# Controlled Release of Fluticasone Propionate after Intra-Articular injection of EP-104IAR in Sheep

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## Introduction

Knee osteoarthritis (KOA) is a degenerative joint disease with a global prevalence of 365 million cases (1). EP-104IAR is a polymer-coated crystal of fluticasone propionate (FP) for the treatment of KOA pain. EP-104IAR achieves extended-release of FP by a diffusion-controlled mechanism resulting in reduced peak FP concentrations, FP exposure extended for weeks and prolonged therapeutic activity. A Phase 2 clinical trial of EP-104IAR in KOA patients has recently been completed (2). We report the results of a pharmacokinetic and tolerability study of EP-104 injected into the stifle of sheep.

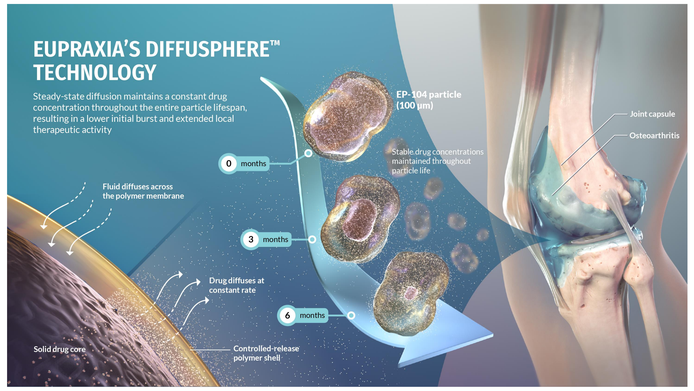


**Figure 1.** Mechanism of action of EP-104IAR.

## Methods

Twelve adult female sheep were randomized and administered by intra-articular (IA) injection into their right stifle joint with 2.0 mL of EP-104IAR. Four sheep received a single IA administration of either 5 mg, 15 mg or 50 mg of EP-104IAR. The contralateral stifle joint served as a control and was not injected. Animals were housed for 40 days with periodic blood sampling for the measurement of plasma FP and both hematology and clinical chemistry. At study termination, sheep were euthanized and the joints recovered and processed for histopathology. Joints were assessed for both macroscopic and microscopic changes using the OARSI scale (3). Plasma and synovial fluid FP was measured using qualified LC/MS-MS assays.

## Results

Fluorescence, scanning electron microscopy and light microscopy images of uniformly sized ≈100 µm EP-104IAR particles (Fig. 2) showing the polymer shells surrounding the FP drug core.

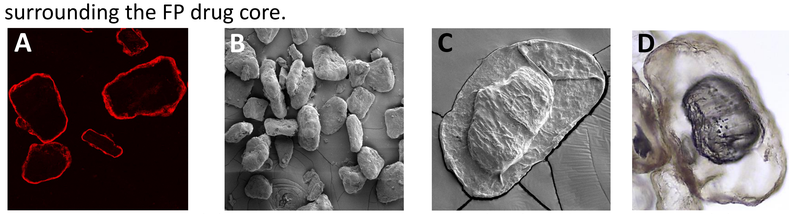


**Figure 2**. Fluorescence (A), scanning electron microscopy (B, C) and light microscopy (D) images of EP-104IAR showing the polymer shell (red fluorescence, A), homogeneous particle size (B) and the FP core after partial release of FP (C, D).

Peak plasma concentrations ($C_{max}$) of FP occurred 24 hours after dosing ($T_{max}$) and the FP concentrations remained elevated for the entire 40-day study (Fig. 3). On study day 40, mean FP plasma concentrations were 11.6, 16.2 and 44.9 pg/mL for the 5, 15 and 50 mg dose groups, respectively. The estimated plasma elimination half-lives of FP between study day 8 to day 40 were 21.6 days, 30.7 days and 27.8 days for the 5, 15 and 50 mg dose groups, respectively (Fig. 3 and Table 1). These estimated elimination half-lives correspond closely to the decrease of FP concentrations in the plasma of human administered with EP-104IAR up to 4 weeks after dosing (2). In the clinical study, plasma concentrations remained unchanged from 4 weeks post-dosing to at least 24 weeks after EP-104IAR administration (2).

