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Clinical Trial

Safety and pharmacokinetics of EP-104IAR (sustained-release fluticasone propionate) in knee osteoarthritis: A randomized, double-blind, placebo-controlled phase 1 trial

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ABSTRACT

Objective: EP-104IAR is a novel, sustained-release, intra-articular (IA) formulation of the corticosteroid fluticasone propionate (FP), in development for the treatment of osteoarthritis (OA) pain. This study evaluated the safety, pharmacokinetics (PK) and efficacy of a single dose of EP-104IAR in patients with OA of the knee.

Design: This was a multi-center, randomized, double-blind, placebo-controlled trial performed at 3 sites in Canada. Subjects with moderate to severe pain received either a single dose of the investigational product EP-104IAR (15 mg) or placebo (vehicle) and were evaluated for up to 42 weeks. The primary outcome measures were safety and PK. The study was not powered to assess efficacy, however patient reported outcome measures were analyzed to evaluate pain and symptom relief.

Results: Thirty-two subjects were randomized (21 women, 11 men, mean age: 64.8 years). EP-104IAR was well tolerated. Average serum cortisol levels showed no clinically significant deviations compared to placebo and remained within the normal range of cortisol variation. Plasma PK concentrations were within acceptable safety margins, compared to marketed FP products. Synovial fluid FP levels were approximately 2 orders of magnitude higher and at efficacious concentrations for most subjects. Efficacy evaluations indicated that EP-104IAR provided an immediate improvement of OA symptoms and these effects persisted for 8–12 weeks consistently across all measures.

Conclusions: This study provides evidence that 15 mg of EP-104IAR is well tolerated and has the potential for efficacy in OA patients. These data support further examination of EP-104IAR in larger clinical studies.

1. Introduction

Current evidence-based treatment guidelines for knee osteoarthritis (OA) recommend intra-artiucular (IA) corticosteroid injections to manage symptoms associated with inflammation [1–3]. Injectable corticosteroids have been widely used for decades; however, currently available immediate release (IR) corticosteroids are suboptimal due to their limited duration of activity and the risk for systemic side effects [4,5]. Evidence is also emerging regarding the risk of adverse joint findings and/or OA progression following repeated injections of IR corticosteroids [6–9].

A sustained-release IA corticosteroid is expected to prolong local residence time and provide increased patient benefit due to a longer duration of efficacy and reduced frequency of injections. By decreasing pharmacokinetic (PK) peak concentrations, greater efficacy might also be achieved with fewer systemic (e.g., flushing, glucose alterations and cortisol suppression) and local (cartilage damage, rapid OA progression) side effects. These aspects are a focus of EP-10IAR development.

Fluticasone propionate (FP) is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity and a well-established safety record in the form of widely used inhaled, intranasal and topical agents. Relative to other corticosteroids, FP has a high affinity for the

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glucocorticoid receptor, low solubility, a low rate of dissociation, and a comparatively long half-life [10]. These characteristics make FP an excellent candidate for prolonged anti-inflammatory effects.

EP-104IAR is a novel, long-acting formulation of FP for IA injection, in development to treat OA pain. EP-104IAR contains FP crystals coated with a very thin layer (2–4 μm) of the polymer polyvinyl alcohol (PVA), comprising approximately 6% of the drug product. PVA is used extensively in the medical industry and has a 30-year record of safe use in various human tissues, including for meniscus/cartilage tissue replacement [11–16]. The PVA-coated particles are heat-treated to crosslink the polymer, forming a membrane through which the low solubility FP slowly diffuses over several months. The combination of a highly-potent, low-solubility corticosteroid with low levels of crosslinked polymer is expected to provide prolonged, stable drug delivery, with substantially less polymer injected into the joint.

To date, EP-104IAR has shown favorable local and systemic safety profiles in non-clinical studies [17]. Here, we report results of the first clinical study evaluating the safety, PK and preliminary efficacy of EP-104IAR in patients with moderate to severe knee OA pain.

2. Methods

2.1. Study design

This was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 3 Canadian sites between May 2016 and December 2017. Participants were randomly allocated to a single dose of 15 mg EP-104IAR or placebo (vehicle) and were evaluated for up to 42 weeks, or until they returned to baseline pain (whichever occurred earlier). Assessments were performed at site visits and telephone calls.

The study was approved by each site's independent ethics committee and all participants provided written informed consent. The protocol is registered on www.clinicaltrials.gov (NCT02609126).

The study was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki and is reported here in accordance with the 2010 CONSORT statement. The protocol was amended several times during conduct. Amendments included a revised dose procedure and minor changes to eligibility criteria.

2.2. Study population

Eligible participants included ambulatory males and females aged 40–80 with primary OA in at least one knee (diagnosed using American College of Rheumatology [18] and radiographic criteria [19]) experiencing unsatisfactory pain control using non-opioid medications. The following eligibility criteria also applied: Kellgren-Lawrence [19] Grade 2 or 3; body mass index $\leq$40 kg/m^2; pain in the treated knee $\geq$4 to $\leq$9 (on a 0–10 numeric rating scale) at Screening and Baseline. In subjects with bilateral knee OA, the knee with the greatest pain was selected for treatment; the pain score in the non-treated knee had to be $<$ 6.

