This is an author produced version of Phase 2b trial of a novel extended-release microsphere formulation of triamcinolone acetonide for intra-articular injection in knee osteoarthritis.

White Rose Research Online URL for this paper: http://eprints.whiterose.ac.uk/122874/

Article:
Running head: Microsphere formulation of triamcinolone acetonide in knee osteoarthritis

Title: Phase 2b trial of a novel extended-release microsphere formulation of triamcinolone acetonide for intra-articular injection in knee osteoarthritis

Authors and affiliations: Philip G Conaghan MBBS PhD FRACP FRCP,1 Stanley B Cohen MD,2 Francis Berenbaum MD PhD,3 Joelle Lufkin MPH,4 James R Johnson PhD,5 Neil Bodick MD PhD6

1Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Biomedical Research Centre, Leeds, UK (p.conaghan@leeds.ac.uk); 2Rheumatology, University of Texas Southwestern Medical School, Dallas TX, USA (scohen@arthdocs.com); 3Rheumatology, Pierre & Marie Curie University, Paris, France (francis.berenbaum@aphp.fr); 4Clinical Operations, Flexion Therapeutics Inc., Burlington, MA, USA (jlufkin@flexiontherapeutics.com); 5Biostatistics, Summit Analytical LLC, Cary, NC, USA (jjohnson@summitanalytical.com); 6Clinical Research and Medical Affairs, Flexion Therapeutics Inc., Burlington, MA, USA (nbodick@flexiontherapeutics.com)

Financial support: Flexion Therapeutics, Inc. sponsored and funded this study. Together with guidance from regulatory authorities, a subset of the authors (including the corresponding author) worked with the sponsor to develop the study design, study protocol, statistical analysis plan, and subsequently to interpret study data. Site management and monitoring were provided by contract research organizations (CROs). Data collection and database maintenance were performed by a CRO. A full audit trail was maintained from the time of data entry to database lock. The database was then securely transferred to a separate CRO for the conduct of statistical analyses. All authors participated in data interpretation and manuscript development in
collaboration with a professional medical writer/editor funded by the sponsor. All authors had full access to the study data, and the corresponding author takes final responsibility for the decision to submit for publication. No author external to the sponsor received financial compensation to write this manuscript.

**Potential conflicts of interest:** Philip G Conaghan has received compensation for consultancies from AbbVie, Flexion Therapeutics, Inc., Infirst, Medivir, Merck Serono, Novartis, and ONO Pharmaceutical Co. (all <$10,000). Stanley B Cohen has received research support, paid to Metroplex Clinical Research, and consulting fees (<$10,000) from Flexion Therapeutics, Inc. Francis Berenbaum has received research grants (paid to institution) from Fondation Arthritis, FOREUM Foundation, Pfizer, Programme Europeen de Recherche, Servier, Societe Francaise de Rhumatologie, and TRB Chemedica; consulting/speaking/board membership fees from AbbVie, Biogaran, Biogen, Expanscience, Flexion Therapeutics, Inc., IBSA, Janssen, Merck Serono, Novartis, Pfizer, Sanofi, Servier, TRB Chemedica, and UCB; and travel/meeting expenses paid by OARSI, Pfizer, and US Arthritis Foundation (all <$10,000). James R Johnson was an employee of Flexion Therapeutics, Inc. at the time of data analyses and manuscript development and is now employed by Summit Analytical, LLC, and has received personal fees for statistical and pharmacokinetic support from Acura Pharmaceuticals, Flexion Therapeutics, Inc., Iroko Pharmaceuticals, IX Biopharma, and Tolmar, Inc. (all >$10,000). Joelle Lufkin and Neil Bodick are employees of Flexion Therapeutics, Inc. and own stock/stock options in Flexion. Neil Bodick has the following issued/pending patents: ‘Corticosteroids for the treatment of joint pain’ (Issued), ‘Corticosteroid formulations for maintaining corticosteroid synovial fluid formulations’ (pending), ‘Corticosteroid formulations and methods for the treatment of joint pain in patients
with type 2 diabetes mellitus’ (pending), and ‘Corticosteroid formulations and methods for the treatment of joint pain in patients with diabetes’ (pending).

