CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208845Orig1s000

SUMMARY REVIEW

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II
Division of Anesthesia, Analgesia, and Addiction Products

Clinical Memorandum

May 23, 2018

To: NDA 208845

From: Sharon Hertz, M.D.
Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

The applicant, Flexion Therapeutics, Inc., recently raised concerns about statements in the Pharmacology/Toxicology NDA Review and Evaluation, dated September 8, 2017, and the Cross-Discipline Peer Review Summary Review, dated October 6, 2017, that refer to ZILRETTA (triamcinolone acetonide extended-release injectable suspension) causing "cartilage loss" or "cartilage reduction."

The concerns raised by the applicant are under review by DAAAP.

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/s/

SHARON H HERTZ
05/24/2018

Cross-Discipline Peer Review
Summary Review

Date	October 6, 2017
From	Robert Shibuya, MD
Subject	Cross-Discipline Peer Review
NDA/BLA # Supplement#	208845
Applicant	Flexion Therapeutics, Inc.
Date of Submission	December 8, 2016
PDUFA Goal Date	October 8, 2017
Proprietary Name / Established (USAN) names	Zilretta
Dosage forms / Strength	Injection, 32 mg
Proposed Indication	1. Management of osteoarthritis pain of (b) (4)
Recommended:	Approval

1. Introduction

Flexion Therapeutics, Inc. ("Applicant") submitted this 505(b)(2) new drug application (NDA), proposing an indication of management of osteoarthritis (OA) pain (b) (4) The drug is administered by intra-articular (IA) injection. Zilretta (known as "FX006" through development) is a reformulation of triamcinolone acetonide (TCA), a synthetic corticosteroid originally approved in 1965. TCA is approved in a wide variety of formulations (topical, injectable, nasal spray, tablets, metered dose inhalers, and syrup for a panoply of corticosteroid indications.

Zilretta is formulated as a suspension of poly(lactic-co-glycolic acid) (PGLA) microspheres and is designed to reside in the joint longer and to reduce systemic exposure to the steroid compared to Kenalog®-40, the immediate-release formulation of TCA injection (IR TCA) approved in 1965. The drug product is a dry powder that is reconstituted with diluent (which contains carboxymethylcellulose sodium (b) (4) Throughout the development process, the to-be-marketed dose was considered to be 40 mg. However, during the review cycle, we learned that the delivered dose is (b) (4) 32 mg (b) (4) mL), not the nominal 40 mg (5 mL). As will be described in greater detail later, the viscosity of the reconstituted drug product has the consequence of a substantial proportion of the volume clinging to the vial and not available for aspiration into the syringe for injection. While the submission and the FDA reviews refer to a 40 mg dose, the labeling will correctly specify a dose of 32 mg.

The Applicant submitted data to address all required elements for a 505(b)(2) NDA. The extended-release formulation has resulted in certain CMC issues as described above. The nonclinical program showed some excess toxicity for the Zilretta formulation vs. IR TCA although it is not clear to what degree the PLGA component affected the observed results. Flexion underwent a GMP inspection in June 2017 to assess the device constituent manufacturing. A 7-item Form FDA-483 was issued documenting deficiencies with validation, design controls, complaint files, CAPA and purchasing controls. The site was able to adequately respond to the inspectional findings.

From the clinical perspective, the application is supported by a single adequate and well-controlled study in patients with OA of the knee and two supportive, dose-finding studies, also in the knee. An efficacy study was required to demonstrate that the PK profile provided by this novel, extended-release formulation was suitable to provide efficacy for the intended indication. The Applicant was required to conduct two pharmacodynamic studies to assess key safety questions. One examined the effect on the hypothalamic-pituitary-adrenal (HPA) axis and the other assessed the effects on blood glucose in diabetic patients in patients injected with Zilretta compared to IR TCA. Given that the development objective of the Applicant was to exploit the properties of the formulation to increase TCA residence time in the joint and reduce systemic exposure, this review will also focus on what conclusions can be drawn from the pharmacokinetic, pharmacodynamic, and clinical trial data submitted. (b) (4)

2. Background

Osteoarthritis (OA) is a very common condition primarily manifested by symptoms of pain and stiffness and signs of cartilage deterioration, bony changes, and inflammation in the affected joints. OA is a major cause of disability, limiting mobility with downstream negative effects on overall health. OA is initially treated with lifestyle modification followed by analgesics with ascending potency and toxicity (acetaminophen (APAP), nonsteroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, and opioids). Affected joints can also be injected with corticosteroids or hyaluronic acid. The other treatment is joint replacement surgery, usually performed after more conservative measures have failed, assuming the patient presents an acceptable surgical risk.

The Applicant has developed Zilretta with the goal of improving one of the accepted OA therapies, injection of IR TCA. The Applicant notes that the literature suggests that the analgesic effect of intra-articular IR TCA appears to be short-lived (Friedman and Moore 1980, Gaffney et al 1995, Bellamy et al 2006). The Applicant also believes that reduction of systemic exposure to the corticosteroid is a clinical benefit of their formulation.

As noted in Section 1 of this review, IR TCA injection (Kenalog-40) is approved for a large number of indications. The wording of the osteoarthritis indication reads, "The intra-articular…administration of Kenalog-40 Injection is indicated as adjunctive therapy for short-term administration (to tide the patient over in an acute episode or exacerbation) in…osteoarthritis." The proposed indication "management of osteoarthritis pain of (b) (4)

[redacted]" varies from the relevant IR TCA indication and one adequate and well-controlled study was required to support a finding of efficacy.

