Efficacy and safety of a diffusion-based extended-release fluticasone propionate intra-articular injection (EP-104IAR) in knee osteoarthritis (SPRINGBOARD): a 24-week, multicentre, randomised, double-blind, vehicle-controlled, phase 2 trial

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For the Danish translation of the abstract see Online for appendix 1

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Summary

Background Corticosteroids are among the few effective treatments for knee osteoarthritis, but short duration of action limits their utility. EP-104IAR, a long-acting formulation of fluticasone propionate for intra-articular injection, optimises the action of fluticasone propionate through novel diffusion-based extended-release technology. The SPRINGBOARD trial assessed the efficacy, safety, and pharmacokinetics of EP-104IAR in people with knee osteoarthritis.

Methods SPRINGBOARD was a randomised, vehicle-controlled, double-blind, phase 2 trial done at 12 research sites in Denmark, Poland, and Czech Republic. We recruited adults aged 40 years or older with primary knee osteoarthritis (Kellgren–Lawrence grade 2–3) who reported Western Ontario and McMaster Universities Osteoarthritis Arthritis Index (WOMAC) pain scores of at least 4 and no more than 9 out of 10. Participants were randomly assigned (1:1) to receive one intra-articular dose of 25 mg EP-104IAR or vehicle control. Randomisation was done via interactive web-based access to a central predefined computer-generated list with block size of six (allocated by clinical site). Participants and assessors were masked to treatment allocation. Participants were followed up for 24 weeks. The primary outcome was the difference between groups in change in WOMAC pain score from baseline to week 12, analysed in all participants who were randomly assigned and received treatment. Safety, including laboratory analyses, and pharmacokinetics from quantification of fluticasone propionate in peripheral blood were assessed in all participants who received a dose of randomly assigned treatment. A person with lived experience of knee osteoarthritis was involved in study interpretation and writing of the report. This trial is registered with ClinicalTrials.gov, NCT04120402, and the EU Clinical Trials Register, EudraCT 2021-000859-39, and is complete.

Findings Between Sept 10, 2021, and Nov 16, 2022, 1294 people were screened for eligibility, and 319 were randomly assigned to EP-104IAR (n=164) or vehicle control (n=155). One participant in the EP-104IAR group was excluded from all analyses because treatment was not administered due to an adverse event. 318 participants (135 [42%] male and 183 [58%] female, 315 [99%] White) received randomly assigned treatment and were included in the primary analysis and safety analysis (EP-104IAR, n=163; vehicle control, n=155). At week 12, least squares mean change in WOMAC pain score from baseline was –2·89 (95% CI –3·22 to –2·56) in the EP-104IAR group and –2·23 (–2·56 to –1·89) in the vehicle control group, with a between-group difference of –0·66 (–1·11 to –0·21; p=0·0044); a significant between-group difference persisted to week 14. 106 (65%) of 163 participants in the EP-104IAR group had one or more treatment-emergent adverse event compared with 89 (57%) of 155 participants in the vehicle control group. Effects on serum glucose and cortisol concentrations were minimal and transient. There were no treatment-emergent deaths or treatment-related serious adverse events. Plasma concentrations of fluticasone propionate showed a blunted initial peak with terminal half-life of approximately 18–20 weeks.

Interpretation These phase 2 results suggest that EP-104IAR has the potential to offer clinically meaningful pain relief in knee osteoarthritis for an extended period of up to 14 weeks, longer than published data for currently marketed corticosteroids. There were minimal effects on glucose and cortisol, and stable fluticasone propionate concentrations in plasma. The safety and efficacy of EP-104IAR will be further evaluated in phase 3 trials, including the possibility of bilateral and repeat dosing with EP-104IAR.

Funding Eupraxia Pharmaceuticals.

Research in context

Evidence before this study

We searched PubMed from date of database inception up to May 21, 2024, using the search terms "fluticasone propionate", "osteoarthritis", and "randomized clinical trial" for publications in English. This search yielded no results. The American College of Rheumatology (ACR) and Osteoarthritis Research Society International (OARSI) recommend that first-line pharmacotherapy for knee osteoarthritis is non-steroidal anti-inflammatory drugs (NSAIDs). However, extended use of NSAIDs has been associated with increases in cardiovascular events, gastrointestinal bleeding, and kidney injury. Opioids are not recommended by the ACR, but are prescribed for pain in more than 15% of patients with knee osteoarthritis despite increased risks of fracture, cardiovascular events, and overall mortality. For advanced knee osteoarthritis, intra-articular corticosteroid injections are recommended by the ACR and conditionally recommended by OARSI for acute and short-term pain relief. Typical corticosteroid injections are immediate release, resulting in high peak plasma concentrations, which can affect regulation of serum glucose and suppress cortisol. The duration of effect for immediate-release corticosteroids is short and chronic use might increase cartilage loss. One extended-release corticosteroid (FX006, a microsphere-based formulation of triamcinolone acetonide) has been approved for use as a single intra-articular injection in people with knee osteoarthritis. Viscosupplementation has been shown to reduce the symptoms of knee osteoarthritis; however, the duration of effect is limited. Some other agents for treatment of knee osteoarthritis, including prolotherapy, platelet-rich plasma injections, and other biologics, are emerging; however, these are currently investigational.