Individuals with the following conditions were excluded: chondrocalcinosis; ipsilateral hip OA; insulin-dependent diabetes; fibromyalgia; chronic pain syndrome; active psychiatric disorder; active malignancy; active infection; history of drug abuse; active alcoholism; pregnancy, or breastfeeding.

Prohibited medications and procedures (prior to and throughout the study) included: oral, nasal, inhaled, or injected steroids, narcotics, CNS-active medications, or participation in another interventional trial within the prior 30 days; glucocorticoid injections in the prior 8-weeks; hyaluronic acid injections or immunosuppressive therapy in the prior 6 months; joint replacement of the contralateral knee in the prior 6 months, any surgery in the treated knee in the prior 12 months, or planned surgery during the study.

2.3. Treatments and blinding

Subjects were randomized to EP-104IAR 15 mg or placebo (vehicle) in a 3:1 ratio using a pseudorandom number generator provided by the study statistician. Randomization was not stratified by site.

EP-104IAR comprises a sterile powder containing cured PVA-coated FP crystals and a sterile liquid containing excipients necessary to prepare a uniform suspension (vehicle). The powder is suspended in the vehicle immediately prior to injection. EP-104IAR is visibly different from placebo, therefore an unblinded pharmacist prepared the injection, an unblinded physician performed the ultrasound-guided injection and blinded study personnel performed all other assessments. Patients were blinded by concealing the syringe during the procedure.

Acetaminophen, up to 2500 mg daily, was permitted as rescue therapy.

2.4. Study procedures

Following screening, subjects stopped their usual pain medications and began weekly recordings of OA pain levels in their treated knee. Dosing took place at the Baseline Visit. Subjects attended clinic visits at 2 days post-dose; at Weeks 1, 3 and 6; and one randomized visit between Weeks 12, 18, 24 and 30 (Supplemental Data: Fig. 1). The end of study visit (or Early Exit visit) occurred at Week 42, or when the subject returned to baseline pain (defined as a return to baseline pain or worse for 2 consecutive weeks).

2.5. Safety measures

Adverse events (AEs) were collected throughout the study. Clinical laboratory parameters (hematology, chemistry, and urinalysis), examination of the treated-knee and vital signs were performed at all visits. Laboratory parameters included serum cortisol. Samples were collected between 8 and 10 a.m. (except for the 2-h post-dose sample) to reduce the impact of diurnal variation.

2.6. Pharmacokinetic measures

Plasma samples for the measurement of FP were collected from all subjects at all post-dose visits. A single synovial fluid sample was collected from EP-104IAR subjects at one randomized visit (either Week 12, 18, 24, or 30 or the Early Exit Visit). Subjects' individual treatment assignments were unblinded when they reached this visit and the aspiration only performed in EP-104IAR subjects.

Used injection kits were retained for residual drug bioanalysis and calculation of the dose administered.

2.7. Efficacy measures

Weekly assessments of Patient Pain (PtPain) and Patient Global Assessment of OA (PtGA) were recorded from Week −2 until completion, both measured on an 11-point numerical rating scale. Each subject's baseline pain was calculated as the mean of the Weeks −1 and 0 PtPain scores, rounded down. Change from baseline was calculated from this value.

Western Ontario and McMaster Universities Arthritis Index (WOMAC version 3.1, a self-administered questionnaire comprising 24 questions in 3 subscales: Pain, Stiffness and Physical Function) [20], a physician's assessment of OA (MDGA, a single question "How would you describe the patient's disease activity today?", rated 0 (none) to 10 (very severe)) and an evaluation of subjects' overall health status (using the Short-Form quality of life questionnaire, SF-36) [21] were collected at scheduled visits/calls.

2.8. Sample size

Study size was not based on formal calculations. A sample size of 32, allocated 3:1 to EP-104IAR or placebo, was deemed suitable to provide reasonable safety, PK and preliminary efficacy data, while minimizing exposure to a new investigational product.

2.9. Statistical analyses

Due to its small size and investigative nature, no formal inferential testing was planned. Data summaries employed descriptive statistics, as appropriate for categorical or numerical data. Data analyses were performed using R (version 3.5.0) [22].

A single analysis population was used, comprising all dosed subjects. Subjects were analyzed based on the treatment actually received, in the event this differed from the allocated assignment; however, all subjects received the randomized treatment.

Summaries were prepared for treatment-emergent AEs, clinical laboratory tests, vital signs, and knee examinations. Treatment-emergent AEs were defined as events that started or worsened after dosing, or had a missing start date.

Plasma and synovial fluid samples were analyzed according to actual sample time. Non-compartmental analysis was used to calculate PK parameters, including maximum concentration in plasma (C_{max}) and time at which maximum concentration is observed (t_{max}). Due to the sparse sampling, terminal phase PK parameters such as AUC to infinity (AUC_{∞}) were calculated using aggregate data.

