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RESEARCH**

APPLICATION NUMBER:

208845Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 208845	Submission Date(s): December 8, 2016
Brand Name	Zilretta
Generic Name	Triamcinolone Acetonide for Extended-Release Injectable
Reviewer	Wei Qiu, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	Flexion Therapeutics, Inc.
Relevant IND	IND 111,325
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	Suspension; 40 mg
Indication	Management of osteoarthritis pain of (b) (4) [REDACTED]
Proposed Dosing Regimen	A single dose (40 mg in 5 mL suspension) of intra- articular injection

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed this submission dated December 8, 2016 and finds it acceptable provided a mutual agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Flexion Therapeutics, Inc. submitted a 505(b)(2) NDA 208845 for FX006 as an intra-articular (IA) injection for the management of osteoarthritis (OA) pain of (b) (4). FX006 is an extended release suspension formulation of triamcinolone acetonide (TCA) in 75:25 poly(D,L-lactic-co-glycolic acid) (PLGA) microspheres. The intention of this formulation design is to maintain prolonged concentrations of TCA in the joint following IA injection and to provide meaningful analgesia and limiting systemic exposure. Flexion intends to market FX006 as a single formulation in a single dose vial that provides a 5 mL injection with 40 mg of TCA, which is the same dose of the LD, Kenalog®-40, an IA immediate-release crystalline suspension of TCA, indicated for IA use in OA.

The sponsor conducted three (3) clinical efficacy/safety studies using FX006, where the to-be-marketed formulation/preparation as an injection volume (the volume of diluent used to re-suspend the FX006 microspheres) of 5 mL was used in Studies FX006-2014-006 and FX006-2014-008, and an injection volume of 3 mL was used in the early study FX006-2011-001. No change in formulation, other than the resuspension volume, was made during development.

In this 505(b)(2) application, the sponsor proposed to rely on in part on the agency's previous findings of systemic safety of the identified listed drug, Kenalog®-40 (triamcinolone acetonide [TCA], injectable suspension) (NDA 14-901) by establishing a pharmacokinetic bridge in the pivotal comparative bioavailability Study FX006-2015-009. Study -009 was conducted in patients with osteoarthritis of the knee to establish PK bridge between a single IA injection of FX006 40 mg and a single IA injection of Kenalog®-40. The same study also evaluated local synovial concentrations of TCA. The to-be-marketed formulation/preparation as an injection volume of 5 mL was used in Study -009.

In addition, plasma PK, local synovial concentrations and PD effects were also evaluated in 3 earlier studies conducted in patients with osteoarthritis of the knee (FX006-2011-001, FX006-2011-002 and FX006-2013-005) where an injection volume of 3 mL was used.

Comparative Bioavailability between 40 mg FX006 and Kenalog-40

A single dose IA injection of 40 mg FX006 (as an injection volume of 5 mL) showed a substantially lower systemic exposure to TCA in comparison with Kenalog-40 (40 mg TCA in a 1 mL injection volume), an immediate release (IR) TCA.

Table 1 Mean (SD) TCA Plasma Pharmacokinetic Parameters for A Single Dose IA Injection of 40 mg FX006 and 40 mg TCA IR and Statistical Analysis (Study -009)

PK Parameter	N	FX006 40 mg	N	TCA IR 40 mg
Tmax (h)	60	7.0 (1, 1008) ^a	18	6.0 (2, 24) ^a
Cmax (pg/mL)	60	1143.7 (611.06)	18	21062.2 (18466.79)
AUC(0-24h) (pg.h/mL)	60	21219.2 (11325.62)	18	297545.3 (222402.77)
AUCt (pg.h/mL)	60	634513.5 (408327.55)	18	1026652.2 (1251334.91)
AUCinf (pg.h/mL)	33	842149.2 (1062004.97)	14	1567565.0 (1246330.95)
T1/2 (h)	33	633.9 (893.0)	14	146.9 (213.29)
Geometric Mean Ratio % (40 mg FX006/40 mg TCA IR) (90% CI)				
Cmax		8.74% (5.90% – 12.94%)		
AUC0-24h		10.31% (7.11% – 14.96%)		
AUC0-inf		43.49% (26.51% – 71.35%)		

^a range; ^b tmax reported as median (min, max)

Source: Table 20, 21, and 22 in study report for protocol FX006-2015-009.

TCA Cmax and AUC values for FX006 40 mg was lower than that for Kenalog 40. The point estimate of the geometric mean ratio (FX006 40 mg/Kenalog-40) for TCA Cmax, AUC0-24h and AUCinf were 8.74%, 10.31%, and 43.49%, respectively. The corresponding 90% confidence intervals (CIs) were 5.90 – 12.94%, 7.11 – 14.96%, and 26.51 – 71.35%, respectively. All of these 90% CIs fell below the lower bound of the 80 to 125% BE limit. Median (min, max) Tmax values were 7.0 (1, 1008) hour for FX006 40 mg and 6.0 (2, 24) hour for Kenalog-40, respectively. These PK results support for bridging to the systemic safety information of Kenalog-40.

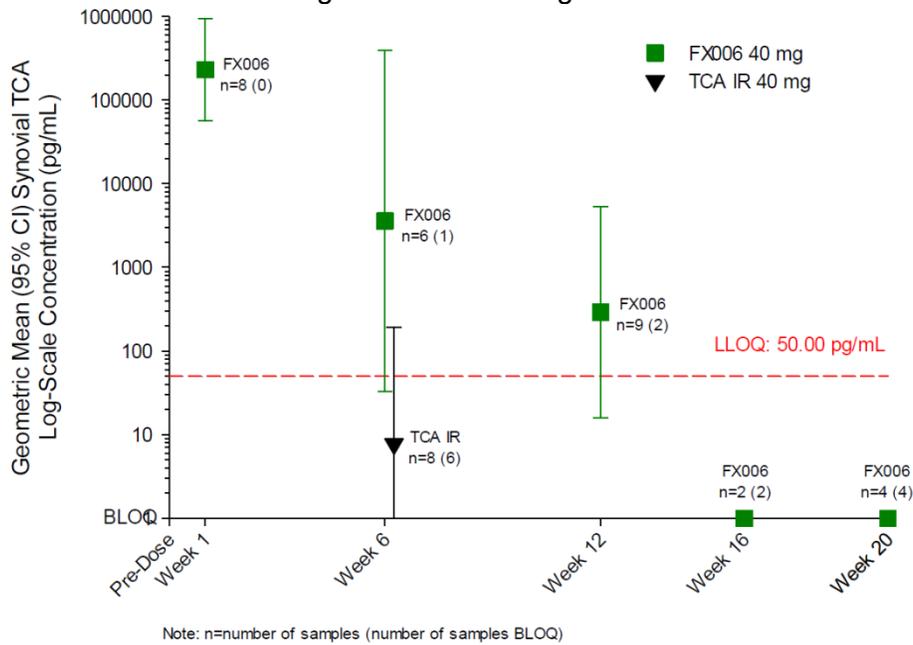
Local Exposure of TCA for FX006 40 mg and Kenalog-40

Geometric mean synovial fluid TCA concentration of 3590 pg/mL (95% CI: 32.89, 391914.74) observed at Week 6 following the administration of 40 mg FX006 was significantly higher than that for Kenalog-40 injection (geometric mean of 7.7 pg/mL (95% CI: 0.31, 191.34)). Six (6) out of 8 subjects following the administration of Kenalog-40 and 1 out of 6 subjects with FX006 40 mg had synovial fluid TCA concentrations below LLOQ of 50 pg/mL at Week 6.

Geometric mean synovial fluid TCA concentration for 40 mg FX006 was 290.6 pg/mL (95% CI: 15.67, 5390.53) at Week 12, where 2 out of 9 subjects had TCA concentrations

below LLOQ of 50 pg/mL. The synovial fluid TCA concentration for all subjects was below the LLOQ of 50 pg/mL at Week 16 (n = 2) and Week 20 (N = 4)).

Figure 1 Synovial Fluid Concentrations following the Administration of a Single dose of 40 mg FX006 and 40 mg TCA IR



Pharmacodynamics Effect (HPA Axis Function):

The 24-hour weighted mean serum cortisol and 24-hour urinary cortisol excretion were determined to evaluate the effects of various doses of FX006 on HPA axis function in comparison to 40 mg TCA IR. Single IA injection of FX006 (10, 40, and 60 mg) appeared to result in dose- and time-dependent decreases in serum cortisol and urinary cortisol excretion.

FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension showed statistically significantly reduced 24-hour weighted mean serum cortisol from baseline. Maximum changes occurring within 24 hour were 42.7% and 59.0% decreases for FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension, respectively. FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension showed statistically significantly reduced 24-hour urinary cortisol excretion from baseline. Maximum changes occurring within 24 hour were 43.8% and 58.5% decreases for FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension, respectively. No significant difference between FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension was observed in 24-hour weighted serum cortisol or 24-hour urinary cortisol excretion within 24 hour, 2 weeks, or 6 weeks post treatment.

2 Question Based Review

2.1 General Attributes of the Drug

1. *What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug product?*

Flexion Therapeutics, Inc. submitted a 505(b)(2) NDA 208845 for FX006 as an IA injection for the management of OA pain of (b) (4) FX006 is an extended release formulation of triamcinolone acetonide (TCA) in 75:25 poly(D,L-lactic-co-glycolic acid) (PLGA) microspheres. The intention of this formulation design was to maintain prolonged concentrations of TCA in the joint following IA injection thereby providing meaningful analgesia and limiting systemic exposure.

The Pre-IND meeting was held on June 15, 2011. The sponsor stated that the extended release product FX006 was not intended to be bioequivalent to the approved immediate release triamcinolone acetonide (IR TCA). DPARP stated that the proposed product was a complex formulation intended for local action and as such, systemic PK and bioequivalence does not apply. The PK data could only be supportive of systemic safety. For the evaluation of HPA axis effect, the Agency recommended serum cortisol and 24 hour urinary cortisol excretion would be appropriate systemic safety assessments. The Agency also recommended that the sponsor designs the evaluation of the HPA axis effect carefully to include an adequate duration of at least six weeks and an active comparator that perturbs the HPA axis.

The sponsor conducted three (3) clinical efficacy/safety studies using FX006, where the to-be-marketed formulation/preparation as an injection volume (the volume of diluent used to re-suspend the FX006 microspheres) of 5 mL was used in Studies FX006-2014-006 and FX006-2014-008, and an injection volume of 3 mL was used in the early study FX006-2011-001. The sponsor stated that the decision to increase the resuspension volume from 3 mL to 5 mL (b) (4)

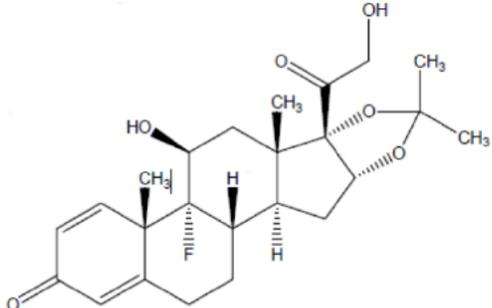
The sponsor stated that there was no change in formulation, other than the resuspension volume, was made during development. FX006 microsphere powder formulation studied in all clinical trials is the same as the proposed to-be-marketed formulation. The sponsor measured the residual amounts in the vials on the clinical batches and consistently obtained a 32 mg delivery for FX006 40 mg dose.

In this 505(b)(2) application, the sponsor proposed to rely on in part on the agency's previous findings of systemic safety of the identified listed drug, Kenalog®-40 (triamcinolone acetonide [TCA], injectable suspension) (NDA 14-901) by establishing a pharmacokinetic bridge. The clinical pharmacology of FX006 was characterized through 4 studies evaluating PK, local synovial concentrations and HPA axis effects in patients with osteoarthritis of the knee. In the pivotal comparative bioavailability Study FX006-2015-009, the to-be-marketed formulation/preparation as an injection volume of 5 mL

was used. An injection volume of 3 mL was used in the other earlier studies (FX006-2011-001, FX006-2011-002 and FX006-2013-005). This clinical pharmacology review focuses on the pivotal comparative bioavailability study -009 and study -002 where the HPA axis effect was evaluated.

2. What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Table 2 Physical-Chemical Properties of Triamcinolone Acetonide

Drug Name	Triamcinolone acetonide
Chemical Name	9-Fluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone
Structure	
Molecular Formula	C ₂₄ H ₃₁ FO ₆
Molecular Weight	434.50 g/mol
Appearance	White to almost white, crystalline powder
Solubility	Practically insoluble in water and very soluble in alcohol

The drug product, FX006, is comprised of 25% (w/w) triamcinolone acetonide, prepared as an extended-release formulation in 75:25 poly(lactic-co-glycolic acid) (PLGA) microspheres. F^{(b) (4)}006 is supplied as a sterile, white to off white powder in a single unit dose, in a Type ^{(b) (4)} glass 5 mL vial with a ^{(b) (4)} rubber stopper, aluminum seal and plastic cap.

Table 3 Components and Composition of FX006 Microspheres

Ingredient	60 mg Strength Nominal amount (mg) per vial	40 mg Strength Nominal amount (mg) per vial	10 mg Strength Nominal amount (mg) per vial	Function	Reference to standards
Micronized Triamcinolone Acetonide	60	40	10	active	USP/Ph. Eur.
75:25 PLGA [Poly(lactic-co- glycolic acid)]	^{(b) (4)}				Supplier's specification

The diluent for suspension of FX006 is supplied as a sterile, clear liquid in a Type ^{(b) (4)} glass 5 mL vial with a ^{(b) (4)} rubber stopper, aluminum seal and plastic cap. Each vial

contains 5 mL of a solution of 0.9% w/w sodium chloride (normal saline) containing 0.5% w/w sodium carboxymethylcellulose, and 0.1% w/w polysorbate-80.

The proposed to-be-marketed formulation of FX006 is reconstituted prior to injection to make a suspension by adding 5 mL of diluent to the drug product vial and (b) (4) tapping and swirling with 5 mL withdrawn and injected intra-articularly. The injection volume of the suspension of 5 mL (i.e., reconstituted with 5 mL of diluent prior to IA injection to deliver 5 mL injection volume) was used in the pivotal bioavailability Study -009 and the primary efficacy/safety Studies -006 and -008. The injection volume of the suspension was 3 mL (i.e., reconstituted with 3.2 mL of diluent prior to IA injection to deliver a 3 mL injection volume) in early PK studies including Studies -001, -002, and -005. According to CMC, the sponsor measured the residual amounts in the vials on the clinical batches and consistently achieved 32 mg delivery for FX006 40 mg dose.

3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Zilretta is an extended release synthetic corticosteroid indicated as an intra-articular injection for the management of osteoarthritis pain of (b) (4)

4. What are the proposed dosage(s) and route(s) of administration?

Zilretta is supplied as a (b) (4) kit containing 40 mg of sterile triamcinolone acetonide extended release microsphere powder, 5 mL of sterile diluent, and a sterile vial adapter. A 40 mg should be administered as a single intra-articular injection (b) (4)

2.2 General Clinical Pharmacology

1. What is known about the PK characteristics of triamcinolone for the listed drug Kenalog-40 Injection?

Kenalog-40 (triamcinolone acetonide injectable suspension, US) is a synthetic glucocorticoid with anti-inflammatory action. This formulation is suitable for intramuscular and intra-articular use only. Each mL of the sterile aqueous suspension provides 40 mg triamcinolone acetonide, with (b) (4)% sodium chloride for isotonicity, 0.99% (w/v) benzyl alcohol as a preservative, (b) (4)% carboxymethylcellulose sodium, and 0.04% polysorbate 80.

According to Kenalog labeling, kenalog-40 injection has an extended duration of effect which may be sustained over a period of several weeks. Studies indicate that following a single intramuscular dose of 60 mg to 100 mg of triamcinolone acetonide, adrenal suppression occurs within 24 to 48 hours and then gradually returns to normal, usually in 30 to 40 days.

2. Were the active moieties in the plasma appropriately identified and measured to assess the pharmacokinetics?

The activity is primarily due to the parent compound triamcinolone. Triamcinolone concentrations were measured in all pharmacokinetic studies.

2.3 Intrinsic Factors

1. What is the pediatric plan?

Division agreed with the full waiver (b) (4) in the communication dated March, 15, 2016 because he pediatrics (b) (4) are rarely diagnosed with osteoarthritis and that recruiting pediatric patients with osteoarthritis is highly impracticable.

2.4 General Biopharmaceutics

1. What is the relative bioavailability of TCA following a single dose administration of the proposed 40 mg FX006 in comparison to the listed drug, Kenalog-40?

A single dose IA injection of 40 mg FX006 (as an injection volume of 5 mL) showed a substantially lower systemic exposure to TCA in comparison with Kenalog-40. The point estimate of the geometric mean ratio (FX006 40 mg/Kenalog-40) for TCA Cmax, AUC0-24h and AUCinf were 8.74%, 10.31%, and 43.49%, respectively. The corresponding 90% confidence intervals (CIs) were 5.90 – 12.94%, 7.11 – 14.96%, and 26.51 – 71.35%, respectively. All these 90% CIs fell below the lower bound of 80 to 125% BE limit. Median (min, max) Tmax values were 7.0 (1, 1008) hour for FX006 40 mg and 6.0 (2, 24) hour for Kenalog-40, respectively.

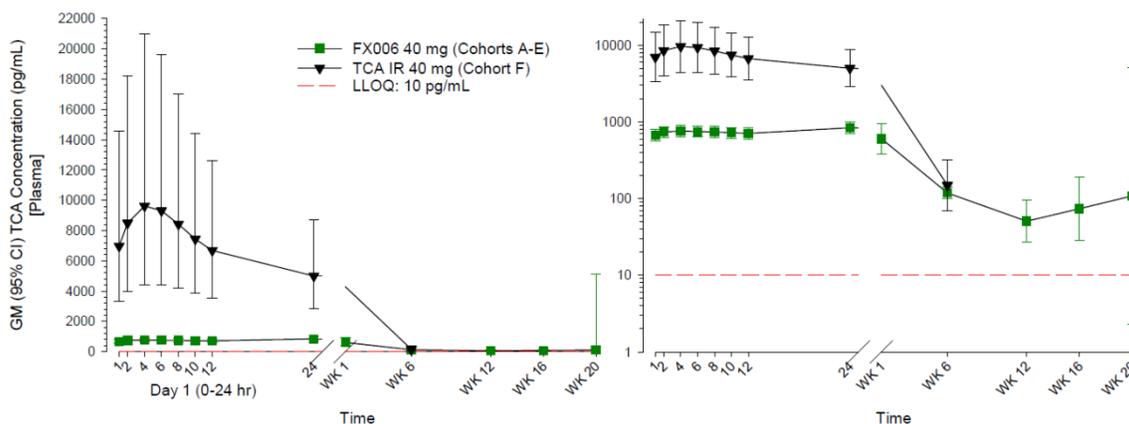
The pivotal comparative bioavailability Study -009 characterized the systemic PK and local exposure of TCA for a single IA injection of FX006 40 mg in comparison to TCA IR 40 mg in patients with osteoarthritis of the knee. The to-be-marketed preparation, FX006 40 mg administered with a 5 mL injection volume, was used in this study. A total of 63 patients were enrolled into five cohorts for treatment with a single IA injection of FX006 40 mg administered in a volume of 5 mL. Blood samples for drug concentration measurements in plasma were collected from all patients prior to administration of study medication, and at 1, 2, 4, 6, 8, 10, 12, and 24 h post-dose, at Week 6 and at the assigned Synovial Fluid Visit (Week 1, 6, 12, 16, or 20). Synovial fluid samples for drug concentration measurements were obtained from all patients via aspiration on Day 1 prior to study medication administration and at the Synovial Fluid Visit (depending on cohort assignment at either Week 1, 6, 12, 16, or 20). A total of 18 patients received the TCA IR 40 mg, blood samples were collected at pre-dose, and at 1, 2, 4, 6, 8, 10, 12, 24 h, and at Week 6, and synovial fluid samples were collected pre-dose and at Week 6.

Table 4 Study Cohorts

Cohort	Treatment	Synovial Fluid Visit
A	40 mg FX006	Week 20
B	40 mg FX006	Week 16
C	40 mg FX006	Week 12
D	40 mg FX006	Week 6
E	40 mg FX006	Week 1
F ¹	40 mg TCA IR	Week 6

The mean TCA plasma concentration-time profiles are shown in **Figure 2**. Descriptive statistics and results of the statistical analyses for FX006 40 mg versus 40 mg TCA IR are summarized in **Table 1**.

Figure 2 TCA plasma concentration (pg/mL) time profiles for a single injection of 40 mg FX006 and TCA IR 40 mg



Mean C_{max} values were 1143.7 pg/mL and 21062.2 pg/mL for a single IA injection of FX006 40 mg and Kenalog 40, respectively. The mean AUC_{inf} values were 842149.2 pg.h/mL and 1567565 pg.h/mL for FX006 40 mg and 40 mg TCA IR, respectively. Median T_{max} (min, max) values were 7.0 (1, 1008) h and 6.0 (2, 24) h for FX006 40 and Kenalog 40, respectively (**Table 1**).

A single dose IA injection of 40 mg FX006 (as an injection volume of 5 mL) showed a substantially lower systemic exposure to TCA in comparison with Kenalog-40. The point estimate of the geometric mean ratio (FX006 40 mg/Kenalog-40) for TCA C_{max}, AUC_{0-24h} and AUC_{inf} were 8.74%, 10.31%, and 43.49%, respectively. The corresponding 90% confidence intervals (CIs) were 5.90 – 12.94%, 7.11 – 14.96%, and 26.51 – 71.35%, respectively. All these 90% CIs fell below the lower bound of 80 to 125% BE limit (**Table 1 in Executive Summary**).

