1. TITLE PAGE

A Double-Blind, Randomized, Placebo-Controlled, Two-Phase Study (a Single Ascending Dose Phase Followed by a Proof of Concept Phase) to Assess the Safety, Efficacy and Pharmacokinetics of FX005 (50:50 PLGA) Microspheres for the Treatment of Pain in Osteoarthritis of the Knee

Protocol:	FX005-2010-001
Development Phase:	1/2a
Investigational Product:	FX005 (50:50 PLGA) Microspheres
EUDRACT Number:	2010-022976-29
Date of Inclusion of First Patient:	February 15, 2011
Date of Completion of Last Patient:	March 7, 2012
Indication Studied:	Treatment of Pain in Osteoarthritis of the Knee
Methodology:	Double-blind, placebo-controlled
Report Version:	Final
Date of Report:	August 30, 2013
Report Written By:	PROMETRIKA, LLC
Sponsor:	Flexion Therapeutics, Inc. 10 Mall Road, Suite 301 Burlington, Massachusetts 01803 USA Tel: 781-305-7777
Sponsor Contact Person:	Neil Bodick, MD, PhD, Chief Medical Officer

2. SYNOPSIS

Name of Company: Flexion Therapeutics **Name of Finished Product:** FX005 (50:50 PLGA) Microspheres **Name of Active Ingredient:** FX005	*(For National Authority Use only)*

Title of Study: A Double-Blind, Randomized, Placebo-Controlled, Two-Phase Study (a Single Ascending Dose Phase Followed by a Proof of Concept Phase) to Assess the Safety, Efficacy and Pharmacokinetics of FX005 (50:50 PLGA) Microspheres for the Treatment of Pain in Osteoarthritis of the Knee

Protocol Number: FX005-2010-001

Investigators and Study Centers: SAD Phase: 4 sites in Canada, 2 sites in Spain, and 1 site in Austria. PoC Phase: 5 sites in Canada, 5 sites in Spain, 4 sites in Austria, and 1 site in the UK.

Publication Reference: Bodick N, Willwerth C, Lufkin J, Kumar A, Blanks RC, Clayman MD. Safety and Efficacy of FX005, an Intra-Articular Extended Release p38MAP Kinase Inhibitor, in Patients with Osteoarthritis of the Knee. Abstract at Orthopedic Research Society Annual Meeting 2013.

Study Period: Approximately 13 months (February 15, 2011 to March 07, 2012)

Phase of Development: 1/2a

Objectives:

Single Ascending Dose (SAD) Phase

Primary Objective:

- Assess the safety and tolerability of single doses of FX005 microspheres in patients with osteoarthritis of the knee

Secondary Objective:

- Characterize the single dose pharmacokinetic (PK) profiles of FX005 microspheres

Proof of Concept (PoC) Phase

Primary Objectives:

- Assess the safety and tolerability of a single dose of FX005 microspheres in patients with osteoarthritis of the knee
- Assess the analgesic effect of a single dose of FX005 microspheres in patients with osteoarthritis of the knee

Secondary Objectives:

- Characterize the single dose PK profiles of FX005 microspheres
- Explore the effect of FX005 microspheres on:
    - functional improvement
    - intermittent and constant osteoarthritis pain
    - patient global assessment (PTGA) of disease status
    - clinical observer global assessment (COGA) of the disease status

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- Outcome Measures in Rheumatoid Arthritis Clinical Trials – Osteoarthritis Research Society International (OMERACT-OARSI) responder status
- consumption of analgesic medications

Methodology:

This study was a multi-center, randomized, double-blind, placebo-controlled design. The study consisted of two phases, a Single Ascending Dose (SAD) Phase followed by a Proof of Concept (PoC) Phase. The study was conducted in male and female patients, ≥ 40 years of age, with symptomatic tibio-femoral osteoarthritis (OA) of the knee. Patients diagnosed with bilateral OA of the knees could be enrolled and have their index knee treated according to the study protocol.

In the SAD Phase, the dose was escalated through 1, 10, and 45 mg and compared to blank poly [lactic-co-glycolic acid] (PLGA) microspheres (matched to each active dose in terms of microsphere content) and Diluent in three cohorts of 12 patients. When the last patient in a given cohort had completed 14 days of follow-up, the Safety Review Committee (SRC) conducted a safety review prior to escalation to the next dose.

The PoC Phase was initiated after the safety review for the final dose of the SAD Phase and a review of drug concentration measurements and PK parameters through Day 3 from the SAD Phase. The Sponsor notified the relevant Competent Authorities and Ethics Committees of the results from the SAD safety reviews and the rationale for the selection of the PoC dose within the 3 doses tested. Where applicable, a justification for its selection was submitted to the relevant Competent Authorities and Ethics Committees prior to implementation of the PoC Phase.

The highest, well-tolerated dose evaluated in the SAD Phase was compared to blank PLGA microspheres (matched to each active dose in terms of microsphere content) and Diluent in the PoC Phase; patients were randomized in a 2:1:1 ratio, respectively. After the Safety Review Committee's review of the safety and pharmacokinetic data for all 3 dose levels from the SAD Phase, the 45 mg dose of FX005 microspheres was determined to be the highest, well-tolerated dose to be used for the PoC Phase of the study.

