investigational drug/biologic use within 6 months of Screening
10. Prior use of FX006
11. Prior arthroscopic or open surgery of the index knee within 12 months of Screening
12. Planned/anticipated surgery of the index knee or any other surgery that would require use of a restricted medication during the study period

Patient-related criteria

13. Known hypersensitivity to any form of triamcinolone
14. History of sarcoidosis or amyloidosis
15. Active or history of malignancy within the last 5 years, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or effectively managed cervical carcinoma
16. Known active or quiescent systemic fungal, bacterial (including tuberculosis), viral or parasitic infections, or ocular herpes simplex
17. Any infection requiring intravenous antibiotics within 4 weeks of Screening or oral antibiotics within 2 weeks of Screening
18. History of osteomyelitis
19. Known or clinically suspected infection with human immunodeficiency virus (HIV), hepatitis B or C viruses
20. Any clinically significant ECG abnormality as judged by the Investigator
21. Patients requiring or likely to require chronic treatment with corticosteroids during the study period based on patient medical history

22. Uncontrolled diabetes as indicated by a hemoglobin A1c (HbA1c) of > 7.5% (> 59 mmol/mol)
23. Active psychiatric disorder including psychosis (e.g., schizophrenia), bipolar disorder, uncontrolled anxiety disorder and major depressive disorder
24. History of or active Cushing's syndrome
25. Positive drug screen (amphetamines, barbiturates, benzodiazepines (indicated as a muscle relaxant), cocaine, opiates, tetrahydrocannabinol (THC))
26. Active substance abuse (drugs or alcohol), history of chronic substance abuse within the past year, or prior chronic substance abuse judged by the investigator as likely to recur during the study
27. Skin breakdown at the knee where the injection would take place
28. Women who are pregnant or nursing
29. Women of child-bearing potential (not surgically sterile or post-menopausal for at least 1 year as documented in medical history) not using a highly effective method of contraception (abstinence; oral, injected or implanted hormonal methods of contraception; intrauterine device (IUD) or intrauterine system (IUS); condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; or male sterilization (vasectomy))
30. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents within 5 years of Screening
31. Has received a live or live attenuated vaccine within 3 months of Screening
32. Use of any other investigational drug or device within 30 days of Screening or an investigational biologic within 60 days of Screening
33. Any other clinically significant acute or chronic medical conditions (e.g., bleeding disorder) that, in the judgment of the Investigator, would preclude the use of an IA corticosteroid or that could compromise patient safety, limit the patient's ability to complete the study, and/or compromise the objectives of the study.

Reviewer Comment: The wording of exclusion criterion 23 regarding psychiatric disorders was ambiguous. In a response to information request submitted 4/14/17, the Applicant clarified that investigators were informed that the intent of the criterion was to exclude active, uncontrolled conditions and to allow patients with conditions that were controlled on a stable treatment regimen. The exclusion of subjects with uncontrolled symptoms of psychosis, mania and depression, is reasonable, as these subjects may be too impaired by their psychiatric condition to participate and provide reliable self-report.

The other exclusion criteria appear reasonable for this study.

Treatments

- FX006 – extended-release formulation of TCA in 75:25 PLGA microspheres
Nominal 40 mg TCA, IA, administered as a 5 mL injection

- Normal saline, sodium chloride (0.9% NaCl) solution, IA, administered as a 5 mL injection
- Commercially available TCA injectable suspension, 40 mg/mL, IA, administered as a 1 mL injection

Reviewer Comment: The volume of commercially available TCA is 1 ml compared to 5 ml of FX006 and the normal saline placebo. The volume administered in the placebo group is the same as that in the FX006 group, which is acceptable.

Subjects were randomized using a 1:1:1 randomization scheme. The randomization was stratified by weekly average baseline pain score 5 to <6, 6 to <7 and 7 or greater.

The treatment was administered by an assigned injector based on standard of care. The position may have been extended or bent, the approach may have been medial or lateral and the numbing agent may have been ethyl chloride or subcutaneous lidocaine and was at the discretion of the injector. The joint was aspirated prior to injection. A 20 or 21-gauge needle was used for aspiration and injection. Patients were told to avoid strenuous and prolonged weight-bearing activities for 24 to 48 hours after injection.

Prohibited medications

The following medications were to be prohibited throughout the study, beginning 5 half-lives prior to Day -7:

- Analgesics including
 - Oral non-steroidal anti-inflammatory drugs (NSAIDs).
 - Aspirin (>325 mg per day).
 - Centrally-acting pain medications (e.g., pregabalin, gabapentin, duloxetine, milnacipran).
 - Opioids.
 - Topical therapies (e.g., NSAIDs, capsaicin, lidocaine patches, other local treatments) applied to the index knee.
- Anesthetic medications injected locally in the index knee (other than subcutaneous lidocaine if used for IA injection procedure).
- Inhaled, intranasal, and topical corticosteroids.
- Muscle relaxants (e.g., cyclobenzaprine, tetrazepam, and diazepam).
- Amphetamines, barbiturates, benzodiazepines (indicated as a muscle relaxant), cocaine, opiates, and THC

Rescue Medication

Patients were to be permitted to take up to 3 g acetaminophen per day (500 mg tablets) as needed to treat worsening pain of any type. Rescue medication use was to be recorded in the interactive voice response system on a daily basis.

Schedule of Assessments

Table 4 Study 008 Schedule of Assessments

Table 6-1: Schedule of Assessments

<i>Procedures</i>	Screen ¹	Baseline Day 1	Wk 4 ² Day 29	Wk 8 ² Day 57	Wk 12 ² Day 85	Wk 16 ² Day 113	Wk 20 ² Day 141	Wk 24 ² / Final Visit ³ Day 169
Informed consent	X ⁴							
Inclusion/Exclusion Review	X	X ⁵						
Medical History/Update	X	X ⁵						
OA Medical History	X							
Prior Treatment & Medications ⁶	X	X ⁵						
Physical Examination	X	X ⁵			X			X
Index Knee X-ray ⁷	X							X
Index Knee Assessment ⁸	X	X ⁵	X	X	X	X	X	X
12-Lead ECG	X							
Vital Signs	X	X ⁹	X	X	X	X	X	X
Height	X							
Weight and BMI	X							X
Hematology & Chemistry ¹⁰	X	X ⁹			X			X
Hemoglobin A1c ¹⁰	X							
HIV, Hepatitis B/C ¹⁰	X							
Urine Drug Screen ¹⁰	X							
Serum Pregnancy Test ^{10,11}	X							

¹ Screening may occur up to 21 days prior to Baseline/Day 1.

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

³ If a patient withdraws from the study early, the patient should return for a Final/Early Termination Visit as soon as possible and follow the procedures noted under Week 24/Final Visit.

⁴ Consent must be obtained prior to any study-specific procedures including wash-out of medications.

⁵ Complete assessment prior to randomization.

⁶ Record any prior medications received 30 days prior to the screening visit

⁷ Standing, fixed flexion PA view, weight bearing X-ray will be taken using a standardized knee positioning device. The Screening X-ray will be read locally for K-L grade. The Screening and Week 24 X-rays will be sent to central imaging vendor for safety assessment.

⁸ Index knee will be assessed for tenderness, heat/redness, swelling, effusion, and Baker's cyst. New clinically significant findings or findings that worsen for the patient's baseline condition should be recorded as AEs.

⁹ Complete assessment prior to dosing.

¹⁰ Via Central Laboratory

<i>Procedures</i>	Screen ¹	Baseline Day 1	Wk 4 ² Day 29	Wk 8 ² Day 57	Wk 12 ² Day 85	Wk 16 ² Day 113	Wk 20 ² Day 141	Wk 24 ² / Final Visit ³ Day 169
Urine Pregnancy Test ¹¹		X ⁵						X
Daily Diary Calls (by patient) ¹²	-----X-----							
Review of Patient Diary ¹³	X ¹⁴	X ^{5,15}	X	X	X	X	X	X
Rescue Medication (dispense/return) ¹⁶	X	X	X	X	X	X	X	X
Stable Lifestyle Assessment	X	X	X	X	X	X	X	X
WOMAC® LK 3.1 ¹⁷		X ⁴	X	X	X	X	X	X
PGIC ¹⁷			X	X	X	X	X	X
CGIC			X	X	X	X	X	X
KOOS QOL subscale ¹⁸		X	X	X	X			X
SF-12 ¹⁸		X	X	X	X			X
Randomization		X ⁷						
Treatment Administration		X						
Adverse Events ¹⁹		-----X-----						
Concomitant Medications ¹⁹		-----X-----						

¹¹Conduct for women of childbearing potential only.

¹² Starting at the screening visit and continuing through to Week 24/Final Visit, patients are to call into the diary system on a daily basis between 4 pm and midnight local time. See [Appendix 2](#) for Sample Patient Diary Card.

¹³ Review of daily pain diary data and rescue medication data (if applicable) since previous visit to monitor compliance and re-train patient if needed

¹⁴ Instruct the patient on use of the patient diary system; print diary confirmation sheet so that patient will be able to access the system that evening.

¹⁵ Review the Subject Eligibility Report to assure that there is at least 5 of the previous 7 days of data and that the patient meets inclusion criterion for average pain score

¹⁶ Rescue medication will be dispensed to patients at the Screening visit. At each subsequent visit, rescue medication accountability will be performed and additional rescue medication will be returned/dispensed as needed.

¹⁷ WOMAC and PGIC to be completed prior to all other assessments.

¹⁸ KOOS QOL subscale and SF-12 to be completed at end of visit.

¹⁹ AEs and Concomitant Medications will be captured from Day 1 (post injection) to Week 24/Final Visit.

Source: p. 46 and 47 Study 008 protocol

Study Procedures

There was to be a review of eligibility, including medical history, prior treatment, medications, and physical exam including an index knee assessment that assessed tenderness, heat/redness, swelling, effusion, and Baker's cyst at the screening visit and baseline visit. An x-ray of the index knee, 12-lead ECG, hematology, chemistry, HbA1c, urine drug screen and serum pregnancy test were to be done at the screening visit.

Patient Diary entries were to be made by the patient daily from screening through week 24 between 4 pm and midnight local time to report their daily average and worst pain intensity scores on a 0 to 10 NRS and their rescue medication use.

Patient and blinded assessor questionnaires were to be completed at study visits as noted in the schedule of assessments. The patient questionnaires were to be the WOMAC LK 3.1, PGIC, KOOS, and SF-12 and the blinded assessor questionnaire was to be the CGIC.

Adverse events were to be collected by blinded study staff at each study visit. Study visits were to occur at weeks 4, 8, 12, 16, 20, and 24. At the baseline visit a blinded assessor was to be present as soon as the study drug administration procedure was complete to assess the patient for any adverse events.

Analysis populations

The safety population was to be all patients who receive study medication.

The protocol states that the full analysis set was to be all patients who receive study medication and have baseline and at least one post-dose pain evaluation. However, the statistical analysis plan (SAP) states that the full analysis set is to be all randomized patients who receive study medication.

The ITT analysis set was to be all patients who were randomized into the study.

The primary efficacy endpoint was to be the change from baseline to week 12 in the weekly mean of the average daily pain intensity score for FX006 relative to placebo

According to the SAP the following key secondary efficacy endpoints were to be evaluated in order using a step-down testing procedure:

- Area Under the Effect curve (AUE) of change from Baseline in weekly mean of the average daily (24-hr) pain intensity scores from baseline to Week 12 for FX006 relative to placebo.
- AUE of change from Baseline in weekly mean of the average daily (24-hr) pain intensity scores from baseline to Week 12 for FX006 relative to TCA IR.
- Change from Baseline to Week 12 in the weekly mean of the average daily (24-hr) pain intensity scores for FX006 relative to TCA IR
- AUE of change from Baseline in weekly mean of the average daily (24-hr) pain intensity scores from baseline to Week 24 for FX006 relative to placebo

Reviewer Comment: The key secondary endpoints are all variations of analysis of the same pain intensity score data as the primary endpoint and are not independent of the primary endpoint. The order of testing is not relevant in this case (b) (4)

The following additional efficacy endpoints were to be exploratory:

- Responder status as defined by: Proportion of patients experiencing a >20%, >30%, or >50% decrease in pain from baseline in weekly mean of the average daily (24-hr) pain intensity scores at each week (e.g. week 1, 2, 3, etc.)
- Percent of responders (defined as patients with high improvement in pain or function) according to Outcome Measures in Rheumatology (OMERACT)-Osteoarthritis Research Society International (OARSI) criteria at Weeks 4, 8, 12, 16, 20 and 24
- Change from Baseline to each week in weekly mean of the average daily (24-hr) pain intensity scores
- AUE of change from Baseline in weekly mean of the average daily (24-hr) pain intensity scores over the time intervals (e.g., Weeks 1 to 4, Weeks 1 to 8, Weeks 1 to 16, Weeks 4 to 12, Weeks 12 to 24).
- Change from Baseline over time for Western Ontario and McMaster Osteoarthritis Index (WOMAC) A (pain subscale), A1 (pain on walking question), B (stiffness subscale), C (function subscale), and total scale at Weeks 4, 8, 12, 16, 20 and 24
- Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) at Weeks 4, 8, 12, 16, 20 and 24
- Change from Baseline over time for Knee Injury and Osteoarthritis Outcome Score (KOOS Quality of Life (QOL) subscale and SF-12 at Weeks 4, 8, 12 and 24
- Change from Baseline to each week in the weekly mean of the worst daily (24-hr) pain intensity scores
- Time to onset of pain relief defined as the time from administration of study treatment to the first daily pain assessment showing >30% improvement from the weekly mean of the average daily (24-hr) pain intensity scores at Baseline
- Average weekly and total consumption of rescue medications

Reviewer Comment: The WOMAC function subscale and PGIC are included in the exploratory endpoints (b) (4)

The analysis of the primary efficacy endpoint and continuous secondary endpoints was to be conducted with a model that included baseline pain and study site as covariates. The primary efficacy endpoint was to be tested using a longitudinal mixed effects model for repeated measures (MMRM) with fixed effects for treatment group, study week, treatment-by-week interaction, study site and baseline pain and subject as the random effect and using a two-sided alpha of 0.05. The analysis was to include all weeks of

study data and treatment differences from control were to be estimated via least squares means from the analysis model.

Multiplicity of testing for the key secondary endpoints was to be controlled by following a hierarchy and only testing the next endpoint if the previous result was statistically significant with a p-value of <0.05.

Reviewer Comment: [REDACTED] (b) (4)

Missing average daily pain intensity scores were not to be imputed.
The study results pertaining to the efficacy review are discussed in section 6 below.

Study 006

FX006-2014-006: A DOUBLE-BLIND, RANDOMIZED, PARALLEL GROUP, DOSE-RANGING STUDY TO ASSESS THE SAFETY AND EFFICACY OF FX006 FOR THE TREATMENT OF PAIN IN PATIENTS WITH OSTEOARTHRITIS OF THE KNEE

There was one amendment of the original protocol dated September 12, 2014, which extended the follow-up period from 20 weeks to 24 weeks after the single study treatment.

Primary Objective: assess the magnitude and duration of pain relief of a single IA injection of two doses (20 and 40 mg) of FX006, an extended release formulation of TCA, relative to normal saline (placebo control)

Secondary Objectives:

- To assess the effect of FX006 on function, responder status, global impressions of change, stiffness, and consumption of analgesic medications.
- To assess the safety and general tolerability of a single IA injection of two doses (20 and 40 mg) of FX006

The study was to be double-blinded, randomized, parallel group with three treatment arms:

FX006 20 mg

FX006 40 mg

Normal saline (placebo)

The study population was to be males and females age 40 and above with OA of the knee. There were no clinically important differences between the enrollment criteria in study 008, which are summarized in the description of study 008 above, and study 006.

Subjects were to receive a single injection of study medication in the index knee and return for six outpatient visits at weeks 4, 8, 16, 20 and 24.

The schedule of assessments is below:

Table 5 Study 006 Schedule of Assessments

<i>Procedures</i>	<i>Screen¹</i>	<i>Baseline Day 1</i>	<i>Wk 4² Day 29</i>	<i>Wk 8² Day 57</i>	<i>Wk 12² Day 85</i>	<i>Wk 16² Day 113</i>	<i>Wk 20² Day 141</i>	<i>Wk 24² Day 169</i>
Informed consent	X ³							
Inclusion/Exclusion Review	X	X ⁴						
Medical History/Update	X	X ⁴						
Prior Treatment & Medications	X	X ⁴						
Physical Examination	X	X ⁴			X			X
Index Knee X-ray	X ⁵							
Index Knee Assessment ⁶	X	X ⁴	X	X	X	X	X	X
12-Lead ECG ⁷	X	X ⁴			X			X
Vital Signs	X	X ⁸	X	X	X	X	X	X
Height	X							
Weight and BMI	X							X
Hematology & Chemistry	X	X ⁸			X			X
HIV, Hepatitis B/C	X							
Urine Drug Screen	X							
Serum Pregnancy Test ⁹	X							
Urine Pregnancy Test ⁹		X ⁴						X
Daily Pain Score		-----X-----						
Review of Patient Diary	X	X	X	X	X	X	X	X
Stable Lifestyle Assessment	X	X	X	X	X	X	X	X
WOMAC [®] LK 3.1 ¹⁰		X ⁴	X	X	X	X	X	X
PGIC ¹⁰ and CGIC			X	X	X	X	X	X
Randomization		X ⁸						
Treatment Administration		X						
Adverse Events ¹¹		-----X-----						
Concomitant Medications ¹¹		-----X-----						

¹ Screening may occur up to 21 days prior to Baseline/Day 1.

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

³ Consent must be obtained prior to any study-specific procedures including wash-out of medications.

⁴ Complete assessment prior to randomization.

⁵ Screening X-ray must be sent to the central imaging vendor for K-L grading required for eligibility.

⁶ Index knee will be assessed for tenderness, heat/redness, swelling, effusion, and Baker's cyst. New clinically significant findings or findings that worsen for the patient's baseline condition should be recorded as AEs.

⁷ ECGs must be read in real time, if QTc > 450 msec for male patients or > 470 msec for female patients, repeat two additional ECGs.

⁸ Complete assessment prior to dosing.

⁹ For women of childbearing potential only.

¹⁰ Patient reported pain assessments (i.e., WOMAC and PGIC) should be completed prior to all other assessments.

¹¹ AEs and Concomitant Medications will be captured from Day 1 (post injection) to Week 24/Final Visit.

Source: Table 6-1 study 006 protocol v.2

The study procedures were similar to those summarized in the description of study 008 above. However, unlike study 008, there was no additional imaging taken of the index knee after the baseline assessment.

The planned analysis of the primary efficacy endpoint was to be the change from baseline to week 12 in the weekly mean of the average daily pain intensity score for the 40 mg FX006 group versus placebo and was to use the same model and covariates as the primary analysis for study 008.

The study results pertaining to the efficacy review are discussed in section 6 below.

6 Review of Efficacy

Efficacy Summary

The pivotal efficacy study 008 was a double-blind, placebo- and active-controlled study that enrolled patients with knee osteoarthritis in North America, Europe, Asia, and Australia. Forty-two percent of subjects were enrolled in U.S. sites. The primary efficacy endpoint was change in baseline to week 12 on the weekly mean of the average daily pain score on the 11-point NRS scale, which is an acceptable endpoint to evaluate pain that has been frequently used in drug development programs. The results of the primary efficacy analysis demonstrate that FX006 40 mg is statistically significantly superior to placebo and supports an efficacy finding for the product. These results appeared robust in that the results remained statistically significant on sensitivity analyses. Rescue medication use was also lower in the FX006 group compared to placebo, which supports the finding of efficacy. Additionally, the WOMAC pain and function subscales and Patient Global Impression of Change endpoints that have been frequently evaluated in osteoarthritis studies, while not tested in a manner that controlled for multiplicity, were numerically supportive of the primary analysis results.