Reviewer’s Comment: The lower systemic exposure for FX006 40 mg in comparison to Kenalog-40 was also demonstrated in studies -001, 002, and -005 where 3 mL injection was used. Among studies -001, -002, and -009 where PK parameters of TCA were determined, TCA C_{max} and AUC_{inf} values for FX006 40 mg were 3.4% to 9.7% and 43.5% to 51.5% of the values for Kenalog-40, respectively. All studies showed that FX006 40 mg has lower TCA systemic exposure of compared to Kenalog-40.

2. Local exposure for FX006 in comparison with Kenalog-40?

Local extent and duration of exposure of TCA from FX006 was determined and compared to Kenalog-40 in patients with OA of the knee in the pivotal comparative bioavailability study -009. Study -009 was a Phase 2, open label, single dose study. Synovial fluid samples for drug concentration measurement were obtained from all patients on Day 1 prior to study medication administration, and at the Synovial Fluid Visit (depending on cohort assignment at either Week 1, 6, 12, 16, or 20) for patients receiving FX006 40 mg or at Week 6 for patients received Kenalog-40.

Geometric mean synovial fluid TCA concentration of 3590 pg/mL (95% CI: 32.89, 391914.74) observed at Week 6 following the administration of 40 mg FX006 was significantly higher than that for Kenalog-40 injection (mean of 7.7 pg/mL (95% CI: 0.31, 191.34)) (Figure 1, Tables 5 and 6). Of note, majority of the subjects (6 out of 8) following the administration of Kenalog-40 had synovial fluid TCA concentrations below LLOQ of 50 pg/mL at Week 6. In addition, geometric mean synovial fluid TCA concentration for 40 mg FX006 was 290.6 pg/mL (95% CI: 15.67, 5390.53) at Week 12. The TCA concentration was below the LLOQ of 50 pg/mL for all patients at Week 16 (N = 2) and Week 20 (N = 4).

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

Treatment Time	Number Below LLOQ		Mean	SD	Geometric Mean	Log-Scale SD	95 % CI	Median	Min, Max
	N ¹	N							
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		Mean	SD	Geometric Mean	Log-Scale SD	95 % CI	Median	Min, Max
	N ¹	N							
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.

Reviewer Comment: Greater local TCA exposures from FX006 than TCA IR 40 mg at Week 12 were also demonstrated in Study -005. Study -005 was a Phase 2, open label, single dose study in patients with OA of the knee. Patients were enrolled into four FX006

cohorts with one cohort receiving 10 mg FX006 (synovial fluid sample was collected at Week 12) and three cohorts receiving FX006 40 mg (synovial fluid samples were collected at Week 12, 16, and 20, respectively, for three different cohorts), and one cohort receiving TCA IR 40 mg (synovial fluid sample was collected at Week 12). At Week 12, geometric mean synovial fluid TCA concentrations for patients (n = 6) following the administration of 40 mg FX006 was 923.7 pg/mL (95% CI: 74.24, 11492.46). However, all patients (5 of 5) received Kenalog-40 injection had concentrations below the LLOQ of 50 pg/mL. In addition, at Week 16, 6 out of 8 patients who received 40 mg FX006 had measureable concentration with a geometric mean of 224.3 (95% CI: 37.42, 1344.70) pg/mL. At Week 20, most patients (9 of 11) who received FX006 40 mg had concentration below the LLOQ of 50 pg/mL.

3. How does FX006 40 mg on HPA axis function in comparison to Kenalog 40?

The 24-hour weighted mean serum cortisol and 24-hour urinary cortisol excretion were determined to evaluate the effects of various doses of FX006 on HPA axis function in comparison to 40 mg TCA IR. Single IA injection of FX006 (10, 40, and 60 mg) appeared to result in dose- and time-dependent decreases in serum cortisol and urinary cortisol excretion.

FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension showed statistically significantly reduced 24-hour weighted mean serum cortisol from baseline. Maximum changes occurring within 24 hour were 42.7% and 59.0% decreases for FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension, respectively. FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension showed statistically significantly reduced 24-hour urinary cortisol excretion from baseline. Maximum changes occurring within 24 hour were 43.8% and 58.5% decreases for FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension, respectively. No significant difference between FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension was observed in 24-hour weighted serum cortisol or 24-hour urinary cortisol excretion within 24 hour, 2 weeks, or 6 weeks post treatment.

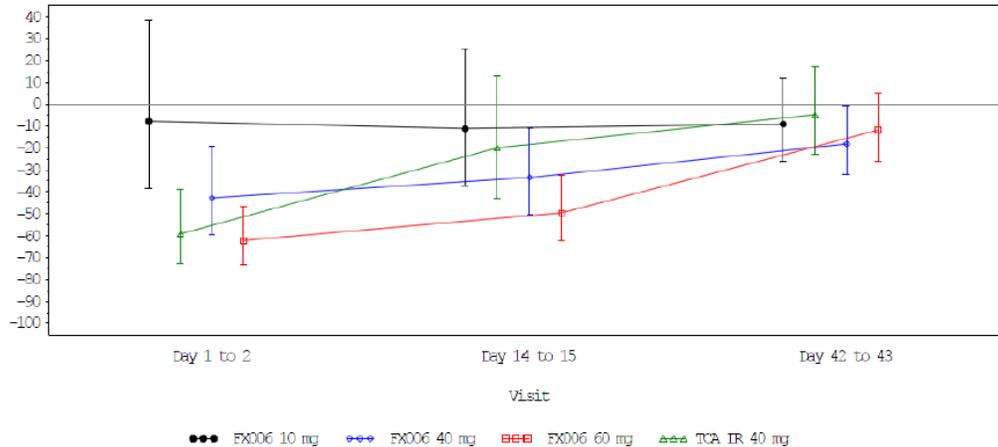
The HPA axis effect of various doses of FX006 (10, 40, and 60 mg) in comparison to TCA IR 40 mg was evaluated in Study -002. This was a Phase 2, double blind, randomized, active comparator study in patients with OA of the knee. Study -002 evaluated safety and tolerability of FX006, the PK of FX006 relative to 40 mg TCA IR, and effects on HPA axis of FX006 relative to 40 mg of TCA IR. Twenty-four patients were randomized into one the four treatment groups and treated with a single IA injection of 10, 40, or 60 mg of FX006 or 40 mg of TCA IR. The three FX006 doses were administered in a volume of 3 mL and the TCA IR 40 mg was administered in a volume of 1 mL.

Blood samples for TCA PK were collected at pre-dose, and at 1, 2, 4, 6, 8, 12, and 24 h post dose and on Days 3, 4, 5, 8, 15, 22, 29, 36, and 43. Serial blood samples for serum cortisol measurement were obtained from all patients during the in-patient periods from Day -1 to Day 1, Day 1 to Day 2, Day 14 to Day 15, and Day 42 to Day 43. For each time period, the first sample was collected on the day starting the in-patient period (Time 0) and then at 1, 2, 4, 6, 8, 12, and 24 hours post dose. Single blood samples for serum cortisol measurements were also obtained at Screening and Days 3, 4, 5, 8, 22, 29, and 36. Twenty-four hour urine collections for evaluation of urinary free cortisol excretion, 6-

beta-hydroxycortisol and creatinine were obtained from all patients during the in-patient periods from Day -1 to Day 1, Day 1, to Day 2, Day 14 to Day 15, and Day 42 to Day 43.

Change from Baseline in the 24-hour weighted mean serum cortisol suggested that a single IA injection of FX006 results in a dose- and time-dependent effect. Serum cortisol suppression with 40 mg and 60 mg FX006, and TCA IR 40 mg peaked in the first 24 hours and gradually returned to near Baseline levels by Week 6 (**Figure 3** and **Table 7**). Cortisol suppression appeared to return to near Baseline levels earlier for TCA IR 40 mg than 40 mg and 60 mg FX006. FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension showed statistically significantly reduced 24-hour weighted mean serum cortisol from baseline. Maximum changes occurring within 24 hour were 42.7% and 59.0% decreases for FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension, respectively.

Figure 3 Geometric Mean Percent Difference from Baseline in 24-hour Weighted Mean Serum Cortisol (nmol/L) by Visit



1 LSMs are back transformed to obtain the ratio of on treatment response to baseline and then converted to percentage change from baseline as $(\text{ratio}-1)*100\%$ within each treatment group.

Table 7 Geometric Mean Percent Change from Baseline in 24-Hour Weighted Mean Serum Cortisol (nmol/L) by Visit

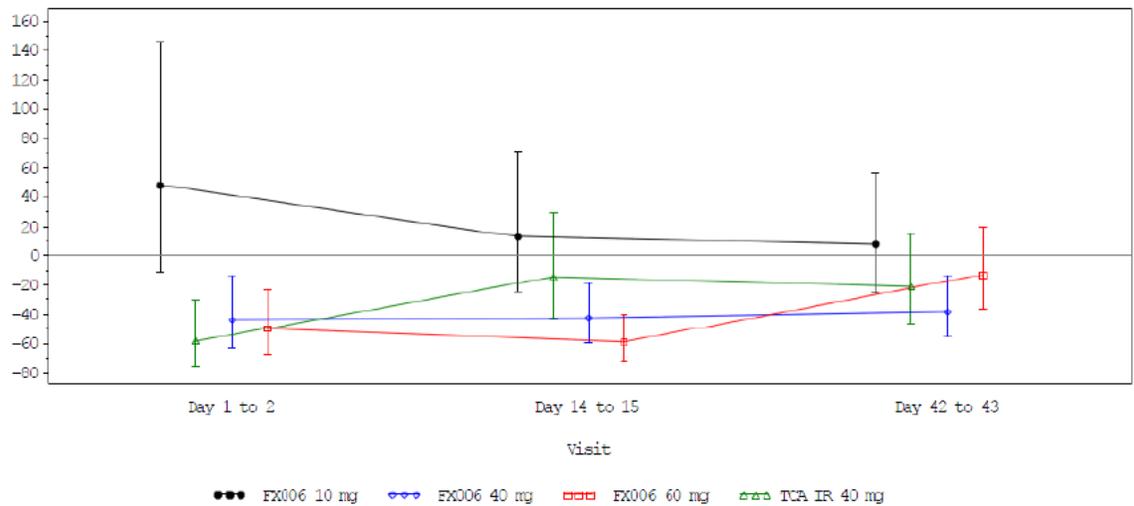
LS Means [1] 95% CI	FX006 10 mg (N = 5)	FX006 40 mg (N=7)	FX006 60 mg (N=7)	TCA IR 40 mg (N=5)
% Change from Baseline at Day 1 to 2	-7.7 (-38.4, 38.3)	-42.7 (-59.2, -19.4)	-62.2 (-73.2, -46.8)	-59.0 (-72.6, -38.6)
% Change from Baseline at Day 14 to 15	-11.1 (-37.0, 25.5)	-33.4 (-50.2, -10.9)	-49.5 (-62.3, -32.4)	-19.7 (-43.0, 13.3)
% Change from Baseline at Day 42 to 43	-9.0 (-26.2, 12.3)	-18.0 (-32.2, -0.7)	-11.8 (-26.1, 5.4)	-4.8 (-22.7, 17.4)

[1] Least squares (LS) means are back transformed to obtain the ratio of on treatment response to baseline and then converted to percentage change from baseline as $(\text{ratio}-1)*100\%$ within each treatment group.

This table is reproduced from Table 14.4.3 Change from Baseline in Weighted Mean Serum Cortisol (nmol/L) by Visit - Analysis of Covariance - Primary Analysis Population: Full Analysis Set in Study Report for Protocol: FX006-2011-002

The results from analyses of the change from Baseline in 24-hour urinary free cortisol excretion were similar in terms of FX006 dose- and time-dependency to the change from baseline in weighted mean serum cortisol (**Figure 4** and **Table 8**). FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension showed statistically significantly reduced 24-hour urinary cortisol excretion from baseline. Maximum changes occurring within 24 hour were 43.8% and 58.5% decreases for FX006 40 mg and 40 mg triamcinolone acetonide injectable suspension, respectively.

Figure 4 Geometric Mean Percent Difference from Baseline in 24-Hour Urinary Free Cortisol Excretion (nmol/24h) by Visit



1. LSMeans are back transformed to obtain the ratio of on treatment response to baseline and then converted to percentage change from baseline as $(\text{ratio}-1)*100\%$ within each treatment group.

Table 8 Geometric Mean Percent Change from Baseline in 24-Hour Urinary Free Cortisol Excretion (nmol/24h) by Visit

LS Means [1] 95% CI	FX006 10 mg (N = 5)	FX006 40 mg (N=7)	FX006 60 mg (N=7)	TCA IR 40 mg (N=5)
% Change from Baseline at Day 1 to 2	47.9 (-11.1, 146.2)	-43.8 (-63.5, -13.6)	-50.1 (-67.7, -23.0)	-58.5 (-75.2, -30.5)
% Change from Baseline at Day 14 to 15	13.0 (-25.3, 70.8)	-42.4 (-59.3, -18.3)	-59.0 (-72.0, -40.0)	-14.7 (-43.9, 29.6)
% Change from Baseline at Day 42 to 43	7.7 (-25.8, 56.3)	-38.3 (-56.1, -13.3)	-13.1 (-36.7, 19.3)	-21.3 (-46.0, 14.8)

[1] Least squares (LS) means are back transformed to obtain the ratio of on treatment response to baseline and then converted to percentage change from baseline as $(\text{ratio}-1)*100\%$ within each treatment group.

This table is reproduced from Table 14.4.6 Change from Baseline in Weighted Mean Serum Cortisol (nmol/L) by Visit - Analysis of Covariance - Primary Analysis Population: Full Analysis Set in Study Report for Protocol: FX006-2011-002

Table 9 summarizes the difference between the LSM of each FX006 group and the TCA IR group as well as the 90% confidence interval for the LSM difference (LSMD) and the associated p-value.

The LSMD of 40 mg FX006 and TCA IR 40 mg with respect to change in 24-hour weighted mean serum cortisol from Baseline to Day 1-2, Day 14-15, and Day 42-43 were not statistically significant (p=0.1999, p=0.3948, and p=0.2832, respectively). The LSMD of 40 mg FX006 and TCA IR with respect to change in 24-hour urinary free cortisol excretion from Baseline to Day 1-2, Day 14-15, and Day 42-43 were not statistically significant (p=0.3565, p=0.1485, and p=0.3291, respectively).

Table 9 Summary of the Difference between the LSM of Each FX006 group and the TCA IR Group as well as the 90% confidence interval for the LSM difference (LSMD) and the associated p-values

	LSMD vs TCA IR (90% CI)		
	10 mg FX006	40 mg FX006	60 mg FX006
Change from Baseline in Weighted Mean Serum Cortisol			
Day 1 to 2	125.1 (40.4, 260.9) p = 0.0078	39.8 (-9.6, 116.3) p = 0.1999	-7.8 (-40.4, 42.7) p = 0.7513
Day 14 to 15	10.7 (-26.0, 65.5) p = 0.6670	-17.1 (-42.8, 20.3) p = 0.3948	-37.1 (-56.7, -8.8) p = 0.0440
Day 42 to 43	-4.4 (-25.1, 22.1) p = 0.7525	-13.9 (-31.8, 8.8) p = 0.2832	-7.3 (-26.1, 16.2) p = 0.5664
Change from Baseline in 24-Hour Urinary Free Cortisol Excretion			
Day 1 to 2	256.5 (96.2, 548.0) p=0016	35.5 (-22.3, 136.1) p=0.3565	20.2 (-31.6, 111.0) p=0.5790
Day 14 to 15	32.4 (-18.4, 114.9) p=0.3279	-32.4 (-56.9, 6.0) p=0.1485	-52.0 (-70.1, -22.9) p=0.0150
Day 42 to 43	36.9 (-11.5, 111.7) p=0.2277	-21.6 (-48.6, 19.4) p=0.3291	10.5 (-26.8, 66.5) p=0.6809

Reviewer’s Comment:

(1) The 24-hour weighted mean serum cortisol and 24-hour urinary free cortisol excretion are commonly used to evaluate the HPA axis effects. In the communication during drug development (meeting minutes dated 7/15/11), the Agency recommended serum cortisol and 24 hour urinary cortisol excretion would be appropriate safety assessments to evaluate the HPA Axis effect. The Agency also recommended that the sponsor designs the evaluation of the HPA axis effect carefully to include an adequate duration of at least six weeks and an active comparator that perturbs the HPA axis. The sponsor decided to use TCA IR 40 mg as the active control for study -002 because when administered intra-articularly, 40 mg of TCA IR produced a substantial adrenal effect in the first few days following administration (70-80% reduction in serum cortisol) (Derendorf et al, Clin Pharmacol Ther 1986;39:313-7) and therefore was able to establish assay sensitivity and allow for comparison with the effect of FX006 on the HPA axis. Study results showed no significant difference between FX006 40 mg and 40 mg

triamcinolone acetonide injectable suspension in 24-hour weighted serum cortisol or 24-hour urinary cortisol excretion within 24 hour, 2 weeks, or 6 weeks post treatment.

(2). The lower systemic exposure for FX006 40 mg in comparison to Kenalog-40 was also demonstrated in study -002 where 3 mL injection was used (**Table 10**). TCA C_{max} and AUC_{inf} values for FX006 40 mg were 3.4% and 51.5% of the values for Kenalog-40, respectively. In the pivotal comparative BA study -009, a single dose IA injection of 40 mg FX006 (as an injection volume of 5 mL) showed a lower systemic exposure to TCA in comparison with Kenalog-40. TCA C_{max} and AUC_{inf} values for FX006 40 mg were 8.7% and 43.5% of the values for Kenalog-40, respectively. Thus, the PK results from studies -002 and -009 are consistent. In addition, the sponsor measured the residual amounts in the vials on the clinical batches and consistently obtained a 32 mg delivery for FX006 40 mg dose. Therefore, the HPA axis effect results obtained from study -002 can be applied to the final to-be-marketed product.

Table 10 Mean (CV%) Plasma Pharmacokinetic Parameters of TCA (Study -002)

TCA PK Parameters	Mean (CV%)			
	FX006 10 mg	FX006 40 mg	FX006 60 mg	TCA IR 40 mg
	N = 5	N = 7	N = 7	N = 5
AUC ₀₋₄ (pg•h/mL)	89289 (52.9)	388012 (44.0)	698583 (42.1)	843834 (46.5)
AUC _{0-inf} (pg•h/mL)	133019 ² (33.6)	473116 (43.6)	803143 (38.6)	919128 (34.5)
AUC ₀₋₂₄ (pg•h/mL)	6027 (41.0)	20837 (49.9)	32878 (44.0)	440304 (66.9)
CL/F (mL/h)	85682 ² (49.0)	117663 (85.0)	92695 (64.2)	47566 (31.1)
C _{max} (pg/mL)	322 (33.6)	1028 (45.7)	1734 (48.1)	30132 (61.7)
t _{1/2} (h)	317 ² (64.4)	370 (27.2)	363 (26.2)	387 (116.4)
t _{max} ¹ (h)	94.9 (6.00, 95.4)	4.0 (2.00, 6.00)	8.0 (2.00, 94.4)	4.0 (1.00, 8.00)
MRT _{inf} (h)	428 ² (51.3)	569 (26.2)	508 (22.1)	313 (136.9)

Source: [Table 14.4.2](#)
¹ Median (Min, Max)
² N = 4

2.5 Analytical Section

1. Do the bioanalytical methods adequately validated for determining concentrations of TCA?

A validated LC-MS/MS method was used for the determination of TCA in human plasma samples in Studies -001, -002, -005, and -009 and synovial fluid measurements in Studies -005 and -009. The accuracy and precision are summarized in **Table 11**.

Table 11 Summary of Accuracy and Precision Data for TCA

Study		LLOQ Calibration Range	QCs	QC Precision (%CV)	QC Accuracy (%Bias)
Study -001	plasma	LLOQ: 50 pg/mL Calibration Range: 50 to	150, 375, 2500, and 3750 pg/mL	2.59 to 5.69%	-0.79 to 0.88%

		5000 pg/mL			
Study -002	Plasma	LLOQ: 50 pg/mL Calibration Range: 50.00 to 5000.00 pg/mL	150.00, 375.00, 2500.00, and 3750.00 pg/mL	1.56 to 7.02%	-1.29 to 1.37%
Study -005	plasma	LLOQ: 10 pg/mL Calibration Range: 10 to 1000 pg/mL	30, 75, 500, and 750 pg/mL	2.54 to 5.57%	-1.60 to 4.11%
	Synovial fluid	LLOQ: 50 pg/mL Calibration Range: 50 to 50000 pg/mL	150, 2500, 25000, and 37500 pg/mL	1.82 to 10.01%	-2.96 to 10.91%
Study -009	Plasma	LLOQ: 10 pg/mL Calibration Range: 10 to 5000 pg/mL	30, 250, 2500, and 3750 pg/mL	2.98 to 6.44%	-1.83 to 1.93%
	Synovial fluid	LLOQ: 50 pg/mL Calibration Range: 50 to 50000 pg/mL	150, 2500, 25000, and 37500 pg/mL	2.30 to 7.78%	-4.32 to 4.08%

Note: The bioanalytical reports are in the following locations in the NDA:

Project No. 110538 for Study FX006-2011-002: See module 5.3.3.2 under the leaf for the study, Study Report Body/Bioanalytical Report 1b

Project No. 1304111 for Study FX006-2013-005: See module 5.3.3.2 under the leaf for the study, Study Report Body/Bioanalytical Study Report

Project No. 150421 for Study FX006-2015-009: See module 5.3.3.2 under the leaf for the study, Study Report Body/Bioanalytical Study Report

3 Detailed Labeling Recommendations

As of August 8, 2017, labeling negotiation is still ongoing. The following changes are recommended for Pharmacodynamics in Section 12.2 and pharmacokinetics in Section 12.3. (Deletion is shown by ~~Red Strike through~~, addition is shown by blue underline)

12.2 Pharmacodynamics

Studies indicate that following a single intramuscular dose of 60 to 100 mg of immediate release triamcinolone acetonide injectable suspension, adrenal suppression occurs within 24 to 48 hours and then gradually returns to normal, usually in 30 to 40 days. To assess potential effects of the systemic levels of triamcinolone acetonide associated with a single intra-articular (IA) administration of ZILRETTA on hypothalamic pituitary adrenal (HPA) axis function, serum and urine cortisol levels were monitored over 6 weeks post injection. (b) (4)

(b) (4)

adrenal suppression occurred within 12-24 hours and then gradually returned to normal, within 30-42 days.