**Address correspondence and reprint requests to:** Professor Philip G Conaghan, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Biomedical Research Centre, Leeds, UK, 2nd Floor Chapel Allerton Hospital Chapeltown Road, Leeds LS7 4SA, UK; Ph: +44 11339 24883 or 24884; Fax: +44 1133924991; Email - p.conaghan@leeds.ac.uk

**Author contributions:** Philip G Conaghan: 1a, 1c, 2, 3; Stanley B Cohen: 1c, 2, 3; Francis Berenbaum: 1c, 2, 3; James R Johnson: 1a, 1c, 2, 3; Joelle Lufkin: 1a, 1b, 1c, 2, 3; Neil Bodick: 1a, 1b, 1c, 2, 3.
**ABSTRACT**

**Objective:** FX006 is a novel, microsphere-based, extended-release formulation of triamcinolone acetonide (TA) for intra-articular injection designed to maintain TA joint concentration and provide prolonged analgesic benefits in patients with osteoarthritis (OA) of the knee. The aim of this study was to compare the analgesic benefits of two FX006 doses with saline-placebo injection.

**Methods:** In this Phase 2b study, participants with knee OA (Kellgren-Lawrence Grade 2–3) and average daily pain (ADP)-intensity ≥5 to ≤9 (0–10 Numeric Rating Scale) were randomized (1:1:1) and received single IA injections of FX006 32 mg (N=104) or 16 mg (N=102) or saline-placebo (N=100). The primary endpoint was least-squares-mean (LSM) change from baseline to Week 12 in weekly mean ADP-intensity scores for FX006 32 mg versus saline-placebo.

**Results:** The primary endpoint was not met (FX006 32 mg versus saline-placebo LSM-change at Week 12: −3.1 versus −2.5; LSM-difference [95% confidence interval] of −0.58 [−1.22, 0.07]; P = 0.08). However, FX006 32 mg improvements were significant versus saline-placebo at Weeks 1–11 and Week 13. FX006 16 mg improvements were significant versus saline-placebo at Weeks 1–9. A dose-response was evident in duration of maximal analgesic effect (32 mg: 13 weeks versus 16 mg: 9 weeks), with FX006 32 mg providing increased therapeutic benefit relative to FX006 16 mg. All treatments were well-tolerated.

**Conclusion:** Although the primary endpoint was not met, FX006 demonstrated a prolonged reduction in symptoms with an evident dose response and a safety profile similar to that of saline-placebo.
INTRODUCTION

Osteoarthritis (OA) of the knee is characterized by pain, progressive cartilage destruction, subchondral bone changes and joint inflammation (1). Treatment guidelines recommend intra-articular (IA) corticosteroids (2). Standard IA corticosteroids provide moderate pain improvements, but the magnitude of benefit rapidly wanes post-injection (3). FX006, an extended-release formulation of triamcinolone acetonide (TA) in 75:25 poly(lactic-co-glycolic acid) (PLGA) microspheres, was designed to maintain prolonged TA joint concentrations, with the intent to improve analgesic effect and reduce systemic exposure versus commercially available TA crystalline suspension (TAs). In a pharmacokinetic study (NCT02637323), FX006 demonstrated prolonged residency in synovial fluid and reduced systemic exposure following IA injection versus TAs in people with knee OA (4).

In the first clinical study of efficacy following a single IA injection of FX006 (target low-, mid-, and high-doses: 10 mg, 40 mg, or 60 mg) in people with knee OA (NCT01487161) (5), FX006 mid-dose yielded pain relief superior to TAs 40 mg with treatment differences achieving statistical significance at Weeks 5–10 (all P < 0.05) and numerical improvement at each of Weeks 2–12. Pain relief with the FX006 high-dose compared with TAs was similar to that for the mid-dose through Week 6, but diminished from Weeks 7–12. Pain relief was numerically improved with the FX006 low-dose compared with TAs at each of Weeks 2–12, but the effect did not achieve statistical significance. Hence, the mid-dose of FX006 was concluded to be the most efficacious tested in that trial (5) and further evaluation was deemed appropriate.