Like study 008, study 006 was a double-blind, placebo-controlled study in patients with knee osteoarthritis. The primary comparison between FX006 and placebo was for the same endpoint as study 008 and FX006 was not statistically significantly superior to placebo. The endpoint trended in favor of FX006 and the magnitude of change in the FX006 40 mg group was nearly the same as in study 008. However, the placebo response was larger than in study 008, which drove the lack of a statistically significant difference between FX006 and placebo in the primary comparison.

Because the Applicant has referenced a previous finding of efficacy for Kenalog for osteoarthritis and has provided evidence of efficacy from one adequate and well controlled study, I conclude that the application meets the standard for having provided substantial evidence of efficacy.

6.1 Indication

(b) (4)
The single Phase 3 study and two dose-ranging studies submitted in the application studied subjects who had received an injection in the knee only. (b) (4)

(b) (4)

(b) (4)
I recommend that the product label state that the product has not been evaluated in treatment of hip or shoulder OA and that due to the injection volume of the product, it is not appropriate for use in small joints.

6.1.1 Methods

The efficacy studies 008 and 006 are reviewed individually.

6.1.2 Demographics

Study 008

Study conducted from January 29, 2015 to January 21, 2016.

Report released June 24, 2016.

41 study centers

Two-hundred three of the four-hundred eighty-six patients enrolled (42%) were enrolled at U.S. sites.

Table 6 Study 008 Study Sites

	Center No	# patients enrolled
US	010	8
	012	9
	021	1
	022	9
	026	4
	028	1
	033	40
	036	4
	039	0
	053	22
	058	12
	061	6
	062	8
	064	4
	065	0
	066	40
	067	10
	068	7
	069	12
	070	4
Canada	073	2
	078	0
	081	15
	083	26
	084	11
Australia	100	10

	102	4
	103	4
	104	3
New Zealand	131	19
	132	2
	133	5
	134	14
	135	28
Hong Kong	200	34
Denmark	210	12
	211	22
	212	19
Romania	220	36
Estonia	230	14
Lithuania	240	5

In study 008 the demographic and baseline characteristics summarized in the clinical study report are as follows:

Table 7 Study 008 Demographic and Baseline Characteristics

Parameter/Statistics	Treatment Group			Total (N=484)
	40 mg FX006 (N=161)	Placebo (N=162)	TCA IR 40 mg (N=161)	
Gender - n (%)				
Male	58 (36.0)	66 (40.7)	64 (39.8)	188 (38.8)
Female	103 (64.0)	96 (59.3)	97 (60.2)	296 (61.2)
Primary Race - n (%)				
American Indian or Alaska Native	0	0	0	0
Asian	18 (11.2)	13 (8.0)	16 (9.9)	47 (9.7)
Black or African American	9 (5.6)	4 (2.5)	12 (7.5)	25 (5.2)
Native Hawaiian or Other Pacific Islander	4 (2.5)	1 (0.6)	2 (1.2)	7 (1.4)
White	130 (80.7)	144 (88.9)	131 (81.4)	405 (83.7)
Other	0	0	0	0
Ethnicity - n (%)				
Hispanic or Latino	21 (13.0)	25 (15.4)	19 (11.8)	65 (13.4)
Not Hispanic or Latino	140 (87.0)	137 (84.6)	142 (88.2)	419 (86.6)
Age at Consent (years)				
n	161	162	161	484
Mean (SD)	61.5 (9.52)	62.4 (8.89)	62.3 (10.08)	62.1 (9.49)
Median	61.0	62.0	63.0	62.0
Min ; Max	40 ; 83	40 ; 83	40 ; 85	40 ; 85
Height (cm) at Baseline				
n	161	162	161	484
Mean (SD)	166.31 (9.747)	167.01 (9.709)	167.73 (10.982)	167.02 (10.158)
Median	165.10	166.19	168.00	167.00
Min ; Max	147.2 ; 195.0	139.9 ; 190.5	142.0 ; 194.0	139.9 ; 195.0

Parameter/Statistics	Treatment Group			Total (N=484)
	40 mg FX006 (N=161)	Placebo (N=162)	TCA IR 40 mg (N=161)	
Weight (kg) at Baseline				
n	161	162	161	484
Mean (SD)	83.31 (16.203)	84.53 (16.867)	85.56 (17.740)	84.47 (16.938)
Median	83.00	83.49	86.50	83.95
Min ; Max	47.2 ; 126.4	49.9 ; 135.9	43.1 ; 132.0	43.1 ; 135.9
Body Mass Index (kg/m ²) at Baseline				
N	161	162	161	484
Mean (SD)	30.06 (5.011)	30.18 (4.687)	30.25 (4.819)	30.16 (4.831)
Median	29.78	30.00	30.20	29.94
Min ; Max	19.2 ; 40.0	18.8 ; 39.9	19.9 ; 39.8	18.8 ; 40.0
Body Mass Index (kg/m ²) Category at Baseline - n (%)				
Underweight (BMI <18.5 kg/m ²)	0	0	0	0
Normal (BMI 18.5 to 24.9 kg/m ²)	28 (17.4)	22 (13.6)	25 (15.5)	75 (15.5)
Overweight (BMI 25.0 to 29.9 kg/m ²)	57 (35.4)	58 (35.8)	53 (32.9)	168 (34.7)
Obesity Class I (BMI 30.0 to 34.9 kg/m ²)	45 (28.0)	52 (32.1)	55 (34.2)	152 (31.4)
Obesity Class II (BMI 35.0 to 39.9 kg/m ²)	31 (19.3)	30 (18.5)	28 (17.4)	89 (18.4)
Obesity Class III (BMI ≥40.0 kg/m ²)	0	0	0	0
Baseline Weekly Average for Daily Pain Intensity Score Category - n (%)				
5 to <6	68 (42.2)	68 (42.0)	68 (42.2)	204 (42.1)
6 to <7	52 (32.3)	52 (32.1)	51 (31.7)	155 (32.0)
≥7	41 (25.5)	42 (25.9)	42 (26.1)	125 (25.8)

Source: Table 12 study 008 CSR

There were more female than male subjects in all treatment groups (around 60% female overall). Race was predominantly white (around 84% overall) and races were fairly evenly distributed between treatment groups. The ages of subjects ranged from 40 to 85 with a mean and median age of 62 and were similar in all treatment groups. The study population as a whole had a high BMI, with only 15% of subjects of a normal weight and around half of subjects having BMI in the obese range, which is likely to be generalizable to the U.S. population. The percentage of patients in each BMI category was similar between treatment groups. The weekly average pain intensity at baseline was also similar between treatment groups.

Study 006

Study conducted from April 29, 2014 to August 7, 2015.
Report released March 22, 2016.

Forty-eight study centers in the U.S. and Canada screened patients. Five study centers in Canada enrolled a total of 45 patients, with the remaining 43 study centers in the U.S. enrolling the other 265 patients (85% of enrolled subjects were enrolled at U.S. sites).

The sex demographics in study 006 were similar to those in study 008. There was a similar percentage of white subjects but there were less Asian (2% compared to 10%) and more African American (16% compared to 5%). The mean age was slightly younger (59 compared to 62). The average BMI of subjects in study 006 was 0.7 mg/m² higher than that in study 008, which would be like subjects in study 006 on average being about 5 lbs heavier than subjects of the same height in study 008.

Table 8 Study 006 Demographic and Baseline Characteristics

Parameter/Statistics	Treatment Group			Total (N=306)
	FX006 20 mg (N=102)	FX006 40 mg (N=104)	Placebo (N=100)	
Gender - n (%)				
Male	40 (39.2)	53 (51.0)	39 (39.0)	132 (43.1)
Female	62 (60.8)	51 (49.0)	61 (61.0)	174 (56.9)
Primary Race - n (%)				
American Indian or Alaska Native	0	0	1 (1.0)	1 (0.3)
Asian	2 (2.0)	3 (2.9)	2 (2.0)	7 (2.3)
Black or African American	17 (16.7)	16 (15.4)	15 (15.0)	48 (15.7)
Native Hawaiian or Other Pacific Islander	1 (1.0)	0	0	1 (0.3)
White	81 (79.4)	85 (81.7)	82 (82.0)	248 (81.0)
Other	0	0	0	0
Multiple	1 (1.0)	0	0	1 (0.3)
Ethnicity - n (%)				
Hispanic or Latino	16 (15.7)	21 (20.2)	20 (20.0)	57 (18.6)
Not Hispanic or Latino	86 (84.3)	83 (79.8)	79 (79.0)	248 (81.0)
Not Reported	0	0	1 (1.0)	1 (0.3)
Age at Consent (years)				
n	102	104	100	306
Mean (SD)	58.2 (8.34)	58.7 (8.06)	59.7 (8.23)	58.8 (8.20)
Median	57.5	58.0	60.0	59.0
Min ; Max	43 ; 83	41 ; 79	40 ; 80	40 ; 83
Height (cm) at Baseline				
n	102	104	100	306
Mean (SD)	169.5 (9.61)	170.2 (11.32)	168.7 (10.91)	169.5 (10.62)
Median	167.6	170.2	168.9	169.0
Min ; Max	149 ; 196	132 ; 196	122 ; 192	122 ; 196
Weight (kg) at Baseline				
N	102	104	100	306
Mean (SD)	88.1 (17.36)	89.7 (16.15)	89.2 (18.24)	89.0 (17.21)
Median	87.0	90.1	87.4	87.7
Min ; Max	47 ; 131	55 ; 136	46 ; 141	46 ; 141

Body Mass Index (kg/m ²) at Baseline				
n	102	104	100	306
Mean (SD)	30.6 (4.86)	31.0 (4.55)	31.2 (5.11)	30.9 (4.84)
Median	30.9	30.8	31.0	30.9
Min ; Max	17 ; 39	20 ; 42	19 ; 43	17 ; 43
Body Mass Index (kg/m ²) at Baseline, n (%)				
Underweight (BMI <18.5 kg/m ²)	2 (2.0)	0	0	2 (0.7)
Normal weight (BMI 18.5 to 24.9 kg/m ²)	12 (11.8)	10 (9.6)	10 (10.0)	32 (10.5)
Overweight (BMI 25.0 to 29.9 kg/m ²)	32 (31.4)	35 (33.7)	33 (33.0)	100 (32.7)
Obesity Class I (BMI 30.0 to 34.9 kg/m ²)	37 (36.3)	39 (37.5)	29 (29.0)	105 (34.3)
Obesity Class II (BMI 35.0 to 39.9 kg/m ²)	19 (18.6)	18 (17.3)	27 (27.0)	64 (20.9)
Morbid Obesity (BMI ≥40.0 kg/m ²)	0	2 (1.9)	1 (1.0)	3 (1.0)

Source: Table 11 006 CSR

The following table summarizes the demographics for studies 001, 006 and 008. These studies were pooled together for the purposes of summarizing the overall efficacy findings in subpopulations in section 6.1.7 Subpopulations.

Table 9 Demographic and Baseline Characteristics (Studies 001, 006, and 008)

Parameter/Statistics	FX006 40 mg (N = 324)	Placebo (N = 262)	TCA IR 40 mg (N = 212)
Gender - n (%)			
Male	139 (42.9)	105 (40.1)	86 (40.6)
Female	185 (57.1)	157 (59.9)	126 (59.4)
Primary Race - n (%)			
American Indian or Alaska Native	0	1 (0.4)	0
Asian	23 (7.1)	15 (5.7)	18 (8.5)
Black or African American	26 (8.0)	19 (7.3)	13 (6.1)
Native Hawaiian or Other Pacific Islander	4 (1.2)	1 (0.4)	2 (0.9)
White	269 (83.0)	226 (86.3)	178 (84.0)
Other	2 (0.6)	0	1 (0.5)
Race Groups - n (%)¹			
White	271 (83.6)	226 (86.3)	178 (84.0)
Asian	23 (7.1)	15 (5.7)	19 (9.0)
Non-White/Non-Asian	30 (9.3)	21 (8.0)	15 (7.1)
Ethnicity - n (%)			
Hispanic or Latino	42 (13.0)	45 (17.2)	19 (9.0)
Not Hispanic or Latino	282 (87.0)	216 (82.4)	193 (91.0)
Not Reported	0	1 (0.4)	0
Country - n (%)			
US	158 (48.8)	160 (61.1)	64 (30.2)
Canada	74 (22.8)	29 (11.1)	56 (26.4)
Australia/New Zealand	41 (12.7)	32 (12.2)	42 (19.8)
Hong Kong	16 (4.9)	6 (2.3)	12 (5.7)
Europe	35 (10.8)	35 (13.4)	38 (17.9)
Age at Consent (years)			
Mean (SD)	60.5 (9.16)	61.4 (8.73)	62.1 (10.06)
Age at Consent (years) Category - n (%)			
40 - 50	46 (14.2)	36 (13.7)	31 (14.6)
51 - 64	163 (50.3)	133 (50.8)	90 (42.5)
65 - 75	97 (29.9)	82 (31.3)	72 (34.0)
> 75	18 (5.6)	11 (4.2)	19 (9.0)

Parameter/Statistics	FX006 40 mg (N = 324)	Placebo (N = 262)	TCA IR 40 mg (N = 212)
Height (cm) at Baseline			
Mean (SD)	167.89 (10.336)	167.65 (10.195)	167.55 (10.543)
Weight (kg) at Baseline			
Mean (SD)	86.33 (16.176)	86.31 (17.516)	85.47 (17.709)
Body Mass Index (kg/m ²) at Baseline			
Mean (SD)	30.55 (4.771)	30.58 (4.871)	30.15 (4.864)
Body Mass Index Category at Baseline – n (%) ²			
Underweight	0	0	0
Normal	43 (13.3)	32 (12.2)	34 (16.0)
Overweight	114 (35.2)	91 (34.7)	69 (32.5)
Obesity 1	100 (30.9)	81 (30.9)	72 (34.0)
Obesity 2	65 (20.1)	57 (21.8)	37 (17.5)
Morbid Obesity	2 (0.6)	1 (0.4)	0
Weekly Daily Average Pain Intensity Score at Baseline – n (%)			
5-5.9	118 (36.4)	99 (37.8)	82 (38.7)
6-6.9	107 (33.0)	78 (29.8)	70 (33.0)
≥ 7	99 (30.6)	85 (32.4)	60 (28.3)

Source: Table 14.13.B

¹ Race such as Middle East, Palestinian, Egyptian classified as Other or Multiple, have been assigned the White category in the race group, while Cambodian has been assigned the Asian category.

² Underweight is defined as < 18.0 kg/m², Normal as 18.0 to < 25 kg/m², Overweight as 25.0 to < 30 kg/m², Obesity 1 as 30.0 to < 35 kg/m², Obesity 2 as 35.0 to < 40 kg/m² and Morbid Obesity as ≥ 40.0 kg/m².

Abbreviations: SD = standard deviation; TCA IR = triamcinolone acetonide injectable suspension, immediate release; US = United States

Source: Table 13, ISE

6.1.3 Subject Disposition

Study 008

There were 695 screen failures in the study. The reasons for patient ineligibility are tabulated below:

Table 10 Study 008 Screen Failures

Inclusion or exclusion criterion	Criterion not met for inclusion or criterion met for exclusion	N
I6	Kellgren-Lawrence (K-L) Grade 2 or 3 in the index knee per Screening X-ray	310
I8	Mean score of ≥ 5 and ≤ 9 on the 24-hr average pain score (0-10 NRS) using the average daily ratings for at least 5 of the 7 days prior to Day 1	271
I9	No more than one 24 hr average pain score (0-10 NRS) reported as "10" during the 7 days prior to Day 1	94
I5	Currently meets ACR Criteria (clinical and radiological) for OA as follows: 1) Knee	77

	Pain 2) at least 1 of the following: Age>50 years, Stiffness<30 minutes, Crepitus 3) Osteophytes	
I2	Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions	69
E25	Positive drug screen (amphetamines, barbiturates, benzodiazepines (indicated as a muscle relaxant), cocaine, opiates, tetrahydrocannabinol (THC))	54
E19	Known or clinically suspected infection with human immunodeficiency virus (HIV), hepatitis B or C viruses	32
E22	Uncontrolled diabetes as indicated by a hemoglobin A1c (HbA1c) of > 7.5% (> 59 mmol/mol)	32
E20	Any clinically significant ECG abnormality as judged by the Investigator	19
E33	Any other clin. sig. acute/chronic med. cond. precluding, in the judgment of the Inv., use of an IA corticosteroid or compromising patient safety or ability to complete and/or compromise study obj	18
I11	Body mass index (BMI) <= 40 kg/m2	13
I7	Index knee pain for >15 days over the last month (as reported by the patient)	11
E1	Any condition that could possibly confound the patient's assessment of index knee pain in judgment of the investigator	9
I13	Willingness to abstain from use of protocol-specified restricted medications and non-pharmacological therapies during the study	9
I10	If bilateral OA exists, pain in the contralateral knee must be less than pain in the index knee as reported by the patient	8
E15	Active or history of malignancy within the last 5 years, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or effectively managed cervical carcinoma	7
E23	Active psychiatric disorder including psychosis (e.g., schizophrenia), bipolar disorder, uncontrolled anxiety disorder and major depressive disorder	7
E21	Patients requiring or likely to require chronic treatment with corticosteroids during the study period based on patient medical history	7
E26	Active substance abuse (drugs or alcohol), history of chronic substance abuse within the past year, or prior chronic substance abuse judged by the investigator as likely to recur during the study	5
I12	Ambulatory and in good general health	4
E16	Any infection requiring intravenous antibiotics within 4 weeks of Screening or oral antibiotics within 2 weeks of Screening	4
E8	Intramuscular or oral corticosteroids (investigational or marketed) within 1 month of Screening	4
E6	IA corticosteroid (investigational or marketed) in any joint within 3 months of Screening	3
E12	Planned/anticipated surgery of the index knee or any other surgery that would require use of a restricted medication during the study period	2
I1	Written consent to participate in the study	2
E2	Fibromyalgia, chronic pain syndrome or other concurrent medical or arthritic	1

	conditions which could interfere with the evaluation of the index knee	
E7	IA hyaluronic acid (investigational or marketed) in the index knee within 6 months of Screening	1
E16	Known active or quiescent systemic fungal, bacterial (including tuberculosis), viral or parasitic infections, or ocular herpes simplex	1
I3	Male or female ≥ 40 years of age	1
E11	Prior arthroscopic or open surgery of the index knee within 12 months of Screening	1
E27	Skin breakdown at the knee where the injection would take place	1
I4	Symptoms associated with OA of the knee for ≥ 6 months prior to Screening (patient reported is acceptable)	1
E32	Use of any other investigational drug or device within 30 days of Screening or an investigational biologic within 60 days of Screening	1

Source: IETEST dataset

Reviewer comment: The vast majority of screen failures did not meet the criteria for osteoarthritis diagnosis, osteoarthritis severity, or the criteria for pain. Exceeding the criteria for body mass index of 40 or below only occurred in 13 potential subjects and limiting the study population in this way does not appear to have affected the subjects that were selected for the study in a significant way. Likewise, only 7 subjects were found to be ineligible based on an active psychiatric disorder, indicating that the criterion was not overly restrictive.

Two subjects were randomized but did not receive study drug. Four-hundred eighty-six subjects were randomized and the prespecified sample size described in the statistical analysis plan was 450.

