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Effects of a Single Intra-Articular Injection of a Microsphere Formulation of Triamcinolone Acetonide on Knee Osteoarthritis Pain

A Double-Blinded, Randomized, Placebo-Controlled, Multinational Study

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Background: Intra-articular corticosteroids relieve osteoarthritis pain, but rapid systemic absorption limits efficacy. FX006, a novel, microsphere-based, extended-release triamcinolone acetonide (TA) formulation, prolongs TA joint residence and reduces systemic exposure compared with standard TA crystalline suspension (TAcS). We assessed symptomatic benefits and safety of FX006 compared with saline-solution placebo and TAcS.

Methods: In this Phase-3, multicenter, double-blinded, 24-week study, adults ≥ 40 years of age with knee osteoarthritis (Kellgren-Lawrence grade 2 or 3) and average-daily-pain (ADP)-intensity scores of ≥ 5 and ≤ 9 (0 to 10 numeric rating scale) were centrally randomized (1:1:1) to a single intra-articular injection of FX006 (32 mg), saline-solution placebo, or TAcS (40 mg). The primary end point was change from baseline to week 12 in weekly mean ADP-intensity scores for FX006 compared with saline-solution placebo. Secondary end points were area-under-effect (AUE) curves of the change in weekly mean ADP-intensity scores from baseline to week 12 for FX006 compared with saline-solution placebo, AUE curves of the change in weekly mean ADP-intensity scores from baseline to week 12 for FX006 compared with TAcS, change in weekly mean ADP-intensity scores from baseline to week 12 for FX006 compared with TAcS, and AUE curves of the change in weekly mean ADP-intensity scores from baseline to week 24 for FX006 compared with saline-solution placebo. Exploratory

continued

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end points included week-12 changes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Injury and Osteoarthritis Outcome Score Quality of Life (KOOS-QOL) subscale scores for FX006 compared with saline-solution placebo and TAcS. Adverse events were elicited at each inpatient visit.

Results: The primary end point was met. Among 484 treated patients ($n = 161$ for FX006, $n = 162$ for saline-solution placebo, and $n = 161$ for TAcS), FX006 provided significant week-12 improvement in ADP intensity compared with that observed for saline-solution placebo (least-squares mean change from baseline: -3.12 versus -2.14 ; $p < 0.0001$) indicating $\sim 50\%$ improvement. FX006 afforded improvements over saline-solution placebo for all secondary and exploratory end points ($p < 0.05$). Improvements in osteoarthritis pain were not significant for FX006 compared with TAcS using the ADP-based secondary measures. Exploratory analyses of WOMAC-A, B, and C and KOOS-QOL subscales favored FX006 ($p \leq 0.05$). Adverse events were generally mild, occurring at similar frequencies across treatments.

Conclusions: FX006 provided significant, clinically meaningful pain reduction compared with saline-solution placebo at week 12 (primary end point).

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

In 1955, intra-articular injection of corticosteroids (particularly hydrocortisone acetate) was reported to be effective in 80% of arthritic joints, but the transitory nature of the effect “limited its practical value as a therapy.”¹ Subsequently, more potent synthetic corticosteroids replaced hydrocortisone for intra-articular indications; controlled clinical studies of these analogs also demonstrated short-term effects^{2,3}. Pharmacokinetic study indicated the efflux of corticosteroids from the joint within hours of injection⁴.

Osteoarthritic pain represents a major health problem for aging and increasingly obese populations⁵. Modern evidence-based management guidelines from the American Academy of Orthopaedic Surgeons (AAOS) and the American College of Rheumatology (ACR) recommend a combination of pharmacological and non-pharmacological therapies, including joint replacement^{6,7}. In practice, the utility of oral pharmacotherapy is limited by modest efficacy and side effects^{6,8,9}, and the treatment effect of intra-articular hyaluronic acid preparations has been questioned^{6,10,11}. Despite the short-term efficacy, and perhaps reflecting the paucity of effective alternatives, intra-articular corticosteroid use is common. Among beneficiaries with knee osteoarthritis identified from a 1999 to 2013 Medicare 5% sample, $>25\%$ of the nearly 12 million people with knee osteoarthritis received intra-articular corticosteroid injections; the fraction of newly diagnosed knee patients receiving intra-articular corticosteroids increased from 0.27 to 0.45 during the time period¹².

FX006 is a novel, microsphere-based, extended-release formulation of triamcinolone acetonide (TA) for intra-articular injection. Within each 35-to-55- μm microsphere, small ($<5 \mu\text{m}$) TA crystals are embedded in a poly(lactic-co-glycolic acid) (PLGA) matrix (Fig. 1-A). Pharmacokinetic assessments have demonstrated that measurable TA concentrations persist in the joint for ≥ 12 weeks¹³, indicative of long duration of release as compared with other marketed PLGA small-molecule formulations¹⁴. Typically, PLGA microspheres exhibit a triphasic drug-release profile, with an initial burst, a subsequent lag phase with minimal drug release, and a zero-order-release phase via bulk

polymer erosion¹⁵⁻¹⁸. In vitro, FX006 does not exhibit a burst or lag phase; rather, release commences immediately and is continuous (data on file). In the early-release phase, scanning electron microscopy reveals small channels approximately 500 nm in diameter on the smooth, largely intact, microsphere surface (Fig. 1-B). These nanochannels are unique to FX006 and presumably limit both TA egress from the microsphere's interior and polymer hydration, slowing bulk erosion and prolonging drug release. PLGA is degraded to oligomeric poly-acid units and then to lactic and glycolic acids¹⁹, followed by elimination as carbon dioxide and water.