The package insert for IR TCA contains Warnings and Precautions language appropriate for all systemic corticosteroids. However, IR TCA is approved via both the IA and intramuscular routes and for a wide variety of indications for which corticosteroids are used. The approved IR TCA labeling does not inform the level of risk for systemic corticosteroid side effects when IR TCA is administered via the IA route. As required in a 505(b)(2) submission, the Applicant conducted pharmacokinetic studies to inform the local and systemic levels of TCA. Those data show less systemic exposure to the TCA molecule when 32 mg of Zilretta is injected into the knee compared to 40 mg of IR TCA. The level of TCA systemic exposure that would be expected to result in a clinically meaningful decrease in systemic corticosteroid risk is not established. Thus, Flexion has provided data to indirectly inform potential safety benefits. The efficacy, adverse event, and laboratory data from clinical trials and the two pharmacodynamic studies do not appear to be sufficiently clinically meaningful [redacted]

3. CMC/Device

- General product quality considerations

Drug substance
Sukhamaya Bain, PhD conducted the drug substance review with secondary concurrence by Donna Christner, PhD and they have recommended approval.
The manufacture, release and stability of the drug substance, triamcinolone acetonide, is referenced to DMF [redacted] The DMF is adequate in support of the use of TCA in the preparation of the Zilretta® drug product. The retest date of [redacted] is assigned to triamcinolone acetonide drug substance, [redacted]

The process review of the drug product manufacture recommends the manufacture of Zilretta as adequate. Sufficient data is provided to ensure the adequacy of the drug product from the biopharmaceutics prospective.

Drug product
Valerie Amspacher, PharmD conducted the drug product review with secondary concurrence from Julia Pinto, PhD. The drug product components are the [redacted] drug powder and sterile diluent that are both contained in clear glass vials with clear labels. The carton also contains a vial adapter to allow the direct connection of a luer-lock syringe to the vial containing drug. The Instructions For Use (IFU) indicate that vials are cleaned, the vial adapter is attached to the drug vial, diluent is drawn into the syringe, the needle is removed, the diluent is delivered to the drug vial using the vial adapter, drug is reconstituted and mixed, the suspension is drawn back into the syringe,

a new needle is attached, and the drug is injected. The vial adapter is used in several other drug products and healthcare providers are familiar with its use. Thus, no human factors study was required or conducted.

For the convenience of the reader, the assembled vial adapter, drug vial, and syringe are shown below in this figure.

(b) (4)

The reconsitituted drug product for injection is a thick, viscous suspension. The drug vial is reconstituted with 5 mL of diluent. As some of this viscous suspension will cling to the vial, it is not possible to aspirate the full volume of the vial into a syringe for injection. The CMC team had cycles of Information Requests and responses with the Applicant to adequately define the dose delivered and the Applicant was able to address the concerns of the CMC team. The remainder of the application was acceptable from the CMC perspective.

- Facilities review/inspection

  Drug substance and drug product facilities have been inspected with a recommendation of adequate. CDRH/OC has reviewed the vial adapter manufacturing for compliance of

the 820 regulations. The CDRH/OC reviewer recommends the manufacturer as adequate in support of this NDA but with a post-marketing inspection required.

- Other notable issues

  The CMC microbiology review was conducted by Maria Martin Manso, PhD with secondary concurrence by John Metcalfe, PhD. No microbiology deficiencies were identified and the microbiology team has recommended the application for approval on the basis of sterility assurance.

  LCDR Keith Marin and CDR Alan Stevens of CDRH reviewed the risk analysis and data related to the vial adapter and have recommended approval.

  OPQ's final recommendation is as follows:

Adequate data [are] provided to ensure the identity, quality and purity of the drug substance and drug product manufactured as described in this NDA. Further the overall facilities recommendation is adequate. Therefore this NDA is recommended for approval by the OPQ review team.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was conducted by Misol Ahn, PhD with secondary concurrence by Jay Chang, PhD and Dan Mellon, PhD. The pharm/tox team has recommended approval for the proposed single-use indication.

With the exception of the PLGA microspheres, the excipients in Zilretta are qualified for safety via the intraarticular (IA) route. Due to the PLGA component, the Applicant conducted single- and repeat-dose IA toxicity studies. Briefly, the studies showed microscopic changes (multinucleated macrophages, lymphoplasmacytic infiltration, and hyperplasia) associated with Zilretta. Similar changes were also observed with IR TCA although they were of shorter duration. The pharm/tox team believes that the TCA itself may be contributing to these changes. Special stains showed dose-related cartilage reduction which was severe at the highest Zilretta dose tested compared to slight to moderate changes with IR TCA. The cartilage damage recovered by 4 months for IR TCA compared to almost complete recovery at 9 months (end-of-study) for Zilretta. The pharm/tox team writes, "Therefore, the data may not adequately support the safety of Zilretta if the Applicant pursues a repeat use or chronic indication in the future from a nonclinical perspective." The container-closure system was justified for safety based on adequate extractables and leachables data. Flexion is referencing Kenalog for the other aspects of the nonclinical package, augmented with a literature search to address the effects of TCA on reproduction and embryonic development. The nonclinical team has recommended inclusion of some of the reproductive toxicology data from the literature into labeling.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by Wei Qiu, PhD with secondary concurrence from Yun Xu, PhD. The clinical pharmacology team has recommended approval of this NDA.

As a 505(b)(2) application, the Applicant was required to conduct a bridging pharmacokinetic (PK) study to Kenalog®-40 (IR TCA), the identified listed drug. This was accomplished in Study FX006-2015-009 (Study 009), an open-label, comparative bioavailability study using a single IA injection of Zilretta 40 mg (delivered 32 mg) vs. IR TCA, 40 mg in patients with OA of the knee. In Study 009, both plasma and synovial fluid were sampled for TCA. The sample size for this study was large for a Phase 1 PK study because, in the Zilretta-treated patients, synovial fluid was sampled for TCA concentration at 1, 6, 12, 16, and 20 weeks post injection and the Applicant wanted to avoid serial arthroscentesis. This required five cohorts for patients randomized to Zilretta. One cohort of 18 patients was used for the IR TCA arm who underwent synovial fluid sampling at Week 6 only. Plasma was sampled at close intervals for 12 hours following injection, then at Hour 24 and Week 6 and the corresponding late synovial fluid sampling visit (where applicable).

Key pharmacokinetic data for the plasma TCA levels are summarized below from Dr. Qiu's review.

