Poster #: P2209

Pharmacokinetics and Local Tolerability of EP-104GI, an Extended-Release Formulation of Fluticasone for Treatment of Eosinophilic Esophagitis, after Intra-Esophageal Injection in Mini-Pigs

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Introduction

EP-104GI is an extended-release formulation of Fluticasone Propionate (FP) in development for treatment of Eosinophilic Esophagitis (EoE). EP-104GI consists of polymer-coated crystals of FP that release at a pre-defined rate via diffusion at the injection site, reducing peak concentrations while prolonging the therapeutic window (Fig. 1). We report results from a 6-week study in mini-pigs comparing the pharmacokinetics, tissue distribution and local safety of submucosal injection of EP-104GI with an oral gavage of an FP solution.

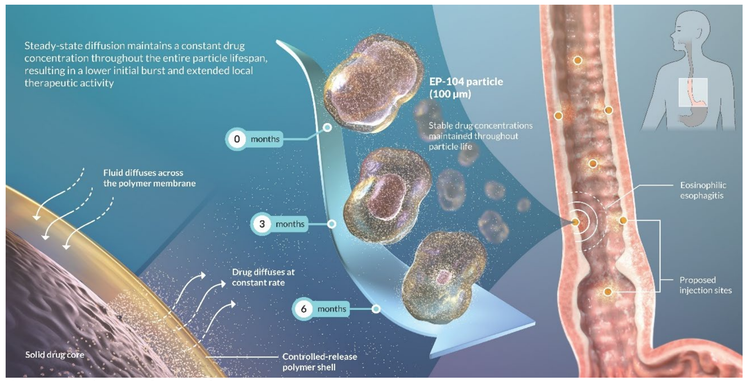

Figure 1. Mechanism of action of EP-104GI.

Methods

Twelve male mini-pigs having an average weight of 31 kg received EP-104GI by 4 circumferential 2.5 mg submucosal injections 5 cm from the gastroesophageal junction, for a total dose of 10 mg FP. Injections of 1.0 mL per site were achieved by endoscopy using a catheter with a 23G needle and a 4 mm needle length. Twelve other male mini-pigs received 10 mg of an FP solution (25 mL) by oral gavage using a feeding tube. Blood was collected at 1, 4, 24 hours and days 2, 3, 5, 7, 10, 14, 21, 28 and 42 and plasma FP measured by an LC/MS-MS method. On days 1, 7, 21 and 42 after dosing, 3 animals per group were euthanized and esophageal tissue was recovered from the injection site at 1, 2, 3 and 4 cm from the injection site. FP in esophageal tissue was measured by an LC/MS-MS assay and tissue biopsy samples were examined for histopathology using hematoxylin and eosin (H&E) and polymer-specific Verhoeff-Van Gieson (VVG) stains.

Results

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

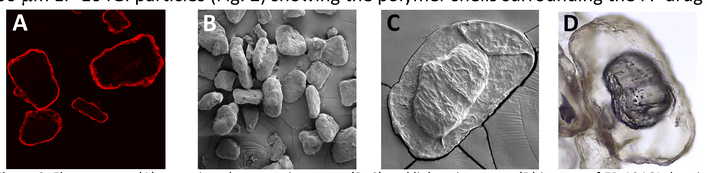

Figure 2. Fluorescence (A), scanning electron microscopy (B, C) and light microscopy (D) images of EP-104GI showing the polymer shell (red fluorescence, A), homogeneous particle size (B) and the FP core after partial release of the drug (C, D).

Results

A plasma C_{max} of 26 pg/mL was observed 4 hours after injection of EP-104GI in the esophagus (Fig. 3A and Table 1). Subsequently, plasma FP was stable from 9-15 pg/mL for the next 6 weeks (Fig. 3A), showing EP-104GI achieved extended FP release. For an FP solution given by oral gavage, C_{max} of 300 pg/mL was at 4 hours and thereafter decreased rapidly with concentrations below 4 pg/mL by Day 10. EP-104GI extended the elimination half-life of FP from 3.0 days when given as an oral suspension to 142.3 days, a 47-fold increase (Fig. 3A and Table 1).

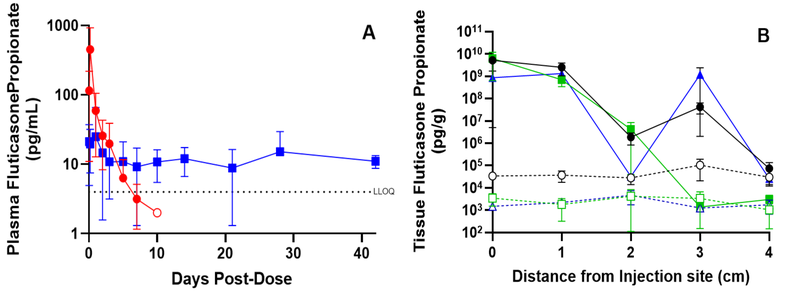

Figure 3. Panel A: Mean plasma concentrations of after FP oral gavage (●) or submucosal injection of EP-104GI (■). **Panel B:** Mean concentrations of FP in esophageal tissue with distance from the injection site at 1 day (●, ○), 3 weeks (■, □) and 6 weeks (▲, △) after dosing of either EP-104GI (●, ■, ▲) or oral FP (○, □, △).