The current study (NCT02116972) was conducted to confirm the appropriate target dose of FX006 and further assess FX006 efficacy and safety. Two notable differences exist between the
previous dose-ranging study (5) and the present one with regard to administration and dosing of
FX006. First, the injection volume increased to 5 mL following adjustment of the diluent volume
to enhance microsphere dispersion and reduce aggregation. Second, the FX006 doses as reported
here (16 mg, 32 mg) reflect the amount of drug received by patients following an approximate
20% reduction during reconstitution, as determined by dose-delivery studies.
METHODS

In this Phase 2b, double-blind, parallel-group, dose-ranging, single-injection study, participants were randomized (1:1:1, block of 6; centralized interactive web randomization system) to receive a single 5-mL IA injection of FX006 16 mg, FX006 32 mg, or saline-placebo. Participants/assessors were blinded to treatment administered by an unblinded injector. Details related to randomization, blinding, and the injection procedure are provided in the Online Supplement. Post-screening, participants were seen at Day 1 (baseline) and Weeks 4, 8, 12, 16, 20, and 24.

Eligible participants (≥40 years, BMI ≤40 kg/m²) had knee OA per American College of Rheumatology clinical/radiological criteria (6) for ≥6 months pre-screening; Kellgren-Lawrence Grade-2/3 on the centrally read screening radiograph (7); index-knee (defined as most painful knee by participants with bilateral disease) pain on >15 days of the previous month; and a mean average daily pain (ADP)-intensity score ≥5 and ≤9 (11-point Numeric Rating Scale [NRS]). People were excluded if they had ipsilateral hip osteoarthritis, other arthritic/immune-mediated inflammatory disorders, or unstable knee joints (e.g., torn anterior cruciate ligament) within 12 months of screening, or received prior IA corticosteroids within 3 months of screening; prior IA hyaluronic acid injections in the index knee within 6 months of screening; prior FX006 at any time; or intramuscular, oral, inhaled, intranasal or topical corticosteroids prescreening.

From screening through Week 24, participants logged daily ADP-intensity scores via an interactive voice response system, using a 0–10 (“no pain” to “pain as bad as you can imagine”) NRS. Participants completed the Western Ontario and McMaster Universities Osteoarthritis
Index (WOMAC) (8) on Day 1 prior to randomization and at Weeks 4, 8, 12, 16, 20, and 24, and
the Patient Global Impression of Change (PGIC) (9) at Weeks 4, 8, 12, 16, 20, and 24.

Safety was evaluated via adverse events (AEs) spontaneously reported or discovered by the
investigator from information obtained via patient electronic diaries, routine physical/laboratory
evaluations, and index-knee assessments by a blinded assessor.

Following informed consent, and for ≥7 days pretreatment, analgesic medications for index-knee
pain were not to be taken or used during the study with the exception of study-issued
acetaminophen/paracetamol (≤3,000mg/day; Sponsor-provided 500-mg tablets) as rescue pain
treatment.

The primary efficacy endpoint, Week 12 change from baseline in weekly mean ADP-intensity
scores for FX006 32 mg versus saline-placebo in the full analysis set (all randomized and treated
participants), was analyzed using longitudinal mixed-model-repeat-measures methodology
(MMMR) on observed data with no imputation for missing data (see Online Supplement). A
sample size of approximately 300 participants (100 per treatment arm) was estimated to provide
80% power (alpha=0.05, 2-sided) if the true underlying primary endpoint treatment effect was
1.0 on the 0–10 NRS for the primary endpoint.