Efficacy measures were summarized using standard summary statistics. WOMAC measures were normalized to a 0–10 scale prior to statistical manipulation. Both (linear) mid-profile and a mixed Baseline/Last Observation Carried Forward (BOCF/LOCF)-type imputations were used for missing efficacy data. All analyses were pre-defined in a statistical analysis plan prior to database lock.

3. Results

3.1. Patient disposition and baseline characteristics

Of 64 patients screened, 32 were randomized. Twenty-four received EP-104IAR and 8 received placebo. Two EP-104IAR subjects and 1 placebo subject prematurely discontinued due to a protocol deviation; all other subjects completed the study with either a return to baseline pain (18 subjects, 56%) or 42 weeks of follow-up (11 subjects, 34%). See Fig. 1. Demographics and OA histories were similar between treatment groups (Table 1) and considered representative of the Canadian knee OA patient population [23,24].

3.2. Dose administered

As EP-104IAR is a suspension prepared before dosing, some variability in delivered dose is expected as particles can settle and adhere to the vial or syringe. The median administered dose was 13.2 mg (interquartile range: 10.7–13.9 mg), approximately 88% of the intended 15 mg dose. The actual dose administered ranged between 3.9 and 14.2 mg. The injection technique was revised following dosing the first five subjects and variability in the delivered dose was substantially reduced in the

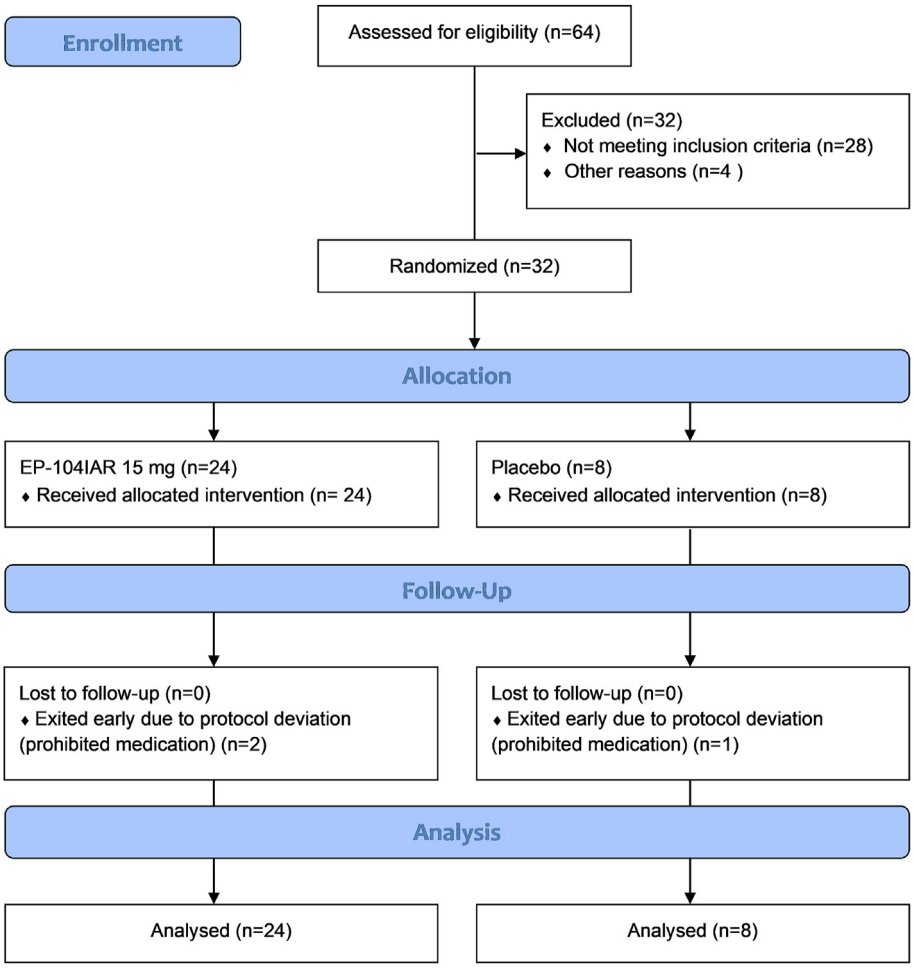

Fig. 1. Subject flow through study.

Table 1
Demographics and baseline OA characteristics.

Characteristic	EP-104IAR (N = 24)	Placebo (N = 8)	Total (N = 32)
Age (years), mean (SD)	65.9 (8.0)	61.4 (8.6)	64.8 (8.3)
Gender, n (%)			
Male	8 (33%)	3 (38%)	11 (34%)
Female	16 (67%)	5 (62%)	21 (66%)
Race, n (%)			
White	22 (92%)	8 (100%)	30 (94%)
Other	2 (8%)	0	2 (6%)
BMI, mean (SD)	29.7 (4.6)	32.7 (5.5)	30.4 (5.0)
ACR criteria at diagnosis, n (%)			
Knee pain? (yes)	24 (100%)	8 (100%)	32 (100%)
Age >50 years (yes)	22 (92%)	4 (50%)	26 (81%)
Morning stiffness <30 min (yes)	18 (75%)	4 (50%)	22 (69%)
Crepitus? (yes)	9 (38%)	3 (38%)	12 (38%)
Osteophytes? (yes)	24 (100%)	8 (100%)	32 (100%)
Bilateral knee OA, n (%)	16 (67%)	6 (75%)	22 (69%)
Time since diagnosis, median (IQR) (Years)	1.7 (0.8–2.6)	4.9 (1.8–11.1)	1.9 (0.8–3.5)
Kellgren-Lawrence Grade			
Grade 2	7 (29%)	3 (38%)	10 (31%)
Grade 3	17 (71%)	5 (62%)	22 (69%)