FP concentrations in esophageal tissues achieved by EP-104GI were 10 to 10,000-fold higher than oral gavage of FP for the entire 6-week study (Fig. 3B). Tissue FP levels decreased with increasing distance from the injection site but remained 10 to 100-fold higher than those achieved by oral gavage of FP, even at 4 cm from the injection site, and for up to 6 weeks post-dosing (Fig. 3B).

The ratio of Tissue FP/Plasma FP concentrations shows EP-104GI particles achieved high local FP concentrations and minimal systemic drug exposure compared to oral FP (Fig. 4A). Within 1 cm of the injection site, this ratio for the FP-releasing depot of EP-104GI was 10^4-10^5 higher than that for oral FP. The tissue/plasma ratio with EP-104GI was 10^2- to 10^3-fold higher than for oral FP even 1 week after administration and 2 cm from the injection site (Fig. 4A). Concentrations of FP at the EP-104GI injection site were very stable over the 6-week study (Fig. 4B), further indicating EP-104GI achieved continuous FP release for the 6-week study duration.

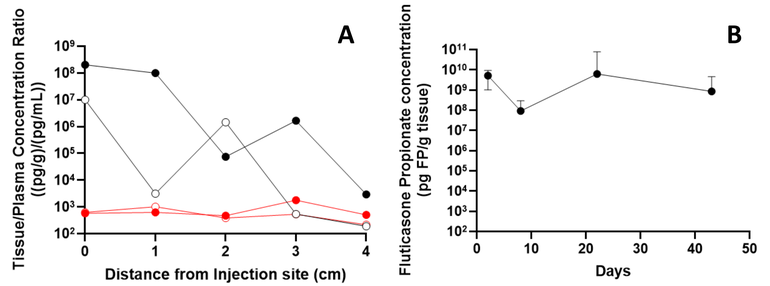

Figure 4. Panel A: Ratio of FP concentrations in esophagus tissue to plasma FP concentrations as a function of distance from the injection site at 1 day (●, ●) and 1 week (○, ○) after submucosal dosing of EP-104GI (●, ○) or oral dosing of FP (●, ○). **Panel B:** Mean concentrations of FP at the esophageal injection site up to 6 weeks after submucosal injection.

Table 1. Summary plasma pharmacokinetic parameters of submucosal EP-104GI compared to oral FP. Values were estimated from a best-fitting polynomial spline fit.

Test Article	Formulation	Total dose (mg)	C_{max} (pg/mL)	T_{max} (h)	$AUC_{0\text{-}14d}$ (pg·d/mL)	Absorption $T_{1/2}$ (h)	Elimination $T_{1/2}$ (d)
EP-104GI	Particle suspension	10	26	4	99.9	1.5	142.3
FP	Microfine suspension	10	300	4	214	0.8	3.0

Histopathology examination of the EP-104GI injection sites showed depots of particles that were present for at least 6 weeks after administration (Fig. 5). The depots of EP-104GI particles at the injection sites (Fig. 5) facilitated extended FP release (Fig. 3A) and drug diffusion throughout the esophagus (Fig. 3B). The significant amount of FP remaining at the injection site, even 6 weeks after injection (Fig. 4B), suggests that extended drug release from these depots would be expected for much longer durations.

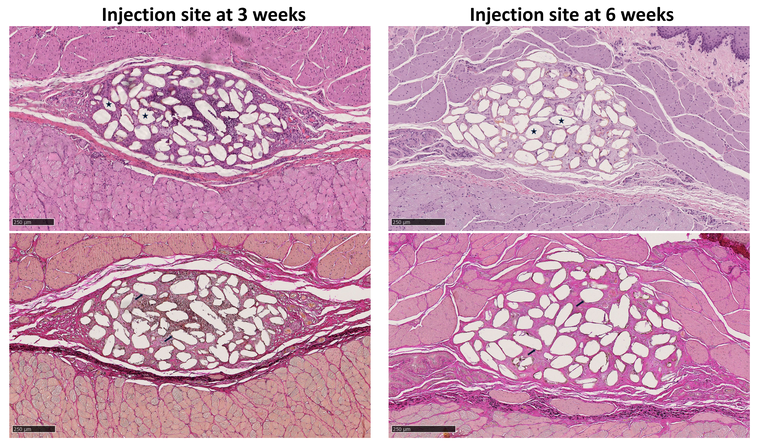

Figure 5. Injection site depots of EP-104GI particles at 3 weeks and 6 weeks after submucosal administration. Sections were stained with hematoxylin and eosin (H&E) or Verhoeff-Van Gieson (VVG) stains. Mild acute inflammatory infiltrate and interstitial fibrosis were observed (Grade 1). Several representative EP-104GI particles are indicated by a ★ and the VVG-stained polymer shell by arrows. Scale bars represent 250 µm.

Discussion & Conclusions

EP-104GI, an extended-release formulation of FP, achieves continuous release of FP for at least 6 weeks after submucosal injection in the esophagus. FP release provides both high local FP concentrations and minimal systemic drug exposure. Plasma FP has been observed for up to 6 months after a single IE injection in EoE patients in a parallel clinical trial (Poster P3911). Tissue concentrations of FP given by submucosal injection of EP-104 GI are orders of magnitude higher than achieved by FP given orally, even at distances up to 4 cm from the injection sites. Injection of EP-104GI in the esophagus was well tolerated. These data show that EP-104GI has significant potential as a safe, effective and long-duration treatment for eosinophilic esophagitis.

MW, AL, CB, LM & AM: employees of Eupraxia Pharmaceuticals.