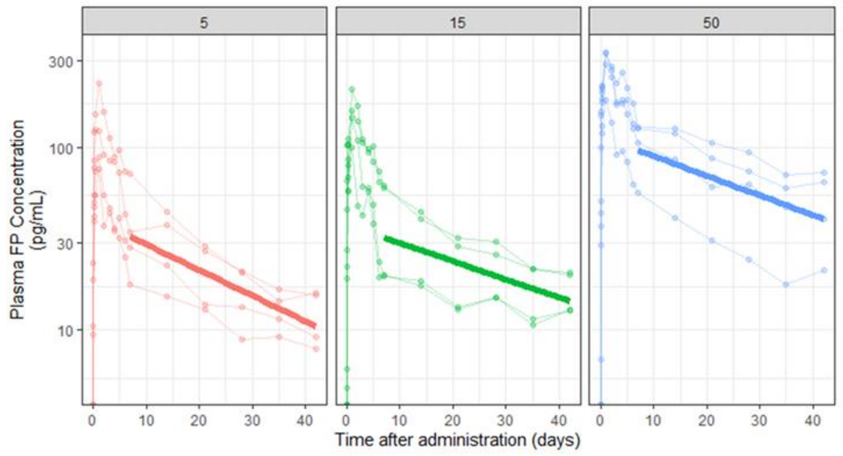


**Figure 3.** Plasma concentrations of FP in sheep after IA administration of EP-104IAR at 5 (left), 15 (middle) or 50 (right) mg per animal doses. Data shown are the individual animal data values and the mean values starting at Day 8 used for the estimation of FP half-life.

Key pharmacokinetic parameters are summarized in Table 1. $C_{max}$ and $AUC_{0-t}$ increased linearly ($r^2$ = 0.70-0.75) with the actual dose of EP-104IAR administered in each animal (Fig. 4A, 4B). Dose-proportionality was sub-linear, with a 2-fold increase of dose associated with a 1.3-fold increase of $C_{max}$ and a 1.4-fold increase of $AUC_{0-t}$.

**Table 1. Summary plasma pharmacokinetic parameters of EP-104IAR after IA administration in the stifle of sheep.** Values of $C_{max}$ and AUC are geometric means estimated from a best-fitting polynomial spline fit.

| Group dose (mg) | $C_{max}$ (pg/mL) | $T_{max}$ (d) | $AUC_{0-t}$ (pg·d/mL) | FP Half-Life Days 8-40 (d) |
|---|---|---|---|---|
| 5 | 117 | 1 | 1150 | 21.6 |
| 15 | 149 | 1 | 1342 | 30.7 |
| 50 | 274 | 1 | 3468 | 27.8 |

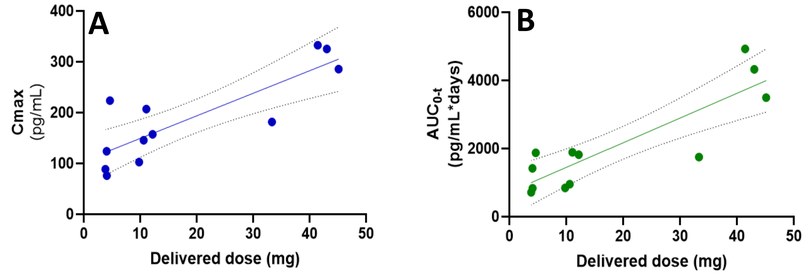


**Figure 4. Panel A:** linear regression (with 95% confidence interval; dotted lines) of administered dose vs. $C_{max}$ ($r^2$ = 0.70). **Panel B:** linear regression (with 95% confidence interval; dotted lines) of administered dose vs. $AUC_{0-t}$ ($r^2$ = 0.75).

EP-104 was well tolerated in all animals with no clinical observations or adverse events noted in the study. No abnormal findings were identified by histology and there were difference in the OARSI histopathology scores between control (un-injected) joints and the EP-104IAR-treated joints (Table 2). No macroscopic structural findings indicative of EP-104IAR-related joint degeneration or inflammation. No changes were noted in the hematology or clinical chemistry results.

**Table 2. Summary histopathology scores of cartilage integrity and synovial structure change by dose group.** Scores represent the average (± standard deviation, n=4/group) scores on the OARSI scale of 0-25 (cartilage) or 0-12 (synovial structure) (3).

| Dose (mg) | EP-104IAR-treated Joint | Control Joint |
|---|---|---|
| **Cartilage Integrity** | | |
| 5 | 4.5 (± 3.4) | 5.3 (± 4.6) |
| 15 | 2.4 (± 2.3) | 4.0 (± 3.4) |
| 50 | 3.0 (± 3.4) | 4.1 (± 3.9) |
| **Synovial Structure** | | |
| 5 | 4.8 (± 4.1) | 3.3 (± 1.2) |
| 15 | 3.8 (± 0.5) | 3.0 (± 0.9) |
| 50 | 4.4 (± 0.9) | 4.4 (± 1.1) |

## Conclusions

EP-104IAR achieves controlled release of FP for at least 40 days after a single IA injection in sheep. EP-104IAR provides both high local FP concentrations and minimal systemic drug exposure and had no observed local or systemic adverse effects. EP-104IAR has significant potential as a safe, effective and durable treatment for KOA.

**References**
(1) WHO OA fact sheet (www.who.int/news-room/fact-sheets/detail/osteoarthritis).
(2) Malone A et al. Lancet Rheumatol. 2024: 6(12) E860-E870.
(3) Little CB et al. Osteoarthritis and Cartilage 2010:18 S80-S92

AL, LM, CB, MW and AM are employees of Eupraxia Pharmaceuticals.