Reviewer Comment: The randomized sample is slightly higher than the planned enrollment. The slight increase in sample size would not be expected to make an important impact on the power of the study or the treatment effect size observed.

Forty-one out of 484 (8%) subjects that received study treatment discontinued. The reasons for discontinuation by study treatment were as follows:

Table 11 Study 008 Disposition

	FX006 N=161		Placebo N=162		TCA N=161	
	n	%	n	%	n	%
All discontinuations	17	10.6%	13	8.0%	11	6.8%
Lack of Efficacy	7	4.3%	4	2.5%	5	3.1%
Withdrew consent	5	3.1%	3	1.9%	1	0.6%
Other	3	1.9%	0	0.0%	4	2.5%

Lost to follow up	1	0.6%	3	1.9%	0	0.0%
Adverse event	0	0.0%	1	0.6%	1	0.6%
Protocol noncompliance	1	0.6%	1	0.6%	0	0.0%
Withdrawn by investigator or sponsor	0	0.0%	1	0.6%	0	0.0%

Source: Reviewer generated from ADSL dataset

Lack of efficacy was the most common reason for discontinuation in all groups and occurred with similar frequency in all treatment arms. Both adverse events that led to discontinuation were worsening of knee pain.

Reviewer Comment: I reviewed the text describing the reasons for discontinuation categorized as “withdrew consent” and “other” included in the dataset. One of the subjects that was reported as withdrawing due to withdrawal of consent in the TCA group by the Applicant was reclassified in the table above as lack of efficacy because in the clinical study report on p. 67 the reason given was dissatisfaction with the degree of improvement of symptoms. The other discontinuations categorized as “withdrew consent” and “other” appeared appropriately classified. Discontinuations were low overall in the study and were highest in the FX006 group. The reasons for discontinuation were similarly distributed in each treatment arm and no patterns emerged that affect the interpretation of the efficacy results.

Study 006

There was a high completion rate in the study with only 8% of subjects discontinuing prior to week 12 overall. There was the highest discontinuation rate in the placebo group and the lowest discontinuation rate in the FX006 40 mg group.

Table 12 Study 006 Disposition

Disposition	Treatment Group			Total (N=310) n (%)
	FX006 20 mg (N=102) n (%)	FX006 40 mg (N=104) n (%)	Placebo (N=104) n (%)	
Randomized	102	104	104	310
Treated ¹	102 (100.0)	104 (100.0)	100 (96.2)	306 (98.7)
Completed	83 (81.4)	87 (83.7)	85 (81.7)	255 (82.3)
Early Terminated	19 (18.6)	17 (16.3)	19 (18.3)	55 (17.7)
Prior to Week 12	9 (8.8)	3 (2.9)	12 (11.5)	24 (7.7)
Prior to Week 24	19 (18.6)	17 (16.3)	19 (18.3)	55 (17.7)
Reason for Early Termination Prior to Week 12	9	3	12	24
Adverse Event	1 (1.0)	2 (1.9)	1 (1.0)	4 (1.3)
Patient Withdrew Consent	1 (1.0)	0	4 (3.8)	5 (1.6)
Withdrawn by the Investigator or Sponsor	0	0	0	0
Protocol Non-Compliance (After injection)	0	0	0	0
Lost to Follow-Up	3 (2.9)	0	1 (1.0)	4 (1.3)
Termination of Study or by Sponsor	0	0	0	0
Patient Death	0	0	0	0
Lack of Efficacy	3 (2.9)	1 (1.0)	3 (2.9)	7 (2.3)
Patient did not consent to Protocol v2.0	0	0	0	0
Other	1 (1.0)	0	3 (2.9)	4 (1.3)

Source: 006 CSR Table 9

Reviewer Comment: Discontinuations were low overall in the study and no patterns emerged that affect the interpretation of the efficacy results.

6.1.4 Analysis of Primary Endpoint(s)

Study 008

In study 008, the single pivotal study in the program, the primary efficacy endpoint, the change from baseline to week 12 in the weekly mean of the average daily pain (ADP) intensity score on an 11-point numeric rating scale for FX006 relative to placebo, was calculated as the least square mean change from baseline to week 12 in weekly mean ADP intensity scores. There was no imputation of missing data.

Table 13 Study 008 Primary Efficacy Analysis

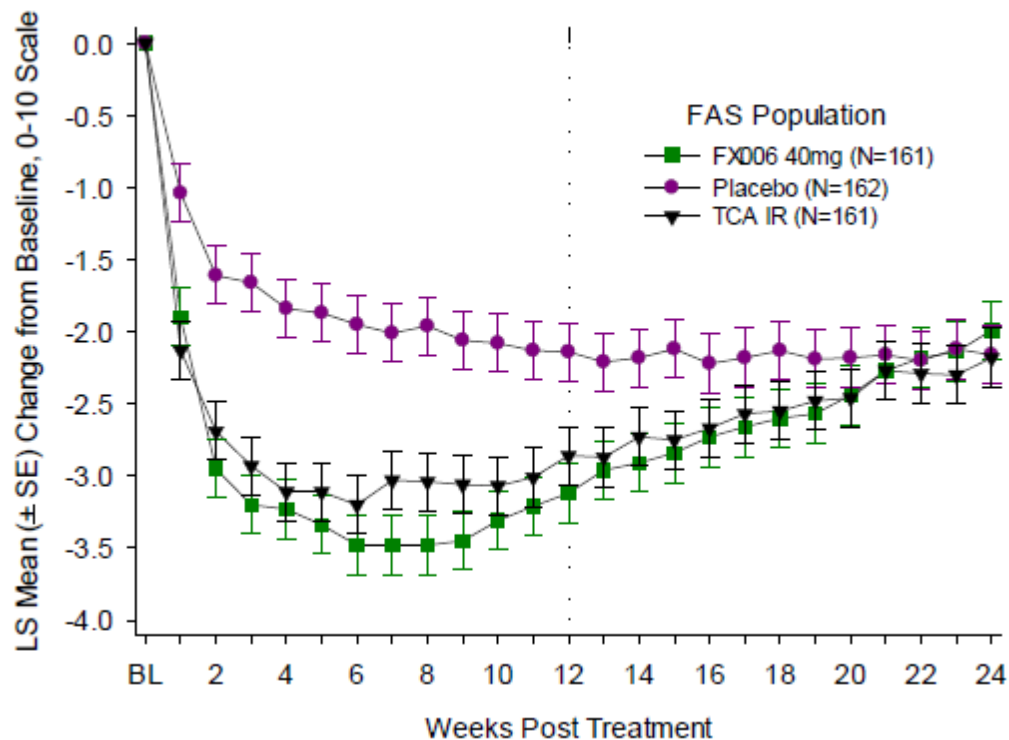
	LSM difference and P-value	Primary endpoint point estimate 40 mg FX006	Primary endpoint point estimate placebo
Primary analysis	-0.98, p<0.0001	-3.12	-2.14
BLOCF/LOCF	-0.99, p= 0.0002	-2.97	-1.98
Multiple imputation	-1.03, p <0.0001	-3.05	-2.19
Removing site as covariate	-0.88, p= 0.0003	-3.07	-2.19

The sensitivity analyses used to examine the impact of missing data indicate that the observed treatment effect is robust.

The mean and median baseline pain score was 6 in each treatment group. The mean pain scores were already one point lower on the 11-point NRS at week 1 in the FX006 and TCA IR groups compared to placebo (mean of 4 in the active groups versus mean of 5 for placebo) and at week 1 the active treatments had a mean change from baseline of 2 points on the 11-point NRS compared to a mean change from baseline of 1 point in the placebo group.

As illustrated in the graph below, the largest improvement from baseline and the largest difference between active and placebo treatments was around week 7 of the treatment period. This improvement was around 3.5 points on the 11-point scale for FX006 and around 3 points for TCA IR. At week 7 the improvement was only 2 points in the placebo group. At week 12, the mean change from baseline for FX006 and TCA IR was 3 points and continued to be 2 points for placebo. By week 24 the treatment effect of FX006 and TCA was no longer evident compared to placebo.

Figure 1 Study 008 Least Squares Mean Change from Baseline in the Weekly Mean of ADP Score



Source: Figure 2 008 CSR

Study 006

The primary efficacy endpoint was the change from Baseline in the weekly mean of the average daily (24-hour) pain intensity score through Week 12 for 40 mg FX006 vs placebo.

Table 14 Study 006 Primary Efficacy Endpoint

	FX006 40 mg	FX006 20 mg	placebo
LSM difference	-3.08	-2.59	-2.50

Source: Table 14.2.1.1.1, 006 CSR

The analysis was to be a longitudinal mixed effects model for repeated measures (MMRM) with fixed effects for treatment group, study week, treatment-by-week interaction and baseline covariate using the full analysis population.

Table 15 Study 006 Primary Efficacy Analysis

	LSM difference and P-value
20 mg vs. placebo	-0.09 p=0.7916
40 mg vs. placebo	-0.58 p=0.0821

Source: Table 13, 006 CSR

The difference between the 40 mg dose and placebo was not statistically significant. However, the point estimate trended in favor of FX006 and does not contradict the findings from study 008. There was essentially no difference between the 20 mg dose and placebo on this endpoint, which supports the choice of the 40 mg dose for study 008.

6.1.5 Analysis of Secondary Endpoints(s)

Study 008

The key secondary endpoints that were tested were comparisons of the area under the effect curves (AUE) for the weekly mean of the ADP scores.

Table 16 Study 008 Key Secondary Endpoints

Endpoint	Comparison	LSM 40 mg FX006	LSM placebo	LSM 40 mg TCA IR	LSM difference	P-value
AUE Weeks 1-12	40 mg FX006 vs. Placebo	-247.3	-145.3		-102.0	<0.0001
AUE Weeks 1-12	40 mg FX006 vs. TCA IR	-247.3		-231.9	-15.3	0.3827

Source: Table 17 008 CSR

Only two of the four prespecified key secondary endpoints were tested based on the planned step-down testing procedure because the p-value for the difference in AUE for weeks 1-12 between FX006 and TCA IR was not <0.05. The results of these secondary

analyses support the finding in the primary analysis that FX006 is superior to placebo and do not show a statistically significant difference in the treatment effect in the first 12 weeks following treatment between FX006 and TCA IR.

Study 006

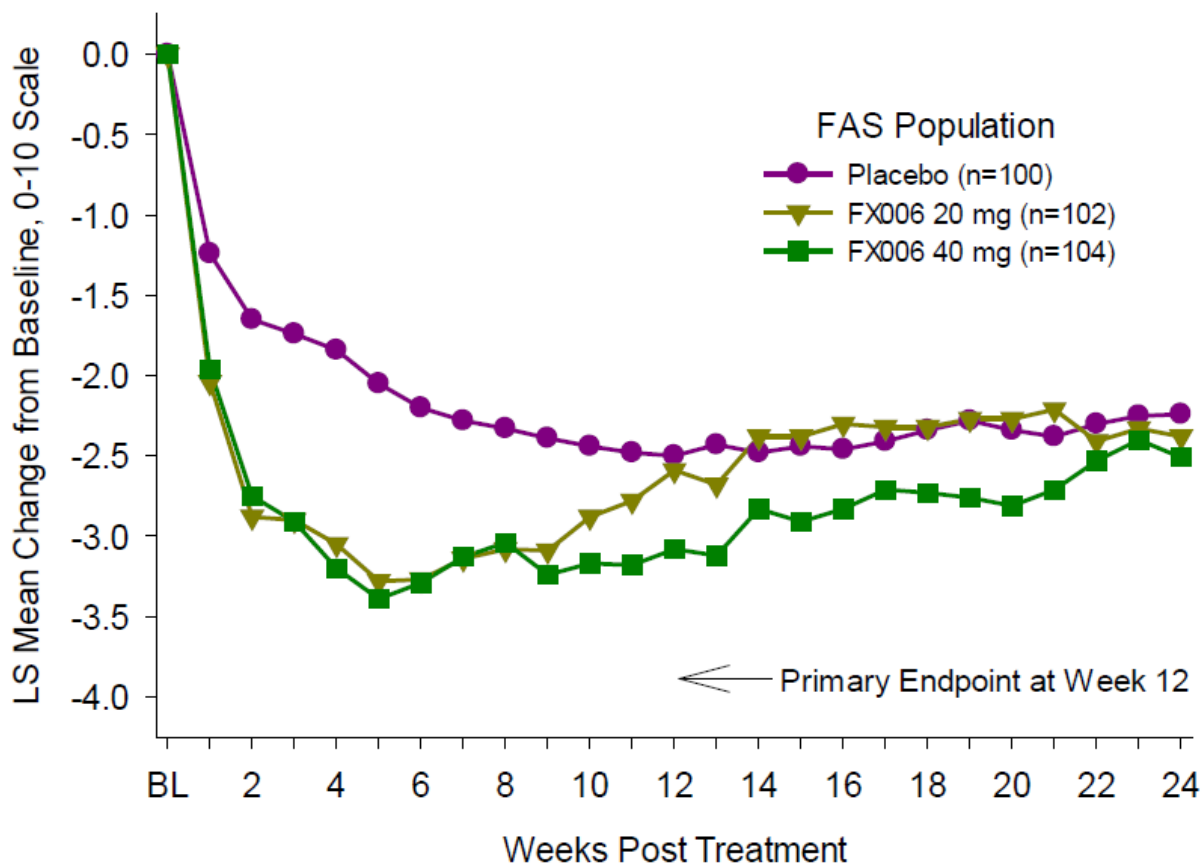
The statistical analysis plan stated that the following endpoints would be analyzed using step-down testing:

- Western Ontario and McMaster Universities (WOMAC®) Osteoarthritis Index C (function): Change from Baseline to Week 12
- Patient Global Impression of Change (PGIC): 7-point scale at Week 12
- Change from Baseline to Week 16 and then Week 20 and then Week 24 in the weekly mean of the average daily (24-hr) pain intensity scores on a 0 to 10 NRS scale

However, the study report did not report these secondary outcomes as key or report the results of step-down testing. Results of the WOMAC function subscale and PGIC are presented in section 6.1.6 along with other endpoints of interest.

The figure below shows the change from baseline for the weekly mean of the average daily pain score by weeks post-treatment for all treatment groups in the FAS population, including weeks 16, 20 and 24, which were planned as secondary endpoints.

Figure 2 Study 006 Least Squares Mean Change from Baseline in the Weekly Mean of ADP Score



Source: Table 14.2.1.1.1.

Source: Figure 2 006 CSR

Reviewer Comment: The FX006 40 mg LSM change from baseline continues to be separated from FX006 20 mg and placebo at week 16 and 20, indicating the persistence of an effect, though the separation in the curves is less than it was at week 12. No between-group differences are evident by week 24.

6.1.6 Other Endpoints

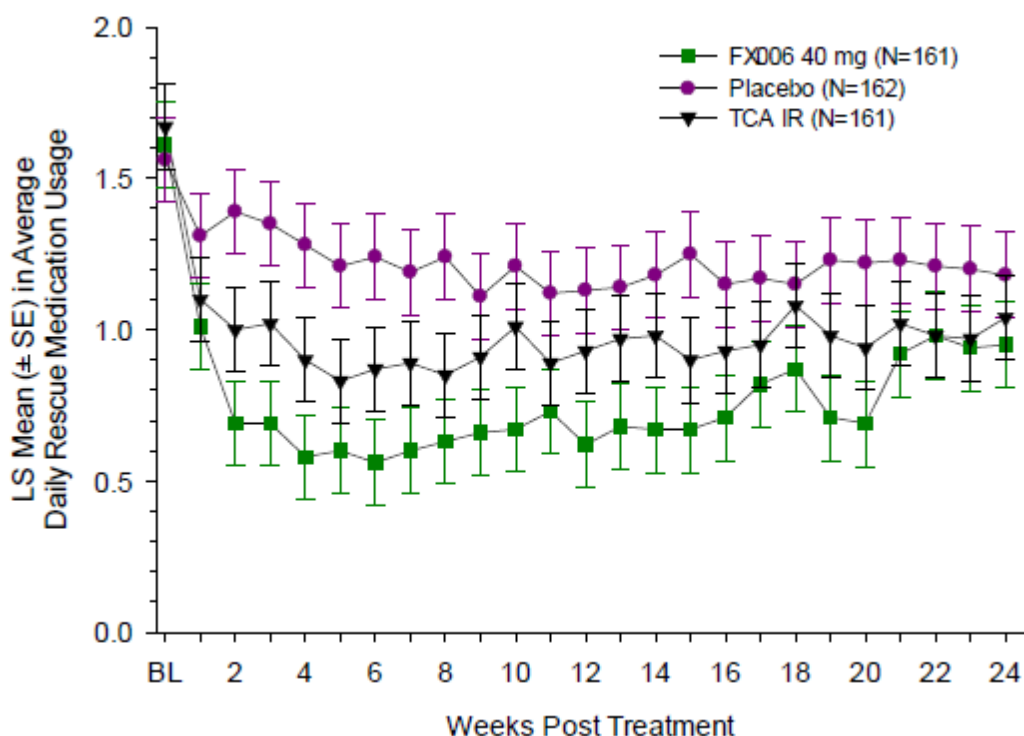
Rescue Medication Use

Study 008

The LS Mean in average daily rescue medication use (acetaminophen as needed up to 3 g per day) supports the primary analysis results in that the placebo group use was

greater than the FX006 group use over the entire 24-week study period as shown in the graph below.

Figure 3 Study 008 Rescue Medication Use



Source: Figure 17 008 CSR

The mean rescue medication use in the week prior to study treatment was a mean of 1.7 and a median of 1 acetaminophen 500 mg tablets per day in all treatment groups. During the treatment period, the mean use decreased to between 1.1 and 1.4 tablets per day at week 1 and continued to be less than at baseline in all groups for the entire study period. This level of rescue use is modest and supportive of a treatment effect from the study treatment.

Study 006

During the baseline period, the mean number of daily rescue medication tablets taken was 1.7 in the FX006 20 mg and 40 mg group and 1.5 in the placebo group. The mean number of daily rescue medication tablets (acetaminophen 500 mg) taken over the entire 24 week treatment period was highest in the FX006 20 mg group (1.27), followed by the placebo group (1.09), and lowest in the FX006 40 mg group (0.95). The decrease in daily rescue medication use compared to baseline during the treatment period and the lower use in FX006 40 mg group compared to placebo during the treatment period despite higher use in the FX006 40 mg group compared to placebo in the baseline

period support the benefit suggested by the numerical trend favoring FX006 40 mg over placebo in the magnitude of decrease in mean 11-point NRS scores from baseline.

WOMAC

Study 008

The pain and physical function subscales are frequently used in clinical trials of OA and the data from these scales were analyzed as exploratory endpoints in this study and are supportive of the primary analysis result.