In a rat model of localized synovitis, FX006 was demonstrated to significantly ($p < 0.05$ versus vehicle control) reduce pain as assessed by gait scores, with a prolonged effect relative to standard TA crystalline suspension (TAcS); significantly improved ($p < 0.05$ versus vehicle control) histological joint scores were observed with effective doses of FX006 but not with TAcS²⁰. In a clinical study, peak plasma TA concentrations following intra-articular injection in patients with knee osteoarthritis were approximately 11 times lower following the proposed clinical dose of FX006 compared with 40 mg (the routine clinical dose) of TAcS; measurable intra-articular TA concentrations were observed for ≥ 12 weeks¹³. In Phase-2 testing, FX006 administered at the proposed clinical dose produced statistically significant improvements in osteoarthritis average-daily-pain (ADP) intensity as compared with TAcS 40 mg (weeks 5 to 10)²¹, and provided meaningful diminution of pain intensity, with maximal effects observed at week 5 and persisting through week 13, compared with saline-solution placebo²².

In this article, we describe a Phase-3, randomized controlled trial comparing FX006 with saline-solution placebo, primarily, and TAcS, secondarily, with respect to efficacy and safety in patients with knee osteoarthritis.

Materials and Methods

Trial Design

In this Phase-3, double-blinded, multinational study (41 global sites), participants were centrally randomized

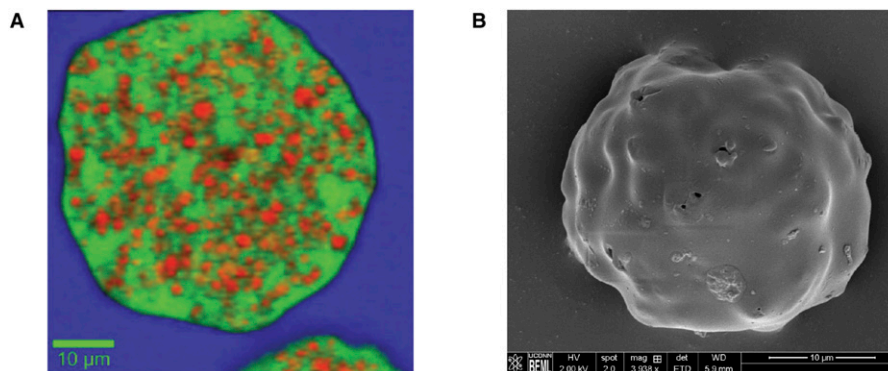


Fig. 1

Figs. 1-A and 1-B FX006, an intra-articular extended-release formulation of triamcinolone acetate (TA). **Fig. 1-A** Raman image of microsphere cross-sections. Within each microsphere, small crystals of TA (red) are embedded in a poly(lactic-co-glycolic acid) matrix (green). **Fig. 1-B** Scanning electron microscopy (SEM) image of a microsphere collected in the initial phase of release. Small channels approximately 500 nm in diameter appear on the smooth, largely intact surface of the microsphere.

(1:1:1, block size = 6; FlexRandomizer [Cytel], with stratification by baseline weekly ADP-intensity score [5 to <6, 6 to <7, or ≥ 7]) to receive a single intra-articular injection of FX006 (32 mg), saline-solution placebo, or a routine dose (40 mg) of TAc. Patients with bilateral disease designated the more painful knee as the index knee at screening. Following informed consent, analgesic medications for index-knee pain were withheld, with the exception of acetaminophen or paracetamol ($\leq 3,000$ mg/day; 500-mg tablets provided as rescue treatment). For details of study blinding, see the Appendix.

This study was registered at clinicaltrials.gov (NCT02357459).

Patients were evaluated at 7 outpatient visits (day 1 [baseline] and weeks 4, 8, 12, 16, 20, and 24). ADP intensity was assessed daily (4:00 P.M. to 12:00 A.M. locally) via an interactive voice-response system. Patients reported pain intensity according to a numeric rating scale (NRS; with 0 indicating no pain and 10 indicating pain “as bad as you can imagine”)^{23,24}. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Likert 3.1, 5-point subscales, with higher scores indicating worse status,²⁵ were employed to assess pain (WOMAC-A), stiffness (WOMAC-B), and physical function (WOMAC-C). The Knee Injury and Osteoarthritis Outcome Score was used to assess quality of life (KOOS-QOL; 0 to 4 Likert scale, with a higher score indicating better quality of life)²⁶. Both instruments were administered as local language-validated questionnaires (see Appendix). Patients recorded rescue medication use daily via an interactive voice-response system and returned medication bottles at study visits. For additional details regarding index-knee radiographic assessment, measurement instruments, and adverse events (AEs), see the Appendix.

Participants

Institutional review board approval was obtained from all study sites. Eligible patients who provided signed informed