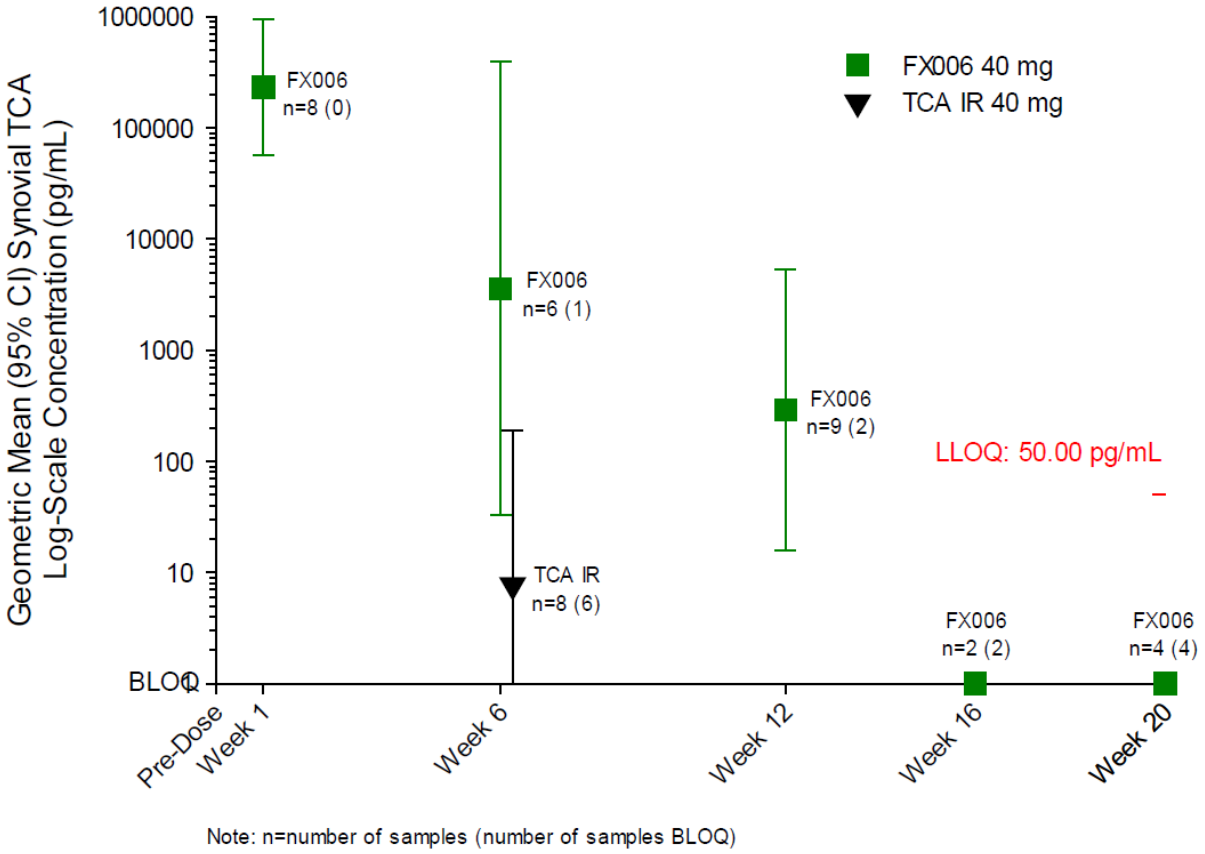
Mean (SD) TCA Plasma Pharmacokinetic Parameters for a Single Dose IA Injection of 40 mg FX006 and 40 mg TCA IR and Statistical Analysis (Study -009)

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%)			

The plasma PK data show that Zilretta (FX006) had lower Cmax and AUC than IR TCA.

The figure below summarizes the synovial fluid levels of TCA from 1 to 20 weeks following injections with Zilretta or IR TCA.

GM [geometric mean] with 95% CI for Synovial Fluid Drug Concentration Curve – FX006 and TCA IR (Synovial Fluid Concentration Population)



Source: Study 009 CSR, Figure 2, p 79/106

The analysis of serial synovial fluid samplings supports the notion that the Zilretta formulation is likely to result in higher synovial fluid TCA concentrations for a longer period of time. However, since synovial fluid in the IR TCA cohort was only sampled once, the findings are not definitive.

Furthermore, I note that Study 009 did not attempt to establish the clinical significance of the observed differences in plasma or synovial fluid pharmacokinetics. As will be discussed later, we can only infer whether the difference in systemic exposure is clinically meaningful indirectly. It is also not known whether the prolonged presence of triamcinolone in the synovial fluid will enhance efficacy over time with repeat injections or result in increased adverse events.

Dr. Qiu notes that plasma PK was also evaluated in Studies FX006-2011-001, FX006-2011-002 and FX006-2013-005. These studies differed from Study 009 in that they used a smaller injection volume of 3 mL compared to the to-be-marketed injection volume of 5 mL. Dr. Qiu notes that these studies also showed lower systemic exposure to TCA compared to IR TCA.

One other study (Study 005) also evaluated synovial fluid. Dr. Qiu notes that, at Week 12, the geometric mean synovial fluid TCA concentrations for patients injected with Zilretta was 923.7 pg/mL (95% CI: 74.24, 11492.46). All patients injected with IR TCA had concentrations below the LLOQ of 50 pg/mL at Week 12. Again, the Applicant did not attempt to correlate these findings with clinical outcomes.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The clinical review was conducted by Pamela Horn, MD. Dr. Horn has recommended approval from the clinical perspective although, among other comments, she notes that the indication (b) (4) to OA of the knee and the labeling should indicate that the approval is for a single injection of drug.

The statistical review was conducted by Katherine Meaker, MS with secondary concurrence by David Petullo, MS. The statistical team has recommended approval.

(b) (4)

As described in the clinical and statistical reviews, the clinical development plan was discussed and agreed upon in several meetings dating to the PIND meeting for IND 111325 in 2011. During the Pre-NDA meeting, the Agency confirmed that one adequate and well controlled study would support a finding of efficacy for this 505(b)(2) application.