The blind-assessor technique was used to maintain double-blind conditions. Treatments were prepared by an unblinded pharmacist, and intra-articular injections were performed by an unblinded injector. The unblinded injector had no other contact with the patient. The patient and the assessor responsible for patient clinical assessments and patient safety monitoring were blinded throughout the study. The injection contents were not visible to the patient. All other site and Sponsor personnel/representatives involved in the conduct of the study were blinded at the patient level with regard to the study treatment being administered with the exception of an unblinded monitor(s) for performing drug accountability, an unblinded radiologist/ultrasound technician (if needed), the Sponsor's SRC representative, and an unblinded statistician for preparing all safety review analyses, and the analyses of the PK data for the SAD Phase prior to the PoC Phase. After the corresponding safety review meeting, certain Sponsor personnel/representatives not directly responsible for blinded site management, data management, or biostatistical analysis may have had access to unblinded by-treatment summary tables for each SAD cohort, but did not have access to unblinded patient-level data until after database lock, to support decision-making and potential regulatory submissions.

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Number of Patients:

Planned: SAD Phase: Up to 36 patients (12 per cohort). PoC Phase: 104 patients (52 patients to receive FX005 microspheres, 26 patients to receive blank PLGA microspheres and 26 patients to receive Diluent).

Analyzed: SAD Phase: 36 patients (12 per cohort). PoC Phase: 104 patients (26 were randomized to the blank PLGA microspheres group, 26 to the Diluent group and 52 to the FX005 microspheres group).

Diagnosis and Criteria for Inclusion

Inclusion Criteria:

- Written consent to participate in the study.
- Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions.
- Male or female ≥40 years of age.
- Diagnosis of unilateral or bilateral OA of the knee for at least 6 months prior to Screening with confirmation of OA according to American College of Rheumatology (ACR) Criteria for Classification of Idiopathic OA of the Knee (clinical and radiological) based on an X-ray performed within 6 months prior to Screening or at Screening.
- Radiographic evidence of OA in the tibiofemoral compartment of the index knee (Kellgren-Lawrence grades II or III) within 6 months prior to Screening or at Screening (PoC only).
- Score of 2 or higher for at least one of the five Western Ontario and McMaster Universities (WOMAC®) Osteoarthritis Index A (WOMAC A) subscale questions for the index knee at Screening (SAD only).
- Index knee pain on most days (> 15) over the last month (PoC only).
- Mean score for the WOMAC A subscale (Likert 3.1) between 2.0 and 3.5 for the index knee at Screening and Baseline (PoC only).
- Score of 2-3 for the WOMAC A1 score (pain on walking) for the index knee at Screening and Baseline (PoC only).
- If bilateral OA existed, the mean score for the WOMAC A subscale for the contralateral knee must have been less than the mean score for the WOMAC A subscale for the index knee at Screening and Baseline.
- Body mass index (BMI) ≤ 40 kg/m^2.
- Willingness to abstain from use of topical pain therapies (e.g., non-steroidal anti-inflammatory drugs [NSAIDS], capsaicin, lidocaine patches, heat patches), intra-articular corticosteroids and intra-articular viscosupplementation during the study.
- Willingness to abstain from use of oral NSAIDs, narcotics and systemic corticosteroids during the study (PoC only).
- Willingness to abstain from the use of the only permitted rescue medication (acetaminophen/paracetamol) for 48 hours prior to the in-clinic period and all out-patient visits with the exception of Visit 1 (Screening; PoC only).

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- No clinically significant results at Screening (clinical significance of values or findings outside of normal ranges will be determined by the Principal Investigator).

Exclusion criteria:

Disease-related criteria:

- Kellgren-Lawrence Grade 0, I or IV radiographic stage of the index knee.
- Clinically apparent tense effusion in index knee (PoC only).
- Ipsilateral hip OA (PoC only).
- Fibromyalgia, chronic pain syndrome or other concurrent medical or arthritic conditions which could interfere with evaluation of the index knee (PoC only).
- History of Reiter's syndrome, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease, sarcoidosis, or amyloidosis.
- Presence of surgical hardware or other foreign body in the index knee.
- Pain in any other area of the lower extremities or back that is equal to or greater than the index knee pain (PoC only).
- Clinical signs and symptoms of active knee infection or crystal disease.

Previous or concomitant OA treatment-related criteria:

- Intra-articular corticosteroid within 3 months of Screening.
- Intra-articular hyaluronic acid within 6 months of Screening.
- Other intra-articular therapy within 3 months of Screening.
- Systemic corticosteroid within 2 weeks of Screening (PoC only).
- Prior arthroscopic or open surgery of the index knee within 12 months of Screening.
- Planned/anticipated surgery of the index knee during the study period.