(b) (4)

(b) (4) The Division recommended deleting the statement (b) (4)

from the sponsor's proposed labeling. (b) (4)

the cortisol data from FX006-2011-002 show evidence of at least mild-moderate suppression in the first few days after FX006 40 mg injection and a gradual return to normal over the course of the 6 week study. (b) (4)

The Division recommended adding the statement (b) (4), adrenal suppression occurred within 12-24 hours and then gradually returned to normal, within 30-42 days." We agree with DMEP's assessment.]

Corticosteroids may increase blood glucose concentrations. (b) (4)

12.3 Pharmacokinetics

ZILRETTA is an extended release dosage form consisting of microspheres of poly(lactic-co-glycolic acid) (PLGA) containing triamcinolone acetonide. (b) (4)

(b) (4)

Plasma pharmacokinetic parameters (b) (4)

into the knee are provided in Table (b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 Appendix

4.1 Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA/BLA Number	208845	Brand Name	Zilretta	
OCP Division (I, II, III, IV, V)	II	Generic Name	Triamcinolone Acetonide for Extended-Release Injectable suspension	
Medical Division	DAAAP	Drug Class	Corticosteroid	
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	Management of osteoarthritis pain of (b) (4)	
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form	(b) (4)	
Pharmacometrics Reviewer		Dosing Regimen	A single dose injection	
Date of Submission	12/8/2016	Route of Administration	Intra-articular injection	
Estimated Due Date of OCP Review	8/20/2017	Sponsor	Flexion Therapeutics, Inc	
Medical Division Due Date	9/3/2017	Priority Classification	Standard	
PDUFA Due Date	10/8/2017			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				

Phase 2:	x	4		FX006-2011-001, FX006-2011-002, FX006-2013-005 and FX006-2015-009
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	x	(1)		FX006-2015-009
alternate formulation as reference:				
Bioequivalence studies -				
traditional design: single / multi dose:				
replicate design: single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	Sponsor stated that the final formulation was used in the pivotal comparative bioavailability study (FX006-2015-009) and primary Phase 3 trials
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			

7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			Sponsor submitted plasma concentration time dataset as well as pharmacokinetic parameter datasets in SAS transport format.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?				
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		x		Agency agreed with the full waiver (b) (4) in the communication dated 3/15/2016.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this	x			

	product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

This NDA submission is fillable from clinical pharmacology perspective.

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

There is no potential review issue to be included in the 74-day letter.

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

Flexion Therapeutics, Inc. submitted a 505(b) (2) NDA for Zilretta (triamcinolone acetonide for extended-release (ER) injection suspension) for the management of osteoarthritis pain of (b) (4). Zilretta is an extended release formulation of triamcinolone acetonide (TCA) in 75:25 poly(D,L-lactic-co-glycolic acid) (PLGA) microspheres. The intention of this formulation design is to maintain prolonged concentrations of TCA in the joint following intra-articular (IA) injection thereby providing meaningful analgesia and limiting systemic exposure. FX006 was used for Zilretta throughout the development program.

As a 505(b)(2) application, Flexion plans to rely in part on the agency's finding of the safety and efficacy of Kenalog®-40 (triamcinolone acetonide injectable suspension) (NDA 14-901), an immediate release (IR) formulation.

The PK data supporting this NDA are generated from 4 Phase 2 studies in OA patients including FX006-2011-001, FX006-2011-002, FX006-2013-005, and FX006-2015-009. The titles of these studies are shown below:

FX006-2011-001: A double-blind, randomized, parallel group, dose-ranging study comparing FX006 to commercially available triamcinolone acetonide injectable suspension in patients with osteoarthritis of the knee

FX006-2011-002: A double-blind, randomized, parallel group, active comparator study to evaluate the safety, pharmacokinetics, and pharmacodynamic effects (HPA Axis) of FX006 in patients with osteoarthritis of the knee

FX006-2013-005: An open-label, single administration study to characterize the local duration of exposure of triamcinolone acetonide from FX006 in patients with osteoarthritis of the knee

FX006-2015-009: An open-label, single administration study to characterize the systemic pharmacokinetics and local extent and duration of exposure of triamcinolone acetonide from FX006 in patients with osteoarthritis of the knee

Study FX006-2011-001: Sponsor stated that mean C_{max} for FX006 40 mg was approximately 10-fold lower than the mean TCA IR C_{max}. Mean AUC_{0-inf} and AUC_{0-t} values for FX006 increased with the dose. Mean AUC_{0-inf} and AUC_{0-t} for TCA IR 40 mg were approximately 2.21- and 2.94-fold higher than that observed for FX006 40 mg.

Study FX006-2011-002: Sponsor stated that following IA injection, FX006 substantially extends the residency of TCA in the joint and reduces systemic TCA exposure relative to an equivalent dose of TCA IR. Furthermore, it was concluded that FX006 will not compromise the ability to mount a stress response in patients without previous impairment of HPA axis function.

Study FX006-2013-005: Sponsor stated that IA administration of FX006 40 mg results in an extended and more controlled and stable overall duration of exposure profile of TCA with FX006 relative to TCA IR at the injected knee joint.

Study FX006-2015-009: Sponsor stated that IA administration of FX006 40 mg with a 5 mL injection volume (the same preparation used in the primary efficacy studies of FX006), resulted in a controlled and stable release of TCA from PLGA microspheres into synovial tissues, where concentrations remain high relative to plasma concentrations for at least 12 weeks. Relative to TCA IR, FX006 40 mg produced substantially lower peak plasma and systemic exposure to TCA. FX006 performed as expected, prolonging the residence of TCA in the joint while minimizing systemic exposure to TCA. Average BE analysis for plasma PK parameters for FX006 40 mg and TCA IR (Kenalog®-40) showed the systemic exposure to TCA when delivered by FX006 40 mg was less than that from the reference product (Kenalog®-40).

4.2 Individual Study Synopsis

4.2.1 Study FX006-2011-001

2. SYNOPSIS

Name of Company: Flexion Therapeutics Name of Finished Product: FX006 Name of Active Ingredient: Triamcinolone acetonide	(For National Authority Use only)
Title of Study: A Double-Blind, Randomized, Parallel Group, Dose-Ranging Study Comparing FX006 to Commercially Available Triamcinolone Acetonide Injectable Suspension in Patients with Osteoarthritis of the Knee	
Protocol Number: FX006-2011-001	
Investigators and Study Centers: This study was conducted at 22 study centers in the United States (US), Australia, and Canada. Investigators and study centers are indentified in Appendix 16.1.4 .	
Publication Reference: Bodick N, Lufkin J, Willwerth C, Lachance P, Jasey G, Gupta A, Chris A, et al. A randomized, double-blind, dose ranging study comparing FX006, an intra-articular (IA) sustained-release formulation of triamcinolone acetonide (TCA), to an approved injectable suspension of TCA in patients with osteoarthritis (OA) of the knee. Abstract 2668. ACR/ARHC Annual Meeting; October 26-30, 2013; San Diego, CA US. Bodick N, Lufkin J, Willwerth C, Kumar A, Bolognese J, Schoonmaker C, et al. Safety and efficacy of FX006 in patients with osteoarthritis of the knee. OARSI Annual Meeting; April 24-27, 2014; Paris, France.	
Study Period: 14 June 2012 to 25 April 2013	
Phase of Development: 2	
Objectives: The primary objectives of this study of patients with osteoarthritis (OA) of the knee treated with a single intra-articular (IA) injection of FX006 included: <ul style="list-style-type: none">• Assessment of the magnitude and duration of pain relief of three doses (10, 40, and 60 mg) of FX006, an extended release formulation of triamcinolone acetonide (TCA), relative to 40 mg of a commercially-available triamcinolone acetonide injectable suspension (TCA IR), and• Assessment of the general tolerability of a single injection of three doses (10, 40, and 60 mg) of FX006. Secondary Objective The secondary objectives of this study were to: <ul style="list-style-type: none">• Explore the effect of FX006 on functional improvement, responder status, time to onset of pain relief, global impressions of change, and consumption of analgesic medications, and• Support the development of the pharmacokinetic (PK) profile for single injection of three doses (10, 40, and 60 mg) of FX006.	

<p>Name of Company: Flexion Therapeutics</p> <p>Name of Finished Product: FX006</p> <p>Name of Active Ingredient: Triamcinolone acetonide</p>	<p>(For National Authority Use only)</p>
<p>Methodology:</p> <p>This study employed a multi-center, randomized, double-blind, active comparator, parallel-group, single dose design. The study was conducted in male and female patients ≥ 40 years of age with OA of the knee.</p> <p>Up to 224 patients with knee OA were planned to be randomized (1:1:1:1) to be treated with a single IA injection of either 10, 40, or 60 mg of FX006 or 40 mg of TCA IR.</p> <p>Each patient was evaluated for a total of 12 weeks following a single IA injection. Following Screening, safety and efficacy and pharmacokinetics (PK) were evaluated at 7 out-patient visits (Day 1 [Baseline], Day 2, and Weeks 1, 2, 4, 8, and 12).</p>	
<p>Number of Patients: A total of 224 patients were planned to be enrolled, with 56 patients in each of four treatment groups.</p>	
<p>Diagnosis and Criteria for Inclusion</p> <p><u>Inclusion Criteria:</u></p> <p>To be included in the study, patients must have fulfilled the following criteria:</p> <ol style="list-style-type: none"> 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. Diagnosis of unilateral or bilateral OA of the knee for at least 6 months prior to Screening with confirmation of OA according to American College of Rheumatology (ACR) Criteria for Classification of Idiopathic OA of the Knee (clinical and radiological), based on an X-ray performed within 6 months prior to Screening or during the Screening period. 5. Radiographic evidence of OA in the tibiofemoral compartment of the index knee (Kellgren-Lawrence grades II or III) within 6 months prior to Screening or during the Screening period. 6. Index knee pain on most days (>15) over the last month. 7. Mean score of ≥ 5 and ≤ 9 on the 24-hour average pain score (0-10 numeric rating scale [NRS]) using the average daily ratings for at least 5 of the 7 days prior to Day 1. 8. No more than one 24-hour average pain score (0-10 NRS) reported as "10" during the 7 days prior to Day 1. 9. If bilateral OA existed, pain in the contralateral knee was less than pain in the index knee, as reported by the patient. 10. Body mass index (BMI) ≤ 40 kg/m². 11. Ambulatory and in good general health. 12. Willingness to abstain from use of the restricted medications and nonpharmacological therapies defined in Section 9.4.8.3 during the study. 	

<p>Name of Company: Flexion Therapeutics</p> <p>Name of Finished Product: FX006</p> <p>Name of Active Ingredient: Triamcinolone acetonide</p>	<p>(For National Authority Use only)</p>
<p><u>Exclusion Criteria</u></p> <p>Patients fulfilling at least one of the following criteria could not be included in the study:</p> <p><i>Disease-related criteria</i></p> <ol style="list-style-type: none"> 1. Ipsilateral hip OA (based on clinical or previous radiological findings). 2. Fibromyalgia, chronic pain syndrome, or other concurrent medical or arthritic conditions that could have interfered with the evaluation of the index knee. 3. History of Reiter's syndrome, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease, sarcoidosis, or amyloidosis. 4. History of arthritides due to crystals (<i>e.g.</i>, gout, pseudogout). 5. History of infection in the index knee. 6. Clinical signs and symptoms of active knee infection or crystal disease of the index knee. 7. Presence of surgical hardware or other foreign body in the index knee 8. Knee pain that was not clinically attributable to OA of the knee (<i>e.g.</i>, radicular low back pain and hip pain that was referred to the knee that could have caused misclassification). 9. Pain in any other area of the lower extremities or back that was equal to or greater than the index knee pain. 10. Unstable joint (such as a torn anterior cruciate ligament). <p><i>Previous or concomitant OA treatment-related criteria.</i></p> <ol style="list-style-type: none"> 11. IA corticosteroid (investigational or marketed) in any joint within 3 months of Screening. 12. IA hyaluronic acid (investigational or marketed) in the index knee within 6 months of Screening. 13. Oral, inhaled, or intranasal corticosteroids (investigational or marketed) within 1 month of Screening. 14. Any other IA investigational drug/biologic within 6 months of Screening or any prior use of an IA investigational PLGA-containing drug/biologic. 15. Prior arthroscopic or open surgery of the index knee within 12 months of Screening. 16. Planned/anticipated surgery of the index knee during the study period. <p><i>Patient-related criteria</i></p> <ol style="list-style-type: none"> 17. Known hypersensitivity to any form of triamcinolone. 18. Known hypersensitivity to ethyl chloride. 19. 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 resected cervical atypia or carcinoma <i>in situ</i>. 20. Known active or quiescent tuberculosis (TB) infection of the respiratory tract; untreated systemic fungal, bacterial, viral or parasitic infections, or ocular herpes simplex. <p>Canada only: history of positive TB test or positive screening tuberculin skin test (TST).</p>	

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<p>defined as 5+ induration.</p> <ol style="list-style-type: none"> 21. History of any infection requiring intravenous antibiotics within 4 weeks of Screening, history of infection requiring oral antibiotics within 2 weeks of Screening, history of chronic infection, or a history of osteomyelitis. 22. Known or clinically suspected infection with human immunodeficiency virus (HIV) or hepatitis B or C viruses. 23. Screening or Baseline 12-lead electrocardiogram (ECG) demonstrating QTc >450 msec in male patients or >470 msec in female patients or any clinically significant ECG abnormality, as judged by the Principal Investigator. 24. Insulin-dependent diabetes. 25. Active psychiatric disorder including psychosis and major depressive disorder. 26. History of or active Cushing's syndrome. 27. Any other clinically significant acute or chronic medical conditions (e.g., uncontrolled diabetes) that, in the judgment of the Investigator, would have precluded the use of an IA corticosteroid or that could have compromised patient safety, limited the patient's ability to complete the study, and/or compromised the objectives of the study. 28. Positive drug or alcohol screen. 29. Skin breakdown at the knee where the injection would have taken place. 30. Women who were pregnant or nursing. 31. 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 (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]). 32. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents within 5 years of Screening. 33. Received a live or live attenuated vaccine within 6 months of Screening. 34. Use of any other investigational drug or device within 30 days of Screening or an investigational biologic within 60 days of Screening. 	
<p>Test Product, Dose and Mode of Administration, Batch Number: FX006 – extended release formulation of TCA in 75:25 poly(lactic-co-glycolic) acid (PLGA) microspheres. Nominal 10, 40, and 60 mg TCA, IA, administered as a 3 mL injection. Batch number: 10 mg FX006: 12-083-001-10; 40 mg FX006: 12-083-001-40; 60 mg FX006: 12-083-001-60</p>	
<p>Reference Therapy, Dose and Mode of Administration, Batch Number: Commercially-available TCA IR injectable suspension, 40 mg/mL, IA, administered as a 1 mL injection. In the US and Canada, the TCA IR suspension (Kenalog[®]) used was manufactured by Bristol-Meyers</p>	

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Squibb supplied as a 1 mL vial, 40 mg/mL, NDC number 0003-0293-05. Batch number: Bristol-Meyers Squibb 1G68770 In Australia, the TCA IR suspension (Kenacort [®]) used was manufactured by Sigma Pharmaceuticals (Australia) Pty Ltd, supplied as a 1 mL ampule, 40 mg/mL, Australian registration number AUST R 49226. Batch number: Sigma Pharmaceuticals 1J65724	
Duration of Treatment: All patients received a single IA injection of study treatment at Baseline (Day 1).	
Criteria for Evaluation: <i>Efficacy</i> <ul style="list-style-type: none">• Weekly mean of the average daily (24-hour) pain intensity score• Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Likert 3.1, 5-point scale)• Patient Global Impression of Change (PGIC)• Clinical Global Impression of Change (CGIC)• Consumption of analgesic medication <i>Safety</i> <ul style="list-style-type: none">• Adverse events• Physical examinations• Index knee examinations• Vital signs• ECGs• Clinical laboratory evaluations <i>Bioanalytical and Pharmacokinetic</i> <ul style="list-style-type: none">• Drug concentration measurements	
Statistical Methods: Statistical analyses were performed using SAS for Windows. Descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum) were calculated by treatment group for continuous variables. Frequencies and percentages were presented by treatment group for categorical and ordinal variables. All study data were presented in by-patient data listings. Safety analyses were performed on the Safety Population. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Incidences (number and percent) of treatment-emergent adverse events (TEAEs), <i>i.e.</i> , those events that started after dosing or worsened in severity after dosing, were presented by treatment group. Incidences of TEAEs also were presented by maximum severity and relationship to study treatment.	

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<p>Laboratory data were summarized by treatment group as summary statistics for value and change from Baseline at each individual time point. Summary statistics included n, mean, median, standard deviation (SD), minimum, and maximum.</p> <p>The primary endpoint was analyzed with a longitudinal mixed effects model with fixed effects for treatment group, study week, treatment-by-week interaction, and Baseline covariate. Patient was the random effect. Treatment differences from control were estimated via least squares-means from the analysis model along with 95% confidence intervals, and associated 1-sided p-values were reported. Multiplicity of dose comparisons to the active comparator was addressed via a step-down procedure at each time point. Multiplicity of time points within each dose comparison to the active comparator was addressed by a sensitivity analysis via Hochberg-adjusted p-values, but not as part of the primary analysis. Secondary endpoints were assessed in a fashion similar to the primary endpoint, except the Hochberg-adjusted p-values were used only for the primary endpoint.</p>	
<p>Disposition and Demographics:</p> <p>A total of 229 patients were enrolled (<i>i.e.</i>, randomized) in this study (58 FX006 10 mg, 59 FX006 40 mg, 60 FX006 60 mg, and 52 TCA IR group). A total of 228 of 229 enrolled patients received their randomized treatment and thus were included in the Safety Population; 1 patient randomized to the TCA IR group withdrew consent to participate prior to the receipt of study treatment and thus was excluded.</p> <p>Treatment arms were well balanced with respect to demographic and baseline characteristics. The 228 treated patients included 108 (47%) males and 120 (53%) females. The majority of patients (n=206, 90%) were white/Caucasian. The mean age at randomization was 62 years (range 40 to 86 years), and mean body mass index was 30.5 kg/m² (range 19.8 to 39.9 kg/m²).</p> <p>All patients had a diagnosis of OA confirmed per ACR criteria. The median time since primary diagnosis was 3.9 years, with a maximum of 45 years. The majority of patients presented to the study with bilateral knee OA (n=139, 61.0%) and with a Kellgren-Lawrence grade of 3 (n=146, 64%) versus a grade of 2 (n=82, 36%). The mean number of days with knee pain in the month prior to Screening was 28.4 days (range 16 to 31 days). Thirty-one percent (n=71, 31%) of the patients had prior OA-related knee surgeries or procedures of the index knee. Thirty-two percent (n=74, 32%) of the patients had a prior IA steroid injection of the index knee, with a mean number of prior injections of 0.7. Eleven percent (n=26, 11%) of patients had a prior IA HA injection of the index knee, with a mean number of prior injections of 0.2. None of these IA steroid or HA injections were within the 3 or 6 months prior to study treatment, respectively. The weekly mean of average daily pain intensity scores at Baseline ranged from 6.4 to 6.6 across the 4 groups.</p>	

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Efficacy Results:

The between-group differences in the weekly mean of the average daily pain score over time are summarized in the following table:

Between-group Difference in Weekly Mean of the Average Daily Pain Score, All Weekly Time Points (FAS; N=228)

Time point [^]		FX006 10 mg (n=58)	FX006 40 mg (n=59)	FX006 60 mg (n=60)
Week 1	LSMD vs. TCA IR p-value*	0.4 0.8903	0.1 0.6466	0.1 0.5919
Week 2	LSMD vs. TCA IR p-value	-0.1 0.4257	-0.4 0.1742	-0.3 0.2103
Week 3	LSMD vs. TCA IR p-value	-0.1 0.3721	-0.5 0.0897	-0.7 0.0412
Week 4	LSMD vs. TCA IR p-value	-0.0 0.4651	-0.6 0.0767	-0.5 0.1077
Week 5	LSMD vs. TCA IR p-value	-0.4 0.1816	-0.8 0.0254	-0.6 0.0618
Week 6	LSMD vs. TCA IR p-value	-0.6 0.0734	-0.9 0.0110	-0.8 0.0260
Week 7	LSMD vs. TCA IR p-value	-0.6 0.0655	-1.1 0.0031	-0.6 0.0657
Week 8	LSMD vs. TCA IR p-value	-0.5 0.0962	-0.9 0.0123	-0.5 0.1249
Week 9	LSMD vs. TCA IR p-value	-0.5 0.1191	-0.9 0.0243	-0.4 0.1860
Week 10	LSMD vs. TCA IR p-value	-0.5 0.1168	-0.9 0.0228	-0.4 0.2002
Week 11	LSMD vs. TCA IR p-value	-0.3 0.2245	-0.5 0.1066	0.1 0.6206
Week 12	LSMD vs. TCA IR p-value	-0.3 0.2657	-0.4 0.2128	0.1 0.5541

LSMD= least squares mean difference; [^]Weeks 8, 10 and 12 were included in the primary endpoint

*p-values are 1-sided and do not take in account multiplicity

Source: Table 14.2.1.1A

There was an apparent dose response in pain relief (as assessed by the change from Baseline in the weekly mean of the average daily pain intensity scores [0-10 NRS]) between 10 and 40 mg FX006. The 40 mg dose of FX006 produced a statistically significant (p<0.05, 1-sided) and potentially clinically meaningful improvement in pain relief relative to TCA IR between Weeks 5 and 10. The 10 mg dose of FX006 produced effects on pain that were consistently improved but not statistically significant relative to TCA IR at Weeks 8, 10 and 12 and of lesser magnitude than those produced by the 40 mg dose. The 60 mg dose did not provide additional benefit relative to the 40 mg dose of FX006.