There are three studies informing the efficacy of Zilretta summarized in the table following which is truncated and modified slightly from Dr. Horn's review.

Study Number	Treatment Arms in Study				
	FX006 10 or 20 mg	FX006 40 mg	FX006 60 mg	Placebo	TCA IR 40 mg
008		X		X	X
006	X (20 mg)	X		X	
001	X (10 mg)	X	X		X

Study 008, the pivotal study, was a randomized, double-blind, active- and placebo-controlled study comparing a single 40 mg IA injection of Zilretta against placebo and 40 mg of IR TCA in adults with OA of the knee. The pharmacist who prepared the syringe for injection and the healthcare provider who performed the injection were unblinded but the patient and all other staff were blinded and contact between blinded and unblinded staff was not permitted. Zilretta and placebo were delivered in a nominal 5 mL volume; IR TCA was delivered in 1 mL. The study enrolled appropriate patients with pain between 5/10 and 9/10 due to knee OA. The protocol excluded patients with a body mass index >40 kg/m^2. Pain intensity data were collected daily for 24 weeks with the primary endpoint being calculated at 12 weeks. Typical OA efficacy data such as WOMAC pain and function and a patient global impression of change were also collected.

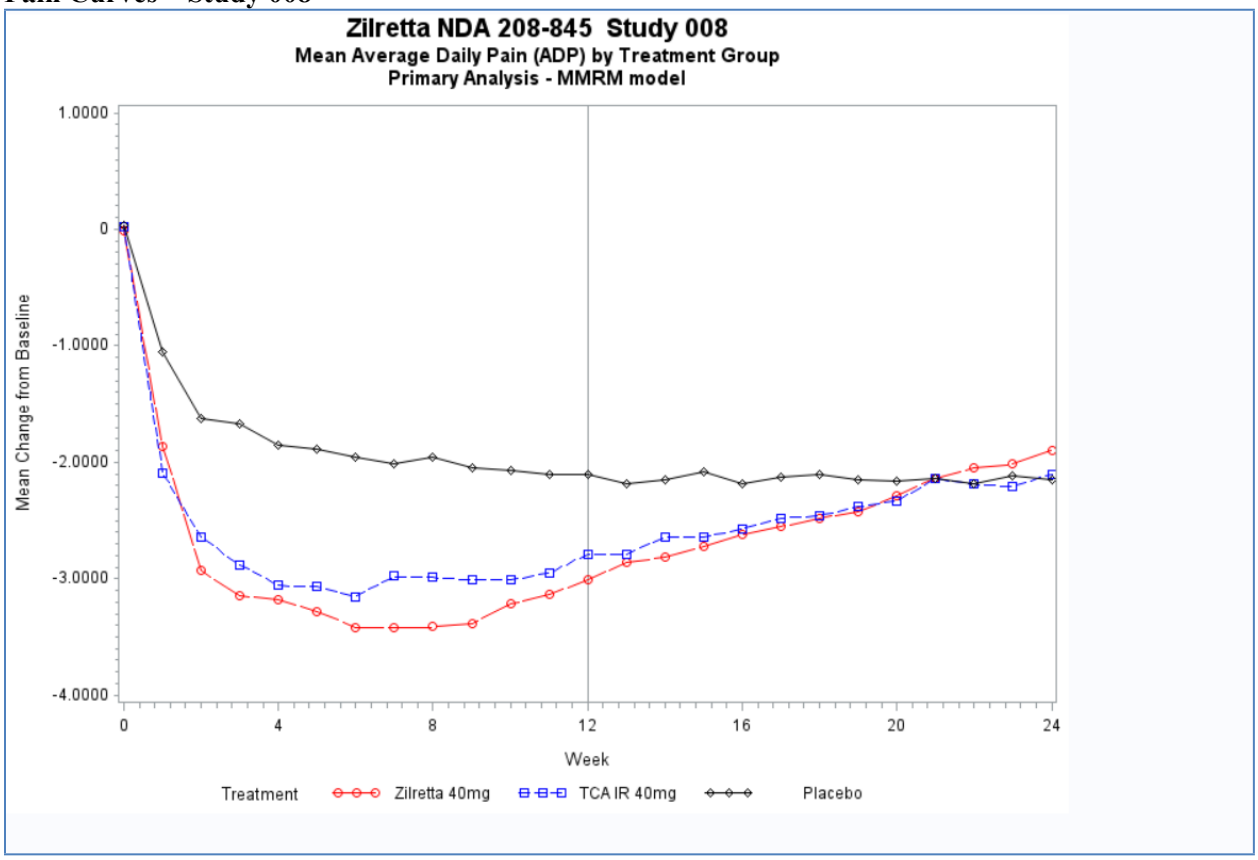
A total of 486 patients were randomized which slightly exceeded the planned sample size of 450. No significant imbalances in the baseline characteristics were noted and there were no issues with study conduct. The primary efficacy endpoint was the change from baseline to Week 12 in the average daily pain scores. The primary comparison was Zilretta vs. placebo with a prespecified secondary endpoint of Zilretta vs. IR TCA.

Efficacy Analysis Results (Study 008)

FAS Pt. Popln.		**Zilretta 40mg N=161**	**Placebo N=162**	**TCA IR 40mg N=161**
Change from Baseline to Week 12 in Average Daily Pain	Baseline Mean (SD)	6.3 (0.9)	6.3 (1.0)	6.2 (0.9)
	Chg Wk 12: Mean (SD)	-3.1 (2.4)	-2.2 (2.1)	-2.8 (2.1)
	LS Mean (SE)	-3.1 (0.2)	-2.1 (0.2)	-2.9 (0.2)
	LSM Diff. from Placebo	-0.98		
	2-sided p-value	<0.0001		
	LSM Diff. from TCA IR	-0.26		
	2-sided p-value	0.296		