Patient-related criteria:

- Clinically significant cardiac disease as judged by the Principal Investigator (e.g., uncontrolled hypertension).
- Screening or Baseline 12-lead electrocardiogram (ECG) demonstrating QT_c > 450 msec in male patients and > 470 msec in female patients (Goldenberg et al, 2006) or any clinically significant ECG abnormality as judged by the Principal Investigator.
- History of malignancy, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or resected cervical atypia or carcinoma in situ.
- Known or clinically suspected infection with human immunodeficiency virus (HIV), hepatitis C or B viruses.
- History of latent or active tuberculosis (TB).
- History of positive TB test or a positive screening Tuberculin Skin Test (TST) defined as 5+

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induration.

- Lived in or visited a country where TB is endemic in the 8 weeks prior to Screening.
- Other serious, non-malignant, significant, acute or chronic medical (e.g., uncontrolled diabetes) or active psychiatric illness that, in the judgment of the Principal Investigator, could compromise patient safety, limit the patient's ability to complete the study, and/or compromise the objectives of the study.
- Increased predisposition for the development of infections.
- Skin breakdown at the knee where the injection would take place.
- History of drug or alcohol dependence in the past 3 years.
- Women who are pregnant, nursing or likely to become pregnant during the time of the study.
- Women of child-bearing potential (not surgically sterile or post-menopausal for at least 1 year as documented in medical history) not using effective contraception (e.g., condoms, oral contraceptives, diaphragm or cervical cap, intrauterine device, tubal ligation or other surgical procedure).
- Known sensitivity to ethyl chloride.
- Known sensitivity to acetaminophen/paracetamol (PoC only).
- Use of any investigational drug or device within 30 days of study start.
- Use of any investigational biologic within 60 days of study start.

Test Product, Dose and Mode of Administration, Lot Number:

SAD: FX005 (50:50 PLGA) Microspheres: nominal 1, 10, or 45 mg* administered as a single, intra-articular injection of 5 mL.

PoC: FX005 (50:50 PLGA) Microspheres: 45 mg administered as a single, intra-articular injection of 5 mL.

Lot number: IL4130A, 10.5 mg strength; IL4130B, 1.0 mg strength

* The active drug load measured at release for the 1 mg vials was 14.5%. The active drug load measured at release for the 10.5 mg vials was 14.2%. Increasing doses reflect an increase in the concentration of microspheres delivered.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Blank 50:50 PLGA Microspheres: administered as a single, intra-articular injection of 5 mL; matched in microsphere content to the FX005 microsphere arm within each cohort, and

Lot number: IL4350A (matched to the 10.5 mg FX006 strength); IL4350B (matched to the 1.0 mg FX006 strength)

Diluent: administered as a single, intra-articular injection of 5 mL.

Lot number: OL0791910

Duration of Treatment: Eligible patients received a single, intra-articular injection.

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Criteria for Evaluation:

Safety (SAD and PoC):

- Adverse events
- Physical examinations
- Index knee examinations
- Vital signs
- ECGs
- Clinical laboratory evaluations

Efficacy (PoC only):

- WOMAC® Osteoarthritis Index (Likert 3.1)
- Intermittent and Constant Osteoarthritis Pain Questionnaire (ICOAP, Version 3)
- PTGA
- COGA
- Responder status as defined by the OMERACT-OARSI criteria
- Consumption of analgesic medications

Bioanalytical and Pharmacokinetic (SAD and PoC):

- Drug concentration measurements
- Peak exposure (C_{max})
- Time from dosing to peak exposure (t_{max})
- Total exposure (AUC_t, AUC_∞)
- Half-life of the terminal log-linear phase ($t_{1/2}$)

Biomarkers of bone and cartilage turnover may also be assessed for research purposes only and will have no bearing on the outcome of study.

Statistical Methods:

Safety parameters (physical examinations, index knee examinations, vital signs, ECGs, clinical laboratory evaluations, and adverse events [AEs]) were analyzed descriptively.

The primary efficacy analysis for the PoC Phase was to compare the mean change in the WOMAC A score (average pain score from 5 questions) from Baseline to Week 4 between FX005 microspheres and Placebo (blank PLGA microsphere and Diluent groups combined and/or Diluent and blank PLGA microsphere groups separately) based on an analysis of covariance (ANCOVA) model with effects for treatment and Baseline WOMAC A score as a covariate. The test for a significant treatment effect was performed using a 0.05 alpha level. Similar analyses were performed for other WOMAC endpoints, intermittent and constant osteoarthritis pain scores (intermittent, constant, and total), global assessment scores (patient and clinical observer), and rescue medication use. The percent of responders at 4, 8, and 12 weeks, according to OMERACT-OARSI criteria, were calculated in each of the treatment groups, and a logistic regression model with effects for treatment, site, and Baseline WOMAC A score were used to test if the likelihood of response differed significantly between FX005 microspheres and Placebo.

Plasma FX005 concentrations were measured using an established, validated method (liquid chromatography with tandem mass spectrometry). Peak exposure (C_{max}), time from dosing to peak exposure (t_{max}), total exposure (AUC_t, AUC_∞), and half-life of the terminal log-linear phase ($t_{1/2}$) were estimated following noncompartmental analysis of plasma concentration time course data. Results

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(plasma concentrations and PK parameters) were analyzed by summary statistics. Plasma concentrations were measured in all patients receiving FX005 microspheres in the SAD and PoC phases.

