The synovial concentrations of TCA produced by 10 mg FX006 at Week 6 was 78.75 ng/ml; 95% CI 50.93, 121.77, and at Week 12 was 0.92 ng/ml; 95% CI 0.74, 1.15. (Figure 2)

At time points beyond Week 12, measurable concentrations of TCA were observed at Week 16 for the 40 mg FX006, 0.22 ng/ml; 95% CI 0.37, 0.11; at Week 20, synovial levels associated with 40 mg FX006 were below LLQ.

Significantly less suppression of morning serum cortisol was observed with 40 mg FX006 than with 40 mg TCA IR at Days 2 and 3 (p=0.0141 and p=0.0027, respectively). (Figure 3)

At Week 6, the suppression of cortisol produced by each of the treatment arms had returned to near-baseline values. (Figure 3)

INTRODUCTION

FX006 is an extended-release formulation of triamcinolone acetonide (TCA) in poly (lactic-co-glycolic) acid microspheres (Figure 1) currently under study for the treatment of OA on the knee.

In a previously reported study of 228 patients with moderate to severe knee OA, 40 mg FX006 demonstrated both prolonged and increased analgesia relative to the 40 mg dose of standard, immediate release TCA (TCA IR).

Two studies (6 and 20 weeks in duration) have subsequently been conducted to characterize systemic pharmacokinetics, local synovial fluid concentrations and effects on cortisol production for FX006 and TCA IR.

Integrating data from these three studies, it is possible to estimate the minimal synovial concentrations of TCA required to achieve and maintain maximal therapeutic effect.

OBJECTIVES

The primary objectives of the 6-Week and the 12-Week Studies in patients with OA of the knee were:

- to characterize systemic pharmacokinetics following single IA injection of comparable doses of FX006 and TCA IR,
- to measure the synovial concentrations of TCA produced by each treatment at 6, 12, 14, and 20 weeks,
- to quantify the effects on the hypothalamic-pituitary-adrenal (HPA) axis for each treatment.

METHODS

The 6-Week Study was a double-blind, randomized, parallel-group, active comparator study in patients with OA of the knee following injection of 10, 40, or 60 mg of FX006 or 40 mg of TCA IR.

The 20-Week Study was an open-label study in patients with OA of the knee following a single IA injection of 10 or 40 mg of FX006, or 40 mg of TCA IR.

In combination these two studies assessed:

- Blood samples for TCA concentration obtained at Baseline, Hours 1, 2, 4, 6, 8, 12, and 24 hours after dosing and at Days 2, 3, 4, 5, 8, 15, 22, 29, 36, 42 and at Weeks 12, 16, 20
- Synovial fluid samples for TCA concentration obtained at Weeks 6, 12, 16, 20
- Change from baseline in morning serum cortisol evaluated on Days 1, 2, 3, 4, 5, 8, 15, 22, 29, 36, 43.
- Plasma and synovial samples were assayed for TCA concentrations using a validated High Performance Liquid Chromatographic Method with Tandem Mass Spectrometry Detection.

RESULTS

- C_{max} for 40 mg FX006 (0.88 ng/ml, 0.71 Log SD) occurred within 4 hours; these levels were approximately 20X lower than the Cmax for 40mg TCA IR (17.54 ng/ml, 1.65 Log SD) which also occurred within 4 hours. (Figure 2)
- Plasma levels associated with 40 mg TCA IR, 10 mg of FX006, and 40 mg of FX006 dropped below LLQ at Weeks 5, 8 and 12, respectively. (Figure 2)
- The synovial concentration of TCA produced by 40 mg of TCA IR was below the lower limit of quantitation (LLQ <0.05 ng/ml) at Week 6 and Week 12. (Figure 2)
- The synovial concentrations of TCA produced by 10 mg FX006 at Week 6 was 6.48 ng/ml; 95% CI 3.17, 13.24, and at Week 12 was 0.47 ng/ml; 95% CI 0.17, 1.40 (Figure 2).

CONCLUSIONS

- Plasma concentrations for 40 mg FX006 are consistently below 1 ng/ml and may confer safety advantage relative to 40 mg TCA IR in diabetics.
- To characterize the relationship between synovial concentrations of TCA and analgesic effect, the synovial concentration data from the 6- and 20-Week Studies have been correlated to efficacy assessments from a companion study of safety and efficacy (assessed as Average Daily Pain on the 11-point Numeric Rating Scale) in which:
  - It took approximately 6 weeks for 10 and 40 mg FX006 to achieve maximal analgesic effect in patients with knee OA.
  - The 40 mg dose of FX006 produced pain relief superior to TCA IR at Weeks 5-10, and between Weeks 2 and 12, the magnitude of the analgesic effect of the 40 mg dose of FX006 exceeded the maximum observed effect of 40 mg TCA IR at Week 4. (Figure 2)
  - Of note, this amplification of the analgesic signal is a new observation.
- It is postulated that the achievement and maintenance of this maximal analgesic effect requires maintenance of a minimal TCA synovial concentration for a period of approximately 6 weeks.
- The effect achieved at six weeks by 40 mg FX006 exceeds that of 10 mg FX006; 60 mg FX006 does not provide any improvement over 40 mg FX006 (data not shown)
- Given these data, the minimal synovial TCA concentration to achieve and maintain maximal therapeutic effect is estimated to be between 6 ng/ml (produced by 10 mg FX006) and 78 ng/ml (produced by 40 mg FX006).
- Importantly, these TCA synovial concentrations are associated with plasma concentrations that will not perturb systemic cortisol production.

Figure 1. Rayman Spectrograph of an individual FX006 microsphere. The green matrix is PLGA; the red islets are You can TCA crystals.

Figure 2. Following a single administration of 40 mg TCA IR, 10 mg FX006 and 40 mg FX006, A, Geometric mean of plasma concentration of TCA over 12 weeks, B, Geometric mean of synovial concentration at Week 6 and Week12 (bar denotes 95% confidence interval), and C, Weekly mean of Average Daily Pain (ADP) on the 11-point Numeric Rating Scale (NRS) (bar denotes standard error) over 12 weeks

Figure 3. Following a single IA injection of 10 mg FX006, 40 mg, 60 mg FX006 and 40 mg TCA IR Geometric Mean Percent Difference from Baseline in Morning Serum Cortisol (nm/L) by visit over six weeks.