All secondary efficacy endpoints were first compared between FX006 32 mg and saline-placebo,
followed by FX006 16 mg versus saline-placebo. Predefined key secondary endpoints (in order
of step-down testing) were: change from baseline to Week 12 in WOMAC-C-function and PGIC
scores, and changes in weekly mean ADP-intensity scores from baseline to Weeks 16, 20, and
24. Additional secondary outcomes included: percent of responders according to Outcomes
Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI)
“Strict” criteria (defined as ≥50% improvement and absolute improvement ≥20 points from baseline in either ADP-intensity or WOMAC-C-function scores) (10) at Weeks 4, 8, 12, 16, 20, and 24; change from baseline to each week (except Weeks 12, 16, 20, and 24 as outlined above, which are specified as the primary and secondary endpoints) in weekly mean of the ADP-intensity scores; change from baseline to each of Weeks 4, 8, 12, 16, 20, and 24 in WOMAC-A-pain; change from baseline to each of Weeks 4, 8, 16, 20, and 24 in WOMAC-C-function and PGIC; and time to onset of pain relief (time to first ADP-intensity assessment showing >30% improvement from baseline).

To quantify the magnitude of difference between FX006 16 mg and 32 mg and saline-placebo, standardized effect sizes (SES) were determined post hoc using methods previously described (11) (see Online Supplement). Safety summaries included treated patients.

This trial was conducted according to Good Clinical Practice guidelines. Each site’s governing ethical body approved the protocol; participants provided written informed consent.
RESULTS

Patient disposition and baseline characteristics

The trial was conducted from 4/29/2014–8/7/2015. Participants were screened at 48 sites (43 in the United States, 5 in Canada) and enrolled at 44 sites (40 in the United States, 4 in Canada). Among 310 randomized participants, 306 were treated (four randomized to saline-placebo were not treated). Approximately 8% and 18% of participants prematurely discontinued participation through Week 12 (primary endpoint) and Week 24 (study completion), respectively (Figure 1). Ultrasound guidance during IA injection was utilized for four patients.

All baseline characteristics, except gender, were generally well-balanced across arms. A higher proportion of men comprised the FX006 32 mg group (51%) compared with the 16 mg group (39%) or saline-placebo group (39%). Baseline ADP-intensity scores (mean = 6.6) indicated substantial daily pain at a moderate level of intensity (Table 1).

Efficacy

The primary endpoint was not met (LSM-difference [95% CI] FX006 32 mg versus saline-placebo at Week 12: \(-0.58 \, [\text{-1.22, 0.07}]\); \(P = 0.08\)). However, FX006 32 mg resulted in significant improvements in ADP-intensity versus saline-placebo at each of Weeks 1–11 (\(P \leq 0.036\)) and Week 13 (\(P \leq 0.039\)) and numerical improvements at each of Week 12 and Weeks 14–24 (Figure 2A). FX006 16 mg improvements achieved significance at Weeks 1–9; thereafter, the difference in pain scores between FX006 16 mg and saline-placebo was small and not statistically significant (Figure 2A). As such, a dose-response effect was evident in the duration of maximal effect. FX006 16 mg and 32 mg had similar median time to onset of analgesic effect.
(Day 4) that was more rapid than saline-placebo (Day 8). The maximum magnitude of analgesic
effect was similar for FX006 16 mg and 32 mg (achieved at Week 4-5; LSM-differences
−1.22/−1.23 and −1.36/−1.34, respectively, Figure 2A).