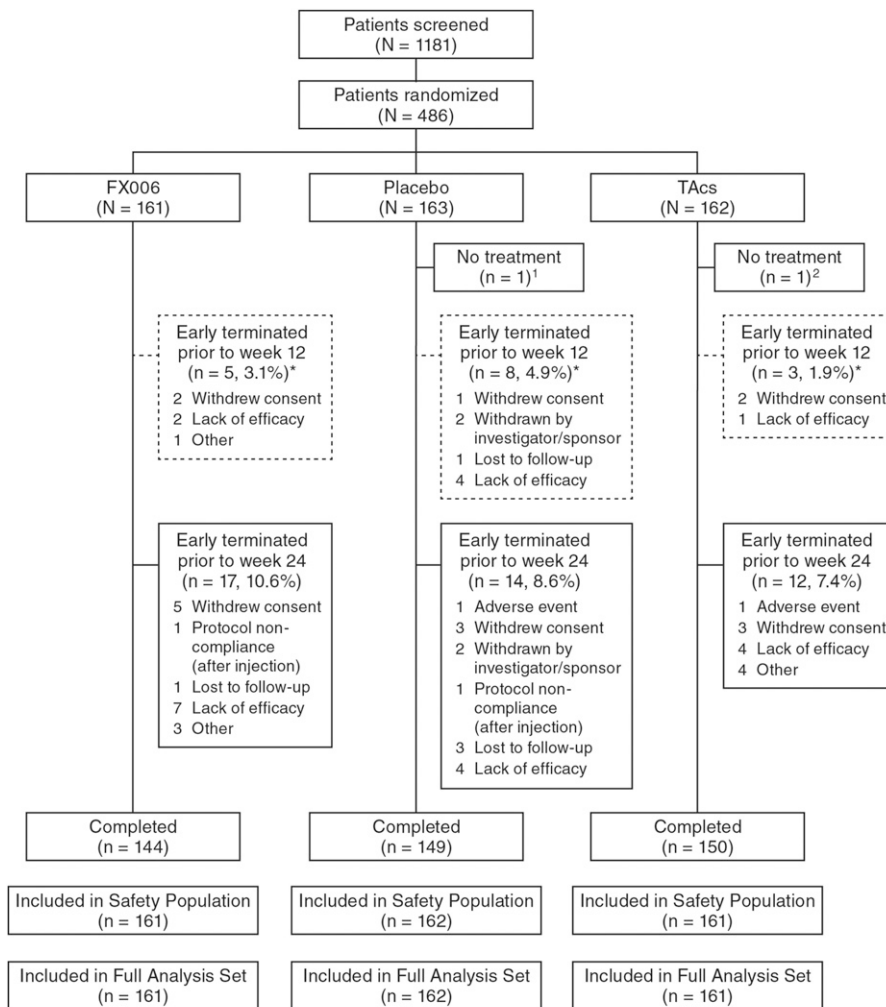
consent (n = 486) were enrolled and randomized at 38 centers in North America (United States and Canada), Australia and New Zealand, Asia (Hong Kong), and the European Union; 484 patients were treated (Fig. 2). Eligible for inclusion were men and women ≥ 40 years of age with symptomatic knee osteoarthritis per ACR criteria²⁷ for ≥ 6 months prior to screening, Kellgren-Lawrence grade-2 or 3²⁸ osteoarthritis in the index knee as assessed on the screening radiograph, patient-reported pain for >15 days in the previous month, and a 24-hour ADP-intensity score of ≥ 5 and ≤ 9 ^{23,24} for ≥ 5 days during the week preceding randomization and intra-articular injection. For the exclusion criteria, see the Appendix.

Interventions

Patients received a single intra-articular injection of FX006 (5 mL injection volume), saline-solution placebo (5 mL), or TAc 40 mg (1 mL), allowing comparisons between FX006 and a current standard of care. FX006 was supplied as a sterile powder for reconstitution; dose-delivery studies indicate that this provides an injection of 32 mg of TA into the joint. For additional details of the study agents and administration, see the Appendix.

Outcomes of Interest and Statistical Methods

The primary outcome, the least-squares mean (LSM) change from baseline to week 12 in weekly mean ADP-intensity scores for FX006 compared with saline-solution placebo in the full analysis set (the randomized and treated patients), was analyzed with a longitudinal mixed-effects model for repeat measures using observed data, with fixed effects for treatment group, study week, treatment-by-week interaction, study site, and baseline pain, and a random patient effect. The SAS/STAT PROC MIXED procedure (2015; SAS Institute) employed an unstructured correlation matrix to model within-patient error. For additional details of the sensitivity analyses, see the Appendix.



- 1 Placebo patient was discontinued by the Investigator after attempts to administer study drug at baseline failed.
 2 TAcS patient withdrew consent to participate after being randomized but before receipt of study drug due to the requirement for blood sample collection in the study.
 * Early terminations prior to week 12 are included in the total early terminations through week 24.

Fig. 2

FX006 Phase-3 study in knee osteoarthritis: patient disposition through week 24. TAcS = triamcinolone acetonide crystalline suspension, and placebo = saline-solution placebo.

Secondary end points were area-under-effect (AUE) curves of the change in weekly mean ADP-intensity scores from baseline to week 12 ($AUE_{\text{week}1-12}$) for FX006 compared with saline-solution placebo, $AUE_{\text{week}1-12}$ for FX006 compared with TAcS, change in weekly mean ADP-intensity scores from baseline to week 12 for FX006 compared with TAcS, and AUE curves of the change in weekly mean ADP-intensity scores from baseline to week 24 for FX006 compared with saline-solution placebo ($AUE_{\text{week}1-24}$). In the step-down testing procedure²⁹ implemented for primary and secondary end points, sequential testing proceeded as long as $p < 0.05$. P values resulting from testing conducted after the first non-significant p value were considered informative only. Changes to secondary end points and sequential testing order during development of the Statistical Analysis Plan after trial initia-

tion were made blinded to any clinical data and results (see the Appendix).