following 19 EP-104IAR subjects (9.6–14.2 mg). As an exploratory analysis, several results are presented both for all subjects who received EP-104IAR; and for the 15 subjects who received at least 12 mg, 80% of the intended dose, and considered to be reflective of higher doses moving forwards in development.

3.3. Safety

Nineteen subjects (59%) experienced at least one AE. A similar AE rate was observed in each treatment group (15 EP-104IAR subjects (62%) and 4 placebo subjects (50%), Table 2). The majority were mild and there were no discontinuations due to AEs. Of note were 3 AEs of arthralgia. These were: a) in the hip; b) different than the presenting index knee pain; and c) following the subject's knee 'popping' while using an elliptical trainer. They are not considered related to EP-104IAR.

One EP-104IAR subject experienced 3 serious adverse events: abdominal distension, upper abdominal pain, and abnormal respiration. Following detailed investigations, these were considered unrelated to study treatment and likely due to the subject's pre-existing Gastro-esophageal Reflux Disease.

The majority of AEs occurred in the first 12 weeks post-dose (31 of 43 events (72%)). This finding was similar between groups (24 of 34 (71%) AEs in EP-104IAR subjects and 7 of 9 AEs (78%) in placebo subjects). There was no apparent relationship between the dose delivered and AE incidence.

Table 2
Summary of treatment-emergent adverse events.

MedDRA System Organ Class Preferred Term	EP-104IAR (N = 24)		Placebo (N = 8)	
	Events, n	Subjects, n (%)	Events, n	Subjects, n (%)
Total number of Treatment Emergent Adverse Events	**34**	**15 (62%)**	**9**	**4 (50%)**
Treatment Emergent Adverse Events occurring in ≥2 Subjects in either Treatment Group				
Infection and Infestations				
Nasopharyngitis	3	2 (8%)	1	1 (12%)
Influenza	3	2 (8%)	0	0 (0%)
Gastroenteritis viral	0	0 (0%)	2	2 (25%)
Nervous System Disorders				
Headache	1	1 (4%)	2	2 (25%)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	3	3 (12%)	0	0 (0%)

There were no clinically meaningful changes in hematology, chemistry, urinalysis or vital signs.

Serum cortisol levels were closely monitored as an early warning signal for the risk of adrenal insufficiency due to EP-104IAR. Cortisol was mildly and transiently suppressed in EP-104IAR subjects, returning to baseline levels between 1- and 3-weeks post-dose (Fig. 2). However, cortisol levels fell below normal ranges in only 5 subjects (21%) and on no more than two occasions. A clear relationship between FP plasma concentration and the degree of cortisol suppression was observed, with plasma levels of approximately 175–200 pg/mL associated with an approximately 50% reduction in serum cortisol compared to baseline (Fig. 3).

AEs, vital signs, and laboratory data were reviewed for signs of the typical symptoms of adrenal insufficiency. These vary from mild, nonspecific symptoms of weakness and fatigue to severe adrenal crises with hypotension and hypoglycemia [25]. No subjects displayed any symptoms of severe adrenal crises, hypotension, or hypoglycemia. Two EP-104IAR subjects reported fatigue or abdominal pain. However, in both cases, cortisol and all other safety measures were within normal ranges, and these events were not considered symptoms of adrenal insufficiency.

The treated knee was examined at each clinic visit. Neither EP-104IAR nor placebo caused any local safety findings of concern. In addition to the lack of adverse examination findings, reported AEs did not indicate any obvious signs of local toxicity.

3.4. Pharmacokinetics

Plasma concentrations were predictable, if somewhat variable. Systemic exposure to the 15 mg of FP in EP-104IAR does not appear to be substantially different than that of inhaled FP. After 6 weeks, plasma concentrations were comparable to, or below, those seen with chronic administration of the lowest starting dose of inhaled FP [26]. EP-104IAR C_{max} was 133 pg/mL. Peak concentrations occurred at either 2 h or 2 days post-dose. Levels initially fell rapidly, to less than 50% of peak averages by 1-week post-dose (41 pg/mL); another third by 3-weeks (27 pg/mL); and another third again by 6-weeks (17 pg/mL). Sampling past this point is sparse, but there appears to be a prolonged release period, with all samples bar one containing detectable amounts of FP out to 42 weeks. The terminal half-life was 11.7 weeks, although examination of individual profiles suggests this might be biased slightly downwards due to the calculation method and the sparse sampling. $AUC_{0–12weeks}$ was 293 pg·weeks/mL, and AUC∞ was 500 pg·weeks/mL. Plasma kinetics appear to be sublinear (calculable due to the range of doses administered), with a doubling in dose associated with a 1.5- to 1.6-fold increase in exposure.