Table 17 Study 008 WOMAC Pain and Function Subscales

Endpoint	Comparison	LSM difference	P-value
WOMAC pain subscale change from baseline to week 12	40 mg FX006 vs. Placebo	-0.37	<0.0001
WOMAC physical function subscale change from baseline to week 12	40 mg FX006 vs. Placebo	-0.38	<0.0001

Source: Figure 7 008 CSR

Study 006

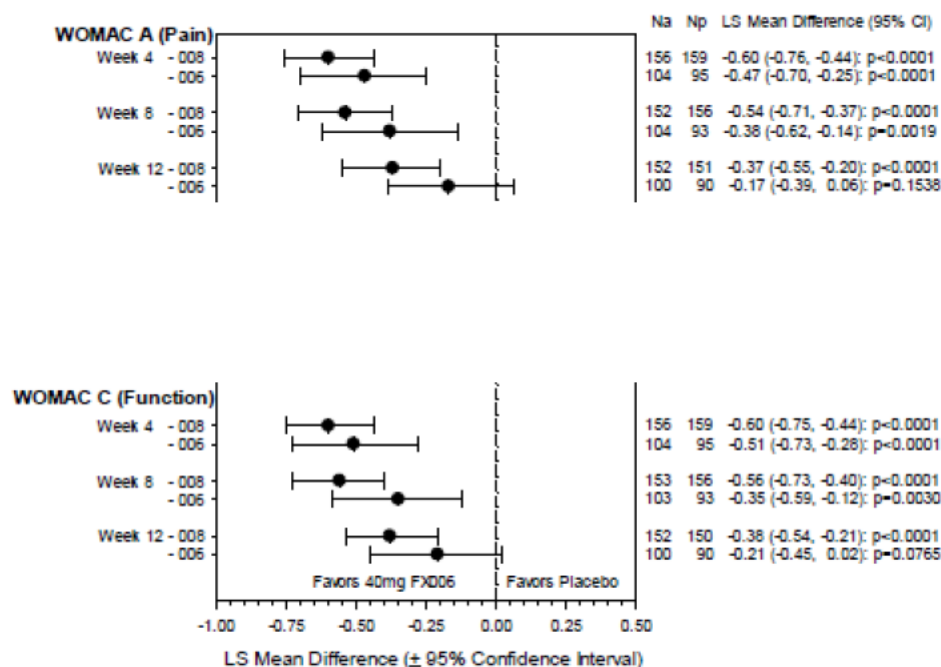
Table 18 Study 006 WOMAC Pain and Function Subscales

Endpoint	Comparison	LSM difference	P-value
WOMAC pain subscale change from baseline to week 12	40 mg FX006 vs. Placebo	-0.2	0.1538
WOMAC physical function subscale change from baseline to week 12	40 mg FX006 vs. Placebo	-0.45	0.0765

As with the primary endpoint, the LSM differences in the WOMAC pain and physical function subscales trended in favor of FX006 40 mg compared to placebo but the difference was not statistically significant.

The following figure presents the WOMAC pain and function subscale scores for both studies 008 and 006 together.

Figure 4 Studies 008 and 006 Differences in WOMAC Pain and Function Subscale Scores (FX006 40 mg versus Placebo)



CI = confidence interval; LS = least square; Na = number of FX006 40 mg patients; Np = number of placebo patients; WOMAC = Western Ontario and McMaster Osteoarthritis Index

Source: Figure 9 of ISE [WOMAC B stiffness removed from figure]

Patient Global Impression of Change (PGIC)

The PGIC is frequently used in clinical trials of OA. The PGIC data from study 008 were analyzed as an exploratory endpoint in this study and are supportive of the primary analysis result.

Study 008

Table 19 Study 008 PGIC

Endpoint	Comparison	LSM difference	P-value
PGIC change from baseline to week 12	40 mg FX006 vs. Placebo	-0.6	0.0003

Study 006

Table 20 Study 006 PGIC

Endpoint	Comparison	LSM difference	P-value
PGIC change from baseline to week 12	40 mg FX006 vs. Placebo	-0.1	>.05

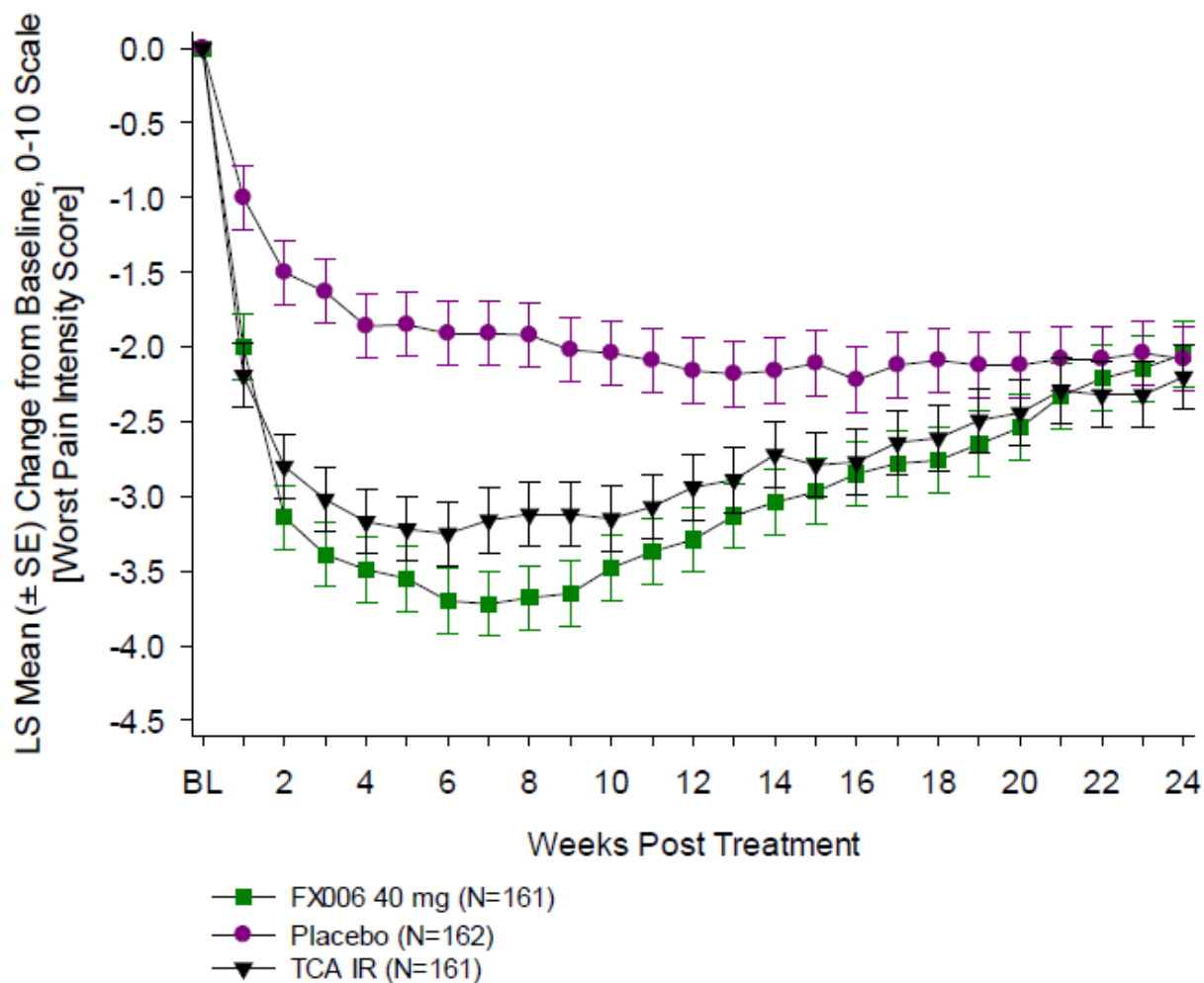
In study 006, the PGIC change from baseline LSM difference between FX006 40 mg and placebo slightly favored FX006 but was not statistically significant.

Weekly mean of the worst daily pain score on 11-point NRS

Study 008

Based on feedback from DAAAP during the development program, the Applicant included measures of pain at its worst in the last 24 hours on the daily patient diary for study 008 and reported the analysis results as an additional exploratory endpoint in the study report. The results support the primary analysis results and are represented graphically below:

Figure 5 Study 008 Weekly Mean of Worst Daily Pain Score



Source: Figure 15, 008 CSR

6.1.7 Subpopulations

Subgroup analyses were conducted using the data from the three double-blind efficacy studies, studies 001, 006, and 008.

Age

In the double-blinded controlled studies, for the primary endpoint, change from baseline to week 12 in weekly mean average daily pain intensity, FX006 had a consistently larger treatment effect than placebo for all age groups (age 40-50 years, age 51-64 years, age 65-75 years and age >75 years). For the WOMAC pain and function subscales, FX006

had a larger treatment effect than placebo for all but the >75 year old age group, where the treatment effect was similar between groups. The subgroup of subjects >75 was very small (<20 subjects per group), which increases the width of the confidence interval and obscures differences between groups.

Sex

In the double-blinded controlled studies, for the primary endpoint, change from baseline to week 12 in weekly mean average daily pain intensity, and the WOMAC pain and function subscales, FX006 had a consistently larger treatment effect than placebo for both men and women.

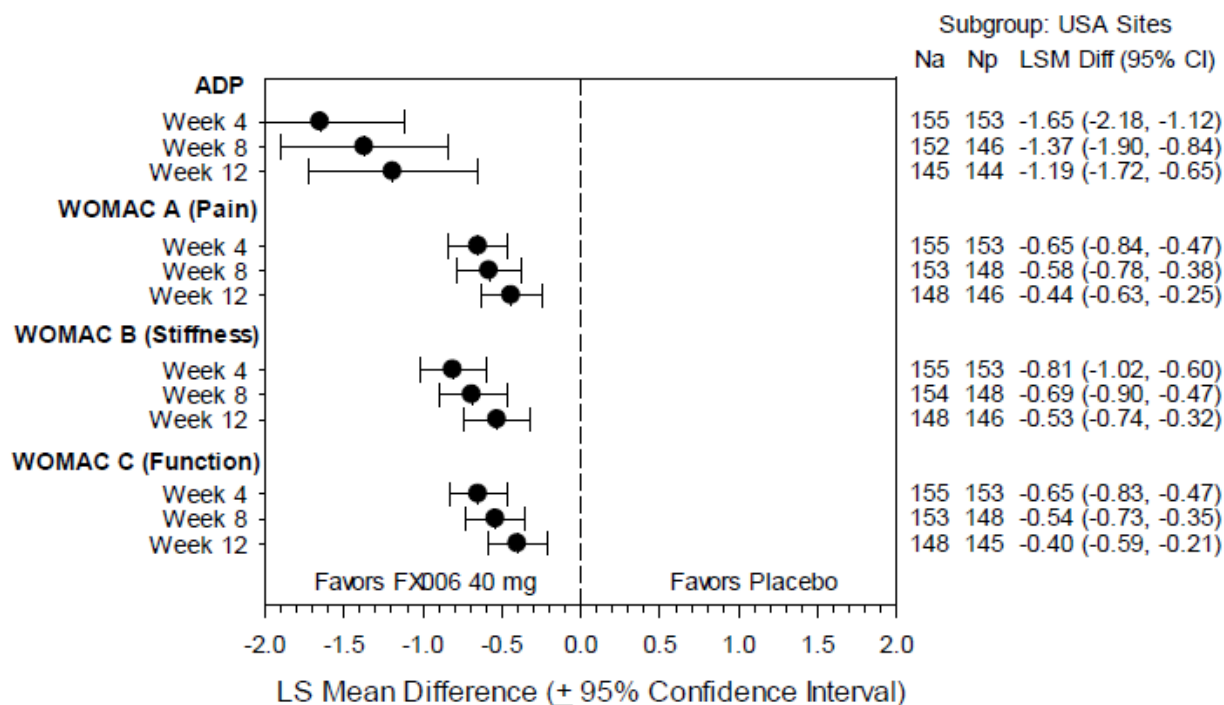
Race

The main efficacy results in the double-blinded controlled studies were also summarized by race. The Applicant only analyzed White and Asian subgroups separately from the other races because they were the two races with the highest number of patients. There were approximately 10 times more White patients in the studies than any other race (around 250 patients per group in the White subgroup analyses compared to around 20 patients per group in the Asian subgroup analyses and around 25 in the non-white, non-Asian subgroup analyses). In the largest subgroup, White patients, the results of the ADP and WOMAC pain and function subscales are like the overall results. There was a small sample size and large confidence interval in the Asian subgroup but the ADP and WOMAC pain and function subscales were generally similar to the overall results with the exception of the week 12 ADP, which had a point estimate favoring placebo and a 95% CI of -1.17 to 1.94. The non-white, non-Asian subgroup also had a small sample size and large confidence intervals for the ADP and WOMAC pain and function subscales. Like the week 12 ADP in the Asian subpopulation, the weeks 4, 8, and 12 ADPs favored placebo and had wide confidence intervals that spanned -0.99 to 2.89. The WOMAC pain and function subscales were similar to the overall results.

Country

For the U.S. sites, the main efficacy results consistently favored treatment with FX006 compared with placebo as shown below:

Figure 6 Change from Baseline in the Weekly Mean of the Average Daily (24-hour) Pain Intensity Scores and WOMAC A, B and C Subscales (Enrollment Site: United States)



Source: [Table 14.2.1.6.1.B](#), [Table 14.2.3.1.6.1.B](#), [Table 14.2.3.3.6.1.B](#), [Table 14.2.3.4.6.1.B](#)

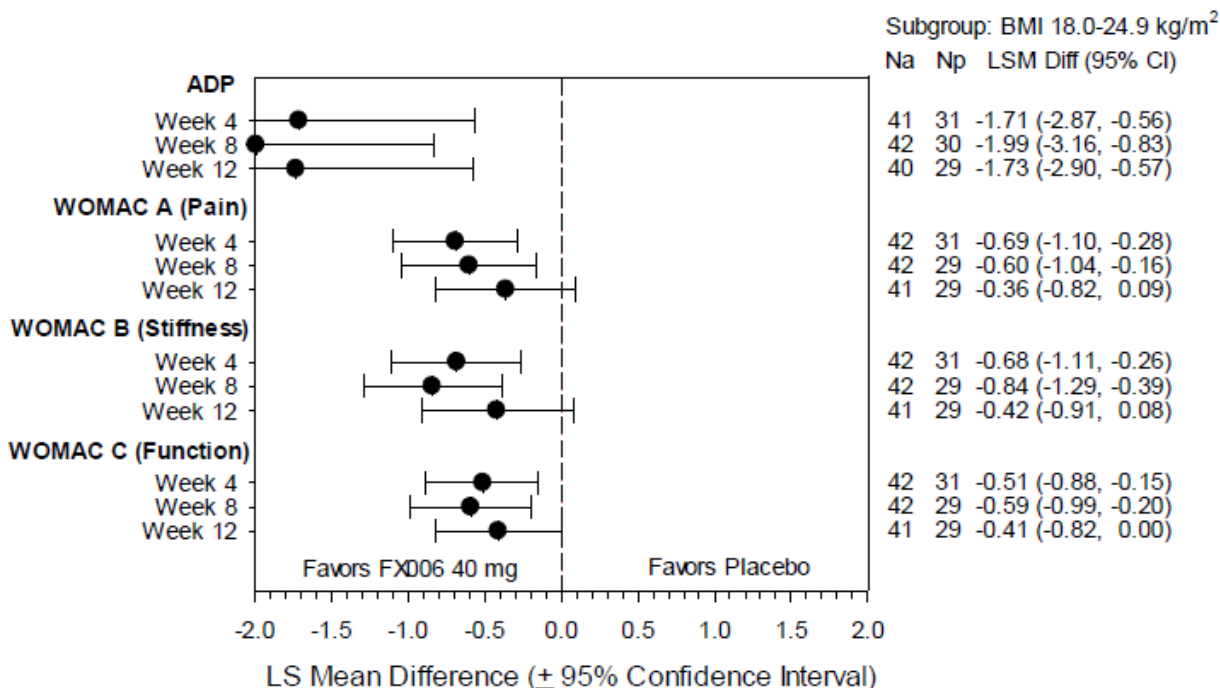
ADP = average daily pain; CI = confidence interval; Diff = difference; LS = least square; LSM = least square mean; Na = number FX006 40 mg patients; Np = number placebo patients; US = United States; WOMAC = Western Ontario and McMaster Osteoarthritis Index

Source: Figure 48 ISE

BMI

The efficacy results from the double-blinded controlled studies were summarized by BMI category. There were no patients with BMI < 18 (underweight) and only 3 with morbid obesity BMI 40 and over. There were less than 50 patients per treatment group in the normal weight category (BMI 18-24.9). FX006 was favored over placebo consistently in all BMI categories with data (normal, overweight, and obesity 1 and 2). The forest plots generated by the Applicant are reproduced below and are very similar across BMI categories:

Figure 7 Change from Baseline in the Weekly Mean of the Average Daily (24-hour) Pain Intensity Scores and WOMAC A, B, and C Subscales (BMI Category: Normal)



Source: [Table 14.2.1.3.2.B](#), [Table 14.2.3.1.3.2.B](#), [Table 14.2.3.3.3.2.B](#), [Table 14.2.3.4.3.2.B](#)

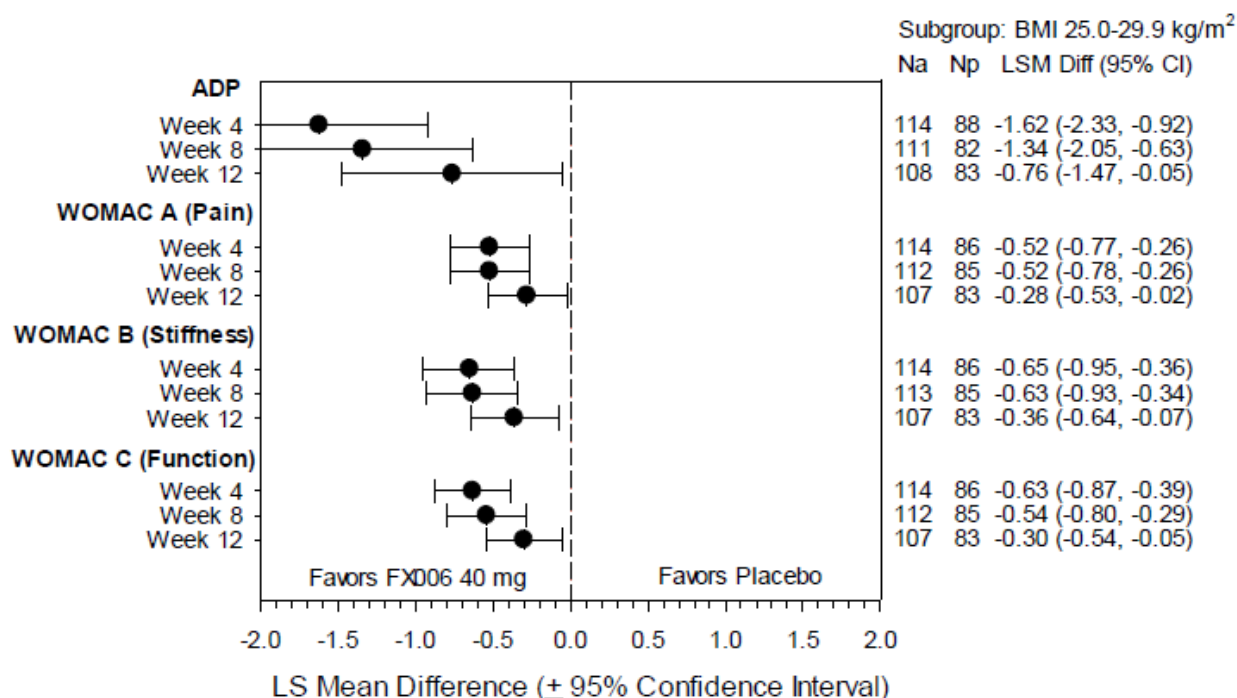
ADP = average daily pain; BMI = body mass index; CI = confidence interval; Diff = difference; LS = least square;

LSM = least square mean; Na = number FX006 40 mg patients; Np = number placebo patients;

WOMAC = Western Ontario and McMaster Osteoarthritis Index

Source: Figure 41 of ISE

Figure 8 Change from Baseline in the Weekly Mean of the Average Daily (24-hour) Pain Intensity Scores and WOMAC A, B, and C Subscales (BMI Category: Overweight)