Analyses conducted for the secondary end points outlined above and additional exploratory end points (changes in WOMAC and KOOS-QOL scores, changes in ADP-intensity scores at additional time points, >30% and >50% improvement in ADP-intensity scores, and rescue medication use) utilized models similar to primary end-point analyses for outcomes involving score changes, summarization of “time-to-event” weekly mean ADP-intensity scores via Kaplan-Meier methodology, and calculation of AUE curves for ADP-intensity score changes over time using linear trapezoidal methodology. The proportions of patients achieving >30% and >50% improvement in ADP-intensity scores were compared using a logistic regression model with study site as a covariate. The

TABLE 1 Baseline Patient Characteristics and Baseline Values for Outcome Measures*

Parameter	Treatment Group			Total, N = 484
	FX006, N = 161	Saline-Solution Placebo, N = 162	TAcS, N = 161	
Female (no. [%])	103 (64.0)	96 (59.3)	97 (60.2)	296 (61.2)
White (no. [%])	130 (80.7)	144 (88.9)	131 (81.4)	405 (83.7)
Age at consent† (yr)	61.5 ± 9.52	62.4 ± 8.89	62.3 ± 10.08	62.1 ± 9.49
BMI† (kg/m ²)	30.1 ± 5.01	30.2 ± 4.69	30.3 ± 4.82	30.2 ± 4.83
BMI category (no. [%])				
Normal (18.5-24.9 kg/m ²)	28 (17.4)	22 (13.6)	25 (15.5)	75 (15.5)
Overweight (25.0-29.9 kg/m ²)	57 (35.4)	58 (35.8)	53 (32.9)	168 (34.7)
Class-I obese (30.0-34.9 kg/m ²)	45 (28.0)	52 (32.1)	55 (34.2)	152 (31.4)
Class-II obese (35.0-39.9 kg/m ²)	31 (19.3)	30 (18.5)	28 (17.4)	89 (18.4)
Type of knee osteoarthritis (no. [%])				
Unilateral	51 (31.7)	60 (37.0)	59 (36.6)	170 (35.1)
Bilateral	110 (68.3)	102 (63.0)	102 (63.4)	314 (64.9)
No. of yr since diagnosis†	7.6 ± 6.56	6.6 ± 5.79	7.5 ± 6.70	7.2 ± 6.37
No. of days with index-knee pain in past month†	28.4 ± 3.86	28.3 ± 3.80	28.0 ± 4.18	28.2 ± 3.95
Kellgren-Lawrence grade (no. [%])				
2	79 (49.1)	69 (42.6)	69 (42.9)	217 (44.8)
3	82 (50.9)	93 (57.4)	91 (56.5)	266 (55.0)
4	0	0	1 (0.6)‡	1 (0.2)‡
ADP-intensity score (0-10)†	6.3 ± 0.93	6.3 ± 0.98	6.3 ± 0.90	6.3 ± 0.94
Weekly ADP-intensity score (0-10) category§ (no. [%])				
5 to <6	68 (42.2)	68 (42.0)	68 (42.2)	204 (42.1)
6 to <7	52 (32.3)	52 (32.1)	51 (31.7)	155 (32.0)
≥7	41 (25.5)	42 (25.9)	42 (26.1)	125 (25.8)
WOMAC score (0-4)†				
A: pain	2.0 ± 0.53	2.0 ± 0.52	2.0 ± 0.52	2.0 ± 0.52
B: stiffness	2.3 ± 0.88	2.4 ± 0.79	2.3 ± 0.87	2.3 ± 0.85
C: physical function	2.1 ± 0.56	2.1 ± 0.51	2.1 ± 0.58	2.1 ± 0.55
KOOS-QOL (0-4)†#	29.9 ± 16.11	31.9 ± 16.64	31.8 ± 15.49	31.2 ± 16.09

*Full analysis set, N = 484. TAcS = triamcinolone acetonide crystalline suspension, BMI = body mass index, ADP = average daily pain, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, and KOOS-QOL = Knee Injury and Osteoarthritis Outcome Score Quality of Life. †The values are given as the mean and the standard deviation. ‡The patient with a Kellgren-Lawrence grade of 4, in violation of the entrance criteria, was included in the full analysis set. §Randomization was stratified by baseline ADP-intensity score category. #Normalized scores (100 indicating no symptoms and 0 indicating extreme symptoms) were calculated as: 100 - AVERAGE(Q1-Q4)/4*100. The numbers of patients with baseline KOOS-QOL assessments were 136, 144, 134, and 414 across the FX006, saline-solution placebo, TAcS, and total groups, respectively.

mean number of daily rescue medication tablets per week was summarized.

For sample size determination, see the Appendix.

Results

Participant Flow and Baseline Characteristics

The study was conducted at 41 sites from January 29, 2015 to January 21, 2016. Among the 486 patients enrolled over

6 months by 38 sites and randomized to FX006 (n = 161), saline-solution placebo (n = 163), or TAcS (n = 162), 2 patients (1 in the saline-solution placebo group and 1 in the TAcS group) were neither treated nor included in the full analysis set or safety populations. Overall, 443 (91.2%) of the patients completed the study through week 24, and 43 (8.8%) discontinued prematurely (n = 17, 14, and 12 across the respective treatment arms; from 21 [55.3%] of the 38 enrolling study sites;