Synovial fluid was collected from all EP-104IAR subjects, but insufficient volumes were obtained from several subjects, resulting in 16 viable samples, collected at 11 different time-points. On average, synovial fluid concentrations were approximately 2 orders of magnitude higher than plasma levels and declined at a similar rate. Inter-individual variability was high, with 3 samples containing extremely low concentrations. These three subjects received doses of 4.4, 13.8, and 14.0 mg and did not exhibit correspondingly low plasma concentrations. At the individual level, there was no clear relationship between synovial fluid and plasma concentrations. Even the extremely low (and high) synovial fluid concentrations did not result in aberrant plasma concentrations (Fig. 4).

3.5. Efficacy

Subjects were assessed until they returned to baseline pain or for 42 weeks post-dose. Return to baseline pain was initially quicker in placebo subjects, with 3 out of 8 subjects (38%) exiting by Week 5. It took until Week 15 for an equivalent proportion of EP-104IAR subjects to return to baseline pain (9 out of 24 subjects, 38%). Of the remaining 5 placebo

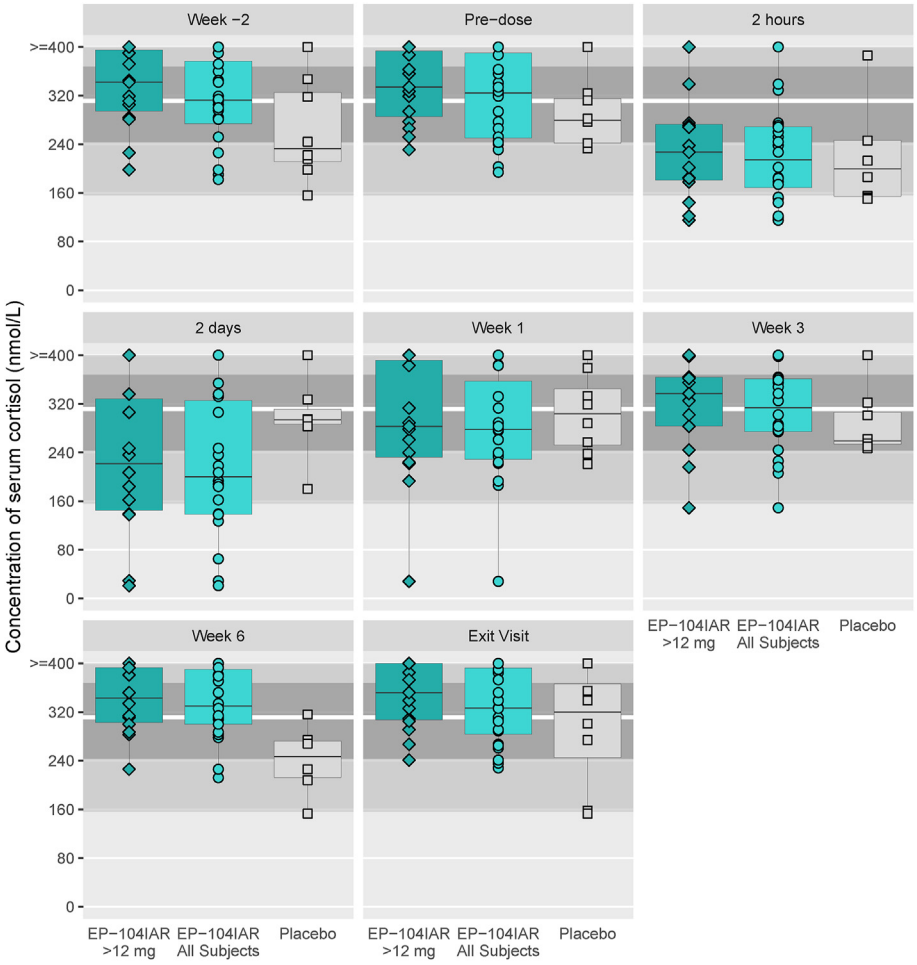

Fig. 2. Mean and Inter-quartile Range (IQR) of Serum Cortisol Over Time. Individual points show individual data. Bars show the inter-quartile range, with the heavy black line showing the median. The shaded background illustrates the range, inter-quartile range and median of all data taken prior to dosing, as a reflection of normal variability in this sample. Cortisol is well known to exhibit diurnal variation; as such all samples are taken at approximately the same time, with the exception of the 2 h sample, which is depressed in all treatment arms as a result of this variability.

subjects: 1 discontinued due to a contraindicated medication; and 4 did not return to baseline pain during the 42-week follow up. The median (IQR) time to return to baseline pain was 21.3 weeks (13 to >42 weeks) in the EP-104IAR group and >42 weeks (4.7 to >42 weeks) in the placebo group (Supplemental Data: Fig. 2). Due to ongoing withdrawals as subjects returned to baseline pain, 18 weeks was selected as a suitable summary period for the efficacy data presented below, as beyond this point >50% of subjects had exited the study, and summaries would be largely based on imputed data.