Source: [Table 14.2.1.3.3.B](#), [Table 14.2.3.1.3.3.B](#), [Table 14.2.3.3.3.3.B](#), [Table 14.2.3.4.3.3.B](#)

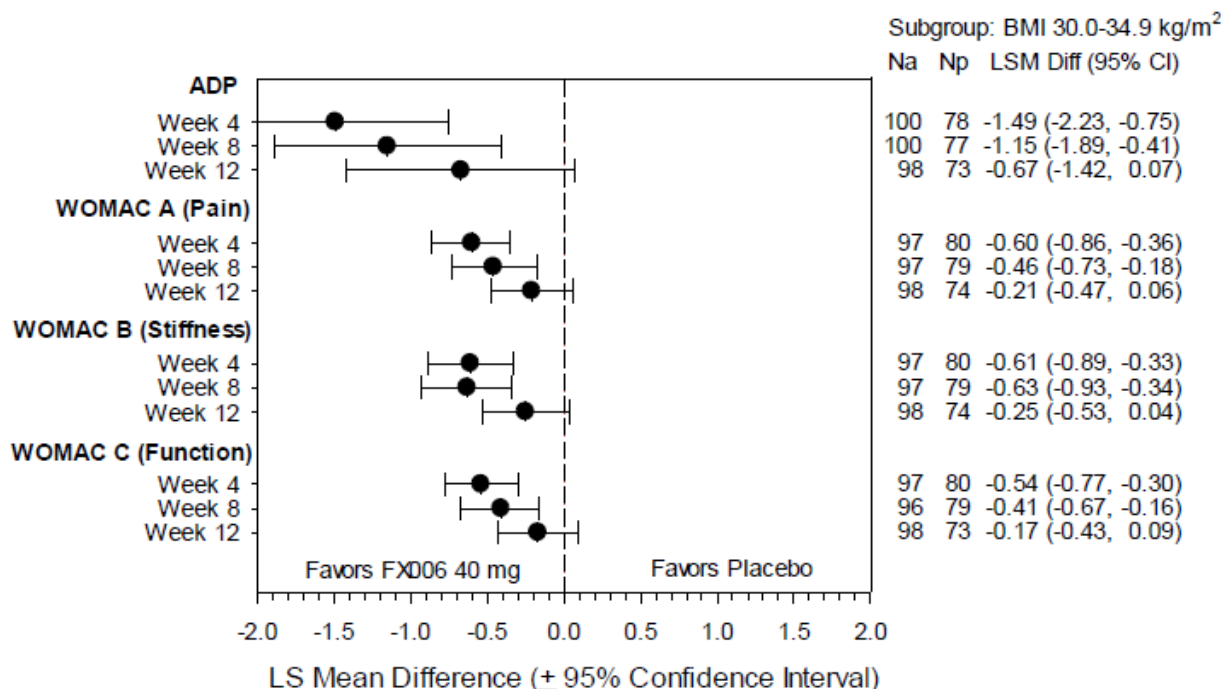
ADP = average daily pain; BMI = body mass index; CI = confidence interval; Diff = difference; LS = least square;

LSM = least square mean; Na = number FX006 40 mg patients; Np = number placebo patients;

WOMAC = Western Ontario and McMaster Osteoarthritis Index

Source: Figure 42 of ISE

Figure 9 Change from Baseline in the Weekly Mean of the Average Daily (24-hour) Pain Intensity Scores and WOMAC A, B, and C Subscales (BMI Category: Obesity 1)



Source: [Table 14.2.1.3.4.B](#), [Table 14.2.3.1.3.4.B](#), [Table 14.2.3.3.3.4.B](#), [Table 14.2.3.4.3.4.B](#)

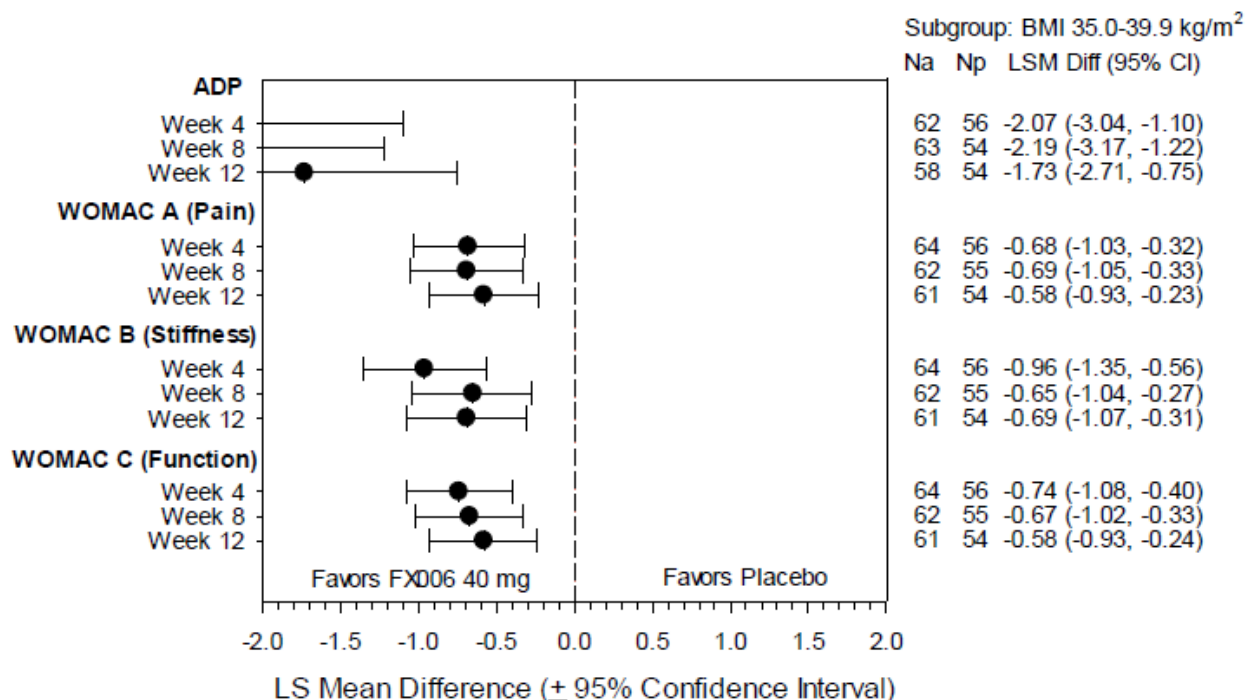
ADP = average daily pain; BMI = body mass index; CI = confidence interval; Diff = difference; LS = least square;

LSM = least square mean; Na = number FX006 40 mg patients; Np = number placebo patients;

WOMAC = Western Ontario and McMaster Osteoarthritis Index

Source: Figure 43 of ISE

Figure 10 Change from Baseline in the Weekly Mean of the Average Daily (24-hour) Pain Intensity Scores and WOMAC A, B, and C Subscales (BMI Category: Obesity 2)



Source: Table 14.2.1.3.5.B, Table 14.2.3.1.3.5.B, Table 14.2.3.3.3.5.B, Table 14.2.3.4.3.5.B

ADP = average daily pain; BMI = body mass index; CI = confidence interval; Diff = difference; LS = least square;

LSM = least square mean; Na = number FX006 40 mg patients; Np = number placebo patients;

WOMAC = Western Ontario and McMaster Osteoarthritis Index

Source: Figure 44 of ISE

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Sponsor cites the dose-ranging study 001 as evidence that there was a dose-response between 10 mg and 40 mg and that there was no additional benefit observed in the subjects that received 60 mg compared to 40 mg.

Study 001 was double-blinded, randomized and active-controlled with no placebo control. Three doses of FX006, 10 mg, 40 mg and 60 mg, and one dose of the active comparator, TCA IR 40 mg, were studied. A single dose was administered and efficacy and safety assessments were collected for 12 weeks following dosing. The average daily pain intensity change from baseline least square mean differences at week 12 are summarized below.

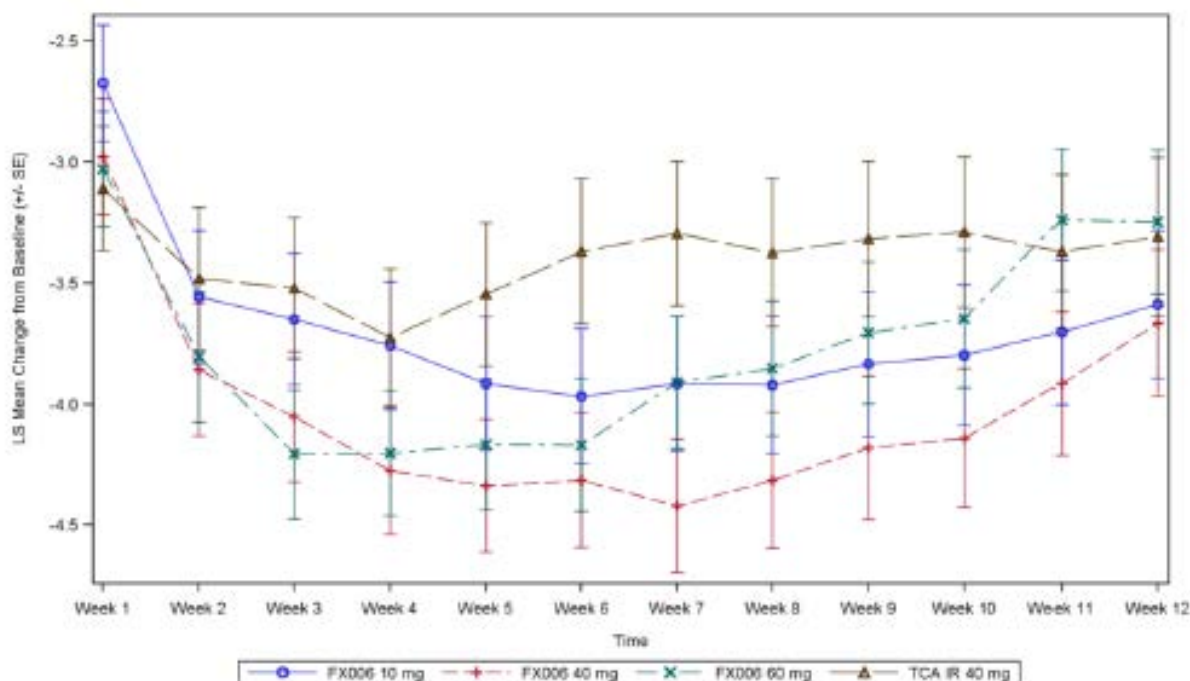
Table 21 Study 001 Primary Efficacy Endpoint

	FX006 10 mg N=58	FX006 40 mg N=59	FX006 60 mg N=60	TCA IR N=51
Change from baseline to week 12 LSM difference	-3.6	-3.7	-3.2	-3.3

Source: Study 001 CSR table 14.2.1.1A

All doses in this study had a similar point estimate for the change from baseline for pain intensity, with no evidence of a dose-response relationship in the week 12 data, and all had a larger change from baseline than placebo in studies 008 and 006 (the placebo average daily pain intensity change from baseline least square mean difference at week 12 was around -2 for study 008 and -2.5 for study 006). However, the trend observed in the weekly data from week 1 to week 12 does appear to show a larger change from baseline for FX006 40 mg compared to FX006 10 mg and does not appear to show any additional benefit from the FX006 60 mg dose compared to the FX006 40 mg dose. These results are supportive of the choice to study the FX006 40 mg dose in the larger Phase 3 study 008.

Figure 11 Study 001 Change from Baseline in the Weekly Mean of the Average Daily (24-hour) Pain Intensity Scores



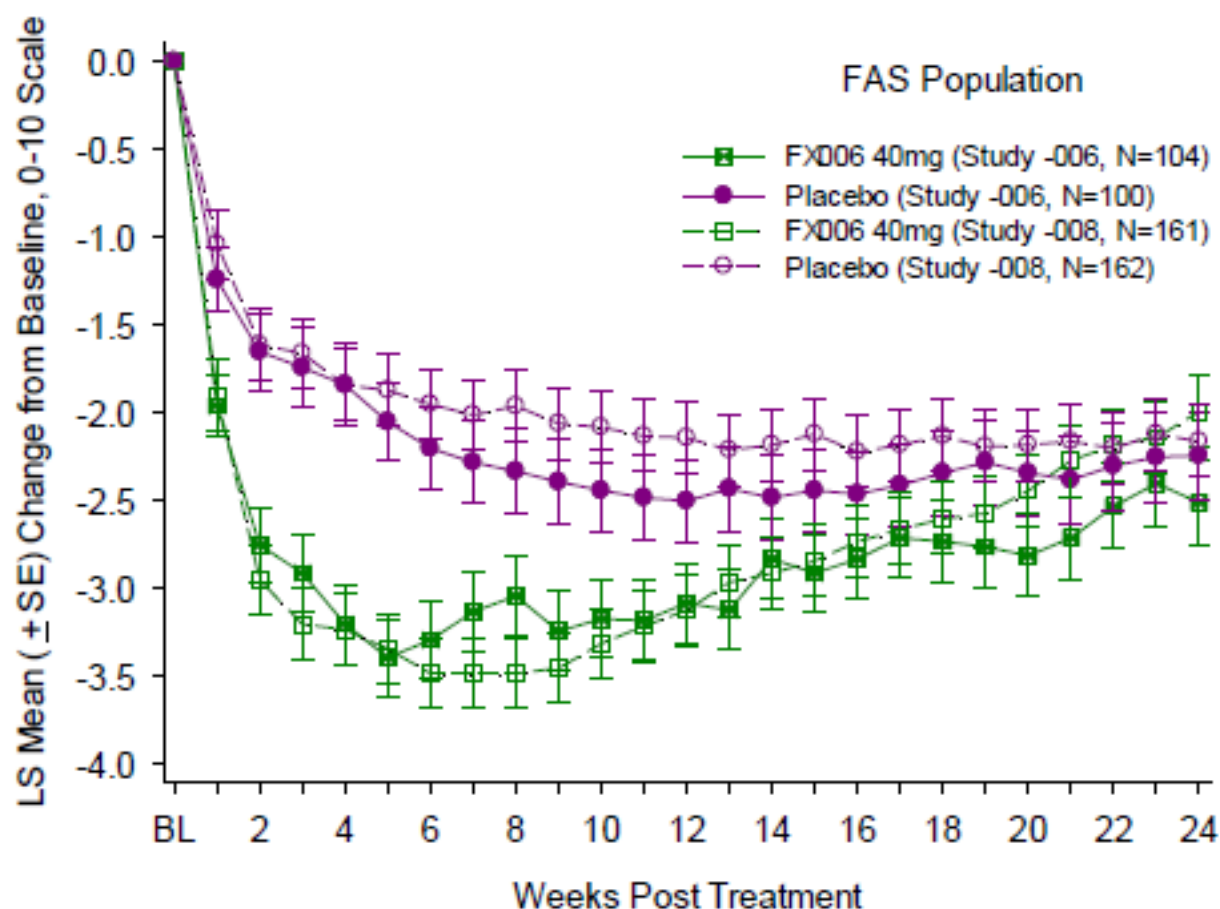
Source: Figure 14.2.1.1A.

Source: figure 11-1, study 001 CSR

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

An effect on the primary efficacy endpoint, as shown below, persisted in both studies 008 and 006 for many weeks past the single injection. In study 008, the effect was statistically significantly different than placebo at the 12-week timepoint generally required for demonstration of a duration of effect that is suitable to support an indication for chronic painful conditions. These results support the proposed indication, which is for management of osteoarthritis pain.

Figure 12 Studies 008 and 006 Change from Baseline in the Weekly Mean of the Average Daily (24-hour) Pain Intensity Scores



Source: FX006-2014-008 Table 14.2.1.1.1; FX006-2014-006 Table 14.2.1.1.1
BL = Baseline; FAS = Full Analysis Population; LS = least square; SE = standard error

Source: ISE Figure 6

7 Review of Safety

Safety Summary

There were no new safety signals identified in the clinical development program. There was adequate evaluation of safety, including follow-up evaluation of the index joint by x-ray at 24 weeks in the pivotal Phase 3 study and evaluation of adrenal suppression in a pharmacodynamics study. The safety experience with FX006 did not distinguish itself from TCA IR and the warnings described in the Kenalog-40 are appropriate for FX006. There were no major differences in the safety experience among subgroups. The findings from study 002 and 010 show that both FX006 and TCA IR elevate blood glucose and cause adrenal suppression and suggest that FX006 could have smaller effects on blood glucose elevation and adrenal suppression than TCA IR. However, the studies had methodologic problems, did not include justification for what would be considered a clinically relevant difference in the measured parameters, and the findings have not been reproduced. Therefore, the clinical importance of the differences observed is unknown (b) (4)

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 22 Studies Used to Evaluate Safety

Study Number	Type of Study	Treatment						Follow-up period
		FX006 10 and 20 mg	FX006 40 mg	FX006 60 mg	FX006 total	placebo	TCA IR 40 mg	
008	Efficacy	0	161	0	161	162	161	24 wk
006	Efficacy	102	104	0	206	100	0	24 wk
001	Efficacy	58	59	60	177	0	51	12 wk
002	PK and PD	5	7	7	19	0	5	6 wk
005	PK	10	30	0	40	0	10	12-20 wk
009	PK	0	63	0	63	0	0	6-20 wks
total		175	424	67	522	262	227	

Source: reviewer-generated from ISS Table 1 and Table 14.1.1.A

There is also information about Study 010 in the ISS but it was not used in the pooling because the study was not complete when the ISS was generated. Study 010 is a PD study.

7.1.2 Categorization of Adverse Events

Adverse events were coded using MedDRA version 18.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The studies were grouped into 2 study pools for analysis purposes.

Pool 1: The six completed studies comprised the All Studies pool. Study 010 was not complete and not included in the pool.

Pool 2: The 3 double-blind studies comprised the Double-blind Studies (i.e., Efficacy Studies) pool.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

All exposures are to single injections. No subjects received multiple injections. There were 424 subjects exposed to the dose proposed for marketing, FX006 40 mg.