Demographics, Disposition, and Exposure:

SAD Phase

A total of 36 patients were enrolled in the SAD Phase. In each cohort (1 mg, 10 mg, and 45 mg FX005), 3 patients were randomized to the blank PLGA microsphere group, 3 patients were randomized to the Diluent group and 6 patients were randomized to the FX005 microsphere group. All patients received their assigned treatment, and all patients completed the study. In all cohorts, the majority of patients were female (range: 58.3% - 75.0%) and white/Caucasian (range: 75.0% - 91.7%). Mean age ranged from 63.3 to 65.5 years, and mean BMI ranged from 30.3 to 32.1 kg/m^2 in the 3 cohorts. There were no statistically significant differences between the blank PLGA microspheres group, the Diluent group, and the FX005 microspheres groups in any cohort for any demographic characteristic.

The mean number of years from diagnosis of knee osteoarthritis to Screening ranged from 6.0 to 8.4 in the 3 cohorts. In the 1 mg and 45 mg cohorts, the majority of patients (58.3% and 75.0%, respectively) presented with bilateral knee osteoarthritis, and in the 10 mg cohort, 58.3% had unilateral knee osteoarthritis. The mean number of days patients experienced knee pain in the month prior to Screening ranged from 27.5 to 30.0 in the 3 cohorts. The mean WOMAC A subscale (Likert 3.1) scores at Screening ranged from 2.17 to 2.28, and mean WOMAC A1 was 2.1 in all cohorts. There were no statistically significant differences between the treatment groups in any cohort with regard to Screening/Baseline index knee characteristics.

PoC Phase

A total of 104 patients were enrolled in the PoC Phase; 26 patients were randomized to the blank PLGA microspheres group, 26 patients to the Diluent group, and 52 patients to the 45 mg FX005 microspheres group. One patient randomized to FX005 microspheres received blank PLGA microspheres in error (Patient # 533016), and is analyzed "as randomized" in the efficacy analyses and "as treated" in the safety and PK analyses. Of the 104 patients, 101 (97.1%) patients completed the study, and 3 (2.9%) prematurely discontinued (1 patient in the Diluent group: withdrew consent; 2 patients in the FX005 group: lost-to-follow-up, personal obligations). The 104 enrolled patients included 33 (31.7%) males and 71 (68.3%) females. The majority of patients (n=92, 88.5%) were white/Caucasian. The mean (SD) age was 62.6 (10.1) years. The mean (SD) BMI (kg/m2) was 31.4 (4.7), and the range was 19.9 - 39.9. There were no statistically significant differences between the blank PLGA microspheres group, the Diluent group, and the FX005 microspheres group for any demographic characteristic.

The mean (SD) number of years from diagnosis of knee osteoarthritis to Screening was 5.9 (5.87). The majority of patients presented to the study with bilateral (60.6%) knee osteoarthritis and with a Kellgren-Lawrence grade of 3 (60.6%) versus a grade of 2 (39.3%). The mean (SD) number of days patients experienced knee pain in the month prior to Screening was 28.9 (3.02). At Screening and Baseline, the mean score for the WOMAC A subscale (Likert 3.1) was 2.44, and the mean WOMAC A1 score was 2.4. There were no statistically significant differences in Baseline index knee characteristics between the treatment groups.

Efficacy Results:

SAD Phase:

Efficacy was not evaluated in the SAD Phase.

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PoC Phase:

Primary efficacy analyses of data from the PoC Phase suggest that FX005 is more effective than Placebo in reducing pain associated with osteoarthritis of the knee. The pre-specified primary endpoint approached statistical significance, that is, the adjusted mean between-treatment difference in WOMAC A was 0.29 with p=0.0535 (two-sided). This was further supported by a sensitivity analysis conducted to remove the impact of rescue or restricted medications which showed that the mean decrease in WOMAC A from Baseline to Week 4 was significantly greater for the FX005 group compared to the Placebo group (p = 0.0069 and 95% CI: 0.117 , 0.721). Additionally, the by-visit analyses of change from Baseline in WOMAC C (function subscale) rendered results that were supportive of efficacy of FX005 in improving function starting within 2 weeks after the intra-articular injection through Week 8. Additionally, a statistically significant treatment effect was observed at Week 4 based on OMERACT-OARSI responder criteria: the odds of being a responder for patients receiving FX005 was approximately 3 times those of patients receiving Placebo (CI for Odds Ratio: 1.341, 7.027; p= 0.0079.). The percentages of responders were 73% for the FX005 group and 46% for the Placebo group at Week 4 (p= 0.0079), 65.4% and 48.1%, respectively, at Week 8 (p-value NS), and 67.3% and 53.8% at Week 12 (p-value NS) in the full population.

Significant ($p<0.10$) Baseline-by-treatment interactions were noted in the analyses of key secondary endpoints. This was manifested as significant (alpha=0.10, 2-sided) Baseline-by-treatment interaction.