Source: Ms Meaker's review, limited to primary endpoint

Pain Curves – Study 008



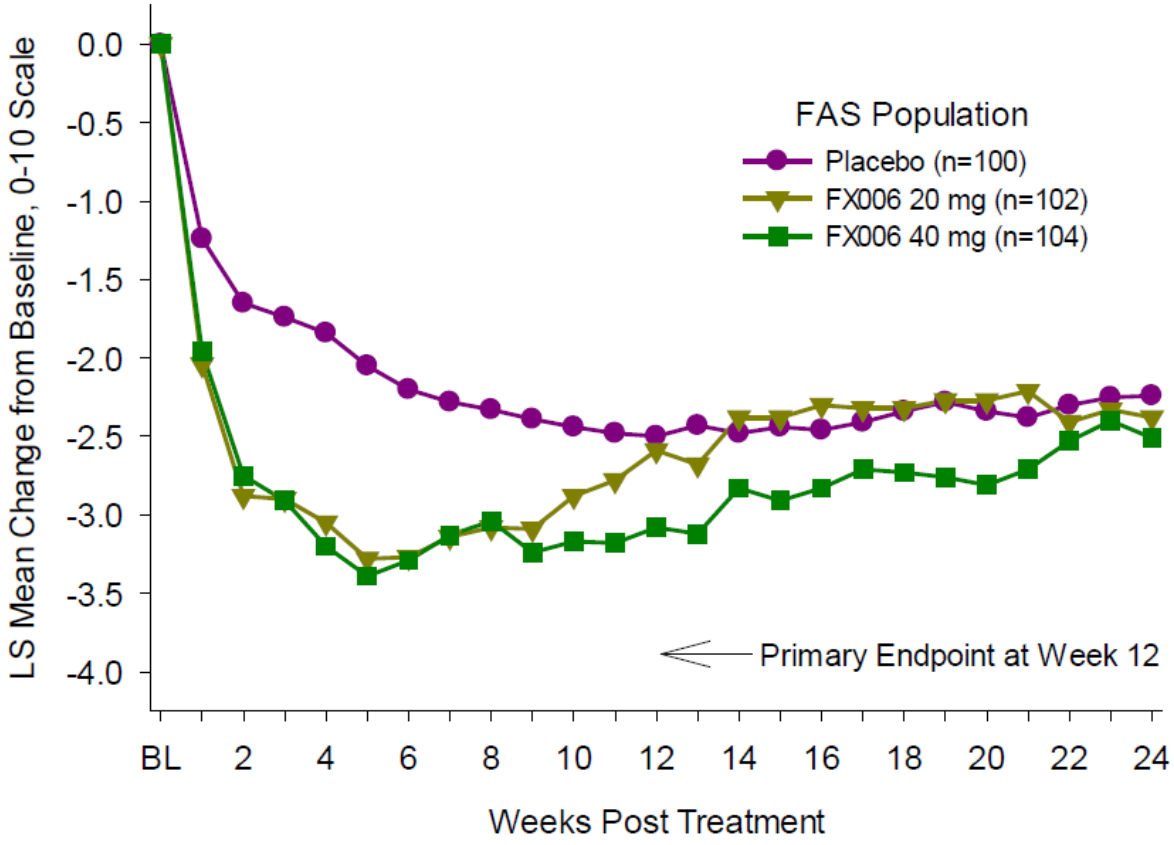
Source: Ms. Meaker's review

The sensitivity analyses for Study 008 supported the primary efficacy analysis.

Two other studies were used to support the choice of dose (40 mg nominal). Study 006 was a randomized, double-blind study similar in most respects to Study 008. As discussed in Ms. Meaker's review, this study showed a trend toward a benefit for Zilretta 40 mg compared to placebo although the p-value calculated (0.08) did not meet statistical significance. Ms. Meaker noted a slightly larger placebo effect in Study 006 compared to Study 008 with similar treatment effect sizes for Zilretta 40 mg and clearly demonstrated the superimposition of the corresponding curves from both studies in Figure 3 from her review. Ms. Meaker and Dr. Horn have opined that Study 006 supports the finding for efficacy from Study 008.

The figure below shows the pain curves for Study 006. The curves for 20 and 40 mg superimpose until Week 8 where the 40 mg dose shows a sustained reduction in pain intensity which supports the choice of the 40 mg for dose for approval.

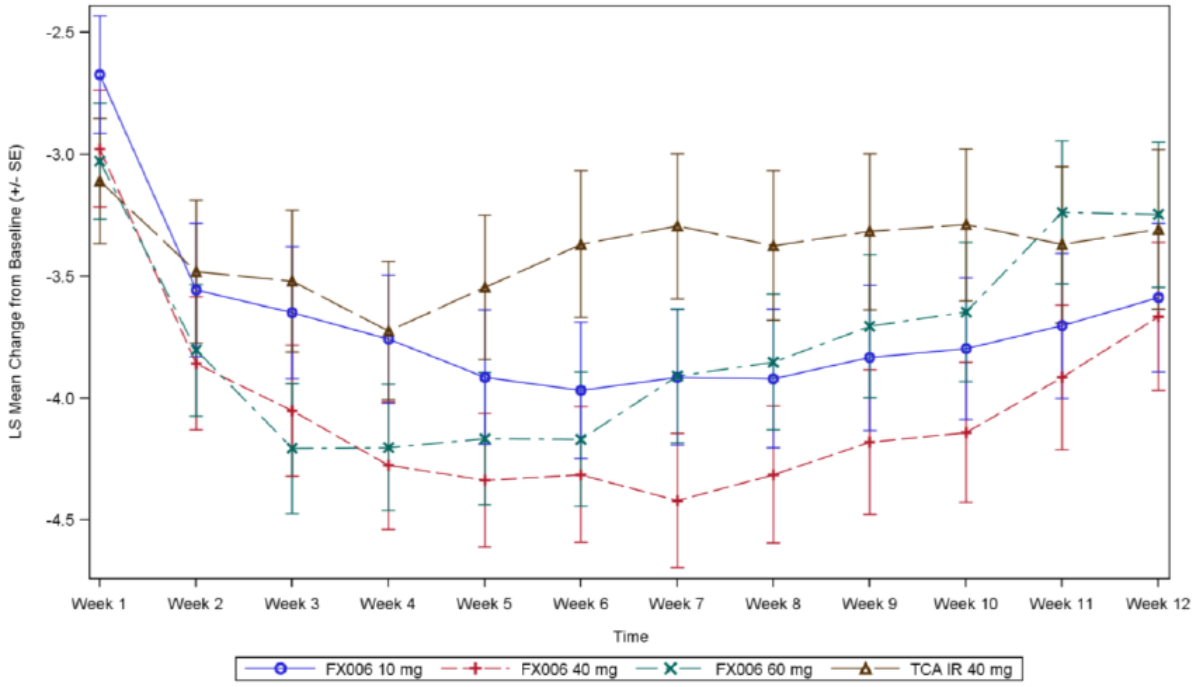
Study 006: Least Squares Mean Change from Baseline in the Weekly Mean of Average Daily (24-hour) Pain Intensity Score through Week 12 (Primary Endpoint) and Week 24 (Secondary Endpoint) (FAS; N=306)