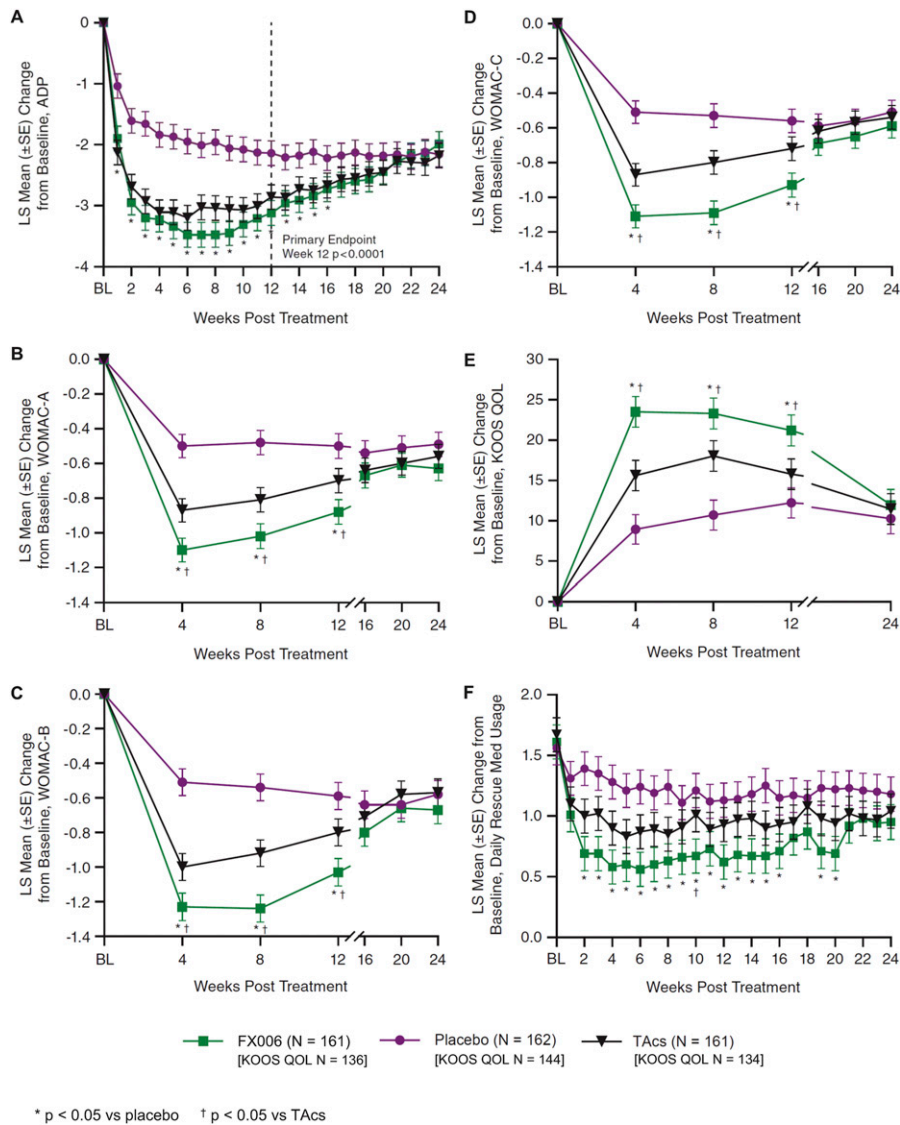


Fig. 3

Figs. 3-A through 3-F Least-squares (LS) mean change from baseline (BL) (and standard error [SE]) for the efficacy end points of weekly mean average daily pain (ADP)-intensity scores (0 to 10 on numeric rating scale) at week 12, the primary end point (n = 484) (**Fig. 3-A**); Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)-A (pain), WOMAC-B (stiffness), and WOMAC-C (physical function) subscale scores (n = 484) (**Figs. 3-B, 3-C, and 3-D**); Knee Injury and Osteoarthritis Outcome Score-Quality of Life (KOOS-QOL) subscale score (n = 414) (**Fig. 3-E**); and rescue medication (med) use (mean number of daily rescue medication [500-mg] tablets per week; n = 484) over time in the full analysis set (**Fig. 3-F**). Primary and exploratory secondary end-point analyses employed an analysis of covariance with model parameters for treatment and covariates of baseline pain-intensity score and study site. TAcS = triamcinolone acetonide crystalline suspension, and placebo = saline-solution placebo.

≤5 of the patients from any site). Sixteen (3.3%) of the patients (n = 5, 8, and 3 across the groups) discontinued before week 12 (Fig. 2).

The treatment groups were well balanced with respect to baseline patient characteristics and values for outcome measures. Patients ranged from 40 to 85 years of age (mean, 62 years), the majority were female (61.2%), and approximately 50% were obese (body mass index of ≥ 30 kg/m²). The mean number of years between the diagnosis of knee osteoarthritis per the ACR criteria and the start of the study was 7.2 (Table I).

Efficacy

The primary efficacy end point was met. ADP intensity was significantly improved among the patients treated with FX006 compared with those treated with saline-solution placebo (LSM change in weekly mean ADP-intensity scores from baseline to week 12: -3.12 compared with -2.14 , respectively; LSM difference [95% confidence interval (CI)]: -0.98 [-1.47 to -0.49]; p < 0.0001) (Fig. 3-A), indicating that FX006 afforded approximately 50% improvement over saline-solution placebo. The results of prespecified sensitivity analyses allowing

TABLE II Summary of Prespecified Sensitivity Analyses of LSM Change in Weekly Mean ADP-Intensity Scores at Week 12 (Primary End Point)*

	Primary Analysis	BLOCF/LOCF Sensitivity	Multiple Imputation Sensitivity
LSM change from baseline (SE)			
FX006	-3.12 (0.20)	-2.97 (0.22)	-3.05 (0.22)
Saline-solution placebo	-2.14 (0.20)	-1.98 (0.22)	-2.02 (0.22)
LSM difference, placebo vs. FX006 (95% CI)	-0.98 (-1.47, -0.49)	-0.99 (-1.51, -0.48)	-1.03 (-1.53, -0.52)
P value	<0.0001	<0.0002	<0.0001

*Full analysis set, N = 484. LSM = least-squares mean; ADP = average daily pain; BLOCF = baseline observation carried forward, for data missing due to patient discontinuation resulting from adverse event(s)/"other" reasons; LOCF = last observation carried forward, for data missing due to patient discontinuation because of lack of efficacy; SE = standard error; and CI = confidence interval.

for missing-data imputation were consistent with those of our primary analysis (Table II).