Table 23 Study Drug Exposure, Pool 1 (All Completed Studies)

Category	FX006 10 and 20 mg (N=175) n (%)	FX006 40 mg (N=424) n (%)	FX006 60 mg (N=67) n (%)	Total FX006 (N=666) n (%)	Placebo (N=262) n (%)	TCA IR 40 mg (N=227) n (%)
Position of Knee						
Extended	71 (40.6)	242 (57.1)	36 (53.7)	349 (52.4)	114 (43.5)	111 (48.9)
Bent	103 (58.9)	181 (42.7)	31 (46.3)	315 (47.3)	146 (55.7)	115 (50.7)
Other	1 (0.6)	1 (0.2)	0	2 (0.3)	2 (0.8)	1 (0.4)
Approach for Injection						
Lateral	113 (64.6)	260 (61.3)	33 (49.3)	406 (61.0)	168 (64.1)	126 (55.5)
Medial	61 (34.9)	163 (38.4)	34 (50.7)	258 (38.7)	92 (35.1)	101 (44.5)
Other	1 (0.6)	1 (0.2)	0	2 (0.3)	2 (0.8)	0
Aspiration of Synovial Fluid? ¹						
Yes	166 (94.9)	411 (96.9)	64 (95.5)	641 (96.2)	254 (96.9)	212 (93.4)
0 mL	104 (59.4)	262 (61.8)	33 (49.3)	399 (59.9)	175 (66.8)	128 (56.4)
>0 mL - <5 mL	48 (27.4)	122 (28.8)	25 (37.3)	195 (29.3)	62 (23.7)	71 (31.3)
≥5 mL	14 (8.0)	27 (6.4)	6 (9.0)	47 (7.1)	17 (6.5)	13 (5.7)
No	9 (5.1)	13 (3.1)	3 (4.5)	25 (3.8)	8 (3.1)	15 (6.6)
Entire Contents of Syringe Injected?						
Yes	175 (100.0)	424 (100.0)	67 (100.0)	666 (100.0)	262 (100.0)	227 (100.0)
No	0	0	0	0	0	0

Source: Table 9, ISS

Table 24 Study Drug Exposure, Pool 2 (All Double-blind Studies)

Category	FX006 10 and 20 mg (N=160) n (%)	FX006 40 mg (N=324) n (%)	FX006 60 mg (N=60) n (%)	Total FX006 (N=544) n (%)	Placebo (N=262) n (%)	TCA IR 40 mg (N=212) n (%)
Position of Knee						
Extended	57 (35.6)	156 (48.1)	29 (48.3)	242 (44.5)	114 (43.5)	96 (45.3)
Bent	102 (63.8)	167 (51.5)	31 (51.7)	300 (55.1)	146 (55.7)	115 (54.2)
Other	1 (0.6)	1 (0.3)	0	2 (0.4)	2 (0.8)	1 (0.5)
Approach for Injection						
Lateral	105 (65.6)	192 (59.3)	29 (48.3)	326 (59.9)	168 (64.1)	114 (53.8)
Medial	54 (33.8)	131 (40.4)	31 (51.7)	216 (39.7)	92 (35.1)	98 (46.2)
Other	1 (0.6)	1 (0.3)	0	2 (0.4)	2 (0.8)	0
Aspiration of Synovial Fluid?						
Yes	151 (94.4)	312 (96.3)	57 (95.0)	520 (95.6)	254 (96.9)	197 (92.9)
0 mL	99 (61.9)	223 (68.8)	33 (55.0)	355 (65.3)	175 (66.8)	123 (58.0)
> 0 mL - < 5 mL	43 (26.9)	77 (23.8)	19 (31.7)	139 (25.6)	62 (23.7)	63 (29.7)
≥ 5 mL	9 (5.6)	12 (3.7)	5 (8.3)	26 (4.8)	17 (6.5)	11 (5.2)
No	9 (5.6)	12 (3.7)	3 (5.0)	24 (4.4)	8 (3.1)	15 (7.1)
Entire Contents of Syringe Injected?						
Yes	160 (100.0)	324 (100.0)	60 (100.0)	544 (100.0)	262 (100.0)	212 (100.0)
No	0	0	0	0	0	0

Source: Table 10, ISS

The demographics in all studies (Pool 1) are as follows:

Table 25 Demographic and Baseline Characteristics Pool 1 (Safety Population)

Parameter/Statistics	FX006 10 and 20 mg (N=175)	FX006 40 mg (N=424)	FX006 60 mg (N=67)	Total FX006 (N=666)	Placebo (N=262)	TCA IR 40 mg (N=227)	Total (N=1155)
Gender - n (%)							
Male	76 (43.4)	181 (42.7)	30 (44.8)	287 (43.1)	105 (40.1)	91 (40.1)	483 (41.8)
Female	99 (56.6)	243 (57.3)	37 (55.2)	379 (56.9)	157 (59.9)	136 (59.9)	672 (58.2)
Primary Race - n (%)							
American Indian or Alaska Native	0	0	2 (3.0)	2 (0.3)	1 (0.4)	0	3 (0.3)
Asian	3 (1.7)	24 (5.7)	3 (4.5)	30 (4.5)	15 (5.7)	18 (7.9)	63 (5.5)
Black or African American	20 (11.4)	46 (10.8)	2 (3.0)	68 (10.2)	19 (7.3)	16 (7.0)	103 (8.9)
Native Hawaiian or Other Pacific Islander	2 (1.1)	4 (0.9)	0	6 (0.9)	1 (0.4)	2 (0.9)	9 (0.8)
White	148 (84.6)	348 (82.1)	56 (83.6)	552 (82.9)	226 (86.3)	190 (83.7)	968 (83.8)
Other	2 (1.1)	2 (0.5)	4 (6.0)	8 (1.2)	0	1 (0.4)	9 (0.8)
Race Groups - n (%)¹							
White	149 (85.1)	350 (82.5)	58 (86.6)	557 (83.6)	226 (86.3)	190 (83.7)	973 (84.2)
Asian	4 (2.3)	24 (5.7)	3 (4.5)	31 (4.7)	15 (5.7)	19 (8.4)	65 (5.6)
Non-White/Non-Asian	22 (12.6)	50 (11.8)	6 (9.0)	78 (11.7)	21 (8.0)	18 (7.9)	117 (10.1)
Ethnicity - n (%)							
Hispanic or Latino	18 (10.3)	62 (14.7)	0	80 (12.0)	45 (17.2)	19 (8.4)	144 (12.5)
Not Hispanic or Latino	157 (89.7)	361 (85.3)	67 (100.0)	585 (88.0)	216 (82.4)	208 (91.6)	1009 (87.4)
Not Reported	0	0	0	0	1 (0.4)	0	1 (0.1)
Parameter/Statistics	FX006 10 and 20 mg (N=175)	FX006 40 mg (N=424)	FX006 60 mg (N=67)	Total FX006 (N=666)	Placebo (N=262)	TCA IR 40 mg (N=227)	Total (N=1155)
Country - n (%)							
US	95 (54.3)	251 (59.2)	1 (1.5)	347 (52.1)	160 (61.1)	74 (32.6)	581 (50.3)
Canada	61 (34.9)	74 (17.5)	44 (65.7)	179 (26.9)	29 (11.1)	36 (15.9)	264 (22.9)
Australia/New Zealand	19 (10.9)	48 (11.3)	22 (32.8)	89 (13.4)	32 (12.2)	47 (20.7)	168 (14.5)
Hong Kong	0	16 (3.8)	0	16 (2.4)	6 (2.3)	12 (5.3)	34 (2.9)
Europe	0	35 (8.3)	0	35 (5.3)	35 (13.4)	38 (16.7)	108 (9.4)
Age at Consent (years)							
n	175	424	67	666	262	227	1155
Mean (SD)	59.6 (8.75)	60.5 (8.93)	62.2 (9.22)	60.4 (8.93)	61.4 (8.73)	62.1 (9.87)	61.0 (9.09)
Median	59.0	60.0	62.0	60.0	61.0	63.0	61.0
Min; Max	36;83	40;83	44;86	36;86	40;83	40;85	36;86
Age at Consent (years) Category - n (%)²							
40 - 50	27 (15.5)	59 (13.9)	6 (9.0)	92 (13.8)	36 (13.7)	31 (13.7)	159 (13.8)
51 - 64	94 (54.0)	222 (52.4)	35 (52.2)	351 (52.8)	133 (50.8)	102 (44.9)	586 (50.8)
65 - 75	47 (27.0)	121 (28.5)	20 (29.9)	188 (28.3)	82 (31.3)	74 (32.6)	344 (29.8)
> 75	6 (3.4)	22 (5.2)	6 (9.0)	34 (5.1)	11 (4.2)	20 (8.8)	65 (5.6)
Height (cm) at Baseline							
n	175	424	67	666	262	227	1155
Mean (SD)	168.87 (10.250)	167.77 (9.921)	168.00 (11.218)	168.08 (10.140)	167.65 (10.195)	167.35 (10.579)	167.84 (10.235)
Median	167.64	167.64	168.00	167.64	167.64	167.64	167.64
Min; Max	147.0;198.1	132.1;195.6	137.2;193.0	132.1;198.1	121.9;191.7	142.0;194.0	121.9;198.1

Clinical Review
Pamela Horn, MD
NDA 208845
Zilretta (triamcinolone acetonide)

Parameter/Statistic	FX006 10 and 20 mg (N=175)	FX006 40 mg (N=424)	FX006 60 mg (N=67)	Total FX006 (N=666)	Placebo (N=262)	TCA IR 40 mg (N=227)	Total (N=1155)
Weight (kg) at Baseline							
n	175	424	67	666	262	227	1155
Mean (SD)	88.52 (17.237)	87.02 (15.918)	86.62 (17.922)	87.37 (16.471)	86.31 (17.516)	85.30 (17.465)	86.72 (16.916)
Median	88.00	86.70	85.90	86.86	84.60	86.18	86.10
Min; Max	47.3;135.2	47.2;136.4	54.0;136.1	47.2;136.4	46.3;140.6	43.1;132.0	43.1;140.6
Body Mass Index (kg/m²) at Baseline							
n	175	424	67	666	262	227	1155
Mean (SD)	30.88 (4.789)	30.84 (4.822)	30.26 (4.773)	30.80 (4.805)	30.58 (4.871)	30.16 (4.806)	30.62 (4.822)
Median	31.44	30.61	30.00	30.80	30.22	30.00	30.43
Min; Max	16.8;39.5	19.2;41.9	21.0;39.9	16.8;41.9	18.8;43.3	19.8;39.8	16.8;43.3
Body Mass Index Category at Baseline - n (%)¹							
Underweight	1 (0.6)	0	0	1 (0.2)	0	0	1 (0.1)
Normal	20 (11.4)	51 (12.0)	9 (13.4)	80 (12.0)	32 (12.2)	34 (15.0)	146 (12.6)
Overweight	49 (28.0)	145 (34.2)	24 (35.8)	218 (32.7)	91 (34.7)	77 (33.9)	386 (33.4)
Obesity 1	66 (37.7)	132 (31.1)	22 (32.8)	220 (33.0)	81 (30.9)	77 (33.9)	378 (32.7)
Obesity 2	39 (22.3)	92 (21.7)	12 (17.9)	143 (21.5)	57 (21.8)	39 (17.2)	239 (20.7)
Morbid Obesity	0	4 (0.9)	0	4 (0.6)	1 (0.4)	0	5 (0.4)
Weekly Daily Average Pain Intensity Score at Baseline - n (%)⁴							
5-5.9	52 (32.5)	118 (36.4)	20 (33.3)	190 (34.9)	99 (37.8)	82 (38.7)	371 (36.4)
6-6.9	48 (30.0)	107 (33.0)	21 (35.0)	176 (32.4)	78 (29.8)	70 (33.0)	324 (31.8)
≥7	60 (37.5)	99 (30.6)	19 (31.7)	178 (32.7)	85 (32.4)	60 (28.3)	323 (31.7)

Source: Table 14.13.A.

¹ Race such as Middle East, Palestinian, Egyptian classified as Other or Multiple, were assigned the White category in the race group, while Cambodian has been assigned the Asian category.

² One patient in the 10 or 20 mg group was 36 years old thus not assigned to any category.

³ Underweight was defined as <18.0 kg/m², Normal as 18.0–25 kg/m², Overweight as 25.0–30 kg/m², Obesity 1 as 30.0–35 kg/m², Obesity 2 as 35.0–40 kg/m² and Morbid Obesity as ≥40.0 kg/m².

⁴ Denominator is from studies 001, 006, and 008. Studies 002, 005 and 009 did not collect this information.

Source: Table 11, ISS

The demographics in the double-blind controlled studies (Pool 2) are as follows:

Table 26 Demographic and Baseline Characteristics Pool 2 (Safety Population)

Parameter/Statistics	FX006 10 and 20 mg (N=160)	FX006 40 mg (N=324)	FX006 60 mg (N=60)	Total FX006 (N=544)	Placebo (N=262)	TCA IR 40 mg (N=212)	Total (N=1018)
Gender - n (%)							
Male	72 (45.0)	139 (42.9)	26 (43.3)	237 (43.6)	105 (40.1)	86 (40.6)	428 (42.0)
Female	88 (55.0)	185 (57.1)	34 (56.7)	307 (56.4)	157 (59.9)	126 (59.4)	590 (58.0)
Primary Race - n (%)							
American Indian or Alaska Native	0	0	2 (3.3)	2 (0.4)	1 (0.4)	0	3 (0.3)
Asian	3 (1.9)	23 (7.1)	3 (5.0)	29 (5.3)	15 (5.7)	18 (8.5)	62 (6.1)
Black or African American	19 (11.9)	26 (8.0)	2 (3.3)	47 (8.6)	19 (7.3)	13 (6.1)	79 (7.8)
Native Hawaiian or Other Pacific Islander	1 (0.6)	4 (1.2)	0	5 (0.9)	1 (0.4)	2 (0.9)	8 (0.8)
White	136 (85.0)	269 (83.0)	50 (83.3)	455 (83.6)	226 (86.3)	178 (84.0)	859 (84.4)
Other	1 (0.6)	2 (0.6)	3 (5.0)	6 (1.1)	0	1 (0.5)	7 (0.7)
Race Groups - n (%)¹							
White	136 (85.0)	271 (83.6)	51 (85.0)	458 (84.2)	226 (86.3)	178 (84.0)	862 (84.7)
Asian	4 (2.5)	23 (7.1)	3 (5.0)	30 (5.5)	15 (5.7)	19 (9.0)	64 (6.3)
Non-White/Non-Asian	20 (12.5)	30 (9.3)	6 (10.0)	56 (10.3)	21 (8.0)	15 (7.1)	92 (9.0)
Ethnicity - n (%)							
Hispanic or Latino	17 (10.6)	42 (13.0)	0	59 (10.8)	45 (17.2)	19 (9.0)	123 (12.1)
Not Hispanic or Latino	143 (89.4)	282 (87.0)	60 (100.0)	485 (89.2)	216 (82.4)	193 (91.0)	894 (87.8)
Not Reported	0	0	0	0	1 (0.4)	0	1 (0.1)
Country - n (%)							
US	85 (53.1)	158 (48.8)	1 (1.7)	244 (44.9)	160 (61.1)	64 (30.2)	468 (46.0)
Canada	61 (38.1)	74 (22.8)	44 (73.3)	179 (32.9)	29 (11.1)	56 (26.4)	264 (25.9)
Australia/New Zealand	14 (8.8)	41 (12.7)	15 (25.0)	70 (12.9)	32 (12.2)	42 (19.8)	144 (14.1)
Hong Kong	0	16 (4.9)	0	16 (2.9)	6 (2.3)	12 (5.7)	34 (3.3)
Europe	0	35 (10.8)	0	35 (6.4)	35 (13.4)	38 (17.9)	108 (10.6)

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Parameter/Statistics	FX006 10 and 20 mg (N=160)	FX006 40 mg (N=324)	FX006 60 mg (N=60)	Total FX006 (N=544)	Placebo (N=262)	TCA IR 40 mg (N=212)	Total (N=1018)
Age at Consent (years)							
n	160	324	60	544	262	212	1018
Mean (SD)	59.4 (8.51)	60.5 (9.16)	61.9 (9.35)	60.3 (9.01)	61.4 (8.73)	62.1 (10.06)	61.0 (9.19)
Median	59.0	60.0	61.0	60.0	61.0	63.0	61.0
Min; Max	43;83	40;83	44;86	40;86	40;83	40;85	40;86
Age at Consent (years) Category - n (%)							
40 - 50	26 (16.3)	46 (14.2)	6 (10.0)	78 (14.3)	36 (13.7)	31 (14.6)	145 (14.2)
51 - 64	88 (55.0)	163 (50.3)	32 (53.3)	283 (52.0)	133 (50.8)	90 (42.5)	506 (49.7)
65 - 75	41 (25.6)	97 (29.9)	17 (28.3)	155 (28.5)	82 (31.3)	72 (34.0)	309 (30.4)
> 75	5 (3.1)	18 (5.6)	5 (8.3)	28 (5.1)	11 (4.2)	19 (9.0)	58 (5.7)
Height (cm) at Baseline							
n	160	324	60	544	262	212	1018
Mean (SD)	169.71 (10.015)	167.89 (10.336)	168.13 (11.325)	168.45 (10.369)	167.65 (10.195)	167.55 (10.543)	168.06 (10.360)
Median	167.64	167.64	168.46	167.64	167.64	168.00	167.64
Min; Max	149.0;198.1	132.1;195.6	137.2;193.0	132.1;198.1	121.9;191.7	142.0;194.0	121.9;198.1
Weight (kg) at Baseline							
n	160	324	60	544	262	212	1018
Mean (SD)	88.94 (17.402)	86.33 (16.176)	85.88 (18.191)	87.05 (16.787)	86.31 (17.516)	85.47 (17.709)	86.53 (17.165)
Median	88.43	85.90	84.18	86.27	84.60	86.18	85.85
Min; Max	47.3;135.2	47.2;136.4	54.0;136.1	47.2;136.4	46.3;140.6	43.1;132.0	43.1;140.6
Body Mass Index (kg/m²) at Baseline							
n	160	324	60	544	262	212	1018
Mean (SD)	30.72 (4.793)	30.55 (4.771)	29.96 (4.856)	30.53 (4.783)	30.58 (4.871)	30.15 (4.864)	30.47 (4.821)
Median	31.07	30.36	29.40	30.42	30.22	30.08	30.30
Min; Max	16.8;39.5	19.2;41.9	21.0;39.9	16.8;41.9	18.8;43.3	19.8;39.8	16.8;43.3
Parameter/Statistics	FX006 10 and 20 mg (N=160)	FX006 40 mg (N=324)	FX006 60 mg (N=60)	Total FX006 (N=544)	Placebo (N=262)	TCA IR 40 mg (N=212)	Total (N=1018)
Body Mass Index Category at Baseline - n (%)²							
Underweight	1 (0.6)	0	0	1 (0.2)	0	0	1 (0.1)
Normal	19 (11.9)	43 (13.3)	9 (15.0)	71 (13.1)	32 (12.2)	34 (16.0)	137 (13.5)
Overweight	47 (29.4)	114 (35.2)	23 (38.3)	184 (33.8)	91 (34.7)	69 (32.5)	344 (33.8)
Obesity 1	59 (36.9)	100 (30.9)	17 (28.3)	176 (32.4)	81 (30.9)	72 (34.0)	329 (32.3)
Obesity 2	34 (21.3)	65 (20.1)	11 (18.3)	110 (20.2)	57 (21.8)	37 (17.5)	204 (20.0)
Morbid Obesity	0	2 (0.6)	0	2 (0.4)	1 (0.4)	0	3 (0.3)
Weekly Daily Average Pain Intensity Score at Baseline - n (%)							
5-5.9	52 (32.5)	118 (36.4)	20 (33.3)	190 (34.9)	99 (37.8)	82 (38.7)	371 (36.4)
6-6.9	48 (30.0)	107 (33.0)	21 (35.0)	176 (32.4)	78 (29.8)	70 (33.0)	324 (31.8)
≥7	60 (37.5)	99 (30.6)	19 (31.7)	178 (32.7)	85 (32.4)	60 (28.3)	323 (31.7)

Source: Table 14.1.3.B.

¹ Race such as Middle East, Palestinian, Egyptian classified as Other or Multiple, were assigned the White category in the race group, while Cambodian has been assigned the Asian category.

² Underweight was defined as <18.0 kg/m², Normal as 18.0-25 kg/m², Overweight as 25.0-30 kg/m², Obesity 1 as 30.0-35 kg/m², Obesity 2 as 35.0-40 kg/m² and Morbid Obesity as ≥40.0 kg/m².