Source: Study 006 CSR, page 66/133

Briefly, Study 001 was a randomized, double-blind study of Zilretta, 10, 40, and 60 mg against IR TCA, 40 mg. The pain curves shown in the figure below do not show clear dose response. However, the Applicant notes that the 60 mg dose did not perform any better than 40 mg. This study reasonably justifies the 40 mg dose. While there appears to be some curve separation between the IR TCA and Zilretta 40 mg at certain points in the study, the p-value at Week 12 for IR TCA vs Zilretta 40 mg is 0.2128 (Table 11-3 of CSR).

Study 001: LS [least squares] Mean Change from Baseline (±SE) in Weekly Average Daily Pain Intensity Score (0-10 NRS) Over Time (FAS; N=228)



Source: Study 001 CSR, page 86/593

Efficacy Conclusions:

1. The Applicant has met the statutory requirement for substantial evidence of efficacy in the knee.
2. The selected dose of 40 mg is justified, predominantly due to curve separation after 8 weeks compared to 20 mg and no evidence of greater efficacy at 60 mg.
3. There is some suggestion that, compared to 40 mg of IR TCA, 40 mg of Zilretta may offer a small difference in efficacy around Weeks 7 and 8. However, at 12 weeks, the established standard for the comparison of efficacy for products for osteoarthritis, there is no difference between Zilretta and IR TCA.

8. Safety

Safety data from clinical trials in patients with osteoarthritis:

At the Pre-NDA meeting a final safety database size of at least 400 was agreed upon. The final safety database contains 666 patients and subjects who received any dose of Zilretta and 424 at the to-be-marketed dose.

The safety monitoring in the clinical development program was adequate and included standard safety monitoring (physical exams, vital signs, ECG, clinical laboratory evaluations, and adverse event reporting). In light of the route of administration, there were clinical assessments of the index knee at each visit and plain radiographs were conducted at screening and at end-of-study in Study 008.

The demographics of the exposed population were reflective of the patient population eligible for treatment with Zilretta with a mean age of 61 years and slight female predominance. US sites enrolled 46% of the patients. Also typical for OA patients, the Body Mass Index (BMI) was high (median and mean both >30 kg/m^2). Dr. Horn noted that the protocol excluded patients with BMI over 40 kg/m^2. While a substantial proportion of Americans have extreme obesity, there were no trends of greater toxicity with greater BMI in the safety data and the efficacy data also showed no trends by BMI. Thus, I do not recommend any limitation of use for very elevated BMI.

The major safety findings were unremarkable. There were no deaths or problematic cases in the serious adverse events or the adverse events leading to discontinuation although, as a single-dose study, the discontinuation rate would be expected to be low (1.8%). The serious adverse event rate was 2.3% for all Zilretta-treated patients versus 1.1% in placebo and 2.6% in IR TCA-treated patients.

The common adverse events also did not reveal any unexpected signals. In most cases, Zilretta had an adverse event profile similar to placebo and was clearly no worse than IR TCA. The 120-Day Safety Update was submitted on April 7, 2017 and reported that 107 subjects had been enrolled and injected in Study 011 (a repeat injection study). No patients had received a repeat injection. The Applicant reported no deaths, SAEs, or discontinuations due to AE. Flexion also noted that all AEs (n=7) were Grade 1 except for one Grade 2 event of elevated temperature.

To summarize, the safety profile for Zilretta, as inferred from the OA trials, showed no unexpected signals or signals that appeared to be related to the formulation. While Zilretta's adverse event profile did not look worse than IR TCA, it did not look better either. There was no clinically meaningful difference in safety between patients treated with either active agent.

Safety data from special pharmacodynamic studies:

As requested at the Pre-IND meeting, the Applicant conducted a study to assess the effects of Zilretta on the HPA axis. The Applicant also conducted a study in diabetics to assess the effects of Zilretta on blood glucose.