All efficacy measures showed an overall numerical trend for an immediate and substantial distributional shift in the EP-104IAR group relative to placebo (Figs. 5 and 6 and Supplemental Data: Figs. 3–4). This was sustained for 8–12 weeks before achieving parity.

Average baseline (±SD) PtPain scores were similar between groups (EP-104IAR: 6.2 ± 1.7 versus Placebo: 6.5 ± 1.8). PtPain was decreased in both groups through 18 weeks of follow-up. The EP-104IAR group showed an immediate distributional shift that remained numerically superior to placebo for approximately 11–12 weeks (mean trough scores at Week 6 of 3.2 in EP-104IAR versus 5.0 in Placebo). Between Weeks 6 and 18, PtPain scores gradually increased in the EP-104IAR group to 4.6 ± 2.2 (mean ± SD) at Week 18. In contrast, PtPain scores in the placebo group decreased over this part of the study to 3.8 ± 2.9 (mean ± SD) at Week 18. PtGA scores showed a similar trend.

Average (±SD) baseline WOMAC Pain scores were similar between groups (EP-104IAR: 5.7 ± 1.8 and placebo: 5.7 ± 1.9). Mean WOMAC Pain was reduced in both groups through 18 weeks of follow-up, with the EP-104IAR group showing an immediate distributional shift that remained numerically superior to placebo for the first 6 weeks. WOMAC stiffness and function remained numerically superior in the EP-104IAR group compared to placebo for at least 12 weeks. Exploratory analyses of subjects receiving ≥12 mg (80% of the intended dose), showed similar trends, but of slightly greater magnitude and duration (Supplemental Data: Figs. 2–4).

4. Discussion

This was the first clinical study evaluating EP-104IAR in patients with knee OA and was designed to assess safety and PK. Results suggest that EP-104IAR might be a safe and effective treatment for OA knee pain. Adverse events were mostly mild and except for some mild transient cortisol suppression, there were no signs of adrenal suppression.

Transient hypothalamic–pituitary–adrenal (HPA) axis suppression is a known side effect of IA corticosteroids [27]. Cortisol suppression persisting over weeks to months can result in the progressive atrophy of cortisol-producing cells in the adrenal gland, an inability to produce normal levels of cortisol in response to Adrenocorticotropic hormone (ACTH) stimulation and secondary adrenal insufficiency. Average serum cortisol levels in EP-104IAR subjects showed no clinically significant deviations compared to placebo and remain within the normal range of cortisol variation. Two EP-104IAR subjects showed a decrease of greater than 75% from baseline at 2-days post dose; one of which returned to baseline levels by one week and the other by three weeks. These short perturbations in serum cortisol are not expected to lead to adrenal insufficiency [27]. However, adrenal function will continue to be a key safety focus in future studies.

No large, long-term, prospective studies evaluating joint findings following corticosteroid injections have been performed to date, however some studies have questioned the local safety of repeated doses of IR

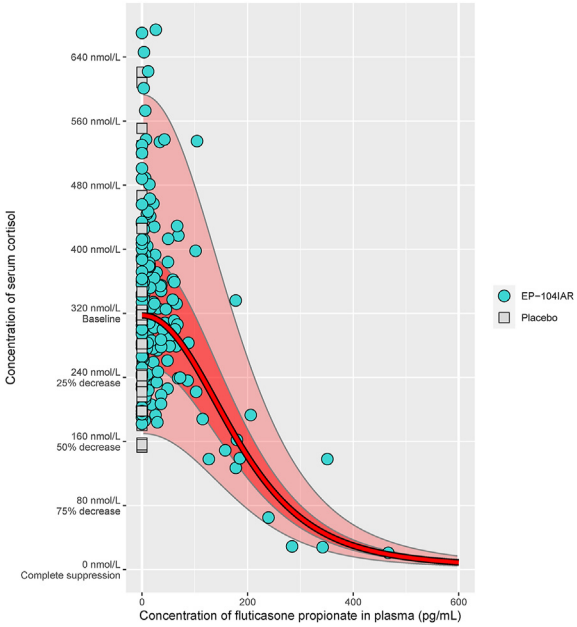

Fig. 3. Relationship Between Plasma Concentrations of Fluticasone Propionate and Serum Cortisol. Individual points show individual plasma concentration/serum cortisol pairs, for both treatment arms. The shaded regions show the 95% and 50% prediction intervals, and the heavy line the median, of a fitted smoothing curve. Average baseline was slightly lower than 320 nmol/L, but for the sake of illustration in this graphic the y-axis approximates this baseline to 320.