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Zilretta (triamcinolone acetonide)

Parameter/Statistics	FX006 10 and 20 mg (N=160)	FX006 40 mg (N=324)	FX006 60 mg (N=60)	Total FX006 (N=544)	Placebo (N=262)	TCA IR 40 mg (N=212)	Total (N=1018)
Age at Consent (years)							
n	160	324	60	544	262	212	1018
Mean (SD)	59.4 (8.51)	60.5 (9.16)	61.9 (9.35)	60.3 (9.01)	61.4 (8.73)	62.1 (10.06)	61.0 (9.19)
Median	59.0	60.0	61.0	60.0	61.0	63.0	61.0
Min; Max	43;83	40;83	44;86	40;86	40;83	40;85	40;86
Age at Consent (years) Category - n (%)							
40 - 50	26 (16.3)	46 (14.2)	6 (10.0)	78 (14.3)	36 (13.7)	31 (14.6)	145 (14.2)
51 - 64	88 (55.0)	163 (50.3)	32 (53.3)	283 (52.0)	133 (50.8)	90 (42.5)	506 (49.7)
65 - 75	41 (25.6)	97 (29.9)	17 (28.3)	155 (28.5)	82 (31.3)	72 (34.0)	309 (30.4)
> 75	5 (3.1)	18 (5.6)	5 (8.3)	28 (5.1)	11 (4.2)	19 (9.0)	58 (5.7)
Height (cm) at Baseline							
n	160	324	60	544	262	212	1018
Mean (SD)	169.71 (10.015)	167.89 (10.336)	168.13 (11.325)	168.45 (10.369)	167.65 (10.195)	167.55 (10.543)	168.06 (10.360)
Median	167.64	167.64	168.46	167.64	167.64	168.00	167.64
Min; Max	149.0;198.1	132.1;195.6	137.2;193.0	132.1;198.1	121.9;191.7	142.0;194.0	121.9;198.1
Weight (kg) at Baseline							
n	160	324	60	544	262	212	1018
Mean (SD)	88.94 (17.402)	86.33 (16.176)	85.88 (18.191)	87.05 (16.787)	86.31 (17.516)	85.47 (17.709)	86.53 (17.165)
Median	88.43	85.90	84.18	86.27	84.60	86.18	85.85
Min; Max	47.3;135.2	47.2;136.4	54.0;136.1	47.2;136.4	46.3;140.6	43.1;132.0	43.1;140.6
Body Mass Index (kg/m ²) at Baseline							
n	160	324	60	544	262	212	1018
Mean (SD)	30.72 (4.793)	30.55 (4.771)	29.96 (4.856)	30.53 (4.783)	30.58 (4.871)	30.15 (4.864)	30.47 (4.821)
Median	31.07	30.36	29.40	30.42	30.22	30.08	30.30
Min; Max	16.8;39.5	19.2;41.9	21.0;39.9	16.8;41.9	18.8;43.3	19.8;39.8	16.8;43.3
Parameter/Statistics	FX006 10 and 20 mg (N=160)	FX006 40 mg (N=324)	FX006 60 mg (N=60)	Total FX006 (N=544)	Placebo (N=262)	TCA IR 40 mg (N=212)	Total (N=1018)
Body Mass Index Category at Baseline - n (%) ²							
Underweight	1 (0.6)	0	0	1 (0.2)	0	0	1 (0.1)
Normal	19 (11.9)	43 (13.3)	9 (15.0)	71 (13.1)	32 (12.2)	34 (16.0)	137 (13.5)
Overweight	47 (29.4)	114 (35.2)	23 (38.3)	184 (33.8)	91 (34.7)	69 (32.5)	344 (33.8)
Obesity 1	59 (36.9)	100 (30.9)	17 (28.3)	176 (32.4)	81 (30.9)	72 (34.0)	329 (32.3)
Obesity 2	34 (21.3)	65 (20.1)	11 (18.3)	110 (20.2)	57 (21.8)	37 (17.5)	204 (20.0)
Morbid Obesity	0	2 (0.6)	0	2 (0.4)	1 (0.4)	0	3 (0.3)
Weekly Daily Average Pain Intensity Score at Baseline - n (%)							
5-5.9	52 (32.5)	118 (36.4)	20 (33.3)	190 (34.9)	99 (37.8)	82 (38.7)	371 (36.4)
6-6.9	48 (30.0)	107 (33.0)	21 (35.0)	176 (32.4)	78 (29.8)	70 (33.0)	324 (31.8)
≥7	60 (37.5)	99 (30.6)	19 (31.7)	178 (32.7)	85 (32.4)	60 (28.3)	323 (31.7)

Source: Table 14.1.3.B.

¹ Race such as Middle East, Palestinian, Egyptian classified as Other or Multiple, were assigned the White category in the race group, while Cambodian has been assigned the Asian category.

² Underweight was defined as <18.0 kg/m², Normal as 18.0-25 kg/m², Overweight as 25.0-30 kg/m², Obesity 1 as 30.0-35 kg/m², Obesity 2 as 35.0-40 kg/m² and Morbid Obesity as ≥40.0 kg/m².

Source: Table 12 ISS

7.2.2 Explorations for Dose Response

The pooled safety data contains data for 4 different doses of FX006. Two studies were controlled and evaluated more than one strength of FX006. Study 006 was a double-blinded study with 20 mg and 40 mg FX006 arms and a placebo arm. Study 001 was a double-blinded study with 10 mg, 40 mg, and 60 mg arms of FX006 and a 40 mg TCA IR arm.

7.2.3 Special Animal and/or In Vitro Testing

There were no special animal or in vitro studies conducted to support the safety of the product.

7.2.4 Routine Clinical Testing

The routine clinical testing in the program was adequate. In the double-blinded controlled studies, laboratory testing was done at screening, baseline, week 12, and week 24 visits for studies 008 and 006. In study 001, the laboratory assessment timing differed from studies 008 and 006. Additional timepoints for laboratory testing were included and there was no week 24 testing done. These additional timepoints corresponded to PK sampling timepoints and were on Day 2, week 1, week 2, week 4 and week 8. Laboratory testing consisted of hematology and clinical chemistry labs, as follows:

Hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, white blood cell count, platelets, and absolute counts of: neutrophils, lymphocytes, monocytes, eosinophils, and basophils

Sodium, potassium, bicarbonate, chloride, calcium, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, uric acid, glucose, total protein, albumin, total cholesterol, triglycerides, high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol

Specific systemic safety concerns requiring laboratory testing for evaluation were evaluated in separate pharmacodynamics studies (see 4.4.2 Pharmacodynamics).

7.2.5 Metabolic, Clearance, and Interaction Workup

No metabolism, clearance, or drug-drug interaction assessments were part of the drug development program. Drug-drug interaction information from the Kenalog-40 label has been proposed for inclusion in the label.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during any of the clinical studies in the development program.

7.3.2 Nonfatal Serious Adverse Events

All studies included in Pool 1 studied OA patients, which is the target population and were single dose administrations. For the purposes of examining incidence of serious adverse events, all data from the target population can be summarized together.

Table 27 SAEs (Pool 1)

	FX006 10 and 20 mg N=175	FX006 40 mg N=424	FX006 60 mg N=67	FX006 all N=666	Placebo N=262	TCA IR N=227
All SAEs	1 (0.6%)	13 (3.1%)	1 (1.4%)	15 (2.3%)	3 (1.1%)	6 (2.6%)
SAEs in index knee joint	1 (0.6%) femur fracture	2 (0.5%) arthralgia and rheumatoid arthritis	0	0	0	0

Source: Table 30, ISS

The subject that had a serious adverse event of rheumatoid arthritis was originally thought to have Klebsiella pneumonia infection of the injected joint 21 days after injection based on a culture of synovial fluid that grew Klebsiella pneumonia after 2 days. However, the clinical course of the patient and investigation by the Sponsor of the sterility of the batch of study drug and procedures used during drug administration revealed that she likely never had septic arthritis and that the Klebsiella that grew out of the culture was from post-collection contamination of the sample and that the clinical presentation was consistent with rheumatoid arthritis.

The other serious adverse events in the FX006 groups were coronary artery stenosis, stroke, left ankle osteoarthritis worsening, myocardial infarction, pneumonia, dizziness, colonic polyps, rectal cancer, pulmonary embolism, left axillary abscess, and two cases of atrial fibrillation. The SAEs in the placebo group were cholangitis, abdominal hernia, and sepsis. The SAEs in the TCA group were chest pain, food poisoning and seizure.

Three serious adverse events occurred in the index joint: the aforementioned rheumatoid arthritis case and an event of worsening left knee pain around 17 weeks after study treatment that resulted in hospitalization and joint replacement occurred in FX006 40 mg treated patients and a patient that received 20 mg of FX006 slipped and

had a fall that resulted in a left distal femur fracture. There were a very small number of serious adverse events and the incidence was similar between the FX006 groups and the placebo and active control groups.

7.3.3 Dropouts and/or Discontinuations

In the double-blinded studies all but one discontinuation due to an adverse event occurred in the index knee. One subject discontinued due to worsening OA in the left ankle. The remaining discontinuations are summarized in the table below by treatment group.

Table 28 Discontinuations due to AEs (Pool 2)

	FX006 10 and 20 mg N=160	FX006 40 mg N=324	FX006 60 mg N=60	FX006 all N=544	Placebo N=262	TCA IR N=212
Discontinued due to AE in index knee	5 (3.1%)	4 (1.2%)	0	9 (1.7%)	2 (0.8%)	1 (0.5%)

CSR study 001, ADAE study 008, ADAE study 006, table

There was a higher incidence of discontinuations in the FX006 treated subjects in the double-blinded studies overall, but few discontinuations for adverse events overall. The adverse events that led to discontinuation in the 10 and 20 mg group were pain for 3 subjects, effusion for one subject and swelling for one subject. In the 40 mg group the adverse events were swelling, synovitis, worse OA, and pain. In the placebo group the adverse events were pain and arthralgia. In the TCA IR group the adverse event was arthralgia. There were no discontinuations for adverse events in the other studies in the development program. The differences in incidence are small and do not appear to be indicative of a meaningful safety difference between FX006 and the comparators.

7.3.4 Significant Adverse Events

The Applicant did not designate any adverse events in the studies as significant adverse events. Based on the ICH E3 Guideline, significant adverse events should be considered “marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events”.

Severe adverse events for pools 1 and 2 are summarized below. The tables from the ISS do not include adverse events that were classified as severe rather than as toxicity

grade 3 in the data and thus the counts of severe adverse events are higher in the tables below than in the ISS because they include adverse events that were coded as severe and as toxicity grade 3.

Table 29 Severe TEAEs (Pool 1)

	FX006 10 and 20 mg N=175	FX006 40 mg N=424	FX006 60 mg N=67	FX006 all N=666	Placebo N=262	TCA IR N=227
Severe TEAEs	7 (4.0%)	11 (2.6%)	0	18 (2.7%)	13 (5.0%)	7 (3.1%)

Source: Table 26 ISS, AE datasets studies 001, 002, 005, 006, 008, 009 and DM datasets studies 001 and 002

Table 30 Severe TEAEs (Pool 2)

	FX006 10 and 20 mg N=160	FX006 40 mg N=324	FX006 60 mg N=60	FX006 all N=544	Placebo N=262	TCA IR N=212
Severe TEAEs	6 (3.8%)	11 (3.4%)	0	17 (3.1%)	13 (5.0%)	6 (2.8%)

Source: ADAE datasets studies 006, 008, AE and DM datasets study 001

There do not appear to be clinically relevant differences in the incidence of severe adverse events between treatment groups.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The following two tables summarize the adverse events by treatment group in all pooled studies (Pool 1) and in the double-blinded studies (Pool 2).

Table 31 TEAEs (Pool 1)

	FX006 10 and 20 mg N=175	FX006 40 mg N=424	FX006 60 mg N=67	FX006 all N=666	Placebo N=262	TCA IR N=227
Patients with at least one	79 (45.1%)	195 (44.1%)	40 (59.7%)	314 (45.9%)	129 (49.2%)	132 (50.8%)

TEAE						
Patients with at least one index knee TEAE	27 (15.4%)	64 (14.5%)	9 (13.4%)	100 (14.6%)	37 (14.1%)	25 (9.6%)
Patients with moderate index knee TEAE	8 (4.6%)	25 (5.7%)	2 (3.0%)	35 (5.1%)	15 (5.7%)	7 (2.7%)
Patients with severe index knee TEAE	3 (1.7%)	3 (0.7%)	0	6 (0.9%)	5 (1.9%)	2 (0.8%)

Source: Table 14.3.1.1.A ISS

Table 32 TEAEs (Pool 2)

	FX006 10 and 20 mg N=160	FX006 40 mg N=324	FX006 60 mg N=60	FX006 all N=544	Placebo N=262	TCA IR N=212
Patients with at least one TEAE	70 (43.8)	168 (51.9)	34 (56.7)	272 (50.0)	129 (49.2)	119 (56.1)
Patients with at least one index knee TEAE	25 (15.6)	53 (16.4)	7 (11.7)	85 (15.6)	37 (14.1)	22 (10.4)
Patients with moderate index knee TEAE	7 (4.4)	19 (5.9)	2 (3.3)	28 (5.1)	15 (5.7)	7 (3.3)
Patients with severe index knee TEAE	3 (1.9)	3 (0.9)	0	6 (1.1)	5 (1.9)	2 (0.9)

Source: Table 14.3.1.1.B ISS

In both pools the incidence of TEAEs and the subcategories of TEAEs summarized in the table were similar in the active groups compared to placebo. These common TEAEs and TEAEs in the index knee did not appear to occur disproportionately in the FX006 groups compared to the placebo or active control groups.

The most commonly reported TEAEs that were higher in the FX006 40 mg group than placebo or the same in these two groups overall are summarized in the table below:

Table 33 Common TEAEs (Pool 1)

Preferred Term	FX006 40 mg N= 424	Placebo N=262
Headache	26 (6%)	15 (6%)
Joint Swelling	14 (3%)	8 (3%)
Upper Respiratory Tract Infection	9 (2%)	6 (2%)
Contusions	10 (2%)	2 (1%)

Source: Table 14.3.1.3.A ISS

The most commonly reported TEAEs in the index knee in the FX006 40 mg group and placebo group are summarized below:

Table 34 Common TEAEs in Index Knee (Pool 1)

Preferred Term	FX006 40 mg N= 424	Placebo N=262
Arthralgia	40 (9%)	25 (10%)
Joint Swelling	11 (3%)	6 (2%)
Contusions	6 (2%)	2 (1%)

Source: Table 14.3.1.10.A ISS

The incidence between FX006 40 mg and placebo are similar and suggest that the injection procedure itself contributed to the most common adverse events in the studies.

7.4.2 Laboratory Findings

The Applicant summarized shifts from baseline to post-baseline for all hematology and chemistry parameters measured (see 7.2.4 Routine Clinical Testing for a list of the parameters measured). There were few treatment-emergent laboratory abnormalities and shifts overall in the safety population. With the exception of hyperglycemia, there were no notable imbalances in incidence of treatment-emergent laboratory

abnormalities or shifts between treatment groups. There was no CTCAE grade 4 hyperglycemia¹.

The Pool 1 data for patients with a worsening in CTCAE grade from baseline for hyperglycemia by CTCAE grade was as follows:

Table 35 Hyperglycemia Worsening by CTCAE Grade (Pool 1)

	FX006 10 mg and 20 mg N=175	FX006 40 mg N=424	FX006 60 mg N=67	Placebo N=262	TCA IR N=227
0 to ≥1	18 (11%)	32 (8%)	17 (25%)	9 (4%)	25 (11%)
1 to ≥2	1 (1%)	1 (<1%)	1 (<1%)	0	0
2 to ≥3	2 (1%)	3 (1%)	2 (3%)	1 (<1%)	1 (<1%)

Source: Table 14.3.4.2.A ISS

The placebo-treated patients had the lowest incidence of worsening of CTCAE grade for hyperglycemia and the highest incidence was in patients who received 60 mg of FX006. The patients that received FX006 10 mg, 20 mg, 40 mg, and TCA IR had a similar incidence of worsening in hyperglycemia grade. These findings are consistent with the known safety profile of corticosteroids and consistent with the reference product label for Kenalog-40.

In addition to summarizing shifts in laboratory values, the Applicant evaluated the laboratory data for patients with values that met criteria for Hy's law and none met criteria.

7.4.3 Vital Signs

Overall, there was no imbalance in incidence of treatment-emergent vital sign abnormalities in the FX006 40 mg, TCA IR 40 mg and placebo. The most common treatment-emergent vital sign abnormality observed was elevated systolic and diastolic blood pressure as defined by SBP ≥ 160 mmHg and DBP ≥ 100 mmHg. The incidence was not higher in the to-be-marketed 40 mg dose than placebo, but there was a higher incidence than placebo in patients that received 60 mg, suggesting a dose-response relationship, as shown in the table below:

¹ CTCAE criteria for hyperglycemia Grade 1 >ULN – 160 mg/dL, Grade 2 >160 – 250 mg/dL, Grade 3 >250 – 500 mg/dL, Grade 4 >500 mg/dL

Table 36 Treatment-Emergent Vital Sign (Blood Pressure) Abnormalities (Pool 1)

Category	FX006 10 and 20 mg N=175 n (%)	FX006 40 mg N=424 n (%)	FX006 60 mg N=67 n (%)	Total FX006 N=666 n (%)	TCA IR 40 mg N=227 n (%)	Placebo N=262 n (%)
Number of Patients with Post Baseline Assessment	175	423	67	665	227	258
At Least One Treatment-Emergent Abnormality	12 (6.9)	27 (6.4)	15 (22.4)	54 (8.1)	17 (7.5)	19 (7.4)
Treatment-Emergent Systolic Blood Pressure $\geq$ 160 mmHg	12 (6.9)	22 (5.2)	11 (16.4)	45 (6.8)	15 (6.6)	19 (7.4)
Treatment-Emergent Diastolic Blood Pressure $\geq$ 100 mmHg	1 (0.6)	9 (2.1)	6 (9.0)	16 (2.4)	5 (2.2)	3 (1.2)

Source: [Table 14.3.5.1.A](#).

Source: Table 34 ISS

The referenced and proposed label includes warning language that corticosteroids can cause elevations of blood pressure and I concur with this language.

7.4.4 Electrocardiograms (ECGs)

ECG assessments were conducted post-baseline in studies 001, 002, 005, and 006. Changes from baseline were assessed for heart rate, PR interval, QRS duration, QT interval, QTc interval, and RR interval. There were eight ECG abnormalities detected and they were evenly distributed among the treatment groups. No pattern emerged from these findings and none of the abnormalities appeared to be attributable to study treatment.

7.4.5 Special Safety Studies/Clinical Trials

See section 4.4.2 Pharmacodynamics for a discussion of the studies that evaluated the effects on the HPA axis and blood glucose levels.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

From the adverse event data collected in the program, there appeared to be a higher incidence of treatment-emergent blood pressure elevation and hyperglycemia² with the FX006 60 mg dose than with the FX006 40 mg dose (see 7.4.3 Vital Signs and 7.4.2 Laboratory Findings). These results are consistent with the known effects of corticosteroids.

² Study 010 also evaluated blood glucose levels but did not evaluate more than one dose of FX006.

Study 002 evaluated the effects of multiple strengths of FX006 on the HPA axis. Dr. Abraham concluded in her draft consult review that there was a dose-dependent cortisol suppression from a single injection of FX006. Adrenal suppression is also a known effect of corticosteroids. Also see 4.4.2 Pharmacodynamics.

7.5.2 Time Dependency for Adverse Events

To account for the variation between studies in follow-up period duration, the Applicant calculated adverse event rates per person year.