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A summary of secondary endpoints is presented in the following table:				
Summary of Secondary Efficacy Endpoints at Week 8 Comparing FX006 vs. TCA IR				
Parameter / Statistic	FX006 10 mg (n=58)	FX006 40 mg (n=59)	FX006 60 mg (n=60)	TCA IR 40 mg (n=51)
WOMAC A (pain)				
LSM change from BSL (SE)	-1.23 (0.099)	-1.33 (0.098)	-1.16 (0.097)	-0.96 (0.108)
LSMD vs. TCA IR	-0.27	-0.37	-0.20	
90% CI	-0.51, -0.03	-0.61, -0.13	-0.44, 0.04	
1 sided p-value	0.0327	0.0058	0.0836	
WOMAC A1 (pain on walking)				
LSM change from BSL (SE)	-1.2 (0.12)	-1.2 (0.12)	-1.1 (0.11)	-0.8 (0.13)
LSMD vs. TCA IR	-0.3	-0.4	-0.2	
90% CI	-0.6, -0.1	-0.7, -0.1	-0.5, 0.1	
1 sided p-value	0.0245	0.0098	0.0928	
WOMAC B (stiffness)				
LSM change from BSL (SE)	-1.37 (0.113)	-1.49 (0.112)	-1.24 (0.111)	-0.99 (0.124)
LSMD vs. TCA IR	-0.38	-0.49	-0.24	
90% CI	-0.65, -0.10	-0.77, -0.22	-0.52, 0.03	
1 sided p-value	0.0126	0.0018	0.0737	
WOMAC C (function)				
LSM change from BSL (SE)	-1.22 (0.096)	-1.31 (0.096)	-1.13 (0.095)	-0.94 (0.106)
LSMD vs. TCA IR	-0.28	-0.37	-0.19	
90% CI	-0.52, -0.04	-0.61, -0.14	-0.42, 0.05	
1 sided p-value	0.0259	0.0049	0.0936	
OMERACT-OARSI Responders				
n (%)	52 (91.2%)	53 (89.8%)	47 (79.7%)	32 (69.6%)
2 sided p-value	0.0076	0.0118	0.2368	
OR (90 % CI)	4.5 (1.8, 11.6)	3.9 (1.6, 9.3)	1.7 (0.8, 3.6)	
Responder >50% Improvement				
n (%)	35 (63.6%)	40 (72.7%)	34 (60.7%)	23 (53.5%)
2 sided p-value	0.3114	0.0507	0.4713	
OR (90 % CI)	1.5 (0.8, 3.0)	2.3 (1.1, 4.7)	1.3 (0.7, 2.6)	
Responder >30% Improvement				
n (%)	42 (76.4%)	47 (85.5%)	45 (80.4%)	27 (62.8%)
2 sided p-value	0.1467	0.0119	0.0548	
OR (90 % CI)	1.9 (0.9, 4.0)	3.5 (1.5, 7.9)	2.4 (1.1, 5.2)	
Responder >20% Improvement				
n (%)	47 (85.5%)	49 (89.1%)	48 (85.7%)	30 (69.8%)
2 sided p-value	0.0650	0.0205	0.0590	
OR (90 % CI)	2.5 (1.1, 5.9)	3.5 (1.4, 8.7)	2.6 (1.1, 6.0)	
PGIC				
LSM change from BSL (SE)	1.9 (0.16)	1.8 (0.16)	2.4 (0.16)	2.5 (0.17)
LSMD vs. TCA IR	-0.6	-0.7	-0.1	
90% CI	-1.0, -0.2	-1.1, -0.3	-0.5, 0.3	
1 sided p-value	0.0058	0.0013	0.3354	
CGIC				
LSM change from BSL (SE)	1.9 (0.16)	1.8 (0.16)	2.5 (0.16)	2.6 (0.17)
LSMD vs. TCA IR	-0.6	-0.7	-0.1	
90% CI	-1.0, -0.2	-1.1, -0.3	-0.5, 0.3	
1 sided p-value	0.0049	0.0013	0.3233	

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Parameter / Statistic	FX006 10 mg (n=58)	FX006 40 mg (n=59)	FX006 60 mg (n=60)	TCA IR 40 mg (n=51)
Rescue Medication Consumption				
LSM change from BSL (SE)	1.0 (0.22)	1.0 (0.22)	1.1 (0.22)	1.2 (0.24)
LSMD vs. TCA IR	-0.2	-0.3	-0.1	
90% CI	-0.7, 0.3	-0.8, 0.3	-0.7, 0.4	
1 sided p-value	0.2620	0.2039	0.3226	

BSL=baseline; CI=Confidence interval; LSM=least-squares mean; LSMD=least-squares mean difference; OR=Odds ratio; SE=standard error

Sources: [Table 14.2.4.1a](#), [Table 14.2.5](#), [Table 14.2.4B](#), [Table 14.2.4.1C](#), [Table 14.2.6](#), [Table 14.2.2](#), [Table 14.2.8](#), [Table 14.2.9](#), and [Table 14.2.10A](#)

Consistent with the analysis of the primary outcome measure, the 40 mg dose also demonstrated significant improvement over TCA IR ($p < 0.05$, 1-sided) at Week 8 in secondary outcomes that assessed pain, stiffness, function, patient and clinical global impressions of change and responder status. The 10 mg dose of FX006 also showed statistically significant improvement compared with TCA IR in the key secondary outcomes at Week 8, although the between-group differences or odds ratios were smaller than those observed between 40 mg FX006 and TCA IR. As observed with the primary outcome measure, the performance of the 60 mg dose in the secondary outcome measures did not represent an improvement relative to the 40 mg dose in these assessments.

The median time to onset of pain relief (defined as the time from first dose to the first daily pain assessment showing $>30\%$ improvement from the weekly mean of the average daily pain intensity scores at Baseline) was similar across all treatments, occurring 1 to 2 days following injection.

Pharmacokinetic Results:

PK analysis were performed on the PK Population, defined as all patients who received study treatment and provided sufficient PK data (as defined in the Statistical Analysis Plan): all 228 patients in the FAS were included.

Analysis of plasma TCA levels showed that the FX006 formulation demonstrated a slower release of TCA into the systemic circulation compared to TCA IR, resulting in substantially lower peak concentrations of TCA with IA injection of FX006 as compared to TCA IR at matched doses (40 mg) and prolonged retention of TCA at the site of injection. The variability of TCA concentration in plasma was high ($\geq 60.0\%$) throughout the study without an obvious trend across treatment groups.

For FX006 at doses of 10, 40, and 60 mg, mean AUC_{0-inf} and AUC_{0-t} values for TCA ranged from 182390 to 856411 $pg \cdot h/mL$ and from 74832 to 640987 $pg \cdot h/mL$, respectively, and mean C_{max} values ranged from 264 to 2218 pg/mL , with the highest value at the FX006 40 mg dose level. In this treatment group, one patient had a C_{max} value of 80876 pg/mL which was high when compared to the mean C_{max} of the same treatment group (2218 pg/mL).

Median t_{max} values were longer in the FX006 treated groups (21.67 – 23.27 h post dose) compared to TCA IR (2.02 h post dose). Mean C_{max} for FX006 40 mg was approximately 10-fold lower than mean TCA IR C_{max} , resulting in a peak in concentration for TCA IR 40 mg at approximately 2 hours post-dose while FX006 40 mg displayed a plateau phase concentration from 22 hours post-dose to Day 85. This supports the difference in release rates ([Gabrielsson and Weiner, 2006](#)) and the retention of TCA at the site of injection for FX006, where the FX006 microspheres provided a slower release of the drug in the systemic circulation which in turn resulted in an apparent plateau of concentrations.

The systemic elimination half-life of TCA after intravenous administration (2 mg) is reported to be 2.0 h ([Derendorf et al., 1995](#)), and the lowest half-life value measured in this study was 35.1 h. It is clear that

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<p>for most subjects, the terminal $t_{1/2}$ was controlled by absorption into the systemic circulation from the site of injection once released from its respective formulation (“flip-flop kinetics”). This is consistent with the overlap between $t_{1/2}$ observed between patients administered FX006 and patients administered TCA IR.</p> <p>Mean CL values were similar at the 10 and 60 mg dose levels with values of 91112 and 89278 mL/h, respectively, while a slightly higher value was observed at the 40 mg dose level (117449 mL/h). Despite a higher mean CL value at the 40 mg dose level, exposure (AUC and C_{max}) to FX006 increased with dose in a relatively dose proportional manner.</p> <p>Mean CL/F of TCA IR 40 mg (38304 mL/h) was lower than that observed for the FX006 40 mg (117449 mL/h). The difference between the CL/F of the TCA IR and FX006 may be attributed to a lower bioavailability (relative availability was ~45% between the 2 formulations). Lower bioavailability for FX006 would support the lower systemic exposure to TCA, and therefore a greater retention of the drug at the site of injection. This would be consistent with the controlled release nature of FX006.</p>	
<p>Safety Results:</p> <p>A total of 54% (122 of 228) of patients experienced at least 1 TEAE during the study. Review of the incidence of TEAEs across treatment groups showed that the incidence was 47%, 56%, 57%, and 55% in the 10 mg, 40 mg, 60 mg FX006 groups and TCA IR group, respectively. Overall, among the 177 FX006-treated patients, the most frequently reported TEAEs were arthralgia (10%); upper respiratory infection (URI) and headache (each 5%); and blood glucose increased (3%). An increased incidence of arthralgia was noted at the 40 mg FX006 dose (1.6- to 3.5-fold higher) relative to other FX006 doses and TCA IR group. However, if relatedness to study drug as judged by the investigator is taken into account, the frequency of arthralgia was relatively similar (3 to 5%) across all treatment groups. With the exception of arthralgia, no dose relationship was apparent with regard to the other most frequently reported TEAEs. All other TEAEs were reported for ≤ 2 FX006-treated patients.</p> <p>For the majority of patients who experienced at least 1 TEAE, all TEAEs were assessed by the Investigator as unrelated to study drug. Overall, 12% (28 of 228) of patients experienced a study drug-related TEAE, including 12% (7 of 58), 8% (5 of 59), 12% (7 of 60), and 18% (9 of 51) of patients in the 10 mg, 40 mg, and 60 mg FX006 groups and TCA IR group, respectively. Among the 177 FX006-treated patients, the only study drug-related TEAEs reported for >2 patients were arthralgia (5%) and joint stiffness (2%).</p> <p>No patient deaths were reported. Three patients, 2 (3%) of 59 in the 40 mg FX006 group and 1 (2%) of 60 in the 60 mg FX006 group experienced an SAE. SAEs reported included mild coronary artery stenosis requiring cardiac catheterization (Patient 30006; 40 mg FX006); mild cerebrovascular accident requiring hospitalization (Patient 30022; 40 mg FX006); and moderate subcutaneous abscess requiring hospitalization (Patient 52017; 60 mg FX006). None of these events involved the index knee or were considered by the Investigator to be related to the study drug administration procedure or to study drug.</p> <p>Most TEAEs were assessed by the Investigator as mild or moderate in intensity. Three patients, 2% (1 of 58) in the FX006 10 mg group and 4% (2 of 51) in the TCA IR group, experienced a severe TEAE. Severe TEAEs included cholecystitis (Patient 54004; 10 mg FX006); worsening of OA in the index knee (Patient 31054; TCA IR); and synovial rupture (Patient 53001; TCA IR). None of these events were considered by the Investigator to be related to the study drug administration procedure or to study drug.</p> <p>One patient in the 10 mg FX006 group (Patient 12004) discontinued from the study because of a TEAE, moderate arthralgia in the index knee, which was considered by the Investigator to be unrelated to the study drug administration procedure and to study drug. This event was ongoing at last follow-up.</p>	

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<p>Thirty-two (14%) of 228 patients experienced at least 1 index knee-related TEAE, with all such event being non-serious and all but one being mild or moderate in intensity. (As described previously, Patient 31054 in the TCA IR group experienced severe worsening of OA in the index knee.) The only index knee-related TEAEs reported for >2 of the 177 FX006-treated patients were arthralgia (8%) and joint stiffness (2%). For 8% (18 of 228) of patients, 9% (5 of 58) in the 10 mg FX006 group, 7% (4 of 59) in the 40 mg FX006 group, 7% (4 of 60) in the 60 mg FX006 group, and 10% (5 of 51) in the TCA IR group, at least 1 index knee-related TEAE was considered by the Investigator to be study drug-related.</p> <p>Analyses of changes from Baseline for hematology and chemistry parameters did not reveal any remarkable trends, with the exception of transient increases in white blood cell count and absolute neutrophil count after study treatment. In general, mean and median changes from Baseline were small and similar across groups. Laboratory changes reported as TEAEs occurred in all groups; none of these changes were reported in any group at an incidence of >5%.</p> <p>There were no clinically significant changes in vital signs or ECG parameters observed following administration of the study drug in any cohort and changes were similar between FX006 and TCA IR groups.</p>	
<p>Summary – Conclusions:</p> <p>The preliminary efficacy of IA injection of FX006 was demonstrated in this study, as evidenced primarily by a reduction in weekly means of average daily pain intensity scores and supported by secondary outcomes that assessed pain, stiffness, function, patient, and clinical global impressions of change, and responder status. The apparent clinically meaningful prolongation and amplification of pain relief demonstrated in the current study coupled with a favorable safety profile provide strong rationale for further clinical study of FX006 to confirm these findings.</p>	
<p>Date of Report: 29 January 2016</p>	

4.2.2 Study FX006-2011-002

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2. SYNOPSIS

Name of Company: Flexion Therapeutics Name of Finished Product: FX006 Name of Active Ingredient: Triamcinolone acetonide	<i>(For National Authority Use only)</i>		
Title of Study: A Double-Blind, Randomized, Parallel Group, Active Comparator Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamic Effects (HPA Axis) of FX006 in Patients with Osteoarthritis of the Knee			
Protocol Number: FX006-2011-002			
Investigators and Study Centers: <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> Dr. Anita Lee Cmax Level 5, East Wing Royal Adelaide Hospital North Terrace Adelaide SA 5000 Australia </td> <td style="width: 50%; vertical-align: top;"> Prof. Charles Inderjeeth Linear Clinical Research Ltd. 1st Floor, B Block, Hospital Avenue Nedlands WA 6009 Australia </td> </tr> </table>		Dr. Anita Lee Cmax Level 5, East Wing Royal Adelaide Hospital North Terrace Adelaide SA 5000 Australia	Prof. Charles Inderjeeth Linear Clinical Research Ltd. 1 st Floor, B Block, Hospital Avenue Nedlands WA 6009 Australia
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Publication Reference: NA			
Study Period: July 10, 2012 – October 17, 2012			
Phase of Development: 2			
Objectives: The primary objectives of this study were, for 3 doses of FX006 delivered as a single intra-articular injection (IA) in patients with osteoarthritis (OA) of the knee, to: <ul style="list-style-type: none"> • Assess safety and tolerability of FX006 • Characterize the systemic pharmacokinetics (PK) of triamcinolone acetonide (TCA) from FX006 relative to 40 mg of triamcinolone acetonide immediate release (TCA IR) • Characterize the effects on the hypothalamic-pituitary-adrenal (HPA) axis of FX006 relative to 40 mg of commercially available TCA IR This study was also designed to begin evaluating the local pharmacokinetics of FX006 on an exploratory basis only.			
Methodology: This study was a double-blind, randomized, parallel-group, active comparator design. The study was conducted in male and female patients ≥35 years of age with symptomatic osteoarthritis of the knee. Twenty-four (24) patients with knee OA were randomized (1:1:1:1) and treated with a single IA injection of 10, 40, or 60 mg of FX006 or 40 mg of TCA IR. TCA IR is commonly used to treat pain and inflammation associated with OA of the knee and contains the same active pharmaceutical ingredient as FX006. TCA IR also served as and was an appropriate active control for this study. When administered intra-articularly, 40 mg of TCA IR produces a substantial adrenal effect in the first few days following administration (70-80% reduction in serum cortisol) and therefore is able to establish assay sensitivity and allow for comparison with the effect of FX006 on the HPA axis. Each patient was evaluated for a total of 6 weeks following a single IA injection. Following screening, safety, PK and pharmacodynamics (PD) were evaluated during one (1) 48-hour in-patient period			

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<p>(Day -1 to Day 2), two (2) 24-hour in-patient periods (Day 14-15 and Day 42-43) and seven (7) out-patient visits (Days 3, 4, 5, 8, 22, 29 and 36).</p>	
<p>Number of Subjects: Planned: Twenty-four patients were planned to be randomized in this study (6 patients per treatment group). Analyzed: Twenty-four patients were randomized in this study (n=5, FX006 10 mg; n=7, FX006 40 mg; n=7, FX006 60 mg; n=5, TCA IR 40 mg).</p>	
<p>Diagnosis and Criteria for Inclusion Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. 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 ≥ 35 years of age 4. Diagnosis of unilateral or bilateral OA of the knee for at least 6 months prior to Screening with confirmation of OA according to American College of Rheumatology (ACR) Criteria for Classification of Idiopathic OA of the Knee (clinical and radiological) based on an X-ray performed within 6 months prior to Screening or during the Screening period 5. Index knee pain on most days (>15) over the last month 6. Body mass index (BMI) ≤ 40 kg/m² 7. Morning serum cortisol result within normal range at Screening 8. Ambulatory and in good general health 9. Willingness to abstain from use of the following during the study: <ul style="list-style-type: none"> • Oral, inhaled or intranasal corticosteroids • IA corticosteroids in any joint • IA viscosupplementation (hyaluronic acid) in the index knee <p>Exclusion criteria: <i>Disease-related criteria</i></p> <ol style="list-style-type: none"> 1. History of Reiter's syndrome, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease, sarcoidosis or amyloidosis 2. History of arthritides due to crystals (<i>e.g.</i>, gout, pseudogout) 3. History of infection in the index joint 4. Clinical signs and symptoms of active knee infection or crystal disease of the index knee 5. Presence of surgical hardware or other foreign body in the index knee 6. Unstable joint (such as a torn anterior cruciate ligament) <p><i>Previous or concomitant treatment-related criteria</i></p> <ol style="list-style-type: none"> 7. IA corticosteroid (investigational or marketed) in any joint within 3 months of Screening 8. IA hyaluronic acid (investigational or marketed) in the index knee within 6 months of Screening 9. Oral, inhaled and intranasal corticosteroids (investigational or marketed) within 1 month of Screening 10. Any other IA investigational drug/biologic within 6 months of Screening 11. Prior arthroscopic or open surgery of the index knee within 12 months of Screening 12. Planned/anticipated surgery of the index knee during the study period 	

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<p>Patient-related criteria</p> <ol style="list-style-type: none"> 13. Known hypersensitivity to any form of triamcinolone 14. Known hypersensitivity to ethyl chloride 15. History of or active malignancy, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or resected cervical atypia or carcinoma in situ within 5 years 16. Known active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, viral or parasitic infections, or ocular herpes simplex 17. History of any infection requiring intravenous antibiotics within 4 weeks of Screening, history of infection requiring oral antibiotics within 2 weeks of Screening, history of chronic infection, or a history of osteomyelitis 18. Known or clinically suspected infection with human immunodeficiency virus (HIV), hepatitis B or C viruses 19. Screening or Baseline 12-lead electrocardiogram (ECG) demonstrating QTc >450 msec in male patients and >470 msec in female patients or any clinically significant ECG abnormality as judged by the Principal Investigator 20. Insulin-dependent diabetes 21. History of or active Cushing's syndrome 22. Any other clinically significant acute or chronic medical conditions (<i>e.g.</i>, uncontrolled diabetes) 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 23. Positive drug or alcohol screen. NOTE: a drug screen positive for opioids for patient's admittedly taking prescription opioids for pain was allowed 24. Skin breakdown at the knee where the injection would take place 25. Women who are pregnant or nursing 26. 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 (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]) 27. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents within 5 years of Screening 28. Has received a live or live attenuated vaccine within 6 months of Screening 29. Use of any other investigational drug or device within 30 days of Screening or an investigational biologic within 60 days of Screening 	
<p>Test Product, Dose and Mode of Administration, Batch Number: FX006 – extended release formulation of TCA in 75:25 poly(lactic-co-glycolic) acid (PLGA) microspheres Nominal 10, 40 and 60 mg TCA, IA injection, administered as a 3 mL injection Batch number: 10 mg FX006 product lot 12-083-001-10 40 mg FX006 product lot 12-083-001-40 60 mg FX006 product lot 12-083-001-60</p>	
<p>Reference Therapy, Dose and Mode of Administration, Batch Number: Commercially available triamcinolone acetonide injectable suspension, 40 mg/mL, IA, administered as a 1 mL injection</p>	