With respect to the protocol-defined secondary end points (Table III), we found that $AUE_{\text{week1-12}}$ was significantly greater for FX006 compared with saline-solution placebo (LSM change: -247.3 compared with -145.3, respectively; LSM difference: -102.0; $p < 0.0001$), indicating that FX006 afforded nearly twice the time-averaged reduction in ADP intensity through week 12 compared with saline-solution placebo. Similar findings were observed for $AUE_{\text{week1-24}}$ (LSM change: -432.5 for FX006 compared with -297.0 for placebo; LSM difference: -135.5; $p = 0.0002$).

FX006 demonstrated efficacy advantages over saline-solution placebo for exploratory end points, as evidenced by greater improvements in the WOMAC pain, stiffness, and physical function and KOOS-QOL subscale scores at weeks 4, 8, and 12 (all $p < 0.0001$) (Table IV) (Figs. 3-B through 3-E). Greater proportions of patients treated with FX006 compared with saline-solution placebo achieved the >30% (67.3% compared with 53.0% at week 12; $p < 0.05$ at weeks 1 to 13 among 24 weeks assessed) and more stringent >50% (52.3% compared with 37.1% at week 12; $p < 0.05$ at weeks 1 to 16 and week 18) ADP-intensity score improvement criteria. Significantly fewer rescue medication tablets per week were used by patients treated with FX006 compared with placebo overall (LSM dif-

ference [95% CI]: -0.50 [-0.78 to -0.21]; $p = 0.0006$) and at each of weeks 2 to 16, 19, and 20 ($p \leq 0.0269$) (Fig. 3-F).

Differences between FX006 and TAcS in $AUE_{\text{week1-12}}$ (LSM change: -247.3 for FX006 compared with -231.9 for TAcS; LSM difference: -15.3; $p = 0.3827$) and change from baseline to week 12 in ADP-intensity score (LSM change: -3.1 compared with -2.9; LSM difference: -0.26; $p = 0.2964$) were not significant (Table III).

FX006 performed more favorably than did TAcS with respect to exploratory end points, as evidenced by greater improvements in WOMAC subscale scores for pain ($p \leq 0.0475$), stiffness ($p \leq 0.0182$), and physical function ($p \leq 0.0111$) and the KOOS-QOL subscale score ($p \leq 0.0256$) at weeks 4, 8, and 12 (Table IV) (Figs. 3-B through 3-E). No significant differences were observed between the proportions of FX006 and TAcS-treated patients achieving >30% or >50% improvement in ADP-intensity scores from baseline (not shown). FX006 onset-of-action was similar to that of TAcS: median (95% CI) days to >30% improvement in ADP intensity, 4 (4 to 5) for FX006 and 3 (3 to 5) for TAcS (not shown).

Safety

Overall, 55.3%, 53.1%, and 56.5% of the patients in the FX006, saline-solution placebo, and TAcS treatment groups,

TABLE III Summary of Protocol-Defined Secondary Efficacy End Points*

Secondary End Point	Comparison	LSM Change (SE)			LSM Difference (95% CI)	P Value
		FX006, N = 161	Saline-Solution Placebo, N = 162	TAcS, N = 161		
1. $AUE_{\text{week 1-12}}$	FX006 vs. placebo	-247.3 (14.89)	-145.3 (14.77)	—	-102.0 (-136.8, -67.3)	<0.0001
2. $AUE_{\text{week 1-12}}$	FX006 vs. TAcS	-247.3 (14.89)	—	-231.9 (14.85)	-15.3 (-49.8, 19.2)	0.3827
3. ADP change from baseline to week 12	FX006 vs. TAcS	-3.12 (0.203)	—	-2.86 (0.202)	-0.26 (-0.74, 0.23)	0.2964†
4. $AUE_{\text{week 1-24}}$	FX006 vs. placebo	-432.5 (30.14)	-297.0 (29.90)	—	-135.5 (-205.9, -65.2)	0.0002†

*Full analysis set, N = 484. LSM = least-squares mean, SE = standard error, TAcS = triamcinolone acetonide crystalline suspension, CI = confidence interval, AUE = area under effect, and ADP = average daily pain. †P value derived from sequential testing conducted after a prior end-point treatment difference was ≥ 0.05 .

TABLE IV Summary of Prespecified Exploratory Efficacy End Points *

Exploratory End Point	Week	FX006 Vs. Saline-Solution Placebo		FX006 Vs. TAcS	
		LSM Difference (95% CI)	P Value	LSM Difference (95% CI)	P Value
WOMAC-A (pain)	4	-0.60 (-0.76, -0.44)	<0.0001	-0.23 (-0.39, -0.07)	0.0052
	8	-0.54 (-0.71, -0.37)	<0.0001	-0.21 (-0.38, -0.04)	0.0158
	12	-0.37 (-0.55, -0.20)	<0.0001	-0.17 (-0.34, -0.00)	0.0475
WOMAC-B (stiffness)	4	-0.72 (-0.91, -0.53)	<0.0001	-0.23 (-0.42, -0.04)	0.0179
	8	-0.69 (-0.88, -0.50)	<0.0001	-0.32 (-0.51, -0.13)	0.0009
	12	-0.44 (-0.63, -0.25)	<0.0001	-0.23 (-0.42, -0.04)	0.0182
WOMAC-C (physical function)	4	-0.60 (-0.75, -0.44)	<0.0001	-0.24 (-0.40, -0.08)	0.0029
	8	-0.56 (-0.73, -0.40)	<0.0001	-0.29 (-0.45, -0.12)	0.0007
	12	-0.38 (-0.54, -0.21)	<0.0001	-0.22 (-0.38, -0.05)	0.0111
KOOS-QOL†	4	14.57 (10.01, 19.12)	<0.0001	7.90 (3.29, 12.52)	0.0008
	8	12.60 (8.02, 17.18)	<0.0001	5.28 (0.65, 9.91)	0.0256
	12	8.97 (4.37, 13.57)	<0.0001	5.42 (0.78, 10.06)	0.0222