Because of this pattern of interaction, the exploratory analyses were conducted within subgroups of low (less severe; WOMAC A < 2.4) and high (more severe; WOMAC A ≥ 2.4) Baseline pain. In the subset of patients with less severe Baseline pain (WOMAC A < 2.4), negligible treatment effect was seen (mean between-treatment difference 0.15, $p>0.5$). In the subset with more severe Baseline pain (WOMAC A ≥ 2.4), a statistically significant and large (relative to the full population) treatment effect was seen (mean between-treatment difference 0.51, p=0.024). Similar patterns and magnitudes of response and differences were seen in other endpoints.

For the subset of patients with more severe Baseline pain (WOMAC A ≥ 2.4), the percentage of responders according to OMERACT-OARSI criteria for FX005 was substantially greater than that of Placebo throughout the trial: 75.9% versus 48.3% at Week 4; 65.5% versus 48.3% at Week 8; and 62.1% versus 55.2% at Week 12. As with the full population, for this subset, the odds of being a responder at Week 4 for patients receiving FX005 was approximately 3 times that of patients receiving Placebo. In spite of the small sample size in the high (more severe) Baseline pain subgroup, this difference was statistically significant, p=0.0336 (CI for Odds Ratio: 1.099, 10.318).

Pharmacokinetic Results:

SAD Phase

The mean plasma concentration of FX005 increased with increasing dose. Plasma concentrations were quantifiable at approximately 1 hour post-dose. In the 1 mg FX005 group, the mean (SD) plasma concentration of FX005 at 48 hours, 0.41 (0.107) ng/mL, was similar to that at Day 14, 0.44 (0.292) ng/mL. By the Day 28 assessment, FX005 was below the limit of quantitation (50 pg/mL) in the plasma of all patients in this cohort. In the 10 mg and 45 mg cohorts, the largest mean (SD) plasma concentrations of FX005, 5.50 (2.464) ng/mL and 24.62 (14.981) ng/mL, respectively, were seen at the 48-hour assessment. At the Day 42 assessment, FX005 was still quantifiable in 4/6 patients in the 10 mg FX005 cohort and all patients in the 45 mg FX005 cohort.

The concentration-time plots for individual patients were highly variable. In the 1 mg FX005 cohort, the maximum plasma concentration was seen at 12 hours (1 patient), 24 hours (1 patient), 48 hours (2 patients), and Day 14 (2 patients). In the 10 mg FX005 cohort, the maximum plasma concentration

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was seen at 48 hours (3 patients) and Day 14 (3 patients). In the 45 mg FX005 cohort, the maximum plasma concentration was seen at 24 hours (2 patients), 48 hours (2 patients), Day 14 (1 patient), and Day 28 (1 patient).

Plots of the mean plasma concentrations for each dose group showed that the shapes of the plasma concentration profiles were similar for the 10 mg and 45 mg FX005 doses. The elimination phase was not seen before 42 days. The nominal observed t_{max} occurred at approximately 48 hours in these groups.

Results of the analysis of FX005 PK show that mean C_{max} and AUC_t increased with increasing dose strength. The dose-proportionality assessment using the power model showed C_{max} increased proportionally with dose: slope and 95% CI for slope of 1.04 and (0.91, 1.17), and AUC_t increased nearly proportionally with dose: 1.18 and (1.05, 1.31). Mean t_{max} was 134 hours for the 1 mg FX005 dose group and 192 hours for the 10 mg and 45 mg FX005 groups.

Because only 1 patient in the 1 mg FX005 group and 2 patients in the 10 mg FX005 group had concentration-time profiles for which λ_z could be calculated, no mean values of λ_z and the other PK parameters that depend on it (AUC_∞, $t_{1/2}$, CL/F, and V_d/F) were calculated in these groups. Mean (SD) values for these parameters were calculated in the 45 mg FX005 group based on the results from 4 patients (λ_z : 0.0044 [0.00278] 1/hr; AUC_∞: 10956 [4525.5] hr*ng/mL; $t_{1/2}$: 228.5 [146.99] hr; CL/F: 4671.6 [1874.54] mL/hr; V_d/F: 1664484 [1482919.8] mL).

PoC Phase

Following a 45 mg dose, the mean (SD) plasma concentration of FX005 was highest at Day 7 (19.35 [16.282] ng/mL). At Day 21, the mean (SD) was less than one-fourth the Day 7 value (4.31 [4.931] ng/mL). The mean (SD) peak plasma concentration occurred on Day 7 in both males and females, but the actual concentration was higher in females (21.06 [18.289] ng/mL) than in males (14.95 [8.351] ng/mL). The mean concentration in females remained higher than that in males until approximately Day 56.

Results of the analysis of FX005 PK show the mean (SD) C_{max} was 21.41 (16.652) ng/mL. Mean (SD) t_{max} was 209.9 (116.77) hours, between Day 7 and Day 14; the median and minimum t_{max} were both 144 hours, indicating that maximum concentration of FX005 was seen at the Day 7 assessment in half of patients. Mean (SD) $t_{1/2}$ was 372.8 (287.40) hours, or 15.5 days. No clinically meaningful differences were seen in the results from females and males.