The following table summarizes the TEAEs that occurred in 2% or more of subjects by preferred term per 100 person years for all studies (Pool 1)

Table 37 TEAEs by 100 person years (Pool 1)

Preferred term	FX006 10 and 20 mg (N = 175) n (rate) PY	FX006 40 mg (N = 424) n (rate) PY	FX006 60 mg (N = 67) n (rate) PY	Total FX006 (N = 666) n (rate) PY	Placebo (N = 262) n (rate) PY	TCA IR 40 mg (N = 227) n (rate) PY
Any Adverse Event	79 (184.9) 42.7	193 (177.8) 108.5	40 (495.3) 8.1	312 (195.8) 159.3	129 (167.5) 77.0	128 (228.9) 55.9
Nasopharyngitis	5 (8.5) 58.8	10 (6.4) 155.2	0 15.0	15 (6.5) 229.0	11 (9.8) 112.0	15 (17.7) 84.9
Upper respiratory tract infection	4 (6.8) 58.9	9 (5.8) 153.9	8 (56.1) 14.3	21 (9.2) 227.1	6 (5.3) 113.2	6 (6.9) 87.0
Contusion	3 (5.1) 59.0	10 (6.5) 154.4	2 (13.5) 14.9	15 (6.6) 228.3	2 (1.8) 114.2	2 (2.3) 88.0
Arthralgia (any joint)	16 (28.1) 56.9	46 (31.2) 147.5	4 (27.7) 14.4	66 (30.2) 218.9	36 (34.4) 104.5	17 (19.9) 85.5
Back pain	3 (5.1) 58.5	12 (7.8) 153.7	1 (6.7) 14.9	16 (7.0) 227.1	11 (9.9) 111.2	14 (16.4) 85.1
Joint swelling	4 (6.8) 59.2	14 (9.1) 153.7	1 (6.7) 14.8	19 (8.3) 227.8	8 (7.1) 112.4	3 (3.4) 87.5
Headache	5 (8.6) 58.0	26 (17.3) 150.7	5 (34.6) 14.5	36 (16.1) 223.2	15 (13.5) 110.9	21 (25.4) 82.8

Source: Table 14.3.1.14.A.

Note: Person-years (PY) was calculated as (event start date - dose date + 1)/365.25 for those with the event.

PY was calculated as ((last visit or death date) - dose date + 1)/365.25 for those without the event.

Rate per 100 PY = (# of AE/PY)*100.

PY were calculated separately by treatment arm for each PT.

TCA IR had the lowest rate of joint swelling and FX006 groups and placebo had similar rates. Rates of arthralgia were highest in the placebo group and were lowest in the TCA IR group.

The following table summarizes the overall TEAEs and arthralgia and joint swelling and joint effusion per 100 person years for double-blinded studies (Pool 2)

Table 38 TEAEs by Person Year (Pool 2)

	FX006 10 and 20 mg N=160 N (rate)	FX006 40 mg N=324 N (rate)	FX006 60 mg N=60 N (rate)	FX006 all N=544 N (rate)	Placebo N=262 N (rate)	TCA IR N=212 N (rate)
Any adverse event	70 (172)	168 (193)	34 (436)	272 (201)	129 (168)	119 (221)
Arthralgia	15 (28)	39 (32)	4 (29)	58 (30)	36 (34)	15 (18)
Joint swelling	4 (7)	14 (11)	1 (7)	19 (10)	8 (7)	3 (4)
Joint effusion	2 (4)	4 (3)	0	6 (3)	4 (4)	5 (6)

Source: ISS table 14.3.1.14.B

In the double-blinded controlled studies, the rates of arthralgia were lowest for TCA IR and highest for placebo. Joint swelling rates were highest in FX006 but joint effusion rates were highest in TCA IR.

Time-dependency for adverse event occurrence can also be summarized by TEAEs overall by start day. The following tables summarize the incidence of patients with an index knee TEAE by the study day the adverse event was reported for Pools 1 and 2.

Table 39 TEAEs by Start Day (Pool 1)

	FX006 10 and 20 mg N=175	FX006 40 mg N=424	FX006 60 mg N=67	FX006 all N=666	Placebo N=262	TCA IR N=227
Day 1 to 3	9 (5%)	14 (3%)	7 (10%)	30 (5%)	7 (3%)	7 (3%)
Day 4 to 28	4 (2%)	12 (3%)	4 (6%)	20 (3%)	9 (3%)	6 (3%)
Day 29 to 56	6 (3%)	13 (3%)	0	19 (3%)	8 (3%)	6 (3%)
Day 57 to 84	5 (3%)	18 (4%)	0	23 (3%)	5 (2%)	3 (1%)
Day 85 to 168	6 (3%)	24 (6%)	1 (1.5%)	31 (5%)	15 (6%)	10 (4%)

Source: Table 14.3.1.1.A

Table 40 TEAEs by Start Day (Pool 2)

	FX006 10	FX006 40	FX006 60	FX006 all	Placebo	TCA IR
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	and 20 mg N=160	mg N=324	mg N=60	N=544	N=262	N=212
Day 1 to 3	7 (4%)	9 (3%)	6 (10%)	22 (4%)	7 (3%)	6 (3%)
Day 4 to 28	3 (2%)	8 (2%)	3 (5%)	14 (3%)	9 (3%)	5 (2%)
Day 29 to 56	6 (4%)	12 (4%)	0	18 (3%)	8 (3%)	5 (2%)
Day 57 to 84	5 (3%)	14 (3%)	0	19 (3%)	5 (2%)	3 (1%)
Day 85 to 168	6 (4%)	23 (7%)	1 (2%)	30 (6%)	15 (6%)	10 (5%)

Source: Table 14.3.1.1.B

The distribution of index knee TEAEs by start day was similar between groups and does not indicate that the events were occurring disproportionately early or late in any group.

The distribution of TEAEs of the index knee leading to study discontinuation was also similar between treatment groups as shown in the tables for Pools 1 and 2 below. All incidences were 1% or less.

Table 41 Index Knee-Related TEAEs Leading to Discontinuation by Start Day (Pool 1)

	FX006 10 and 20 mg N=175	FX006 40 mg N=424	FX006 60 mg N=67	FX006 all N=666	Placebo N=262	TCA IR N=227
Day 1 to 3	0	0	0	0	0	0
Day 4 to 28	1	1	0	2	0	0
Day 29 to 56	0	0	0	0	1	0
Day 57 to 84	2	1	0	3	0	0
Day 85 to 168	2	1	0	3	1	1

Source: Table 14.3.1.1.A

Table 42 Index Knee-Related TEAEs Leading to Discontinuation by Start Day (Pool 2)

	FX006 10 and 20 mg N=160	FX006 40 mg N=324	FX006 60 mg N=60	FX006 all N=544	Placebo N=262	TCA IR N=212
Day 1 to 3	0	0	0	0	0	0
Day 4 to 28	1	1	0	2	0	0

Day 29 to 56	0	0	0	0	1	0
Day 57 to 84	2	1	0	3	1	1
Day 85 to 168	2	1	0	3	1	1

Source: Table 14.3.1.1.B

7.5.3 Drug-Demographic Interactions

There were differences in the incidence of adverse events between males and females, with females having a higher incidence in every category of adverse event in the table below except for TEAEs leading to discontinuation. The largest differences between the sexes were in index-knee and injection-procedure related TEAEs. With respect to age, index knee related TEAEs and overall TEAEs appeared to increase in incidence slightly with increasing age. With respect to race, overall TEAEs and index-knee related TEAEs were notably higher in Asian patients.

Table 43 Summary of TEAEs, by Demographic Subgroup (Safety Population; 40 mg FX006): All Studies

Parameter	At least 1:							
	TEAE	Non-serious TEAE	SAE	Grade 3 or 4 TEAE	TEAE leading to Discontinuation	Study drug-related TEAE	Index-knee related TEAE	Injection procedure-related TEAE
Sex								
Male, n=181	73 (40.3)	72 (39.8)	4 (2.2)	5 (2.8)	2 (1.1)	3 (1.7)	17 (9.4)	1 (0.6)
Female, n=243	120 (49.4)	119 (49.0)	7 (2.9)	9 (3.7)	2 (0.8)	18 (7.4)	47 (19.3)	12 (4.9)
Age								
40-50 years, n=59	24 (40.7)	24 (40.7)	1 (1.7)	3 (5.1)	0	6 (10.2)	7 (11.9)	2 (3.4)
51 to 64 years, n=222	102 (45.9)	101 (45.5)	4 (1.8)	8 (3.6)	3 (1.4)	12 (5.4)	34 (15.3)	9 (4.1)
65 to 75 years, n=121	56 (46.3)	55 (45.5)	6 (5.0)	3 (2.5)	1 (0.8)	2 (1.7)	19 (15.7)	2 (1.7)
>75 years, n=22	11 (50.0)	11 (50.0)	0	0	0	1 (4.5)	4 (18.2)	0
Race								
White, n=350	157 (44.9)	155 (44.3)	7 (2.0)	13 (3.7)	4 (1.1)	17 (4.9)	45 (12.9)	10 (2.9)
Asian, n=24	19 (79.2)	19 (79.2)	2 (8.3)	0	0	2 (8.3)	13 (54.2)	2 (8.3)
Other, n=50	17 (34.0)	17 (34.0)	2 (4.0)	1 (2.0)	0	2 (4.0)	6 (12.0)	1 (2.0)

Source: Table 14.3.1.1.1.A, Table 14.3.1.1.2.A, Table 14.3.1.1.2.1.A, Table 14.3.1.1.2.2.A, Table 14.3.1.1.2.3.A, Table 14.3.1.1.3.1.A, Table 14.3.1.1.2.4.A, Table 14.3.1.1.3.2.A, and Table 14.3.1.1.3.3.A.

Source: Table 40 ISS

The following table summarizes TEAEs by BMI and weight categories. Subjects of the lowest weight category had the highest incidence of index-knee related TEAEs. There otherwise did not appear to be any BMI or weight-related trends in incidence of TEAEs.

Figure 13 Summary of TEAEs, by BMI and Weight Subgroups (Safety Population; 40 mg FX006): All Studies

Parameter	At least 1:							
	TEAE	Non-serious TEAE	Serious TEAE	Grade 3 or 4 TEAE	TEAE leading to Discontinuation	Study drug-related TEAE	Index-knee related TEAE	Injection procedure-related TEAE
BMI								
Underweight; n=0	0	0	0	0	0	0	0	0
Normal; n=51	27 (52.9)	27 (52.9)	1 (2.0)	4 (7.8)	0	3 (5.9)	8 (15.7)	3 (5.9)
Overweight; n=145	64 (44.1)	63 (43.4)	5 (3.4)	2 (1.4)	2 (1.4)	6 (4.1)	26 (17.9)	4 (2.8)
Obesity 1; n=132	67 (50.8)	66 (50.0)	3 (2.3)	5 (3.8)	1 (0.8)	9 (6.8)	13 (9.9)	4 (3.0)
Obesity 2; n=92	34 (37.0)	34 (37.0)	2 (2.2)	3 (3.3)	1 (1.1)	3 (3.3)	17 (18.5)	2 (2.2)
Morbid Obesity; n=4	1 (25.0)	1 (25.0)	0	0	0	0	0	0
Weight								
<70 kg; n=60	31 (51.7)	31 (51.7)	2 (3.3)	2 (3.3)	0	2 (3.3)	14 (23.3)	2 (3.3)
70-<85 kg; n=132	67 (50.8)	65 (49.2)	5 (3.8)	6 (4.5)	1 (0.8)	8 (6.1)	22 (16.7)	5 (3.8)
85-<100 kg; n=143	60 (42.0)	60 (42.0)	2 (1.4)	3 (2.1)	2 (1.4)	10 (7.0)	16 (11.2)	5 (3.5)
100-<115 kg; n=71	28 (39.4)	28 (39.4)	1 (1.4)	2 (2.8)	1 (1.4)	1 (1.4)	10 (14.0)	1 (1.4)
≥115 kg; n=18	7 (38.9)	7 (38.9)	1 (5.6)	1 (5.6)	0	0	2 (11.1)	0

Source: 1.11.3 Clinical Information Amendment Table, 8/16/17

7.6 Additional Safety Evaluations

The subsections for additional safety evaluations were not relevant for this product.

7.7 Additional Submissions / Safety Issues

Index knee x-rays were done at baseline and week 24 in study 008 and were to be evaluated for joint space narrowing, subchondral bone changes, osteonecrosis, and insufficiency fracture by a central imaging vendor according to the study protocol. The study report provided the results of the x-ray evaluations. No MRI imaging was done as part of the study. There were no treatment-emergent subchondral bone changes or osteonecrosis identified. There was one treatment-emergent insufficiency fracture (subject ID FX006-2014-008-066-8002) in the TCA IR group. This subject had no other reported AEs.

The percent of subjects with x-ray data at week 24 and the incidence of an increase in joint space narrowing are summarized by treatment group as follows:

Table 44 Study 008 X-ray Findings

	FX006 N=161	Placebo N=162	TCA IR N=161
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Percent subjects with baseline and week 24 x-ray	(140/161) 87%	(148/162) 91%	(145/161) 90%
JSN	(7/140) 5%	(6/148) 4%	(5/145) 3%

Source: Table 14.4.7 Study 008 CSR

There were an additional 18 subjects (roughly equal number of subjects in each treatment group) that had a post-baseline x-ray at the early termination visit. One subject in the FX006 group and one subject in the placebo group had an increase in JSN. There were an additional 3 subjects in the FX006 group and 2 subjects in the TCA IR group that had an x-ray that was after database lock. None of these subjects had an increase in JSN.

Reviewer Comment: The imaging performed does not suggest a difference between treatment groups in the outcomes evaluated. A large proportion of the study population had baseline and post-baseline x-ray images available. The duration of follow-up out to week 24 appear sufficient to evaluate any potential long-term changes in the joint that would be evident on x-ray. These data do not indicate that a single injection of FX006 or TCA IR caused an increase in joint damage over a saline injection. While MRI would have been more sensitive in evaluating the joint structures, including cartilage, the clinical relevance of changes on MRI findings are unclear. Adverse events were also collected over a 24 week period in studies 006 and 008. The adverse events observed in the development program do not suggest that subjects treated with FX006 or TCA IR had symptoms or signs indicative of worsening joint damage in excess of normal disease progression.

8 Postmarket Experience

FX006 is not currently marketed in any country.

9 Appendices

9.1 Literature Review/References

The Applicant submitted the results of a literature review conducted June 29, 2016 to identify any adverse events that were not reflected in the Kenalog-40 label at last update. None of the reports identified suggest the need for modifications to the label for triamcinolone acetonide injectable products for intraarticular injection.

An article published in JAMA on May 16, 2017 titled Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial by McAlindon, et. al. reports on cartilage volume measurements on MRI in patients who received q12 week doses of IA TCA or saline for 2 years. The clinical relevance of cartilage volume measurements on MRI and changes in cartilage volume are unclear and the findings do not change the risk-benefit profile of the product under review.

9.2 Labeling Recommendations

I recommend the following changes to the proposed labeling:

- Section 1:
 - Indication (b) (4) to knee osteoarthritis (b) (4)
See 6.1 (b) (4).
 - The application does not contain nonclinical or clinical safety data to support multiple administrations. Therefore, the indication should include a limitation of use to emphasize that it is only approved for a single administration
- Section 2:
 - Add the following to 2.1 Important Dosage and Administration Information (additions are in bold font):
 - For intra-articular use only (b) (4)
**and should not be administered by the following routes:
Epidural, Intrathecal, Intravenous, Intraocular, Intramuscular,
Intradermal, Subcutaneous**
 - **The efficacy and safety of ZILRETTA for management of
osteoarthritis pain of shoulder and hip have not been
evaluated.**
 - **ZILRETTA is not suitable for use in small joints, such as the
hand**

To avoid inappropriate use of the product, Zilretta should be clearly differentiated from Kenalog, which can be used by the intramuscular route in addition to the intra-articular route. It should also be clear that it is not suitable for use in small joints because of the 5 mL injection volume, which is too large for use in small joints.

- Include information about (b) (4)
[redacted]
- Have a separate multiple-page instructions for use (IFU) portion of labeling (b) (4)
[redacted]
- Section 6: (b) (4)
[redacted] add a table of the ARs with a higher incidence in Zilretta than placebo in the index knee to show comparative data on ARs that occurred in the index knee.
- Section 8: Based on discussions with the Maternal Health and the Clinical Pharmacology reviewers, and a review of other corticosteroid labels, the systemic exposure of triamcinolone from the intra-articular route is similar to that of inhaled fluticasone and much lower than other routes of administration such as the intramuscular route (a labeled route of administration for Kenalog). The label for inhaled fluticasone does not have language about infant hypoadrenalism and I recommend that language about infant hypoadrenalism need not be included in the Zilretta label because of the low systemic exposure observed with intra-articular administration of the product.
- Section 12: Two consultants from the Division of Metabolism and Endocrine Products evaluated the findings from studies 002 and 010 (see 4.4.2 Pharmacodynamics), which are cited in section 12.2 Pharmacodynamics of the proposed label.
 - Regarding study 002, I recommend removing the statement (b) (4)
[redacted]
[redacted] from this section based on Dr. Abraham's findings and recommendations and adding "Adrenal suppression with ZILRETTA occurred within 12-24 hours and then gradually returned to normal, within 30-42 days"
 - Regarding study 010, I recommend removing the statement (b) (4)
[redacted] based on Dr. Archdeacon's findings and recommendations and recommend the following addition "Corticosteroids may increase blood glucose concentrations. In a study where 18 patients with osteoarthritis knee pain and controlled type 2 diabetes mellitus received a (b) (4) [redacted] the change from baseline in average blood glucose over the 72 hours after injection as measured by a continuous glucose monitoring device was 8.2 mg/dL (95% confidence interval 0.1,

29.2).” Dr. Archdeacon also notes that the increases in blood glucose concentrations observed with corticosteroids as a class, including TCA IR, which had numerically higher change in average blood glucose than FX006, may merit a warning in section 5 of labeling. I recommend that if a class-labeling change is considered that it be considered separately from the current application under review, because the blood glucose changes observed with FX006 do not appear to place subjects at increased risk over other intra-articular triamcinolone products and the safety experience for these products should be evaluated as a whole before adding a new warning to the product labels.

- Section 14:
 -  (b) (4)
 - Illustrate the lack of separation in change in average daily pain score between Zilretta and TCA IR, which was the active comparator and reference product. One possible approach would be to add TCA IR data to the figure titled “Weekly Change from Baseline to Week 12 in Average Daily Pain”.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PAMELA J HORN
08/31/2017

ROBERT B SHIBUYA
08/31/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: (b) (4)

Applicant: (b) (4)

Stamp Date: 3/29/16

Drug Name: (b) (4)

NDA/BLA Type: Priority request

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm)	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505b2
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?	X			NDA 14901 Kenalog
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	X			BA
14.	Describe the scientific bridge (e.g., BA/BE studies)	X			BA
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: 006 Study Title: Phase 2b double-blind, randomized (1:1:1), dose-ranging study to assess the magnitude and duration of pain relief of a single IA injection of FX006 at two doses (20 and 40 mg) relative to normal saline (placebo control) Sample Size: 310	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Treatment Arms: FX006 20 mg , FX006 40 mg, Placebo Location in submission: 5.3.5.1				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 008 Indication: OA Pivotal Study #2 Indication:	X			
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dosage (or dosage range) believed to be efficacious?	X			
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary ² used for			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	mapping investigator verbatim terms to preferred terms?				
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			

(verbatim -> preferred and preferred -> verbatim).

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Provide a justification for the applicability of data collected in foreign study sites to the U.S. population or provide its location in the application. In particular, address differences in body mass index (BMI) between the U.S. population and the countries of the foreign study sites and how this may impact the interpretation of the study results.

Reviewing Medical Officer

Date

Clinical Team Leader

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PAMELA J HORN
02/02/2017

ELLEN W FIELDS
02/02/2017