Name of Company: Flexion Therapeutics Name of Finished Product: FX006 Name of Active Ingredient: Triamcinolone acetonide	<i>(For National Authority Use only)</i>
Batch number: Kenacort (Sigma Pharmaceuticals), Lot 1J65724	
Duration of Treatment: Eligible patients received a single, intra-articular injection.	
Criteria for Evaluation: <i>Pharmacodynamic</i> <ul style="list-style-type: none"> • Serum cortisol measurements • 24-hour urinary free cortisol excretion, 6-beta-hydroxycortisol and creatinine measurements <i>Safety</i> <ul style="list-style-type: none"> • Adverse events • Physical examinations • Index knee examinations • Vital signs • ECGs • Clinical laboratory evaluations <i>Bioanalytical and Pharmacokinetic</i> <ul style="list-style-type: none"> • Drug concentration measurements • Maximum observed concentration (C_{max}) • Time at which the maximum observed concentration occurs (t_{max}) • Terminal half-life ($t_{1/2}$) estimated from the slope of the terminal phase (λ_z): $t_{1/2} = \ln(2) / \lambda_z$ • Total exposure (AUC from time of dose to last measurable concentration: AUC_{0-t}, AUC from time of dose to 24 hours: AUC_{0-24}, and AUC from time of dose extrapolated to infinity: AUC_{0-inf}) • Total body clearance (CL/F; Dose/AUC) • Mean residence time (MRT_{inf}: $AUMC_{0-inf} / AUC_{0-inf}$, where AUMC is the area under the moment curve) • Apparent volume of distribution (V_z/F: $Dose / (\lambda_z * AUC_{0-inf})$) 	
Statistical Methods: <p>All statistical analyses were performed using SAS® Software, Version 9.1 or later. Descriptive summaries were provided by treatment cohort. All statistical tests in this study were one-sided and performed at 5% significance level.</p> <p>Continuous endpoint summaries included the number of patients (n) with non-missing values, mean, geometric mean, standard deviation (SD), log-scale SD, median, minimum, and maximum.</p> <p>Categorical endpoint summaries included the frequency and percentage of patients in each category. In general, the denominator for the percentage calculation was based upon the total number of patients in the study population for each treatment, unless otherwise specified.</p> <p>Baseline characteristics and safety tables were presented for the safety population unless otherwise specified. PD tables were presented for the Full Analysis Set (FAS); primary hypothesis tables were also to be presented for the Per Protocol (PP) population. PK tables were presented for the PK population.</p> <p>The primary endpoint, mean change from baseline at Hour 24 in the natural log of 24-hour weighted mean serum cortisol, was analyzed using an analysis of covariance (ANCOVA) model with factors for treatment (10, 40, and 60 mg FX006; 40 mg TCA IR) and the baseline value as a covariate. The response variable for analysis was the natural log of the ratio of the on treatment response to the baseline response. Least squares means (LSM) from the analysis model were back transformed to yield the</p>	

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<p>geometric mean percentage change from baseline within each treatment group and geometric mean ratio of TCA IR to each FX006 dose. Secondary analyses of change from baseline to Week 6 and Week 2 in the natural log of the 24-hour weighted serum cortisol were similarly performed.</p> <p>The PK parameter calculations were generated by using Phoenix WinNonlin (WNL) 6.3 software (Pharsight, Cary, NC). Actual sampling times were used for the estimation of the PK parameters, but mean table summaries and mean figures used scheduled sampling times. PK parameters were summarized by dose. Summary statistics included N, arithmetic mean, mean, SD, median, minimum, maximum, geometric mean, and SD of the natural logs of the observations. (Only N, median, minimum, and maximum were calculated for t_{max}.) No statistical testing of PK parameters was performed.</p> <p>All safety and tolerability endpoints were presented by using the safety population and included adverse events (AEs), clinical laboratory assessments, vital sign measurements, ECG findings, concomitant medication use, physical examination findings, and index knee assessments.</p>	
<p>Disposition and Demographics:</p> <p>Of the 24 patients enrolled, 23 (95.8%) completed the study and 1 (4.2%) (in the 40 mg FX006 group) prematurely discontinued (patient withdrew consent).</p> <p>Overall, 8 (33.3%) patients were male and 16 (66.7%) were female. The majority of patients were Caucasian/white (n=22, 91.7%). The mean (SD) age was 62.5 (10.64) years. All patients had a diagnosis of OA confirmed per ACR criteria, with a mean (SD) number of years from diagnosis of knee OA to Screening of 5.87 (4.718). More patients presented to the study with unilateral (n = 13, 54.2%) versus bilateral (n = 11, 45.8%) knee OA, and nearly 80% of the patients presented with a Kellgren-Lawrence grade of 2 or 3. The mean (SD) number of days patients experienced knee pain in the month prior to Screening was 27.9 (4.2), with a range of 20-31 days.</p>	
<p>Pharmacodynamic Results:</p> <p>The primary and secondary analyses (ANCOVA model) of the primary endpoint, change from Baseline in the 24-hour weighted mean serum cortisol, suggest that a single IA injection of FX006 results in a pattern of cortisol suppression that is dose- and time-dependent. Superiority at Day 1-2 post treatment was achieved for the 10 mg FX006 dose and non-inferiority was concluded for that dose at Weeks 6 and 2. Superiority at 24 hours post-treatment was not achieved for the 40 and 60 mg FX006 dose; therefore, non-inferiority could not be concluded at Weeks 6 and 2. The least square mean difference (LSMD) of 10 mg FX006 and TCA IR with respect to change in weighted mean serum cortisol from Baseline to Day 1-2 was statistically significant (p=0.0078; 90% CI: 40.4%, 260.9%). When comparing 40 mg and 60 mg FX006 to TCA IR for the same endpoint, statistical significance was not achieved; however, 40 mg FX006 resulted in less cortisol suppression (-42.7%; 90% CI: -59.2%, -19.4%) than TCA IR by Day 1-2 while suppression resulting from 60 mg FX006 (-62.2%; 90% CI: -73.2%, -46.8%) was similar to that observed with TCA IR.</p> <p>The results from analyses of the change from Baseline in 24-hour urinary free cortisol excretion and in morning serum cortisol were similar in terms of FX006 dose- and time-dependency to those of the primary endpoint (change from Baseline in weighted mean serum cortisol).</p> <p>To facilitate the comparison of cortisol suppression from IA administration of FX006 observed in this study with that from published clinical studies of single and multiple dose corticosteroids administered by oral, intravenous and inhaled routes, an exploratory analysis of cumulative cortisol suppression (CCS) was performed, with findings showing that the median CCS% values for FX006 and TCA IR were consistent with the analysis of weighted mean serum cortisol.</p>	
<p>Pharmacokinetic Results:</p> <p>Results of analyses of plasma drug concentrations showed that exposure (C_{max} and AUC) to FX006 increased in a proportional manner with dose.</p> <p>FX006 displayed a much wider range of t_{max} when compared to TCA IR, suggesting that FX006 microspheres slowed the release of TCA in the systemic circulation thereby creating a "plateau" of concentrations. FX006 resulted in a lower fluctuation between peak and trough concentrations of TCA</p>	

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<p>as compared to TCA IR, suggesting that IA administration of FX006 resulted in a more controlled and stable release of TCA from the site of injection.</p> <p>Administration of 40 mg FX006 resulted in approximately 2000x more TCA in the joint when compared to TCA IR on Day 43 (82673 pg/mL vs 38.6 pg/mL [geometric means calculated by Sponsor: 78757 pg/mL vs 42 pg/mL]). The TCA synovial fluid/plasma partition coefficient estimated on Day 43 were 426 and 290 and for FX006 40 mg and FX006 60 mg, respectively. All 3 of the FX006 doses produced synovial fluid levels at Day 43 that are potentially therapeutic. (The 90% effective concentration for TCA at the corticosteroid receptor is between 4,000 and 9,000 pg/mL.)</p> <p>Exposure to FX006 increased in a proportional manner with dose, as indicated by the similar CL/F observed across dose levels (85.7 to 118 L/h). In contrast, the CL/F of TCA IR 40 mg was 47.6 L/H. This difference was attributed to a lower relative availability of TCA in the systemic circulation and a greater retention of the drug at the site of injection for FX006 as supported by the long MRT_{inf} and apparent higher TCA concentrations in the joint following FX006 administration.</p>	
<p>Safety Results:</p> <p>All treatments were well tolerated. Overall, 92% of patients experienced at least 1 treatment-emergent adverse event (TEAE), with a similar incidence across the 4 treatment groups. There were no deaths, serious adverse events, or significant adverse events reported, and no patients prematurely discontinued from the study due to an AE.</p> <p>The most common TEAE, headache, occurred in 8 of 24 patients overall including patients from each treatment group. TEAEs that occurred in more than 1 patient in any group included: catheter site haematoma [n=2, TCA IR], vessel puncture site hematoma [n=2, 10 mg FX006], contusion [n=2 each, 40 mg and 60 mg FX006], post-traumatic pain [n=2, 40 mg FX006], arthralgia [n=3, 40 mg FX006], muscle spasms [n=2, 60 mg FX006] and headache [n=3 each, 40 mg and 60 mg FX006].</p> <p>TEAEs not related to the index knee were infrequent and the majority of them were mild or moderate. The most common index knee-related TEAEs, arthralgia and joint stiffness, each occurred in 3 of 24 patients with arthralgia only occurring in the 40 mg FX006 group and joint stiffness occurring in 1 patient each in the 10 mg FX006, 60 mg FX006 and TCA IR groups. Other index knee-related TEAEs that occurred in more than 1 patient in any group included: contusion [n=2, 40 mg FX006], post-traumatic pain [n=2, 40 mg FX006], and injection site pain (n=2, 1 10 mg FX006, 1 40 mg FX006).</p> <p>No remarkable changes in laboratory parameters were noted in any cohort. Overall, with small numbers of patients per group, there were no clear trends demonstrating worsened local inflammation with FX006 versus TCA IR. There were no clinically significant changes in vital signs or ECG parameters observed following administration of the study drug in any cohort and any changes were similar between FX006 and TCA IR groups.</p>	
<p>Summary – Conclusions:</p> <p>Data from this study suggest that following IA injection, FX006 is substantially extends the residency of TCA in the joint and reduces systemic TCA exposure relative to an equivalent dose TCA IR. Further these differences are likely to be clinically meaningful. IA concentrations at Day 42 post injection of 40 mg of FX006 are likely therapeutic, whereas IA concentrations at Day 42 post injection of 40 mg of TCA IR are below levels of detection. Systemic concentrations at in the first days post injection of 40 mg of FX006 have significantly lower impact on HPA axis function relative 40 mg of TCA IR. These data are consistent with an improved efficacy and systemic safety profile for FX006 relative to TCA IR in the treatment of patients with OA of the knee and other inflammatory joint disorders.</p>	
<p>Date of Report: November 21, 2014</p>	

4.2.3 Study FX006-2013-005

2. SYNOPSIS

Name of Sponsor/Company: Flexion Therapeutics	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: FX006		
Name of Active Ingredient: Triamcinolone acetonide (TCA)		
Title of Study: An Open-label, Single Administration Study to Characterize the Local Duration of Exposure of Triamcinolone Acetonide from FX006 in Patients with Osteoarthritis of the Knee		
Principal Investigator: Investigators: This study was conducted at three study centers in the United States (US). Investigators and study centers are identified in Appendix 16.1.4 .		
Study center(s): See above.		
Publications (reference): None.		
Studied period (years): Date first patient enrolled: 07 November 2013 Date last patient completed: 19 May 2014		Phase of development: 2
Objectives: Primary: <ul style="list-style-type: none"> Characterize the local duration of exposure of triamcinolone acetonide (TCA) for 2 doses (10 and 40 mg, single IA injection) of FX006 relative to 40 mg of TCA immediate release (IR) in patients with osteoarthritis (OA) of the knee. Secondary: <ul style="list-style-type: none"> Assess the safety and general tolerability of a single IA injection of two doses (10 and 40 mg, single IA injection) of FX006. 		

Methodology:

This study was an open-label, single administration design, conducted in male and female patients ≥ 40 years of age with OA of the knee.

Patients were enrolled sequentially with eight patients per Cohort as follows:

Cohort	FX006 Dose	Final Visit
A	40 mg	Week 20
B	40 mg	Week 16
C	10 mg	Week 12
D	40 mg	Week 12

Each patient was evaluated for up to 12, 16, or 20 weeks following a single IA injection depending on the assigned Cohort. Following the screening visit, safety was evaluated at 3 out-patient visits and synovial fluid was collected at Day 1 for baseline measurements and the Final Visit for drug concentration measurements. Patients were allowed to be re-assigned to a different cohort (for the Final Visit assignment only) if necessary and with Sponsor approval if it was clear that the patients did not have synovial fluid at the originally assigned Final Visit. Enrollment of 2 additional patients per cohort was allowed following fulfillment of Cohort D. Once enrollment in Cohorts A through D was adequate, 10 patients were enrolled in Cohort E.

Cohort	Treatment	Final Visit
E	TCA IR 40 mg	Week 12

The study was expected to enroll over a period of approximately 1 month.

Number of patients (planned and analyzed):

Up to 50 patients were planned to be enrolled, with 8 to 10 patients in each of the first 4 cohorts and 10 patients in the fifth cohort.

Diagnosis and main criteria for inclusion:***Inclusion Criteria:***

To be included in the study, patients must have fulfilled the following criteria:

1. 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. Had documented diagnosis of OA of the index knee made at least 6 months prior to Screening
5. Met American College of Rheumatology (ACR) criteria (clinical and radiological) for OA as follows:
 - Knee Pain.
 - at least one of the following:
 - Age > 50 years.
 - Stiffness < 30 minutes.

- Crepitus.
 - + Osteophytes.
6. Index knee pain for >15 days over the last month (as reported by the patient).
 7. Body mass index (BMI) ≤ 40 kg/m².
 8. Ambulatory and in good general health.
 9. Willingness to abstain from use of the following during the study:
 - Oral, inhaled, intranasal, or topical corticosteroids.
 - IA corticosteroids in any joint.
 - IA viscosupplementation (hyaluronic acid) in the index knee.

Exclusion Criteria

Patients fulfilling at least one of the following criteria were not included in the study:

Disease-related criteria

1. History of Reiter's syndrome, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease, sarcoidosis, or amyloidosis.
2. History of arthritides due to crystals (*e.g.*, gout, pseudogout).
3. History of infection in the index joint.
4. Clinical signs and symptoms of active knee infection or crystal disease of the index knee.
5. Presence of surgical hardware or other foreign body in the index knee.
6. Unstable joint (such as a torn anterior cruciate ligament) within 12 months of Screening.

Previous or concomitant OA treatment-related criteria

7. IA corticosteroid (investigational or marketed) in any joint within 6 months of Screening.
8. IA hyaluronic acid (investigational or marketed) in the index knee within 6 months of Screening.
9. Intramuscular (IM) corticosteroids within 3 months of Screening or oral corticosteroids (investigational or marketed) within 1 month of Screening.
10. Inhaled, intranasal, and topical corticosteroids (investigational or marketed) within 2 weeks of Screening.
11. Any other IA investigational drug/biologic within 6 months of Screening.
12. Prior use of FX006.
13. Prior arthroscopic or open surgery of the index knee within 12 months of Screening.
14. Planned/anticipated surgery of the index knee during the study period.

Patient-related criteria

15. Known hypersensitivity to any form of triamcinolone.
16. 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 resected cervical atypia or carcinoma in situ.

17. Known active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.
18. History of any infection requiring intravenous antibiotics within 4 weeks of Screening.
19. History of infection requiring oral antibiotics within 2 weeks of Screening.
20. History of chronic infection or a history of osteomyelitis.
21. Known or clinically suspected infection with human immunodeficiency virus (HIV), hepatitis B or C viruses.
22. Screening or Baseline 12-lead electrocardiogram (ECG) demonstrating QTc >450 msec in male patients and >470 msec in female patients or any clinically significant ECG abnormality as judged by the Investigator.
23. Active asthma that may have required periodic treatment with systemic or inhaled steroids during the study period.
24. Type 1 diabetes or Type 2 diabetes requiring insulin.
25. History of or active Cushing's syndrome.
26. Positive drug screen (a positive drug screen result attributable to an allowed medication was not exclusionary).
27. 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.
28. Skin breakdown at the knee where the injection would have taken place.
29. Women who were pregnant or nursing.
30. 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 (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]).
31. Use of immunomodulators, immunosuppressives, or chemotherapeutic agents within 5 years of Screening.
32. Received a live or live attenuated vaccine within 3 months of Screening.
33. Use of any other investigational drug or device within 30 days of Screening or an investigational biologic within 60 days of Screening.
34. Any other clinically significant acute or chronic medical conditions (e.g., bleeding disorder) that, in the judgment of the Investigator, would have precluded the use of an IA corticosteroid or that could have compromised patient safety, limited the patient's ability to complete the study, and/or compromised the objectives of the study.

<p>Test product, dose and mode of administration, batch number: FX006 – extended release formulation of TCA in 75:25 poly(lactic-co-glycolic) acid (PLGA) microspheres. Nominal 10 or 40 mg TCA, IA, administered as a 3 mL injection. Batch number: 12-083-001-10 (10 mg) and 12-083-001-40 (40 mg)</p>
<p>Duration of treatment: All patients received a single IA injection of study drug at Baseline (Day 1).</p>
<p>Reference therapy, dose and mode of administration, batch number: Commercially-available TCA IR injectable suspension, 40 mg/mL, IA, administered as a 1 mL injection. The TCA IR suspension (Kenalog[®]) used was manufactured by Bristol-Meyers Squibb supplied as a 1 mL vial, 40 mg/mL. Batch number: 0003-0293-05 (Sites 10 and 21) and P115012-0001L00 (Site 08).</p>
<p>Criteria for evaluation: <i>Duration of Exposure</i></p> <ul style="list-style-type: none"> • Drug concentration measurements in plasma and synovial fluid <p><i>Safety</i></p> <ul style="list-style-type: none"> • Adverse events (AEs) • Physical examinations • Index knee examinations • Vital signs • ECGs • Clinical laboratory evaluations
<p>Statistical methods: All study data were presented in by-patient data listings. Statistical analyses were performed using SAS for Windows. Descriptive statistics (n, geometric mean, log-scale standard deviation [SD], and median, minimum, maximum) were calculated by cohort and time point for drug concentration levels and mass. Frequencies and percentages of patients with below assay quantification limits were presented by cohort and time point for drug concentration levels from synovial fluid samples for categorical and ordinal variables. Safety analyses were performed on the Safety Population. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Incidences (number and percent) of treatment-emergent adverse events (TEAEs), those events that started after dosing or worsened in severity after dosing, were presented by cohort. Incidences of TEAEs were also presented by maximum severity and relationship to study drug. Laboratory data were summarized by cohort as summary statistics for value and change from Baseline at each time point. Summary statistics included n, mean, median, SD, minimum, and maximum.</p>
<p>SUMMARY – CONCLUSIONS <i>Disposition and Demographics:</i> Fifty patients were enrolled sequentially in this study (10 FX006 10 mg, 30 FX006 40 mg, and 10 TCA IR 40 mg). All 50 of the enrolled patients received their assigned treatment and thus were included in the Safety Population.</p>

Treatment arms were well balanced with respect to demographic and baseline characteristics. The 50 treated patients included 16 (32.0%) males and 34 (68.0%) females. The majority of patients (n=40, 80%) were white/Caucasian. The mean age at randomization was 62.3 years (range 48 to 78 years), and BMI was 33.23 kg/m² (range 20.5 to 40.0 kg/m²).

All 50 patients had a diagnosis of OA confirmed per ACR criteria. The median time since primary diagnosis was 6.0 years, with a maximum of 30 years. The majority of patients presented to the study with bilateral knee OA (n=32, 64.0%) and with a Kellgren-Lawrence grade of 3 (n=27, 54.0%) versus a grade of 2 (n=20, 40.0%). The mean number of days with knee pain in the month prior to Screening was 28.8 days (range 16.0 to 31.0 days). Twenty percent (n=10, 20.0%) of the patients had a total of 13 prior OA-related knee surgeries or procedures of the index knee. Forty percent (n=20, 40.0%) of the patients had a prior IA steroid injection of the index knee, with a mean number of prior injections of 0.6. Eleven percent (n=26, 11%) of patients had a prior IA hyaluronic acid (HA) injection of the index knee, with a mean number of prior injections of 0.6. With the exception of 1 patient, none of these IA steroid or HA injections were within 6 months prior to the Screening visit (as per exclusion criterion #7 and #8). The one exception (Patient 085003) was provided with a waiver to continue participation in the study, as the corticosteroid injection received by this patient fell short of the 6 month requirement by only 6 days.

Efficacy Results

Efficacy was not evaluated in this study.