In a plot of plasma concentrations versus changes in WOMAC A scores, no correlation was observed.

Safety Results:

SAD Phase

In all cohorts, at least 50% of patients experienced at least one treatment-emergent adverse event (TEAE). Arthralgia, the most common TEAE, occurred in 10 of 36 patients overall, including patients in all treatment groups except the blank PLGA group in the 1 mg dose cohort. (Pain events in the index knee that began > 30 minutes after administration of study treatment were coded to arthralgia, and those that began ≤ 30 minutes after administration of study treatment were coded to Injection Site Joint Pain.) TEAEs that occurred in > 5% of all patients included joint swelling (5/36 patients), upper respiratory infection and headache (4/36 patients each), injection site joint pain (3/36 patients), and joint effusion, joint stiffness, and rash (2/36 patients each). There were no significant dose-related trends in the incidence of TEAEs.

In general, almost all TEAEs reported in the SAD Phase were mild. The only moderate TEAEs reported for patients receiving FX005 microspheres in the SAD Phase were injection site joint pain (index knee

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related) and headache, experienced by 1 patient each in the 1 mg dose group. No severe TEAE was reported for patients receiving FX005 at any dose level. The severe TEAEs reported in the SAD Phase were severe arthralgia and severe joint effusion (both index knee related), reported for 1 patient each in the blank PLGA microspheres group of the 10 mg dose cohort. The only occurrences of TEAEs deemed possibly or probably related to study drug in patients receiving FX005 were 1 occurrence each of mild arthralgia in the 1 mg and 10 mg dose groups; 1 occurrence of injection site pain and sensation of pressure in 1 patient in the 10 mg dose group; and 1 occurrence of mild joint swelling in the 10 mg dose group. No patient died or experienced an SAE or a TEAE leading to discontinuation from the study.

Index knee related TEAEs among patients receiving FX005 microspheres occurred in 2/6 patients in the 1 mg group, 3/6 patients in the 10 mg group, and 3/6 patients in the 45 mg group; among patients receiving blank PLGA microspheres, 3/3 patients in the 10 mg group and 2/3 patients in the 45 mg group; and in 3/9 patients receiving Diluent. Arthralgia occurred in the index knee of 9 patients. Other index knee-related TEAEs included joint swelling (5 patients), injection site joint pain (3 patients), joint effusion and joint stiffness (each in 2 patients) and contusion, burning sensation, and sensation of pressure (each in 1 patient). The only index-knee related TEAE that occurred in more than 1 patient in an FX005 dose group was joint swelling, experienced by 2 patients each in the 10 mg and 45 mg dose groups. None of the patients who experienced an event related to the index knee required intra-articular non-drug (aspiration) or drug therapy in response to the event.

Almost all patients in the Safety Population entered the study with all hematology and chemistry parameters within normal range, and these remained within normal range throughout the study. Patients treated with FX005 who started the study with normal hematology Baseline values but showed abnormal results post-treatment were observed in the 10 mg dose group [Normal to Low lymphocytes in 1 patient, Normal to Low RBC counts in 2 patients, and Normal to Low WBC counts in 1 patient] and in the 45 mg dose group (Normal to Low hemoglobin, Normal to High neutrophils, and Normal to High WBC counts in 1 patient each). Two or more patients treated with FX005 who started the study with normal Baseline chemistry values but showed abnormal results post-treatment were observed in the 1 mg dose group (Normal to High CRP in 2 patients, Normal to Low chloride in 2 patients, Normal to High fasting glucose in 3 patients, and Normal to Low HDL-C in 2 patients) and in the 45 mg dose group (Normal to High LDL-C in 2 patients). In general, these shifts are well within the expected variation for a trial of this length and were no more frequent than those seen in the corresponding Placebo group. Analyses of changes from Baseline did not reveal any remarkable trends. There were no clinically significant changes in vital signs, O_2 saturation or ECG parameters observed following administration of the study drug in any cohort and any changes were similar between FX005 and Placebo groups.

PoC Phase

At least one TEAE occurred in 20 (74.1%) patients in the blank PLGA microspheres group, 14 (53.8%) patients in the Diluent group, and 34 (66.7%) patients in the 45 mg FX005 group. The SOC with the highest incidences of TEAEs overall was Musculoskeletal and Connective Tissue Disorders [blank PLGA microspheres group: 14 (51.9%) patients, Diluent group: 7 (26.9%) patients, FX005 group: 23 (45.1%) patients]. The most common TEAEs, those occurring in at least 10% of patients in each group, were arthralgia [blank PLGA microspheres group: 7 (25.9%) patients, Diluent group: 5 (19.2%) patients, FX005 group: 9 (17.6%) patients] and headache [3 (11.1%), 5 (19.2%), and 7 (13.7%), respectively]. The only severe AE, arthritis, occurred in 1 patient each in the blank PLGA microsphere (3.7%) and the FX005 (2.0%) groups. Both events were related to the index knee. No patient died or discontinued from the study during the PoC phase. One patient in the FX005 group (2.0%) experienced an SAE (breast cancer).