Sensitivity analyses of the primary endpoint (Last/Baseline-Observation-Carried-Forward
[LOCF/BLOCF) addressing patient discontinuations prior to Week 12 showed FX006 32 mg
significantly improved ADP-intensity versus saline-placebo at each visit from Weeks 1–13 (all P
< 0.05), including Week 12 (LSM-difference [95% CI]: −0.67 [−1.32, −0.02]; P = 0.042; Figure
2B]). Results of a multiple imputation sensitivity analysis of the primary endpoint demonstrated
consistent differences between FX006 32 mg and saline-placebo in ADP-intensity changes from
baseline to Week 12 (LSM-difference [95% CI]: −0.65 [−1.30, 0.01]; P = 0.053; data not
shown). Consistent results were observed from a post-hoc exploratory primary endpoint analysis
performed with site added to the MMRM as a covariate (Week 12 LSM-difference [95% CI]:
−0.83 [−1.51, -0.16]; P = 0.034, data not shown). Inclusion of the four patients who were
randomized and not treated (i.e., Intention-to-Treat population) yields results identical to those of
the analysis based on the FAS population, because none of these four patients had efficacy data
after their screening visit.

Results from secondary analyses also favored FX006 32 mg compared with saline-placebo.
FX006 32 mg was associated with significantly improved WOMAC-A-pain (Figure 2C),
WOMAC-C-function (Figure 2D), and PGIC (Figure 2E) scores, and resulted in a higher
proportion of patients who achieved OMERACT-OARSI “Strict” responder criteria (Table S1)
versus saline-placebo at Week 4 and Week 8; numerical advantage was maintained at Week 12
for all of these endpoints except OMERACT-OARSI “Strict” responders. Secondary endpoint
findings for FX006 16 mg versus saline-placebo showed a similar pattern, with a reduced
duration of effect, no trend favoring FX006 16 mg over saline-placebo for improvements in
ADP-intensity at Week 12, and lower OMERACT-OARSI “Strict” response rates at Week 8
(Figure 2A, Table S1).

Results from post-hoc SES determinations indicated that the effect sizes based on ADP were
consistently lower than those for WOMAC-A. The ADP effect sizes for FX006 32 mg at Weeks
4, 8, and 12 were 0.27, 0.13, and 0.12, respectively; the effect sizes for WOMAC-A were 0.72,
0.54, and 0.27, respectively. For each instrument, the effect sizes for FX006 16 mg were similar
to those of FX006 32 mg at Weeks 4 and 8. Consistent with pre-specified secondary endpoints,
effect sizes for both ADP and WOMAC-A were markedly lower for FX006 16 mg versus FX006
32 mg at Week 12 (Table S2).

Safety

Similar proportions of participants reported AEs through Week 24 across treatment arms (Table
2). Most AEs were Grade-1/2, non-serious, and considered unrelated to study drug by blinded
investigators. No deaths occurred. Serious AEs occurred in four (1.9%) FX006-treated patients
(16 mg: left distal femur fracture; 32 mg: worsening left ankle OA, myocardial infarction,
rheumatoid arthritis); all were unrelated to study drug. No AE was consistent with post-injection
flare.

AEs causing study discontinuation occurred in eight (3.9%) FX006-treated patients and one
(1.0%) saline-placebo–treated patient (Table 2). The onset of such events was not temporally
associated with study drug administration. All of these events were considered unrelated to study
drug except for one Grade 2 (FX006 16 mg) and one Grade 3 (saline-placebo) AE.
The incidence of index knee-related AEs was relatively low given the study population. AEs related to the injection procedure were observed in 2.0%, 0%, and 6.0% of FX006 16 mg, FX006 32 mg, and saline-placebo patients, respectively.
DISCUSSION

The primary endpoint—Week 12 improvement in ADP-intensity for FX006 32 mg versus saline-placebo—did not achieve statistical significance (P = 0.08); however, improvements were significant at all time points from Weeks 1–11 (P ≤ 0.036) and at Week 13 (P = 0.039). The placebo response at Week 12 (LSM reduction of −2.5) was the largest reported over the 24-week study. Studies show that placebo effects may confound the interpretation of clinical data (13) and are more pronounced with IA versus other routes of administration (14). Differences in saline-placebo response across study sites were noted; a post-hoc exploratory analysis with a site covariate included in the MMRM accounted for the variability in site responses, and the model demonstrated statistical significance for the primary endpoint at Week 12 (P = 0.034). Sensitivity analyses (LOCF/BLOCF) that addressed patient discontinuations prior to Week 12 indicated that FX006 32 mg was significantly superior to saline-placebo from Weeks 1–13 (P ≤ 0.042). Results of a multiple imputation analysis demonstrated consistent differences between FX006 32 mg and saline-placebo in ADP-intensity changes from baseline to Week 12.