*Full analysis set, n = 484 (n = 414 for Knee Injury and Osteoarthritis Outcome Score Quality of Life [KOOS-QOL]). TAcS = triamcinolone acetonide crystalline suspension, LSM = least-squares mean, CI = confidence interval, and WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. †Normalized scores (100 indicating no symptoms and 0 indicating extreme symptoms) were calculated as: $100 - \text{AVERAGE}(Q1-Q4)/4 * 100$.

respectively, reported AEs (see Table V for the most common AEs). Across treatments, most AEs were mild/moderate (grade 1 or 2), nonserious, and unrelated to the study agent.

Serious AEs occurred in 3.1%, 1.9%, and 2.5% of the patients treated with FX006, saline-solution placebo, and TAcS, respectively (Table V). Each type of serious AE occurred in only 1 patient; none was considered related to the study agent. No FX006-treated patient and <1% of the placebo and TAcS-treated patients discontinued because of an AE (Table V). No deaths occurred.

Index knee-related AEs (new and clinically relevant or worsened index-knee findings), most of which were grade 1 or 2, nonserious, and unrelated to the study agent, occurred in 18.6%, 12.3%, and 9.9% of the patients treated with FX006, saline-solution placebo, and TAcS, respectively (Table V). Most index knee-related AEs occurred after day 3; none was consistent with post-injection flare.

Among the patients with baseline and week-24 index-knee radiographs, worsening of joint-space narrowing was uncommon, occurring in 7 (5.0%) of 140, 6 (4.1%) of 148, and 5 (3.5%) of 145 patients who received FX006, saline-solution placebo, and TAcS, respectively. Joint-space narrowing worsened by only 1 grade in these patients, with the exception of 1 patient treated with saline-solution placebo, who demonstrated worsening from grade 0 to grade 2. One patient treated with TAcS had an insufficiency fracture noted at week 24. No subchondral bone change, osteonecrosis, or radiographically documented rapidly progressive osteoarthritis was identified in the patients treated with FX006. One FX006-treated patient underwent uneventful total knee arthroplasty in the treated knee on day 145. At the time of surgery, the patient's ADP-

intensity score had improved from baseline, and the pre-operative knee radiograph showed no change from baseline (Kellgren-Lawrence grade 3).

No joint infections occurred. Non-joint infections occurred in 16.8%, 19.1%, and 21.7% of the patients treated with FX006, placebo, and TAcS, respectively; upper-respiratory tract infection, nasopharyngitis, influenza, sinusitis, and viral upper-respiratory tract infections were common across the groups. Hypertension occurred in 3.1%, 3.7%, and 0% of the patients who received FX006, saline-solution placebo, and TAcS, respectively.

Discussion

In primary analyses, a single intra-articular injection of FX006 demonstrated statistically significant reductions in osteoarthritis pain intensity as compared with saline-solution placebo. Secondary and exploratory analyses further evaluating pain relief, function, and overall well-being consistently favored FX006 over saline-solution placebo. The FX006 analgesic effect persisted for >12 weeks; onset of action was similar to that of TAcS.

The improvements in osteoarthritis pain conferred by FX006 are clinically relevant. Per accepted consensus criteria specifying $\geq 50\%$ improvement versus saline-solution placebo as "substantial" for individual patients³⁰, FX006 provided substantial improvements compared with saline-solution placebo at weeks 1 to 16 and week 18 ($p < 0.05$). In a separate analysis of data from the current study, the LSM improvement afforded by FX006 compared with saline-solution placebo at weeks 4, 8, and 12 exceeded the minimally clinically important improvement thresholds for the WOMAC pain, stiffness, and physical-function subscales

TABLE V Summary of Adverse Events (AEs) by Treatment Group*

	Treatment Group		
	FX006, N = 161	Saline-Solution Placebo, N = 162	TAcS, N = 161
≥1 AE	89 (55.3)	86 (53.1)	91 (56.5)
≥1 common AE (>5% in any treatment group)			
Arthralgia (any joint)	23 (14.3)	20 (12.3)	12 (7.5)
Headache	14 (8.7)	13 (8.0)	15 (9.3)
Back pain	9 (5.6)	9 (5.6)	12 (7.5)
≥1 serious AE	5 (3.1)	3 (1.9)	4 (2.5)
≥1 AE leading to study discontinuation	0	1 (0.6)†	1 (0.6)
AEs by maximum severity†			
Grade 1	37 (23.0)	33 (20.4)	40 (24.8)
Grade 2	45 (28.0)	48 (29.6)	47 (29.2)
Grade 3	6 (3.7)	5 (3.1)	4 (2.5)
Grade 4	1 (0.6)	0	0
AEs by maximum relationship to study agent			
Not related	69 (42.9)	77 (47.5)	78 (48.4)
Unlikely	10 (6.2)	6 (3.7)	9 (5.6)
Possibly, probably, or definitely related	10 (6.2)	3 (1.9)	4 (2.5)
≥1 index knee-related AE‡	30 (18.6)	20 (12.3)	16 (9.9)
≥1 serious index knee-related AE	1 (0.6)	0	0
≥1 index knee-related AE leading to study discontinuation	0	1 (0.6)§	1 (0.6)
Index knee-related AEs by maximum severity†			
Grade 1	18 (11.2)	7 (4.3)	8 (5.0)
Grade 2	11 (6.8)	12 (7.4)	6 (3.7)
Grade 3	1 (0.6)	1 (0.6)	2 (1.2)
Index knee-related AEs by maximum relationship to study agent			
Not related	22 (13.7)	14 (8.6)	10 (6.2)
Unlikely	3 (1.9)	3 (1.9)	5 (3.1)
Possibly, probably, or definitely related	5 (3.1)	3 (1.9)	1 (0.6)
≥1 AE related to injection procedure	5 (3.1)	5 (3.1)	3 (1.9)