Pharmacokinetic Results:

The local duration of TCA exposure in plasma and synovial fluid was evaluated after single IA administration of FX006 or TCA IR in 50 patients with OA of the knee. IA administration of FX006 resulted in a TCA concentration profile that was typical of a long duration extended release from the site of injection relative to TCA IR formulation. The slow release of TCA from PLGA microspheres prolonged the retention of TCA in the synovial space and reduced the availability of TCA to the systemic circulation relative to TCA IR. Specifically, FX006 displayed the following as compared to TCA IR:

- Detectable TCA synovial fluid levels and corresponding plasma levels for up to 16 weeks post-dosing for FX006 40 mg for the majority of patients compared to <12 weeks for the TCA IR 40 mg formulation.
- For FX006 40 mg, TCA synovial fluid to TCA plasma concentration ratios that demonstrated a gradual but proportional decrease in the ratio over a period of up to 20 weeks, whereas the TCA IR 40 mg dose was released from the site of injection in <12 weeks.

The overall drug concentration profile of TCA with FX006 relative to TCA IR suggests that IA administration of FX006 40 mg results in an extended and more controlled and stable release of TCA from the injection site and ultimately may result in prolonged efficacy while minimizing untoward systemic effects associated with steroid use.

Safety Results:

The evaluation of safety data from 40 patients treated with a single IA injection of FX006, 10 with 10 mg and 30 with 40 mg, demonstrates that FX006 was well tolerated. Furthermore, the systemic and local safety profiles of FX006 were similar to those of TCA IR.

- There were no deaths reported on study.
- No patient who received FX006 experienced a serious adverse event (SAE). Two patients who received TCA IR 40 mg reported an SAE, neither of which was attributable to study drug.
- The proportions of patients experiencing at least one TEAE was similar across cohorts, regardless of follow-up duration, and was similar with FX006 10 mg (50.0%), FX006 40 mg (36.7%), and TCA IR (40.0%).

- All TEAEs reported among FX006-treated patients (10 mg or 40 mg) were mild or moderate in intensity.
- Overall, the most frequently reported TEAE was upper respiratory tract infection (URTI) (2 patients; 20.0%) for the 10 patients who received FX006 10 mg, arthralgia (3 patients; 10%) for the 30 patients who received FX006 40 mg, and arthralgia (2 patients; 20.0%) for the 10 patients who received TCA IR 40 mg.
- No dose relationship was apparent with regard to the incidence of other commonly reported TEAEs.
- For patients who experienced at least one TEAE, all of the TEAEs were assessed by the Investigator as unrelated to study drug.
- Analyses of changes from Baseline for hematology and chemistry parameters did not reveal any remarkable trends. In general, mean and median changes from Baseline were small and similar across cohorts. No laboratory changes were reported as TEAEs.
- There were no clinically significant changes in vital signs or ECG parameters observed following administration of the study drug in any cohort and changes were similar between FX006 and TCA IR cohorts.

Safety findings from this study support the continued investigation of FX006 in patients with OA of the knee.

CONCLUSION:

The overall duration of exposure profile of TCA with FX006 relative to TCA IR suggests that IA administration of FX006 results in an extended and more controlled and stable release of TCA from the site of injection. This profile supports the potential for treatment with FX006 to result in prolonged efficacy while minimizing the untoward systemic effects associated with steroid use. This finding, coupled with the favorable safety profile observed in the current study, provides a strong rationale for further clinical development of FX006.

Date of the report:

03 August 2015

4.2.4 Study FX006-2015-009

2. SYNOPSIS

Name of Sponsor/Company: Flexion Therapeutics	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: FX006		
Name of Active Ingredient: FX006		
Title of Study: An Open-Label, Single Administration Study to Characterize the Systemic Pharmacokinetics and Local Extent and Duration of Exposure of Triamcinolone Acetonide from FX006 in Patients with Osteoarthritis of the Knee		
Investigators and Study Centers: Patients were screened for study eligibility at 4 study centers in the United States (US).		
Publications (reference): None to date.		
Studied period (years): Date first patient enrolled: 30 November, 2015 Date last patient completed: 08 September, 2016		Phase of development: 2
Objectives: The objectives of this study were to: <ul style="list-style-type: none"> • characterize the local extent and duration of exposure of triamcinolone acetonide (TCA) from FX006 and triamcinolone acetonide injectable suspension (TCA IR), • characterize the systemic pharmacokinetic (PK) of FX006 and TCA IR, and • assess the safety and general tolerability when FX006 was delivered at a 40 mg dose as a single 5 mL intra-articular (IA) injection or TCA IR was delivered at a dose of 40 mg as a single 1 mL IA injection in patients with osteoarthritis (OA) of the knee.		

Methodology:

This study employed an open-label, single administration design and was conducted in male and female patients ≥ 40 years of age with OA of the knee. Patients were enrolled sequentially with at least 10 patients per Cohort, as follows:

Cohort	Treatment	Synovial Fluid Visit
A	40 mg FX006	Week 20
B	40 mg FX006	Week 16
C	40 mg FX006	Week 12
D	40 mg FX006	Week 6
E	40 mg FX006	Week 1
F ¹	40 mg TCA IR	Week 6

¹ The protocol was amended on 29 June, 2016, after initial database lock for Cohorts A through E had occurred to include an additional cohort, Cohort F, in which patients received a single 1 mL IA injection of 40 mg TCA IR.

Each patient was screened to confirm eligibility and assigned to a cohort on Day 1/baseline. Each patient was evaluated for safety during his/her participation in the study at 6, 12, 16, or 20 weeks following a single IA injection depending on the assigned Cohort, and plasma and synovial fluid was collected for drug concentration measurements. Patients in Cohorts A through E may have been re-assigned to a different cohort dependent on synovial fluid availability (for the Synovial Fluid Visit assignment only), and with the Sponsor's approval. In Cohort F (40 mg TCA IR), patients completed a Week 6 visit for synovial fluid sampling. This cohort could not be reassigned.

Additional patients may have been enrolled (up to 20 patients maximum per cohort), if required, to ensure that there were at least 6 patients with synovial fluid samples available for analysis at each of the Synovial Fluid Visit time points.

Number of patients (planned and analyzed):

No formal sample size computations were completed for this descriptive study. A maximum of 20 patients per cohort were planned to be enrolled in the 6 planned study cohorts; thus, a total of up to 120 patients were planned to be enrolled.

A total of 63 patients were enrolled in Cohorts A through E (40 mg FX006) in this study, 13 in the Week 1 Cohort (E), 20 in the Week 6 Cohort (D), and 10 each in the Week 12 Cohort (C), Week 16 Cohort (B), and Week 20 Cohort (A). All 63 patients enrolled were treated with a single IA injection of 40 mg FX006 on Day 1. Eighteen patients were enrolled in Cohort F (TCA IR); all 18 patients were treated with a single IA injection of 40 mg TCA IR on Day 1. Thus, a total of 81 patients were enrolled and treated in this study.

Diagnosis and main criteria for inclusion:

To be included in the study, patients were required to fulfill the following criteria:

1. 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 is acceptable).
5. Currently met ACR Criteria (clinical and radiological) for OA as follows:
 - Knee pain

<ul style="list-style-type: none"> • at least 1 of the following: <ul style="list-style-type: none"> - Age >50 years - Stiffness <30 minutes - Crepitus • Osteophytes <p>6. Index knee pain for >15 days over the last month (as reported by the patient).</p> <p>7. Body mass index (BMI) ≥ 40 kg/m².</p> <p>8. Ambulatory and in good general health.</p> <p>9. Willingness to abstain from use of the following protocol-restricted medications during the study:</p> <ul style="list-style-type: none"> • Intravenous (IV), Intramuscular (IM), oral, inhaled, intranasal or topical corticosteroids. • IA corticosteroids in any joint. • IA viscosupplementation (hyaluronic acid) in the index knee. • Any investigational drug or device. • Immunomodulators, immunosuppressives, or chemotherapeutic agents. • Live or live attenuated vaccines.
<p>Test product, dose and mode of administration, batch number:</p> <p>Patients assigned to Cohorts A, B, C, D, or E received a single IA injection of 40 mg FX006. FX006 was supplied as a sterile, white to off white powder in a single unit dose 5 mL vial with a butyl rubber stopper, aluminum seal, and plastic cap. FX006 was reconstituted in diluent containing an isotonic, sterile aqueous solution of sodium chloride (NaCl; 0.9% w/w), sodium carboxymethylcellulose (NaCMC) (0.5% w/w) and polysorbate-80 (0.1% w/w) to form a suspension prior to IA injection. Diluent was supplied as a sterile liquid in a 5 mL vial with a butyl rubber stopper, aluminum seal and plastic cap. FX006 was reconstituted in 5.0 mL of diluent to form a suspension immediately prior to IA injection. FX006 was administered as a single 5 mL IA injection.</p> <p>The lot number of 40 mg FX006 used in this study was FL1100, and the lot number of diluent used in this study was 009M14.</p>
<p>Duration of treatment:</p> <p>Patients received a single IA administration of study drug on Day 1 and were followed for up to 20 weeks thereafter, based on cohort assignment.</p>
<p>Reference therapy, dose and mode of administration, batch number:</p> <p>Patients assigned to Cohort F received a single IA injection of 40 mg TCA IR.</p> <p>Kenalog[®]-40 (triamcinolone acetonide, injectable suspension, USP) (i.e., TCA immediate release or TCA IR) is a synthetic glucocorticoid corticosteroid with anti-inflammatory action. Each mL of the sterile aqueous suspension provided 40 mg TCA, with NaCl for isotonicity, NaCMC, and polysorbate 80. A preservative, benzyl alcohol, may have been present. Sodium hydroxide or hydrochloric acid may have been present to adjust pH to 5.0 to 7.5. At the time of manufacture, the air in the container was replaced by nitrogen. TCA IR was administered as a single 1 mL IA injection.</p> <p>The lot number of Kenalog[®]-40 used in this study was 4M58523.</p>
<p>Criteria for Evaluation:</p> <p>Pharmacokinetics:</p> <p>Blood samples (4 mL per sample) for drug concentration measurements were obtained from all patients prior to administration of study drug on Day 1; at Hours 1, 2, 4, 6, 8, 10 and 12 on Day 2 (24 hours</p>

after study drug administration); at the Week 6 visit and at the assigned Synovial Fluid Visit (a total of 10 or 11 samples from each patient).

Plasma TCA concentrations were measured using an established validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantitation (LLOQ) of 10.00 pg/mL.

An attempt to obtain synovial fluid samples for drug concentration measurements was performed for all patients via aspiration on Day 1 prior to study drug administration and at the Synovial Fluid Visit (depending on cohort assignment at Week 1, 6, 12, 16 or 20). Synovial fluid TCA concentrations were measured using a validated LC-MS/MS method with an LLOQ of 50.00 pg/mL.

Safety:

Safety and tolerability was assessed by physical examinations, index knee examinations, vital signs, clinical laboratory evaluations, and adverse events (AEs).

Efficacy:

No efficacy assessments were employed in this study.

Statistical Methods:

Tabulations were produced for appropriate demographic, baseline, PK, and safety parameters.

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

For continuous variables, the number of non-missing values (n), the mean, median, standard deviation (SD), confidence intervals (CI), minimum and maximum were presented by cohort. In addition, for concentration-based parameters the GM and log-scale standard deviation were provided. Additional statistics may have been presented for certain endpoints as described in the following subsections.

All collected data were presented in by-patient listings.

All data listings with evaluation dates contained a relative study day (Rel Day). Pre-treatment and post-treatment study days were numbered relative to the day of the first dose of study treatment, which was designated as Day 1. The preceding day was Day -1, the day before that was Day -2, etc.

For data listings related to PK assessments, for which several assessments were done on the same day, relative day and time were included.

Plasma and Synovial Fluid Drug Concentration Analyses:

Plasma drug concentration analyses were performed using non-compartmental analysis (NCA) models on the Plasma Drug Concentration population. Data were presented by time point pooled across FX006 cohorts and presented separately for the TCA IR cohort. Baseline (pre-dose) plasma concentration values were set to zero for descriptive and NCA analyses. Post-baseline plasma concentration values recorded as below the limit of quantification (BLOQ) were not imputed but rather were set to zero for descriptive and NCA analyses.

Descriptive statistics (n, mean, standard deviation [SD], geometric mean [GM], log-scale SD, 95% confidence interval [CI] median, minimum, maximum) were calculated by time point for drug concentration levels from plasma samples. Frequencies and percentages of patients with BLOQ values were presented by time point for drug concentration levels from plasma drug samples.

Concentration curves were used to present GM with 95% CIs for plasma drug concentrations pooled across cohorts A through E for the FX006 40 mg treatment arm, and for Cohort F for the TCA IR treatment arm.

The synovial fluid concentration analyses were similarly performed, but using sparse sampling NCA models on the Synovial Fluid Concentration population.

Additionally, descriptive statistics were presented for the ratio of synovial fluid to plasma concentrations at the Synovial Fluid Visit. Geometric means with 95% CIs were used to display these

results graphically.

Pharmacokinetic Analyses:

PK analysis was performed on the Plasma and Synovial Fluid populations. PK parameter estimates were completed by the study pharmacokineticist and results integrated into study data tabulation model (SDTM) and analysis data model (ADaM) datasets.

PK parameters were derived using model-independent methods (NCA) as implemented in Phoenix 64, WinNonlin® (version 6.4) and were based on TCA plasma concentrations from patients in the PK Population and Synovial Fluid Drug Concentration Population. Sparse sampling methodology following Day 1 was implemented across the plasma concentration profile to capture population-based profiles at the end of the plasma concentration sampling profile (up to 20 weeks).

Synovial fluid samples across the FX006 treated cohorts A through E were pooled to characterize the PK profile to estimate PK parameter estimates. Population-based PK parameters were estimated across all patients, due to sparse sampling [2 samples per patient: baseline (pre-dose) and 1 sample post-baseline], for the synovial fluid population for TCA concentrations assayed in synovial fluid. No synovial fluid PK parameter estimates from synovial fluid samples were completed for TCA IR treated subjects in Cohort F due to limited sampling at pre-dose and Week 6.

The PK endpoints to be computed on plasma TCA concentration measurements were either observed from those concentration measurements or estimated by WinNonLin® (version 6.4) using the trapezoidal rule for calculation of the area under the plasma concentration time curve (AUC) estimates to the last measureable concentration. Additional estimates of the half-life ($t_{1/2}$), clearance (CL), residence time, volume of distribution, and the extrapolated area for the AUC_{0-inf} and related parameters were estimated using the slope estimate for the terminal elimination rate constant (λ_z) for each patient with WinNonLin® (version 6.4).

Following review of the plasma PK parameter estimates computed for TCA IR (Cohort F), additional partial AUC parameters were defined to provide for a direct comparison of the FX006 and TCA IR treatment arms. Partial AUC parameters were defined as $AUC_{(0-6 \text{ weeks})}$ (FX006 and TCA IR treatment arms), $AUC_{(0-12 \text{ weeks})}$, $AUC_{(0-16 \text{ weeks})}$, and $AUC_{(0-20 \text{ weeks})}$. (FX006 treatment arm only were subjects contributed plasma concentrations at the respective time point.) A comparison of the $AUC_{(0-6 \text{ weeks})}$ parameter was aligned with the sparse sampling completed for Cohort F (TCA IR).

Relative Bioavailability

An assessment of the relative bioavailability computed as the average bioequivalence for PK parameters was requested by the Food and Drug Administration (FDA) as part of the pre-New Drug Application (NDA) meeting response received from the agency. This analysis was completed and the results from this post-hoc analysis are included as an additional analysis.

SUMMARY – CONCLUSIONS

DISPOSITION:

A total of 63 patients were enrolled in Cohorts A through E (40 mg FX006) in this study, 13 in the Week 1 Cohort (E), 20 in the Week 6 Cohort (D), and 10 each in the Week 12 Cohort (C), Week 16 Cohort (B), and Week 20 Cohort (A). All 63 patients enrolled were treated with a single IA injection of 40 mg FX006 on Day 1. Two (3.2%) patients, 1 each in the Week 1 Cohort (E) and Week 6 Cohort (D), were discontinued from the study prematurely; both patients were lost to follow-up.

Eighteen patients were enrolled in Cohort F (TCA IR). All 18 patients were treated with a single IA injection of 40 mg TCA IR on Day 1. One patient in the TCA IR Cohort was discontinued from the study due to protocol non-compliance.

DEMOGRAPHICS:

Overall, among all 63 FX006-treated patients, 31 (49.2%) were male and 32 (50.8%) were female. The mean age at consent was 60 years, with a range of 46 to 78 years. Most (47/63; 74.6%) patients were

white. Review of demographic and baseline characteristics across cohorts revealed some variability, which is not unexpected, given the lack of randomization and relatively small sample size in each cohort.

Among all 18 TCA IR-treated patients, 13 (72.2%) were female and 5 (27.8%) were male. The mean age at consent was 62 years, with a range of 52 to 78 years. Most (13/18; 72.2%) patients were white.

PHARMACOKINETIC RESULTS:

Following a single IA injection of 40 mg FX006, TCA was absorbed systemically, with a plateau in plasma TCA concentrations occurring in the first 24 hours post-dose, and slow elimination from the systemic circulation observed in the weeks thereafter. The observed GM maximum plasma concentration (C_{max}) of 966.7 pg/mL (95% CI: 822.07, 1136.69) was reached at a median time to maximum plasma concentration (t_{max}) of 7 hours. The median $t_{1/2}$ was 347.0 hours, and the GM MRT was (453.7 hours; 95% CI: 316.45, 650.50). The GM last quantifiable plasma concentration (C_{last}) of 106.4 pg/mL was seen at a median time of last quantifiable plasma concentration (t_{last}) of 1008 hours (6 weeks).

Measurable levels of TCA in the synovial tissues persisted for at least 12 weeks. At Week 1, a GM synovial fluid TCA concentration of 231328.9 pg/mL (95% CI: 56460.40, 947798.36) was observed. Thereafter, the GM synovial fluid TCA concentration declined, with values of 3590.0 pg/mL (32.89, 391914.74) at Week 6 and 290.6 pg/mL (15.67, 5390.53) at Week 12. After Week 12, TCA was BLOQ in synovial fluid in any samples obtained.

A single IA injection of FX006 resulted in prolonged joint residency of TCA in the knee and lower systemic absorption of TCA relative to TCA IR (Kenalog[®]-40). GM synovial fluid TCA concentration at Week 6 was significantly higher with 40 mg FX006 relative to 40 mg TCA IR (3590.0 pg/mL versus 7.7 pg/mL, respectively). In contrast, systemic exposure to TCA was lower after a single IA injection of 40 mg FX006 relative to 40 mg TCA IR with GM C_{max} (966.7 versus 11064.7 pg/mL, respectively), GM $AUC_{0-6 \text{ weeks}}$ (508939.6 versus 3082834.8 h*pg/mL, respectively), and GM $AUC_{0-\infty}$ (543115.0 versus 1248903.3 h*pg/mL, respectively).

In response to an FDA request, a post hoc analysis for BE testing of TCA resulting from a single IA injection of 40 mg FX006 versus Kenalog[®]-40 was conducted. As indicated by BE ratios and 90% CI for the GMs of C_{max} , $AUC_{0-24 \text{ hrs}}$, $AUC_{0-6 \text{ weeks}}$, and $AUC_{0-\infty}$, the overall systemic exposure of FX006 40 mg (Test Product) was significantly lower than that of Kenalog[®]-40 (Reference Product).

SAFETY RESULTS:

A single IA injection of 40 mg FX006 was well tolerated in this study. Review of treatment-emergent adverse events (TEAEs) showed that the overall incidence of TEAEs overall was low (11.1% [7/63]). The only individual TEAE reported for >1 patient was hypertension (3.2% [2/63]), with the event representing a worsening of pre-existing hypertension for each patient. All but 1 TEAE were assessed by the Investigator as Grade 1 or 2 in severity. One patient experienced a Grade 4 TEAE (pulmonary embolism); this event, which occurred in a 64-year-old male patient with a prior history of pulmonary embolism at baseline, also was the only serious adverse event (SAE) reported and was considered unrelated to study drug, injection procedure, and index knee.

No Grade 3 or 5 TEAEs were reported among FX006-treated patients.

Two FX006-treated patients experienced an index knee related TEAE, Grade 2 patellofemoral pain syndrome in 1 patient and Grade 1 arthralgia in another patient.

Only 1 FX006-treated patient experienced a TEAE considered by the Investigator to be study drug-related (patellofemoral pain syndrome in the index knee [see above]); no other TEAEs were considered by the Investigator to be related to study drug, the injection procedure, or the index knee.

No FX006-treated patient discontinued from the study because of a TEAE.

Two (11.1%) patients in the TCA IR Cohort experienced a TEAE, Grade 1 flushing in both cases. For both patients, flushing was considered related to study drug and the injection procedure. No patient in

the TCA IR Cohort experienced an SAE or an index knee TEAE. Furthermore, no patient in the TCA IR Cohort discontinued from the study because of a TEAE.

CONCLUSION:

FX006-2015-009 was a Phase 2, open-label, single administration study to characterize the local extent and duration of exposure of TCA from FX006, to characterize the systemic PK of FX006, and to assess the safety and general tolerability of FX006 when delivered at a 40 mg dose as a single 5 mL IA injection in patients with OA of the knee.

Following a single IA injection of FX006, TCA was absorbed systemically, with a plateau in plasma TCA concentrations occurring in the first 24 hours post-dose, and slow elimination from the systemic circulation observed in the weeks thereafter. Measurable levels of TCA in the synovial tissues persisted for at least 12 weeks. A single IA injection of FX006 resulted in prolonged joint residency of TCA and lower systemic exposure to TCA relative to TCA IR (Kenalog®-40).

The evaluation of safety data from 63 patients treated with a single IA injection of 40 mg FX006 suggest that FX006 was well tolerated. No new or unexpected safety concerns were identified with 40 mg FX006 in this study.