Although FX006 16 mg and 32 mg had comparable median times to onset of analgesia (Day 4) and provided similar and significant maximal analgesic effects (beginning at ~Week 5) versus saline-placebo, maximal effect persisted longer with FX006 32 mg (~Week 13) than 16 mg (~Week 9). FX006 32 mg maintained numerically larger pain relief versus saline-placebo at all time points through Week 24. Other measures of OA signs/symptoms (WOMAC-C-function, PGiC, WOMAC-A-pain and OMERACT-OARSI “Strict” responders) were significantly improved with FX006 32 mg through Week 8 with strong trends remaining at Week 12; results for FX006 16 mg versus saline-placebo showed a similar pattern but were not as robust or long-lasting. A previous clinical study of FX006 in people with OA demonstrated a dose-dependent
increase in synovial fluid concentrations of TA at Week 6 following IA injection (15). It is postulated that there is a critical synovial fluid concentration required to maintain analgesic effect and that the loss of analgesic effect after Week 9 with FX006 16 mg is attributable to synovial fluid TA levels dropping below that critical concentration.

The clinical relevance of these findings was assessed with post-hoc analysis of SES (11), a measure used to quantify the magnitude of difference between two treatment groups. An effect size >0.3 is considered an important change for a patient-reported outcome (12). For FX006 32 mg compared with saline-placebo, effect size for the WOMAC-A-pain instrument exceeded 0.30 at Weeks 4 and 8 and approached 0.30 at Week 12. Effect size with the 16-mg dose was comparable to that of the 32-mg dose at Week 4 but was notably lower at Week 8 and showed no active treatment effect at Week 12. Effect sizes assessed with ADP were consistently lower than those for WOMAC-A-pain for both FX006 doses at each of these time points. Across a large number of trials, the multi-item, knee OA-specific WOMAC-A-pain instrument has proved to be a more sensitive measure of treatment effect than the single-item, general purpose ADP-intensity 0–10 NRS (11).

Overall, both FX006 doses demonstrated systemic and local safety profiles similar to saline-placebo. No FX006 dose relationship in AEs was apparent.

In conclusion, although the study’s primary endpoint was not met, the dose effect on duration of analgesic efficacy observed in this Phase 2b study of people with knee OA confirms FX006 32 mg confers increased therapeutic benefit relative to FX006 16 mg with similar safety, and that improvements in pain afforded by FX006 32 mg were of a magnitude that would be important to patients.
REFERENCES


ACKNOWLEDGMENTS

The authors thank the FX006-2014-006 study participants and their enrolling investigators. The authors also thank Karen Ozer and Teresa Curto of Cytel, Inc., Waltham, MA, USA for statistical analyses and Michelle L Perate MS, for professional medical writing and editorial assistance in support of manuscript development and submission. PG Conaghan is supported in part by the National Institute for Health Research (NIHR) Leeds Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.
FIGURE LEGENDS

Figure 1 Patient disposition

Figure 2 LSM (±SE) changes from baseline in weekly mean of ADP-intensity scores per primary (MMRM, observed data, primary endpoint at Week12 and key secondary endpoints at Weeks16, 20, and 24; A) and sensitivity (LOCF/BLOCF, imputed data; B) analyses; WOMAC-A-pain scores (C); WOMAC-C-function scores (key secondary endpoint at Week12, D); and Patient Global Impression of Change scores (key secondary endpoint at Week12, E) through Week24. ADP - average daily pain, BLOCF – baseline observation carried forward, FAS – full analysis set, LSM – least squares mean, LOCF – last observation carried forward, MMRM – mixed-effects-model for repeat measures, WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index