Index knee-related TEAEs were more common in the blank PLGA microsphere group (16 patients, 59.3%) than in the Diluent (5, 19.2%) or FX005 (17, 33.3%) group. Index knee related TEAEs that

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occurred in at least 5% more patients in the blank PLGA group than in either of the other treatment groups included injection site joint pain (4 patients, 14.8%, compared to 1, 2.0%, in the FX005 group and 1, 3.8%, in the Diluent group); arthralgia (5, 18.5%, compared to 5, 9.8%, in the FX005 group and 3, 11.5%, in the Diluent group); and joint effusion (4, 14.8%, compared to 1, 2.0%, in the FX005 group and 0 in the Diluent group). Joint swelling was at least 5% more common in the FX005 group (6 patients, 11.8%) than in the blank PLGA microsphere (1, 3.7%) or Diluent (0) groups. No event related to the index knee occurred at a difference of at least 5% more patients in the Diluent group than any other treatment group. Four (4) of the 16 patients in the blank PLGA microsphere group who experienced an event related to the index knee (arthritis, n=1; joint effusion, n=3) received intra-articular aspiration of the joint, and 2 of those 4 patients also received treatment with intra-articular corticosteroid. Five of the 17 patients in the FX005 group who experienced an event related to the index knee (arthritis, n=2; joint swelling, n=1; osteoarthritis, n=2) required intra-articular aspiration, and 3 of those 5 patients also required treatment with intra-articular corticosteroid.

For hematology testing, shifts from Normal to Low or High values occurred in fewer than 10% of patients in the blank PLGA microsphere group, in fewer than 18% of patients in the Diluent group, and in fewer than 13% of patients in the FX005 group. In chemistry testing, the most common shift was from Normal to High triglycerides (blank PLGA microspheres, 22.7%; Diluent, 38.5%; FX005, 14.9%). Other shifts from Normal to Low or High chemistry values occurred in fewer than 23% of patients in the blank PLGA microsphere group, in fewer than 26% of patients in the Diluent group, and in fewer than 20% of patients in the FX005 group. Mean changes in laboratory values from Baseline to each visit fluctuated over time but were slight in most parameters and were similar between groups by Week 12. None of these data indicate an effect of FX005 or blank PLGA microspheres on hematology, chemistry, or liver function test (LFT) results. There were no clinically significant changes in vital signs, O_2 saturation or ECG parameters observed following administration of the study drug in any cohort and any changes were similar between FX005 and Placebo groups.

In all three treatment groups, the proportion of patients with no signs of inflammation increased from Baseline to Week 12: blank PLGA microsphere group (37.0% to 55.6%), Diluent group (38.5% to 72.0%), and the FX005 group (33.3% to 59.2%). Among the individual signs of inflammation, the proportions of patients with tenderness and swelling decreased in all three treatment groups over the 12 weeks of the study. The proportion of patients with redness increased slightly by Week 4 in the FX005 group, increased slightly by Week 8 in all groups, and was still slightly increased relative to Baseline in the Diluent and FX005 groups by Week 12. In the Diluent and FX005 groups, the proportion of patients with effusion decreased by Week 2 and was relatively unchanged for the remainder of the study.

Summary – Conclusions:

Primary efficacy analyses of data from the PoC Phase suggest that FX005 is more effective than Placebo in reducing pain associated with osteoarthritis of the knee. In the primary and sensitivity analyses, the effect over Placebo is approximately 7 to 12 mm (converted from a 0-4 point Likert scale to a 100 mm Visual Analogue Scale), comparable to the maximal effects seen with NSAIDs but less than the effects of opioids.

Investigation of the nature of significant treatment by Baseline interactions revealed a generally flat relationship between Baseline and response in the Placebo group and increased response with increased Baseline pain severity in the treated group. Hence exploratory analyses were carried out for the WOMAC A, WOMAC C and OMERACT-OARSI responder status endpoints within 2 subgroups – those with high (more severe) Baseline pain values (≥2.4), and those with low (less severe) Baseline pain values (<2.4). The split between the two subgroups was made at the approximate median of the Baseline

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values.

In exploratory analyses of the patients with Baseline WOMAC A greater than or equal to the median score of 2.4, the differences in means between FX005 and Placebo in WOMAC A were generally larger than those of the full population. The overall magnitude of effect in this subpopulation relative to Placebo equates to approximately 13 mm on the 100 mm visual analog scale (VAS), a difference greater than reported values for opioids. Patients with Baseline pain ≥2.4 comprise approximately 56% of the patient population. In contrast, for patients with Baseline WOMAC A <2.4, the mean differences between FX005 and Placebo with respect to change in WOMAC A were not statistically significant at any measured time point.