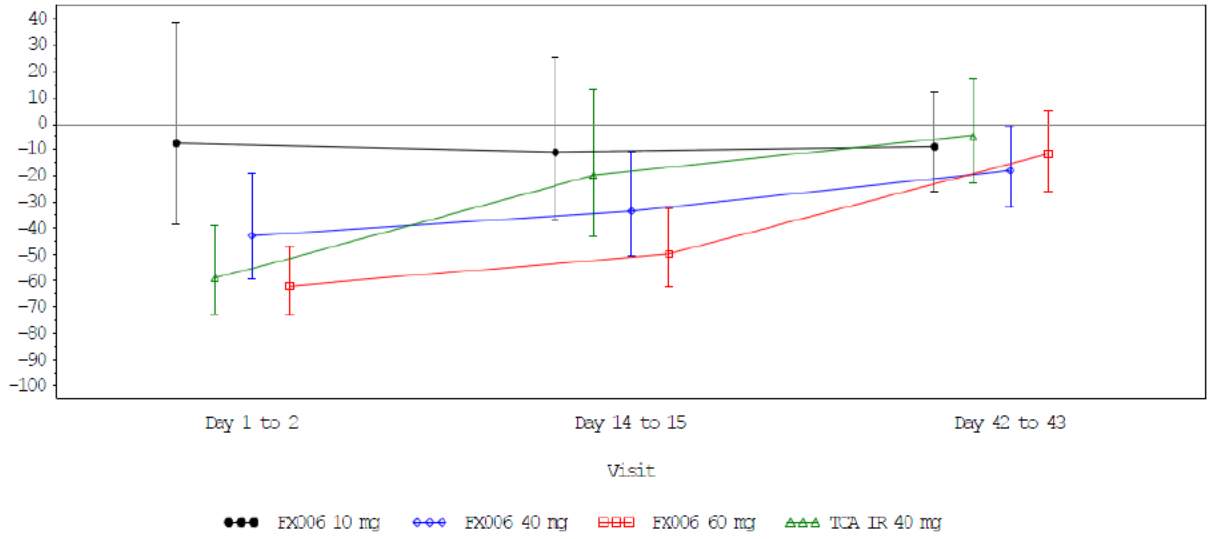
Drs. Horn and Qiu have described both studies in their reviews and the Division obtained consults from the Division of Metabolic and Endocrine Products (DMEP) to provide expert opinion on the interpretation of the results. The studies and DMEP's comments will be summarized here. Please see the corresponding reviews and consults for details.

Study 002

This was a randomized, double-blind, active-controlled study of adults with OA of the knee. A total of 24 patients were enrolled, randomized (1:1:1:1) and treated with a single injection of 10, 40, or 60 mg of Zilretta or 40 mg of IR TCA into the knee. Blood and urine were collected for cortisol levels for six weeks post injection. The DMEP consultants opined the urinary cortisol was not useful to assess HPA suppression in this setting.

The figure below shows the mean suppression of serum cortisol by treatment group over time.

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



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

Note: Cortisol concentrations reported as "xx.x" nmol/L were evaluated as "1/2 xx.x" nmol/L.

Source: CSR, Study 002, page 61/555

DMEP drew the following key conclusions.

1. The study lacked any clinical assessment of adrenal insufficiency, did not employ dynamic cortisol testing, and lacked standardization around serum cortisol collection.
2. The data suggest systemic absorption of Zilretta and some degree of HPA axis suppression with all doses of drug.
3. "The submitted data **does not provide** convincing evidence that clinically relevant HPA axis suppression that puts a patient at risk for development of adrenal insufficiency is **not a** risk associated with FX006 use [emphasis from DMEP]."
4. For labeling, DMEP recommended adding some specific language around this risk and deleting language proposed by the Applicant that reads, (b) (4)

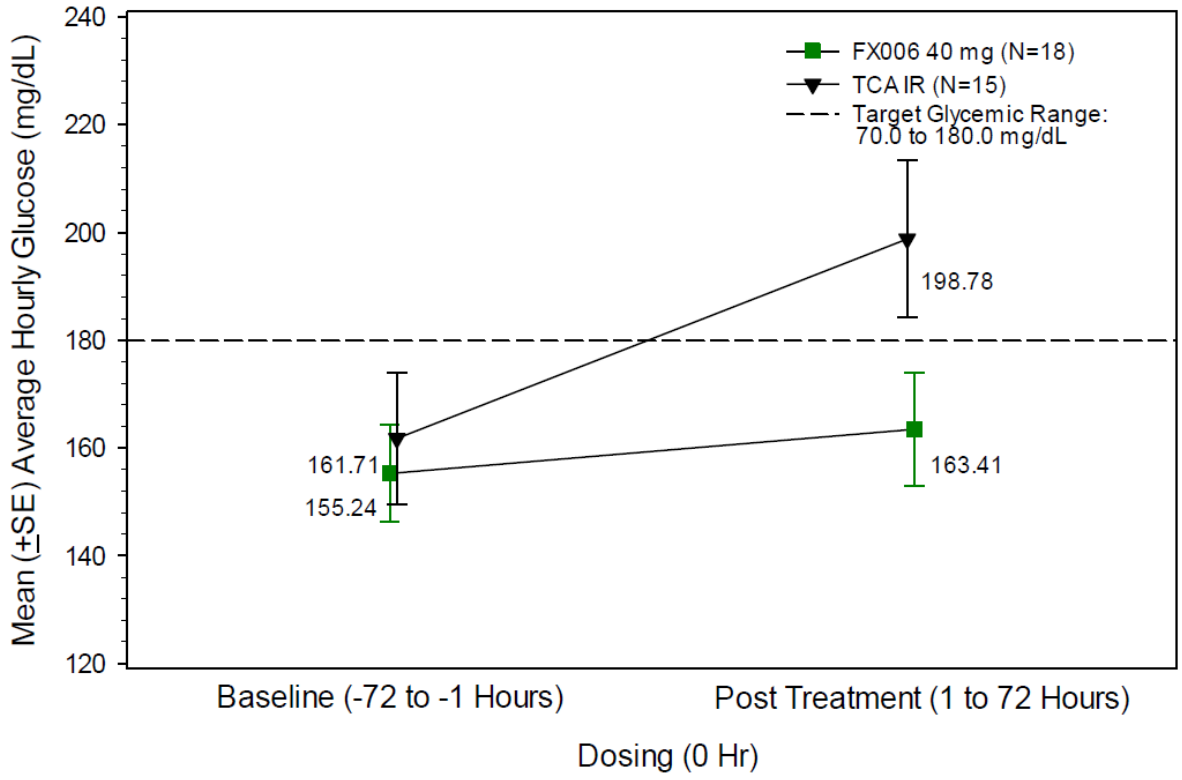
Study 010

This was a randomized, double-blind, active-controlled study in adults with Type 2 Diabetes (T2D) and OA of the knee. A total of 33 patients were randomized (1:1) to receive 40 mg Zilretta or 40 mg of IR TCA as a single knee injection. This study had an issue with study conduct (errors in treatments received vs. assigned). The Applicant presented the results as treatments received, not assigned. Blood glucose levels had been collected for 1 week prior to

injection and for 2 weeks following the injection using a continuous blood glucose monitoring device.