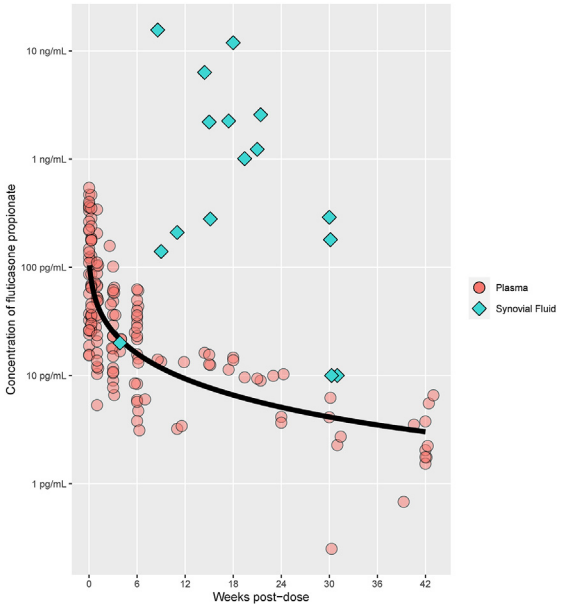

Fig. 4. Concentrations of Fluticasone Propionate in Plasma and Synovial Fluid. Individual points show individual plasma and synovial fluid concentrations of FP from subjects receiving EP-104IAR. The heavy black line shows a simple smoother fit through the plasma data.

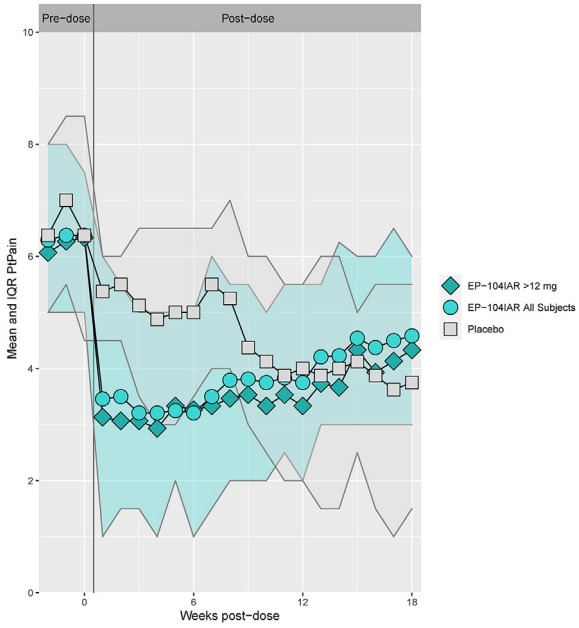

Fig. 5. Patient Pain Scores in the Treated Knee out to Week 18. Average and inter-quartile range PtPain data are shown for EP-104IAR and placebo, using linear mid-profile and LOCF/BOCF post-discontinuation imputation for missing data. The EP-104IAR >12 mg arm shows only the average trace, for simplicity of presentation.

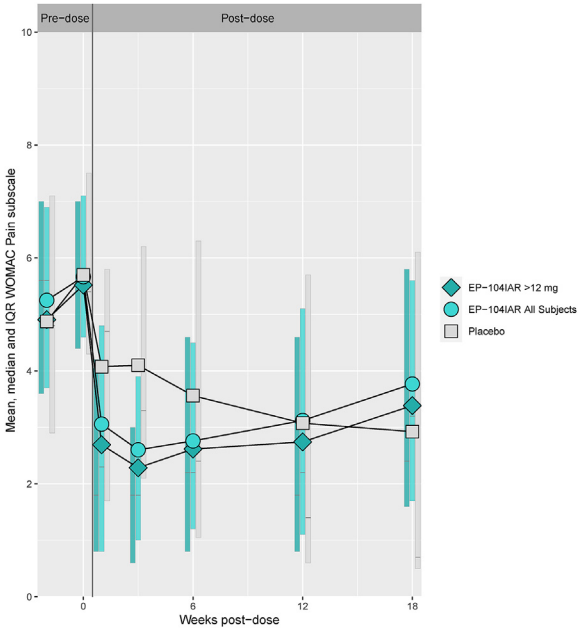

Fig. 6. WOMAC Index Pain Subscale Scores to Week 18. Average, median and inter-quartile range WOMAC Pain data are shown for EP-104IAR and placebo, using linear mid-profile and LOCF/BOCF post-discontinuation imputation for missing data.

corticosteroids [6–9]. The clinical significance of small changes in cartilage volume and other structural changes observed via imaging in these studies is not fully understood [28–30]. However, local safety is anticipated to be a key regulatory focus for any new corticosteroids in development for OA. A Good Laboratory Practice toxicology study of EP-104IAR in 120 beagle dogs [17] demonstrated no changes in Mankin score (a measure of cartilage damage) over 10 months, at any dose, suggesting that EP-104IAR may have a local safety advantage over existing IA corticosteroids. We theorize that local safety is potentially a function of peak corticosteroid concentrations in the IA space. We further theorize that the polymer membrane modulating FP release may prevent an early "burst" release that could be associated with imaging findings observed with IR corticosteroids. Due to its size and exploratory nature, imaging was not performed in this study. Local safety was assessed via adverse events and knee examinations. Although no findings of concern

were noted in any subjects, it is anticipated that future studies will include x-ray and/or MRI imaging modalities to explore the local effects of repeated administrations.