The by-visit analyses of change from Baseline in WOMAC A1 showed similar results to those of WOMAC A with one notable difference: WOMAC A1 demonstrates a maximum difference between FX005 and Placebo group means at Week 2 rather than Week 4. While there were no statistically significant differences between treatment groups in any of the WOMAC A1 analyses, the absolute magnitude can be compared to available therapies. The onset of action of FX005 is as rapid as that of triamcinolone hexacetonide and the overall magnitude of effect and duration of action is greater than that for triamcinolone hexacetonide. The onset of action of FX005 is more rapid than the onset of action of Hylan G-F 20, and the magnitude of effect is greater for the 12-week duration of the study.

The by-visit analyses of change from Baseline in WOMAC C rendered results that were supportive of efficacy of FX005 in improving function starting within 2 weeks after the intra-articular injection through Week 8. There was a significant treatment-by-Baseline interaction (p=0.0343) in the ANCOVA, so an ANOVA model was used.

For patients with Baseline WOMAC A ≥ 2.4, the mean differences between FX005 and Placebo with respect to change in WOMAC C from Baseline to Weeks 2, 4, and 8 were statistically significant (p=0.0404, p=0.0237, and p=0.0403, respectively). The 95% CIs for mean differences between FX005 and Placebo with respect to change in WOMAC C from Baseline to Weeks 2, 4, 8, and 12 were (0.023, 1.011), (0.076, 1.020), (0.024, 1.014), and (-0.215, 0.908), respectively. In contrast, for patients with Baseline WOMAC A < 2.4, the mean differences between FX005 and Placebo with respect to change in WOMAC C were not statistically significant at any measured time point.

The effects on function for FX005 are generally larger than those reported for other intra-articular and for systemic therapies. Hyaluronic acid therapies generally do not show an effect in function. Duloxetine (Cymbalta®), a recently approved oral therapy, demonstrates an effect that is approximately one-third of the magnitude of that observed with FX005.

In the primary and sensitivity analyses of WOMAC A, it is evident that the absolute maximal effect of FX005 is achieved at 2 weeks and that absolute magnitude is maintained for the 12 week duration of the study. However, significance is lost following the 4-week endpoint because the Placebo group improves relative to Week 4, an effect that is especially pronounced at 12 weeks. This marked improvement in the Placebo group is not noted in the WOMAC C analysis; in this analysis, significance was maintained through 8 weeks.

A recent review noted that in studies of pain of 6 weeks or greater duration, an improvement in placebo frequently occurs toward the end of studies and the placebo improvement seems to correlate to the intensity of site interactions with patients and to the expectations of patients at the beginning of the study.

Mean C_{max} and AUC_t increased with increasing dose strength. Mean t_{max} was 134 hours for the 1 mg FX005 dose group and 192 hours for the 10 mg and 45 mg FX005 dose groups.

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The plasma PK evident in the SAD and PoC Phases of the study are noteworthy in that:

- They are dose proportional with relatively little inter- and intra-subject variability.
- There is no evidence of an initial burst, which limits systemic exposure.
- At the highest dose (45 mg) the C_{max} (21.41 ng/mL) is lower than the IC_{50} of FX005 in whole blood (59 ng/mL).
- Throughout the course of the 12-week PoC Phase, plasma levels are consistent with the maintenance of therapeutic levels in the joint predicted from preclinical models (see Study IVOAPT247 in FX005 [50:50 PLGA] Microspheres Investigators Brochure, V1.0, 11 October 2010).

The PK profile demonstrated in the SAD and PoC Phases of the study supports the hypothesis that intra-articular delivery via PLGA microspheres limits systemic exposure and prolongs the maintenance of therapeutic concentrations in the joint.

Across the SAD and PoC Phases of the study, there were few differences in incidence of systemic TEAEs among the active and Placebo arms and none of the differences was indicative of safety liabilities associated with FX005. In particular, the laboratory measures that show the greatest sensitivity to p38 inhibition, hemoglobin, red blood cell count, white blood cell count, and liver function tests, demonstrated no meaningful change from Baseline in the active arms and no meaningful differences from the Placebo arms. These findings strongly support the contention that the low systemic exposure to FX005 is not associated with untoward systemic effects.

In the PoC Phase, TEAEs related to the index knee occurred more frequently in the blank PLGA microsphere group than in the Diluent and FX005 groups and more frequently in the FX005 group than in the Diluent group (blank PLGA microsphere group: 59.3% vs. Diluent group: 19.2% vs. FX005 group: 33.3%). Injection site joint pain, arthralgia, and joint effusion were more common in the blank PLGA microsphere group, while joint swelling was more common in the FX005 group. At this point, an association between these AEs and FX005 and/or PLGA cannot be ruled out. The majority of these events are of mild to moderate severity and all are of limited duration. The overall incidence of index knee related TEAEs in the active arm of the PoC Phase of the study (33.3%) is slightly less than the incidence of index knee related TEAEs in a similar study population treated with Synvisc-One® (35.8%) (refer to Information for Prescribers, Synvisc-One® [hylan GF 20], Genzyme Corporation, January 5, 2010) and is also similar to the incidence associated with other hyaluronic acid injections.

Overall, FX005 was well-tolerated by patients with osteoarthritis of the knee.

Date of Report: 30 August 2013