Flexion showed a difference ($p<0.05$) between Zilretta and IR TCA in mean blood glucose from baseline to Days 1-3 (the primary endpoint) as shown in the figure below.

Mean Average Blood Glucose (mg/dL) at Baseline and 72 Hours Post-Treatment (-72 Hours to 72 Hours)



Source: CSR, Study 010, page 66/94.

DMEP drew the following key conclusions.

1. The results were reported on an "as treated" analysis, deviating from the ITT principle.
2. Continuous blood glucose monitoring has accuracy limitations.
3. The clinical significance of the difference observed is unclear.
4. One key labeling recommendation was deletion of language proposed by the Applicant (b) (4) The relevant text proposed by Flexion is reproduced verbatim below.

(b) (4)

(b) (4)

5. The results of Study 010 are intriguing (b) (4)

In summary, the safety data support the conclusion that Zilretta is similar to both placebo and IR TCA in local toxicity. Regarding hyperglycemia, I note that Table 14.3.1.2.A of the ISS shows "Blood Glucose Increased" in 1 of 442 patients treated with Zilretta compared to 1 in 260 for IR TCA, which is not different. The special pharmacodynamic studies provided some evidence that, compared to 40 mg of IR TCA, 40 mg of Zilretta causes less HPA axis suppression and less elevation of blood glucose in diabetics. However, DMEP has concluded that the effect on HPA axis does not preclude the risk of adrenal insufficiency and the clinical significance of the differences in blood glucose in the three days after injection is uncertain. (b) (4)

9. Advisory Committee Meeting

No advisory committee was held for this application.

10. Pediatrics

Osteoarthritis is on the list of waived indications for pediatric studies. The Pediatric Review Committee agreed with the waiver.

11. Other Relevant Regulatory Issues

Earlier in 2017, McAlindon et al published a randomized, double-blind, placebo-controlled study in 140 patients with Kellgren-Lawrence 2-3 OA of the knee. Patients were randomized to injections of IR TCA, 40 mg or saline to occur every 12 weeks for 2 years. Patients were followed with WOMAC scores and, notably, MRIs of the knee at Months 0, 12, and 24. The authors found little benefit to the injection of active drug and the steroid-injected knees had more cartilage loss as measured by MRI.

On June 7, 2017, staff from DAAAP met with pertinent staff from the Division of Pulmonary, Allergy, and Rheumatology Drugs (DPARP) to discuss this paper. Kenalog-40 (IR TCA) is regulated by DPARP. The consensus was that the findings from this paper were of questionable value because the regimen used did not reflect standard of care and the clinical significance of the difference in cartilage volume was unclear. In Study 008, plain radiographs of the index knee were obtained at baseline and Week 24. The rate of joint space narrowing was similar between the treatment groups (5.0%, 4.1%, and 3.5% for Zilretta, placebo, and IR TCA, respectively).

The Office of Scientific Investigations (OSI) conducted inspections of two investigators who participated in Study 008. OSI concluded that the data generated by the sites was acceptable to support the application.

12. Labeling

The proprietary name, Zilretta, was found acceptable following review by the Division of Medication Error Prevention and Analysis (DMEPA) for either the 40 mg or 32 mg dose. DMEPA and the Office of Prescription Drug Promotion (OPDP) provided recommendations on the proposed labels and labeling. DMEPA opined that no human factors study is required for the vial adapter. Refer to the individual reviews for more details.

Additionally, the Division of Pediatric and Maternal Health (DPMH) was consulted regarding the proposed labeling (i.e., pregnancy and lactation labeling rule [PLLR]). DPMH provided recommendations for the proposed labeling, based on their review.

Millie Shah, PharmD, BCPS of the Division of Medication Error Prevention and Analysis (DMEPA) conducted the review of the IFU and other labeling including the carton and container labeling with secondary concurrence by Otto Townsend, PharmD. See the approved labeling and IFU for details.

I summarize the key changes from the proposed package insert below.

1. The indication (b) (4) to a single injection into the knee, (b) (4)

2. There will be a limitation of use for a single injection of Zilretta based on the uncertainty of the safety of repeated doses. This uncertainty stems from 1) only a single dose was studied in the clinical trial supporting approval of this application and 2) nonclinical data shows the potential for increased local tissue effects and cartilage loss with Zilretta compared to immediate-release triamcinolone. The clinical significance of these findings is not yet clear. Therefore, until adequate data are provided, a limitation of use is appropriate and Zilretta is not for repeated administration.

   The Applicant had proposed (b) (4) (b) (4)

3. During labeling negotiations, the Applicant objected to our deletion of a sentence reading, (b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] neither the Agency nor the Applicant felt that adding language to Warnings and Precautions was appropriate at this time. Flexion agreed with deletion of both sentences.
4. We added (b) (4) [redacted]
5. Section 14 must include the data on triamcinolone from the clinical study so that the efficacy of Zilretta is placed into perspective comparing it to the approved product.
6. We deleted (b) (4) [redacted]
7. Safety language generally retained systemic corticosteroid risks (b) (4) [redacted] the plasma steroid levels are similar to those from other "local" routes of administration (inhaled).

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Approval

- Risk Benefit Assessment

  The Applicant has provided substantial evidence for efficacy for the management of pain in OA of the knee and the safety data support the conclusion that a single injection of Zilretta is not different from IR TCA with regard to safety. (b) (4) [redacted] Zilretta is associated with lower plasma concentrations of TCA when compared to IR TCA. The Applicant generated some interesting data with regard to early changes in blood glucose in diabetics. However, the Division of Metabolic and Endocrine Products questioned the methods used and the clinical significance of the differences seen. (b) (4) [redacted]

The repeat toxicology studies in animals show the potential for additional toxicity. Furthermore, as was discussed in labeling negotiations, (b) (4) When limited to the clinical perspective, the risk-to-benefit assessment for a single-injection into the knee is positive however.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  None

- Recommended Comments to Applicant

  None

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/s/

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10/06/2017

ELLEN W FIELDS
10/06/2017