Date of the report:

01 November, 2016

Table 18. Plasma Drug Concentrations (pg/mL) by Time Pooled across FX006 Cohorts (Plasma Drug Concentration Population)

Treatment Time	Number <LLOQ ¹ N ¹	Statistic							
		N	Mean	SD	Geometric Mean	Log-Scale SD	95 % CI	Median	Min, Max
Baseline (pre-treatment)	51	60	0.0	0.00	NA	NA	NA, NA	0.0	0, 0
Day 1 - Hour 1	0	60	813.6	468.50	670.0	0.71	558.42, 803.97	699.7	35, 2426
Day 1 - Hour 2	0	60	865.1	458.52	736.5	0.60	630.01, 861.03	744.0	151, 2103
Day 1 - Hour 4	0	60	911.0	495.58	759.5	0.65	641.69, 898.87	890.6	125, 1796
Day 1 - Hour 6	0	60	896.5	489.04	747.1	0.66	630.45, 885.28	866.3	109, 1842
Day 1 - Hour 8	0	60	888.2	487.88	740.2	0.65	625.13, 876.36	846.4	129, 1873
Day 1 - Hour 10	0	60	858.6	466.94	720.7	0.64	611.37, 849.66	780.0	139, 1816
Day 1 - Hour 12	0	60	842.6	467.58	706.6	0.63	600.15, 831.91	758.6	149, 1803
Day 2 - Hour 24	0	60	1014.9	587.84	836.4	0.67	703.47, 994.33	922.6	135, 2587
Week 1	0	11	717.4	392.31	600.9	0.67	382.79, 943.25	892.4	204, 1400
Week 6	2	54	137.7	102.35	118.6	0.62	99.93, 140.87	113.3	0, 639
Week 12	4	15	52.3	53.97	53.7	0.84	30.46, 94.74	40.0	0, 156
Week 16	7	15	83.8	209.17	73.8	1.13	28.74, 189.31	19.5	0, 825
Week 20	5	8	90.7	220.34	108.2	1.55	2.30, 5090.25	0.0	0, 633

Source: Table 14.1.6.

Note: All baseline (pre-treatment) values and all post-baseline values that are recorded as below LLOQ are set to zero for analysis and are included in the descriptive mean calculations. Values below LLOQ are not included in geometric mean calculations.

¹ LLOQ = Lower Limit of Quantification (<10 pg/mL).

Table 19. Plasma Drug Concentrations (pg/mL) by Time- TCA IR (Plasma Drug Concentration Population)

Treatment Time	Number		Statistic						
	Below LLOQ ¹	N	Mean	SD	Geo-metric Mean	Log-Scale SD	95 % CI	Median	Min, Max
Baseline (pre-treatment)	18	18	0.0	0.00	NA	NA	NA, NA	0.0	0, 0
Day 1 - Hour 1	0	18	13794.8	12662.89	6968.8	1.49	3329.00, 14588.36	11471.3	477, 43921
Day 1 - Hour 2	0	18	17162.8	15104.57	8494.7	1.54	3954.18, 18248.99	14796.0	519, 49499
Day 1 - Hour 4	0	18	19848.3	18086.25	9628.8	1.57	4420.47, 20973.81	17726.0	587, 65673
Day 1 - Hour 6	0	18	18086.1	15153.87	9314.3	1.50	4423.76, 19611.37	19110.7	644, 53579
Day 1 - Hour 8	0	18	15422.5	12292.37	8421.3	1.42	4166.33, 17021.86	17229.7	691, 40028
Day 1 - Hour 10	0	18	12891.8	9919.83	7439.3	1.33	3845.19, 14392.79	14361.8	688, 31179
Day 1 - Hour 12	0	18	11203.7	8337.85	6678.7	1.28	3535.07, 12617.78	12577.7	642, 26280
Day 2 - Hour 24	0	18	7847.1	5935.43	4991.1	1.13	2851.47, 8736.28	7463.5	779, 19039
Week 6	9	17	88.0	112.29	149.4	0.91	69.70, 320.32	0.0	0, 301

Source: Table 14.1.6.1.

Note: All baseline (pre-treatment) values and all post-baseline values that are recorded as below LLOQ are set to zero for analysis and are included in the descriptive mean calculations. Values below LLOQ are not included in geometric mean calculations.

¹ LLOQ = Lower Limit of Quantification (<10 pg/mL).

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08/25/2017

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08/25/2017

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information			Information
NDA/BLA Number	208845	Brand Name	Zilretta	
OCP Division (I, II, III, IV, V)	II	Generic Name	Triamcinolone Acetonide for Extended-Release Injectable suspension	
Medical Division	DAAAP	Drug Class	Corticosteroid	
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	Management of osteoarthritis pain of (b) (4)	
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form	(b) (4)	
Pharmacometrics Reviewer		Dosing Regimen	A single dose injection	
Date of Submission	12/8/2016	Route of Administration	Intra-articular injection	
Estimated Due Date of OCP Review	8/20/2017	Sponsor	Flexion Therapeutics, Inc	
Medical Division Due Date	9/3/2017	Priority Classification	Standard	
PDUFA Due Date	10/8/2017			
Clin. Pharm. and Biopharm. Information				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Phase 2:	x	4		FX006-2011-001, FX006-2011-002, FX006-2013-005 and FX006-2015-009
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	x	(1)		FX006-2015-009
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	Sponsor stated that the final formulation was used in the pivotal comparative bioavailability study (FX006-2015-009) and primary Phase 3 trials
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			Sponsor submitted plasma concentration time dataset as well as pharmacokinetic parameter datasets in SAS transport format.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?				
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		x		Agency agreed with the full waiver (b) (4) in the communication dated 3/15/2016.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this	x			

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

This NDA submission is fillable from clinical pharmacology perspective.

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

There is no potential review issue to be included in the 74-day letter.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Flexion Therapeutics, Inc. submitted a 505(b) (2) NDA for Zilretta (triamcinolone acetonide for extended-release (ER) injection suspension) for the management of osteoarthritis pain of (b) (4). Zilretta is an extended release formulation of triamcinolone acetonide (TCA) in 75:25 poly(D,L-lactic-co-glycolic acid) (PLGA) microspheres. The intention of this formulation design is to maintain prolonged concentrations of TCA in the joint following intra-articular (IA) injection thereby providing meaningful analgesia and limiting systemic exposure. FX006 was used for Zilretta throughout the development program.

As a 505(b)(2) application, Flexion plans to rely in part on the agency’s finding of the safety and efficacy of Kenalog®-40 (triamcinolone acetonide injectable suspension) (NDA 14-901), an immediate release (IR) formulation.

The PK data supporting this NDA are generated from 4 Phase 2 studies in OA patients including FX006-2011-001, FX006-2011-002, FX006-2013-005, and FX006-2015-009. The titles of these studies are shown below:

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

FX006-2011-001: A double-blind, randomized, parallel group, dose-ranging study comparing FX006 to commercially available triamcinolone acetonide injectable suspension in patients with osteoarthritis of the knee

FX006-2011-002: A double-blind, randomized, parallel group, active comparator study to evaluate the safety, pharmacokinetics, and pharmacodynamic effects (HPA Axis) of FX006 in patients with osteoarthritis of the knee

FX006-2013-005: An open-label, single administration study to characterize the local duration of exposure of triamcinolone acetonide from FX006 in patients with osteoarthritis of the knee

FX006-2015-009: An open-label, single administration study to characterize the systemic pharmacokinetics and local extent and duration of exposure of triamcinolone acetonide from FX006 in patients with osteoarthritis of the knee

Study FX006-2011-001: Sponsor stated that mean C_{max} for FX006 40 mg was approximately 10-fold lower than the mean TCA IR C_{max}. Mean AUC_{0-inf} and AUC_{0-t} values for FX006 increased with the dose. Mean AUC_{0-inf} and AUC_{0-t} for TCA IR 40 mg were approximately 2.21- and 2.94-fold higher than that observed for FX006 40 mg.

Study FX006-2011-002: Sponsor stated that following IA injection, FX006 substantially extends the residency of TCA in the joint and reduces systemic TCA exposure relative to an equivalent dose of TCA IR. Furthermore, it was concluded that FX006 will not compromise the ability to mount a stress response in patients without previous impairment of HPA axis function.

Study FX006-2013-005: Sponsor stated that IA administration of FX006 40 mg results in an extended and more controlled and stable overall duration of exposure profile of TCA with FX006 relative to TCA IR at the injected knee joint.

Study FX006-2015-009: Sponsor stated that IA administration of FX006 40 mg with a 5 mL injection volume (the same preparation used in the primary efficacy studies of FX006), resulted in a controlled and stable release of TCA from PLGA microspheres into synovial tissues, where concentrations remain high relative to plasma concentrations for at least 12 weeks. Relative to TCA IR, FX006 40 mg produced substantially lower peak plasma and systemic exposure to TCA. FX006 performed as expected, prolonging the residence of TCA in the joint while minimizing systemic exposure to TCA. Average BE analysis for plasma PK parameters for FX006 40 mg and TCA IR (Kenalog®-40) showed the systemic exposure to TCA when delivered by FX006 40 mg was less than that from the reference product (Kenalog®-40).

More details are shown in the attached slides.



NDA 208845
Zilretta (triamcinolone ER) for Intra-Articular
Injection
Sponsor: Flexion

Filing Meeting
January 18, 2017

1



Introduction

- FX006 contains TCA formulated in 75:25 poly(lactic-co-glycolic acid) (PLGA) microspheres with a normal drug load of 25% (w/w)
- Indication: management of osteoarthritis (OA) pain of [REDACTED] (b) (4)
- Dosing Regimen: a single dose IA injection
- 505(b)(2)
- Listed drug product: Kenalog®-40 (triamcinolone acetonide [TCA], injectable suspension) (NDA 14901)

2



Pre-NDA (5/25/16)

Additional Comments:

You propose to submit a 505(b)(2) NDA and rely on the Agency's previous findings on safety of Kenalog-40. To rely on the systemic safety of Kenalog-40, you must demonstrate that the systemic exposure of TCA including C_{max} , AUC_t , and AUC_{inf} values for your proposed product are not higher than those from Kenalog-40. For analysis of comparative bioavailability of your proposed product and Kenalog-40 in Studies -002 and -005, use the average bioequivalence approach to determine the geometric mean ratios for C_{max} , AUC_t , and AUC_{inf} and their corresponding 90% confidence intervals.

Clarify if the proposed to-be-marketed product has been used in the clinical and clinical pharmacology studies to support your NDA submission.

3



Clin Pharm/Clinical Development Program

- PK obtained from 3 PK/PD and 1 Phase 3 study (001)

FX006-2011-001: A double-blind, randomized, parallel group, dose-ranging study comparing FX006 to commercially available triamcinolone acetonide injectable suspension in patients with osteoarthritis of the knee

FX006-2011-002: A double-blind, randomized, parallel group, active comparator study to evaluate the safety, pharmacokinetics, and pharmacodynamic effects (HPA Axis) of FX006 in patients with osteoarthritis of the knee

FX006-2013-005: An open-label, single administration study to characterize the local duration of exposure of triamcinolone acetonide from FX006 in patients with osteoarthritis of the knee

FX006-2015-009: An open-label, single administration study to characterize the systemic pharmacokinetics and local extent and duration of exposure of triamcinolone acetonide from FX006 in patients with osteoarthritis of the knee

- Three Phase 3 studies

4

Formulation/Preparation Development

- Comprised of 25% (w/w) triamcinolone acetonide prepared as an extended-release formulation in 75:25 poly(lactic-co-glycolic acid) (PLGA) microspheres.
- Supplied as a sterile, white to off white powder in a single unit dose
- Final resuspension volume changed during the course of development
 - FX006-2011-001, FX006-2011-002, and FX006-2013-005: reconstituted with 3.2 mL of diluent prior to IA injection to deliver a 3 mL injection volume
 - FX006-2015-009, FX006-2014-006, and FX006-2014-008: reconstituted with 5 mL of diluent prior to IA injection to deliver 5 mL injection volume.
 - Proposed TBM formulation/preparation: same as that used in Studies 009, 006, and 008.

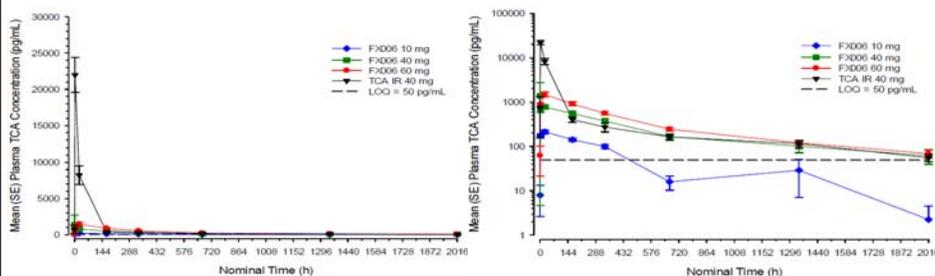
5

Study FX006-2011-001

- Phase 2, R, Active comparator Controlled study in 229 OA patients
- **Objectives:** Magnitude and duration of pain relief, tolerability, and PK of FX006 10, 40 and 60 mg, relative to a commercially available triamcinolone acetonide injectable suspension (TCA IR 40 mg)
- Treatments:
 - 10, 40, or 60 mg FX006 or 40 mg of TCA IR
- PK sampling: pre-dose and within 2 hours post dose on Day 1, and on Day 2 and Weeks 1, 2, 4, 8, and 12.

6

Study FX006-2011-001: Mean (\pm SE) Concentration-Time Profiles of TCA in Plasma (Linear and Semi-Log Scales)



- FX006 shows slower release of TCA into the systemic circulation as compared to TCA IR

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Table 11: Study FX006-2011-001: Mean (CV%) Plasma Pharmacokinetic Parameters of TCA (Pharmacokinetic Population; N=228)^f

TCA PK Parameters	FX006 10 mg N=57	FX006 40 mg N= 59	FX006 60 mg N= 59	TCA IR 40 mg N= 51
AUC _{0-inf} (pg ^a ·h/mL)	182390 ^a (109.9)	511789 ^b (57.7)	856411 ^c (37.7)	1131861 ^d (28.8)
AUC ₀₋₄ (pg ^a ·h/mL)	74832 (125.6)	411301 (76.2)	640987 (58.4)	1210003 (69.2)
CLF (mL/h)	91112 ^a (47.8)	117449 ^b (98.0)	89278 ^c (78.4)	38304 ^d (29.2)
C _{max} (pg/mL)	264 (82.7)	2218 (470.3)	1605 (93.0)	22929 (75.5)
t _{max} ^e (h)	22.58 (1.50 - 1537.33)	21.67 (0.00 - 2061.68)	23.27 (0.00 - 2015.17)	2.02 (1.75 - 289.42)
t _{1/2} (h)	455 ^a (88.3)	542 ^b (94.1)	484 ^c (66.6)	908 ^d (56.3)
MRT _{0-inf} (h)	640 ^a (86.4)	753 ^b (99.4)	630 ^c (71.8)	962 ^d (69.2)
V _{ss} /F (mL)	45420624 ^a (56.9)	75044900 ^b (104.9)	60635073 ^c (127.2)	37281059 ^d (68.6)
V _z /F (mL)	46447588 ^a (55.6)	77678819 ^b (100.2)	65739579 ^c (120.9)	49597525 ^d (58.9)

^a n=11, ^b n=35, ^c n=32, ^d n=24 ^e Median (min-max) ^f two patients (one from the FX006 10 mg group and one from the FX006 60 mg group) were not included in the PK analysis due to all post-baseline plasma samples being below the limit of quantification

- AUC values increased as dose increase for FX006
- Plasma exposures (C_{max} and AUC) for FX006 (10, 40 and 60 mg) are lower than TCA IR 40 mg
- Mean C_{max} for FX006 40 mg was ~ 10-fold lower than the mean TCA IR C_{max}

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Study FX006-2011-002

- Phase 2, DB, R, Active comparator study in 24 OA patients
- **Objectives:** Safety and tolerability, PK and PD effect of FX006 relative to 40 mg TCA IR
- Treatments: Single IA injection of 10, 40, or 60 mg FX006 or 40 mg of TCA IR
- PK blood sampling: pre-dose and at 1, 2, 3, 6, 8, 12, and 24 hours post dose and on Days 3, 4, 5, 8, 15, 22, 29, 36, and 43.
- Synovial fluid: pre-dose and Day 43
- PD assessment (sampling for serum cortisol measurement): 24 h samples during the in-patient periods from Day -1 to Day 1, Day 1 to Day 2, Day 14 to Day 15 and Day 42 to Day 43; single blood samples at Screening and Days 3, 4, 5, 8, 22, 29, and 36.
- PD assessment (urine samples for urinary free cortisol, 6-beta-hydroxycortisol and creatinine): 24 h urine collection from Day -1 to Day 1, Day 1 to Day 2, Day 14 to Day 15, and Day 42 to Day 43.



Study FX006-2011-002: Mean Concentration-Time Profiles of TCA in Plasma (Linear and Semi-Log Scales)

Day 1 to Day 3

Day 3 to Day 43

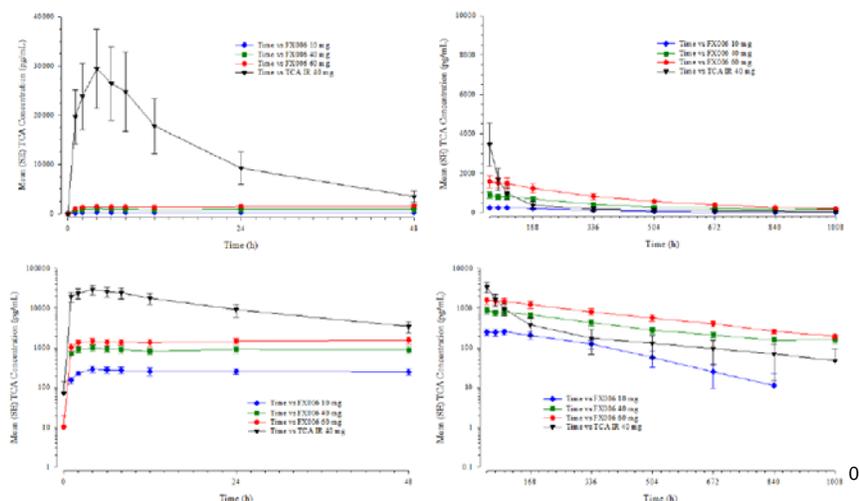


Table 12: Study FX006-2011-002: Mean (CV%) Plasma PK parameters of TCA

TCA PK Parameters	FX006 10 mg N= 5	FX006 40 mg N= 7	FX006 60 mg N= 7	TCA IR 40 mg N=5
AUC _{0-t} (pg* ^a h/mL)	89289 (52.9)	388012 (44.0)	698583 (42.1)	843834 (46.5)
AUC _{0-inf} (pg* ^a h/mL)	133019 ^d (33.6)	473116 (43.6)	803143 (38.6)	919128 (34.5)
AUC ₀₋₂₄ (pg* ^a h/mL)	6027 (41.0)	20837 (49.9)	32878 (44.0)	440304 (66.9)
CL/F (mL/h)	85682 ^d (49.0)	117663 (85.0)	92695 (64.2)	47566 (31.1)
C _{max} (pg/mL)	322 (33.6)	1028 (45.7)	1734 (48.1)	30132 (61.7)
t _{1/2} (h)	317 ^a (64.4)	370 (27.2)	363 (26.2)	387 (116.4)
t _{max} ^b (h)	94.9 (6.00, 95.4)	4.00 (2.00, 6.00)	8.02 (2.00, 94.4)	3.97 (1.00, 8.00)
MRT _{inf} (h)	428 ^b (51.3)	569 (26.2)	508 (22.1)	313 (136.9)

^a n=4, ^b Median (min-max)

- Dose proportional increase in C_{max} and AUC values for FX006
- Plasma exposures (C_{max} and AUC) for FX006 (10, 40 and 60 mg) are lower than TCA IR 40 mg
- Mean C_{max} for FX006 40 mg was ~ 30-fold lower than the mean TCA IR C_{max}

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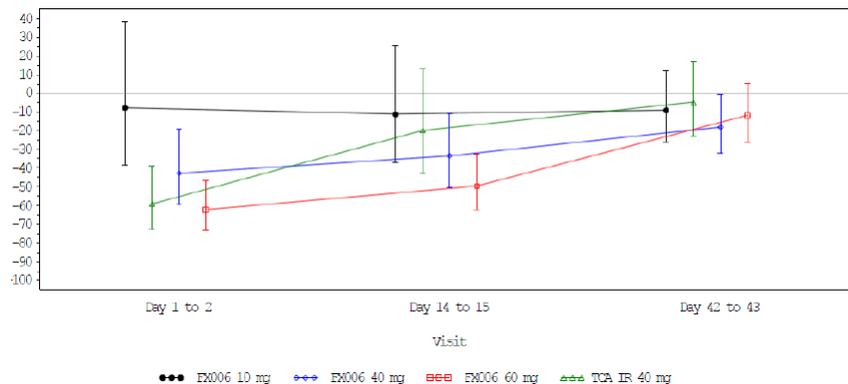
Day 43 Mean Concentration-Time Profiles of TCA in Synovial Fluid



Mean (solid line), Median (dashed line), Interquartile range (25% to 75% of data), Whisker bars (min and max values)

- Synovial samples were analyzed for 17 out of 24 patients (n = 5, FX006 10 mg; n = 5, FX006 40 mg; n = 4, FX006 60 mg; n = 3, TCA IR 40 mg)
- More TCA in the joint when compared to TCA IR administration after 6 weeks (geometric mean of 78757 pg/mL vs 42 pg/mL).