Systemic exposure to 15 mg EP-104IAR was similar to approved inhaled FP products. Synovial fluid concentrations were approximately 2 orders of magnitude higher, with high inter-individual variability. It is theorised that the extremely low synovial fluid concentrations measured in three subjects might be explained by injections that missed the IA space. It is estimated that 10–20% of all injections miss the IA space, even using ultrasound guidance [31,32].

EP-104IAR is a suspension containing 15 mg of FP; the median delivered dose was 13.2 mg, approximately 88% of the intended dose. The wide variation in delivered dose (3.9–14.2 mg) is somewhat explained by a change to administration technique implemented following analysis of used injection kits from the first five EP-104IAR subjects. A syringe rinsing step was added to the procedure, with the rinsing saline being injected into the knee. Dose variability was substantially reduced in the remaining 19 EP-104IAR subjects (9.6–14.2 mg, or 64–95% of the intended dose). Formulation improvements were subsequently initiated to avoid the need for this rinse step in future studies.

The large variability in delivered dose did, however, permit some limited dose proportionality evaluations. Despite the small sample size, there is some evidence of sublinear plasma PK, with a 2-fold increase in delivered dose being associated with an approximately 1.5-fold increase in plasma levels. Care should be taken with this statement, as the distribution of delivered doses is highly clustered with only a few extremes; however, it is largely in line with expectations based on non-clinical PK data in dogs [17]. Future larger studies are planned to further explore these findings.

The study was not powered to detect treatment differences in any efficacy endpoints; however, several assessments were included that permit a preliminary evaluation of efficacy of EP-104IAR in comparison to placebo. Although return to baseline pain was initially quicker in the placebo group, 4 of the 8 placebo subjects (50%) did not return to baseline pain before the end of the follow-up period and showed sustained responses across the various efficacy measurements. OA studies evaluating IA injections typically report higher placebo response rates than less invasive administration routes [33]. The placebo responses here were higher than anticipated, although such a small placebo cohort would be very susceptible to potential bias given the large expected inter-individual variability in pain trials of this type. Use of a vehicle control, while being the most appropriate control to elucidate the true effects of FP, complicates direct comparison to responses observed in other trials using saline controls. Additionally, subjects were permitted to use up to 2500 mg of acetaminophen per day for their OA knee pain. Acetaminophen usage was not tracked; it is not possible therefore to determine if usage differed between groups and if this could have contributed to the observed responses.

Despite the robust placebo response and the small trial size, examination of data and supporting efficacy analyses suggest some clear conclusions – EP-104IAR had an immediate, substantial effect in line with other IA steroids [34]. Graphical data presentations and informal exploratory analyses of the different efficacy measures illustrate a clear analgesic trend for EP-104IAR with distinct numerical separation from placebo for between 8- and 12-weeks in PtPain and WOMAC pain endpoints. Other efficacy endpoints demonstrated similar patterns (e.g., WOMAC stiffness, function and total scores, as well as PtGA, SF-36 and MDGA – data not shown).

Several features of this study design limit full evaluation of EP-104IAR's safety, PK and efficacy: a) Subjects exited when their knee pain returned to baseline, meaning not all subjects were evaluated for the full 42 weeks; b) Clinic visits after Week 6 were randomized, making it difficult to elicit patterns in either treatment group at later time points as data were collected at different visits; c) No imaging endpoints were included; d) Two sites contributed the majority of subjects (15 each) with the third, added late, contributing only 2 subjects; and e) The protocol was amended several times during conduct, including changes to dose administration and to eligibility criteria. Eligibility criteria changes are not believed to have impacted subject heterogeneity. Given the small sample size, no formal analyses were performed to examine either potential site-related differences or eligibility differences between protocol versions.

In conclusion, EP-104IAR 15 mg was well-tolerated. Plasma PK was predictable with concentrations within acceptable safety margins (based on marketed FP products such as Flovent HFA), and with a terminal half-life of approximately 12 weeks. Synovial fluid FP levels were approximately 2 orders of magnitude higher than plasma levels and achieved efficacious concentrations for most subjects. Preliminary efficacy evaluations indicate a clear analgesic trend in favor of EP-104IAR, with distinct numerical separation from placebo for between 8 and 12 weeks depending on the endpoint. Findings were consistent across all measures, supporting examination of further doses of EP-104IAR.

Credit author statement

Malone A: Conceptualization, Methodology, Supervision, Funding acquisition, Writing - Review & Editing. Price J: Software, Formal analysis, Visualization, Writing - Review & Editing. Price N: Project administration, Writing - Original Draft, Writing - Review & Editing. Peck V: Project administration. Getgood A: Investigation, Resources, Writing - Review & Editing. Petrella R: Investigation, Resources, Writing - Review & Editing. Helliwell J: Conceptualization, Methodology, Funding acquisition, Writing - Review & Editing.

Declaration of competing interest

AM, JP, NP, VP and JH are employees of Eupraxia Pharmaceuticals Inc.

AG and RP are investigators of this study and their institutions received fees for participation. AG has received prior research grants from Eupraxia Pharmaceuticals Inc.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2021.100213.

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