*Safety population, N = 484. The values are given as the number of patients, with the percentage in parentheses. TAcS = triamcinolone acetonide crystalline suspension. †If a patient experienced >1 AE in a given category, that patient was counted only once in that category. ‡Any index-knee finding that was new and clinically relevant or had worsened from baseline. §AE was nonserious and unrelated to the study agent.

utilized by the AAOS to assess the “clinical significance” of treatment effects^{6,31,32}. Furthermore, the 95% CIs surrounding the FX006-associated LSM improvement in all WOMAC subscales at weeks 4 and 8 exceeded minimally clinically important improvement thresholds defined by the AAOS for determining a “clinically significant” effect⁶. In a systematic review of pharmacological interventions for symptomatic knee osteoarthritis, the AAOS concluded that no currently available injectable intra-articular treatments

(including corticosteroids and hyaluronic acids) provided a “clinically significant” treatment effect⁶. While there is support for¹⁰, and criticism of¹¹, the AAOS criteria, they represent a systematic approach to identifying clinically meaningful improvements.

Although differences between FX006 and TAcS per protocol-specified ADP-based secondary end points were not significant, FX006 was superior to TAcS on exploratory end points (WOMAC pain, stiffness and physical function and

KOOS-QOL data) at weeks 4, 8, and 12 (Fig. 3). Regarding the inconsistency between the 2 instruments in assessing pain, it is noted that WOMAC pain is a multi-item tool purpose-built for knee osteoarthritis, whereas the NRS is a single-item measure used for numerous indications²³⁻²⁵. A meta-analysis reviewing 125 randomized controlled trials found greater responsiveness for the WOMAC pain subscale compared with single-item pain-intensity measures³³.

FX006 demonstrated an acceptable safety profile. Most AEs across the groups were grade 1 or 2, nonserious, and unrelated to the study drug or injection procedure. Intramuscular delivery of PLGA microspheres is associated with a foreign-body response^{19,34}; in synovial tissues of dogs receiving intra-articular FX006, this was demonstrated to be mild, self-limiting, localized, reversible, and without detectable clinical effect³⁵. The Phase-3 clinical data are consistent with a lack of a clinically relevant foreign-body response, as a single intra-articular FX006 injection demonstrated systemic and local safety profiles generally similar to those of saline-solution placebo and TAcS. Although the numbers of FX006-treated patients to date are limited, the time course of index knee-related AEs in this trial indicated no post-injection flares. Index knee-related arthralgia in the FX006-treated patients was mild and occurred at time points when patients still exhibited improved ADP-intensity scores.

Early case reports associated joint damage with repeated corticosteroid injections^{36,37}. However, final data from 2 controlled imaging studies designed to assess how multiple injections administered over 2 years impact cartilage structure yielded conflicting results^{38,39}. In this study, we found no radiographic evidence of rapidly progressive osteoarthritis in either active arm through 24 weeks.

FX006 has the potential to demonstrate cost-effectiveness as a knee osteoarthritis therapy. In a preliminary evaluation of results from this trial pooled with results from other randomized trials of FX006^{21,22}, observed WOMAC-based clinical benefits of FX006 translated into an increase in quality of life for patients with knee osteoarthritis, demonstrated by an average quality-adjusted-life-years gain per 6 months of 0.189. Employing a hypothetical drug cost of \$500 (USD), FX006 was determined to be cost-effective, with incremental cost-effectiveness ratios (ICERs) of <\$5,000 versus either conventional care or diclofenac. FX006 was the dominant approach compared with intra-articular hyaluronic acid in a further ICER analysis⁴⁰. Additional studies are required to fully understand the cost-benefit and cost-effectiveness implications of managing osteoarthritis knee pain with FX006.

This study had limitations, including differing injection volumes for FX006 and saline-solution placebo (5 mL) versus TAcS (1 mL, as employed in clinical practice). The study was powered to detect significant differences in changes in ADP-intensity scores between FX006 and saline-solution placebo but not significant differences in rapidly progressive osteoarthritis defined by joint-space narrowing or loss of fixed joint space width. Exclusion of diabetics with a hemo-

globin A1c level of >7.5% and the absence of fasting clinical laboratory assessments limit any potential conclusions concerning the effects of FX006 compared with TAcS on serum glucose levels.

In summary, this randomized double-blinded trial demonstrated sustained and clinically meaningful reductions in pain in knee osteoarthritis following a single intra-articular injection of a novel microsphere-based corticosteroid formulation that prolongs TA residency in synovial tissues compared with saline-solution placebo (primary outcome). No osteoarthritis flare or important AE signals were observed. The observed magnitude and persistence of pain-intensity reduction suggest that FX006 may have a place in knee osteoarthritis treatment paradigms.

Appendix

eA Additional details regarding blinding, exclusion criteria, assessments, adverse events, interventions, and outcomes and statistical methods, and a table describing changes made to the study efficacy outcomes during the development of the Statistical Analysis Plan are available with the online version of this article as a data supplement at <http://links.lww.com/JBJS/E646>. ■

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