Geometric Mean Percent Difference from Baseline in Weighted Mean Serum Cortisol (nmol/L) by Visit: FAS Population



- Cortisol suppression that is dose- and time-dependent

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Table 11-3. Summary of Pharmacodynamic Analyses of Covariance: FAS Population

	LSMD vs TCA IR (90% CI)		
	10 mg FX006	40 mg FX006	60 mg FX006
Change from Baseline in Weighted Mean Serum Cortisol			
Day 1 to 2	125.1 (40.4, 260.9) p = 0.0078	39.8 (-9.6, 116.3) p = 0.1999	-7.8 (-40.4, 42.7) p = 0.7513
Day 14 to 15	10.7 (-26.0, 65.5) p = 0.6670	-17.1 (-42.8, 20.3) p = 0.3948	-37.1 (-56.7, -8.8) p = 0.0440
Day 42 to 43	-4.4 (-25.1, 22.1) p = 0.7525	-13.9 (-31.8, 8.8) p = 0.2832	-7.3 (-26.1, 16.2) p = 0.5664
Change from Baseline in 24-Hour Urinary Free Cortisol Excretion			
Day 1 to 2	256.5 (96.2, 548.0) p=0016	35.5 (-22.3, 136.1) p=0.3565	20.2 (-31.6, 111.0) p=0.5790
Day 14 to 15	32.4 (-18.4, 114.9) p=0.3279	-32.4 (-56.9, 6.0) p=0.1485	-52.0 (-70.1, -22.9) p=0.0150
Day 42 to 43	36.9 (-11.5, 111.7) p=0.2277	-21.6 (-48.6, 19.4) p=0.3291	10.5 (-26.8, 66.5) p=0.6809

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Effect on the HPA Axis

$$CCS\% = \frac{AUC_{BASELINE}^{COR} - AUC_{TREATMENT}^{COR}}{AUC_{BASELINE}^{COR}} * 100\%$$

Table 4: Median Cumulative Cortisol Suppression (CCS%)

Median Cumulative Cortisol Suppression (%)	10 mg FX006	40 mg FX006	60 mg FX006	TCA IR
Day 1 to 2 (24-hours)	18.8	43.3	61.4	66.0
Day 14 to 15 (Week 2)	12.5	25.6	33.7	21.4
Day 42 to 43 (Week 6)	10.2	16.8	4.9	6.1

- Sponsor claimed that it is unlikely that the doses of FX006 tested in this study will compromise the ability to mount a stress response in patients without previous impairment of HPA axis function because
 - Smaller CCS% in comparison to that (CSS% 80-90%) for other treatments (e.g., 5-10 mg BID chronic oral methylprednisolone (Meibohm et al., 1999) and chronic oral administration of 20 mg of prednisone for a period of 3 weeks (Xu et al., 2008))
- 40 mg FX006 vs TCA IR: although smaller CSS% in 24 h, greater CCS% at Week 2 and Week 6

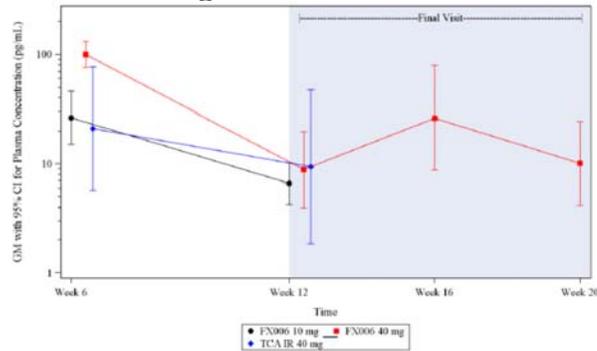
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Study FX006-2013-005

- Phase 2, OL in OA patients
- Objective: Local duration of exposure of TCA for FX006 relative to 40 mg TCA IR
- Treatments:
 - Single IA injection of 10 or 40 mg FX006 or 40 mg of TCA IR
- Blood and synovial fluid samples for drug concentration measurements were obtained from all patients prior to administration of study drug on Day1 and at the final visit. Blood samples were also obtained at Week 6.

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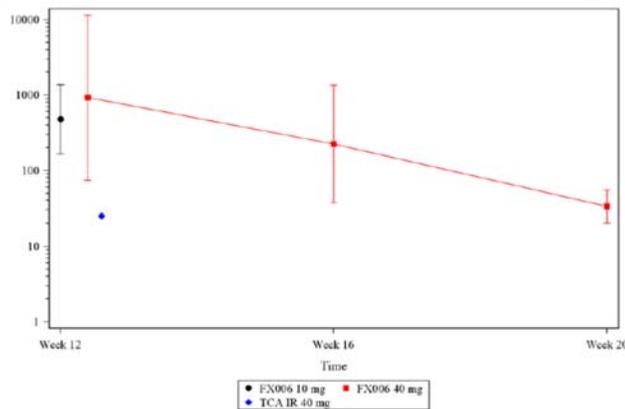
Study FX006-2013-005: GM with 95% CI for Plasma Drug Concentration of TCA



- At Week 6, plasma concentrations higher for FX006 40 mg than TCA IR 40 mg
- At Week 12, 4 of the 7 FX006 40 mg patients and 5 out of 6 TCA IR patients had concentrations below the LLOQ (10 pg/mL)

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Study FX006-2013-005: GM with 95% CI for Synovial



- At Week 12, synovial fluid concentrations higher for FX006 10 mg and 40 mg than TCA IR 40 mg
- All patients in TCA IR cohort had concentrations below the LLOQ (50 pg/mL)

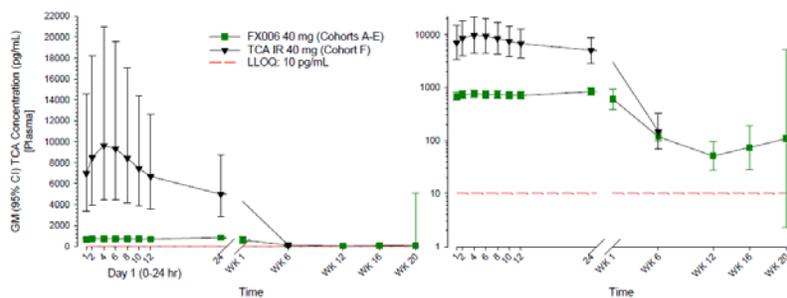
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Pivotal Comparative BA Study FX006-2015-009

- Phase 2, OL in OA patients
- Objective: Systemic PK and local extent and duration of exposure of TCA of a single IA injection of FX006 40 mg
- Treatments:
 - Single IA injection of 40 mg FX006 (5 mL injection volume – preparation used in the primary efficacy studies of FX006 and to-be-marketed preparation)
 - Single 1 mL IA injection of TCA IR (Kenalog®-40)
- Blood samples for PK: pre-dose and at 1, 2, 4, 6, 8, 10, 12, and 24 h, and at Week 6 (last post-treatment time point for TCA IR), 12, 16, or 20.
- Synovial Fluid: pre-dose and Week 1, 6, 12, 16, or 20
- Study results serve as the evidence to support the bioavailability “bridge” to Kenalog®-40, which is the reference listed drug supporting this 505(b)(2) NDA for FX006 40 mg.

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Figure 10: Study FX006-2015-009: Linear and Log Scale GM with 95% CI for Plasma Drug Concentrations (pg/mL) Curve - FX006 and TCA IR (Plasma Drug Concentration Population)



- Systemic exposures for FX006 40 mg were lower than those from the reference product (Kenalog®-40).

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Table 18: Study FX006-2015-009: Summary of Bioequivalence Geometric Mean Ratios (Comparison of FX006 40 mg and TCA IR) using Average Bioequivalence Methods)

Parameter / Statistic	FX006 40 mg (Test)	TCA IR 40 mg (Reference)
C_{max} (pg/mL)		
Geometric Mean (95% CI)	966.66 (822.07, 1136.69)	11064.68 (5406.47, 22644.56)
BE Test	Test/Reference	
BE Ratio (SE) ¹	0.08736 (0.23571)	
Lower 90% CI of Ratio	0.0590	
Upper 90% CI of Ratio	0.1294	
AUC_{0-24 hours} (h*pg/mL)		
Geometric Mean (95% CI)	17908.82 (15230.57, 21058.04)	173690.8 (90320.67, 334015.5)
BE Test	Test/Reference	
BE Ratio (SE) ¹	0.10311 (0.22356)	
Lower 90% CI of Ratio	0.0711	
Upper 90% CI of Ratio	0.1496	

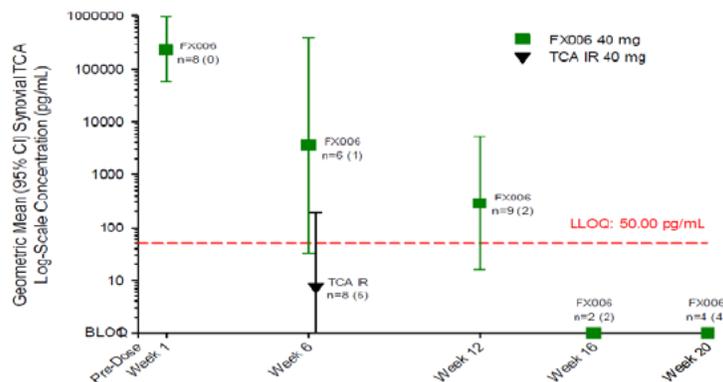
21

Table 18: Study FX006-2015-009: Summary of Bioequivalence Geometric Mean Ratios (Comparison of FX006 40 mg and TCA IR) using Average Bioequivalence Methods)

Parameter / Statistic	FX006 40 mg (Test)	TCA IR 40 mg (Reference)
AUC_{0-6 weeks} (h*pg/mL)		
Geometric Mean (95% CI)	508939.6 (430064.6, 602280.4)	3082835 (1840759, 5163016)
BE Test	Test/Reference	
BE Ratio (SE) ¹	0.16509 (0.20355)	
Lower 90% CI of Ratio	0.1176	
Upper 90% CI of Ratio	0.2317	
AUC_{0-∞} (h*pg/mL)		
Geometric Mean (95% CI)	543115.0 (379530.7, 777207.0)	1248903 (850704.8, 1833491)
Tests	Test/Reference	
BE Ratio (SE) ¹	0.43487 (0.29478)	
Lower 90% CI of Ratio	0.2651	
Upper 90% CI of Ratio	0.7135	

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Figure 11: Study FX006-2015-009: GM with 95% CI for Synovial Fluid Drug Concentration Curve- FX006 and TCA IR (Synovial Fluid Concentration Population)



Note: n=number of samples (number of samples BLOQ)

- At Week 6, synovial fluid TCA concentration for FX006 40 mg greater than that from TCA IR 40 mg

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Recommendation

- Filable from Clin Pharm perspective
 - The Sponsor stated that the to-be-marketed formulation/preparation was used in the pivotal comparative BA study (009) and primary Phase 3 trials
 - PK datasets and bioanalytical reports for all PK studies are included

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Back up Slide

Study 009

Table 20. Plasma PK Parameters Pooled across FX006 Cohorts (Plasma Drug Concentration Population)

Parameter	N	Mean	SD	Statistic				
				Geometric mean	Log Scale SD	95% CI	Median	Min ; Max
$t_{1/2}$ (h)	33	633.9	892.98	434.7	0.77	331.01 ; 570.80	347.0	61 ; 5199
t_{max} (h)	60	28.4	129.03	6.9	1.41	4.76 ; 9.89	7.0	1 ; 1008
C_{max} (pg/mL)	60	1143.7	611.06	966.7	0.63	822.07 ; 1136.69	1084.0	151 ; 2587
t_{last} (h)	60	1402.0	852.02	980.1	1.21	717.89 ; 1338.05	1008.0	24 ; 3360
C_{last} (pg/mL)	60	205.6	357.28	106.4	1.00	82.10 ; 137.94	100.9	18 ; 1865
$AUC_{(0-)} (h^*pg/mL)$	60	634513.5	408327.55	440718.6	1.19	324074.58 ; 599346.14	594399.7	3212 ; 1959054
$AUC_{(0-)}(Observed) (h^*pg/mL)$	33	842149.2	1062004.97	543115.0	1.01	379530.69 ; 777207.04	604588.3	26980 ; 6072359
$V_{(0)}(Observed) (mL/kg)$	33	0.0612	0.0536	0.0462	0.7320	0.0356 ; 0.0599	0.0393	0.0157 ; 0.2694
CL ([mL/h)/kg)	33	0.0002	0.0003	0.0001	1.0107	0.0001 ; 0.0001	0.0001	0.0000 ; 0.0015
MRT(Observed) (h)	33	874.2	1590.30	453.7	1.02	316.45 ; 650.50	369.3	90 ; 8944
$AUC_{(0-24\text{ hours})} (h^*pg/mL)$	60	21219.2	11325.62	17908.8	0.63	15230.57 ; 21058.04	20246.9	3212 ; 44992
$AUC_{(0.5-4\text{ weeks})} (h^*pg/mL)$	60	612105.0	355051.62	508939.6	0.65	430064.56 ; 602280.44	578785.9	69544 ; 1511471
$AUC_{(0.12\text{ weeks})} (h^*pg/mL)$	14	834563.1	639893.04	512607.9	1.33	237335.03 ; 1107155.94	14	834563.1

Source: Table 14.1.9.

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Table 21. Plasma PK Parameters- TCA IR (Plasma Drug Concentration Population)

Parameter	N	Mean	SD	Geometric mean	Statistic			Median	Min : Max
					Log Scale SD	95% CI			
$t_{1/2}$ (h)	14	146.9	213.29	62.9	1.40	21.05 ; 140.82		72.5	11 ; 810
t_{max} (h)	18	7.3	6.54	5.6	0.72	3.90 ; 3.00		6.0	2 ; 24
C_{max} (pg/mL)	18	21062.2	18466.79	11064.7	1.44	5466.47 ; 22644.50		20080.3	966 ; 65673
$t_{1/2}$ (h)	18	461.3	503.13	126.4	1.91	41.86 ; 326.89		24.0	24 ; 1008
$C_{1/2}$ (pg/mL)	18	6531.4	6876.80	1508.6	2.29	483.18 ; 4710.31		3662.6	18 ; 19039
$AUC_{(0-24)}$ (h*pg/mL)	18	1026652.2	1251334.91	594276.8	1.18	330930.30 ; 1067188.32		562754.5	18129 ; 4942351
$AUC_{(0-24)}$ (Observed) (h*pg/mL)	14	1567565.0	1246330.95	1248903.3	0.66	850704.77 ; 1833490.93		912554.0	454269 ; 4944898
$V_{(0)}$ (Observed) (mL/kg)	14	0.0073	0.0138	0.0029	1.2283	0.0014 ; 0.0059		0.0020	0.0008 ; 0.0519
CL (mL/h/kg)	14	0.0000	0.0000	0.0000	0.6650	0.0000 ; 0.0000		0.0000	0.0000 ; 0.0001
MRT(Observed) (h)	14	145.2	266.88	60.9	1.23	29.92 ; 124.00		47.8	14 ; 1027
$AUC_{(0-24 \text{ hours})}$ (h*pg/mL)	18	297545.3	222402.77	173699.8	1.31	90320.67 ; 334015.53		344196.3	17249 ; 686369
$AUC_{(0-6 \text{ weeks})}$ (h*pg/mL)	17	4415320.5	2997266.30	3082834.8	1.00	1840759.35 ; 5163016.13		4942351.4	548536 ; 9767522

Source: Table 14.1.5.1.

Figure 1: Overlay of Plasma Concentration Curves for FX006 40 mg

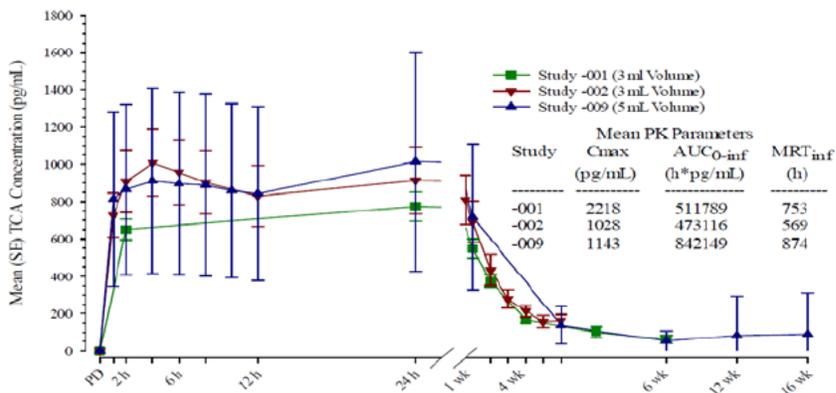


Table 6: FX006-2011-001 Bioanalytical Methods

Bioanalytical Report Number	FX006-2011-001
Species/matrix	Human plasma
Analyte/metabolite name(s)	Triamcinolone acetonide
Internal standard name(s)	Triamcinolone-6-d ₁ -acetonide-d ₆
Method description	LC-MS/MS
LLOQ (pg/ mL)	50.00
Standard curve concentration (pg/mL)	50.00 – 5000.00
QC concentrations (pg/mL)	150.00, 375.00, 2500.00, 3750.00
Within run precision (%CV)	1.98 to 6.39
Within run accuracy (%Bias)	-0.88 to 0.89
Between run precision (%CV)	2.59 to 5.69
Between run accuracy (%Bias)	-0.79 to 0.88

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Table 7: FX006-2011-002 Bioanalytical Methods

Bioanalytical Report Number	FX006-2011-002	
Species/matrix	Human plasma	Synovial fluid
Analyte/metabolite name(s)	Triamcinolone acetonide	Triamcinolone acetonide
Internal standard name(s)	Triamcinolone-6-d ₁ -acetonide-d ₆	Triamcinolone-6-d ₁ -acetonide-d ₆
Method description	LC-MS/MS	LC-MS/MS
Regression (weighing)	Linear (1/C ²)	Linear (1/C ²)
Sample Volume	0.100 mL	0.100 mL
LLOQ (pg/ mL)	50.00	49.74
Standard curve concentration (pg/mL)	50.00-5000.00	49.74-49740.00
QC concentrations (pg/mL)	150.00, 375.00, 2500.00, 3750.00	-
Within run precision (%CV)	1.88 to 7.15	-
Within run accuracy (%Bias)	-2.65 to 5.48	-
Between run precision (%CV)	1.56 to 7.02	-
Between run accuracy (%Bias)	-1.29 to 1.37	-

Note: Validation in human synovial fluid is non-GLP and no validation report is available

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Table 8: FX006-2013-005 Bioanalytical Methods

Bioanalytical Report Number	FX006-2013-005	
Species/matrix	Human plasma	Synovial fluid
Analyte/metabolite name(s)	Triamcinolone acetonide	Triamcinolone acetonide
Internal standard name(s)	Triamcinolone-6-d ₁ -acetonide-d ₆	Triamcinolone-6-d ₁ -acetonide-d ₆
Method description	LC-MS/MS	LC-MS/MS
LLOQ (pg/ mL)	<10.00	<50.00
Standard curve concentration (pg/mL)	10.00-1000.00	50.00-50000.00
QC concentrations (pg/mL)	30.00, 75.00, 500.00, 750.00	150.00, 2500.00, 25000.00, 37500.00
Within run precision (%CV)	0.47 to 7.47	1.31 to 3.93
Within run accuracy (%Bias)	-5.32 to 0.79	-1.11 to 4.53
Between run precision (%CV)	3.78 to 12.53	3.18 to 11.84
Between run accuracy (%Bias)	-3.28 to 0.82	-8.05 to -1.85

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Table 9: FX006-2015-009 Bioanalytical Methods

Bioanalytical Report Number	FX006-2015-009	
Species/matrix	Human plasma	Synovial fluid
Analyte/metabolite name(s)	Triamcinolone acetonide	Triamcinolone acetonide
Internal standard name(s)	Triamcinolone-6-d ₁ -acetonide-d ₆	Triamcinolone-6-d ₁ -acetonide-d ₆
Method description	LC-MS/MS	LC-MS/MS
LLOQ (pg/ mL)	<10.00	<50.00
Standard curve concentration (pg/mL)	10.00 to 5000.00	50.00-50000.00
QC concentrations (ng/mL)	30.00, 2500.00, 3750.00	150.00, 25000.00, 37500.00
Within run precision (%CV)	2.48 to 11.68	1.31 to 3.93
Within run accuracy (%Bias)	-2.93 to 1.85	-1.11 to 4.53
Between run precision (%CV)	3.78 to 12.53	3.18 to 11.84
Between run accuracy (%Bias)	-3.28 to 0.82	-8.05 to -1.85

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During study FX006-2015-009, a partial validation study of human plasma was required due to truncated range in several runs. Details of that partial validation method are provided below in [Table 10](#).

Table 10: FX006-2015-009 Partial Validation Methods

Bioanalytical Report Number	FX006-2015-009 Partial Validation Method
Species/matrix	Human plasma
Analyte/metabolite name(s)	Triamcinolone acetonide
Internal standard name(s)	Triamcinolone-6-d ₁ -acetonide-d ₆
Method description	LC-MS/MS
LLOQ (pg/ mL)	<10.00
Standard curve concentration (pg/mL)	10.00 to 1000.00
QC concentrations (ng/mL)	30.00, 500.00, 750.00
Within run precision (%CV)	0.47 to 7.47
Within run accuracy (%Bias)	-5.32 to 0.79

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02/06/2017

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