Added value of this study

This trial examined the efficacy, safety, and pharmacokinetics of EP-104IAR (an extended-release fluticasone propionate injection) in patients with knee osteoarthritis. EP-104IAR uses a novel diffusion-based extended-release formulation and is the first agent to use fluticasone propionate in an intra-articular injection for knee osteoarthritis. The primary endpoint was met, with a significant difference between the EP-104IAR group and vehicle control group in the reduction in Western Ontario and McMaster Universities Osteoarthritis Arthritis Index (WOMAC) pain score from baseline to week 12. The first two key secondary endpoints were also met: the difference between EP-104IAR and vehicle control groups in change in WOMAC function score from baseline to week 12 and the difference between the EP-104IAR and vehicle control groups in the area under the curve for WOMAC pain score change from baseline to week 12. Pharmacokinetic analyses estimated the maximum plasma concentration (C_{max}) of fluticasone propionate as 90·1 pg/mL at 22·3 h post-dose. Concentrations were maintained at 66% to 33% of peak, for weeks 2–24 at near constant levels. EP-104IAR was well tolerated, without serious treatment-emergent adverse events or discontinuations related to EP-104IAR. A few participants with shifts to low serum cortisol concentrations after EP-104IAR showed a return to normal concentrations by week 2 in most cases. Post-dose changes in glucose concentrations for participants with non-insulin-dependent diabetes were minimal and similar to those in the overall population; no participants developed adrenal insufficiency.

Implications of all the available evidence

EP-104IAR provides stable delivery of fluticasone propionate over an extended period (estimated terminal phase half-life of approximately 18–20 weeks), with fewer reported systemic side effects than those previously reported for immediate-release corticosteroids and clinically meaningful benefit in terms of pain and stiffness as defined in current literature. Therefore, EP-104IAR has potential to address a substantial unmet medical need of symptom reduction in knee osteoarthritis, with the additional possibility of bilateral or repeat dosing and safe use in patients with non-insulin-dependent diabetes. The safety and efficacy of EP-104IAR will be further evaluated in phase 3 trials.

Introduction

Knee osteoarthritis is a leading cause of disability and is the most common site of osteoarthritis. The global prevalence of knee osteoarthritis was estimated at 4712 cases per 100 000 people in 2020 and is projected to increase by approximately 75% between 2020 and 2050.[1,2] Disability associated with knee osteoarthritis is substantial, particularly among those dependent on manual labour or walking.[3] Reduced physical activity associated with knee osteoarthritis has also been associated with increased mortality because of greater risk of cardiovascular disease and reduced ability to self-manage diabetes and hypertension.[3] The health burden associated with knee osteoarthritis is extensive, including increasing rates of arthroplasty and high levels of anxiety and depression in patients.[4–6] Pathological features of osteoarthritis include cartilage damage and loss, osteophyte formation, and synovial inflammation.[7,8]

Treatment for knee osteoarthritis should begin with conservative interventions (lifestyle changes and physiotherapy), with pharmacotherapy as a potential treatment adjunct.[5] Oral non-steroidal anti-inflammatory drugs (NSAIDs) are conditionally recommended by Osteoarthritis Research Society International (OARSI) for knee osteoarthritis, with limitations for use by people with gastrointestinal or cardiovascular comorbidities because of heightened risk of adverse effects.[9] Opioids are not a recommended treatment but continue to be prescribed for pain management in more than 15% of patients with knee osteoarthritis despite association with fracture and cardiovascular events.[10]

Intra-articular corticosteroid injections are recommended by the American College of Rheumatology (ACR) and conditionally recommended by OARSI for acute (1–2 weeks) and short-term (4–6 weeks) pain relief.[9,11] Injections are typically immediate-release formulations, resulting in high peak plasma concentrations of corticosteroid followed by a rapid decline and loss of effect.[5,9] Systemic corticosteroid exposure, particularly with a high initial peak plasma concentration, can affect regulation of serum glucose and suppress cortisol.[12] These effects are of particular concern for the 40–50% of patients with knee osteoarthritis managing comorbid non-insulin-dependent diabetes or hypertension, or both, which further limits safe use of corticosteroids as currently offered.[13,14] Patients who are managing moderate to severe knee osteoarthritis pain are prescribed more pain medication and have a higher number of clinical interactions, yet report lower treatment satisfaction and decreased quality of life, compared with their counterparts with mild pain.[15] These reports further highlight the unmet medical need in this patient population and the limitations with current overall treatment options for knee osteoarthritis.

See Online for appendix 2

EP-104IAR, a long-acting formulation of fluticasone propionate for intra-articular injection, uses a novel delivery system intended to optimise the action of fluticasone propionate through extended-release technology, controlling circulating concentrations of the drug outside the intended treatment space while maximising intra-articular residence time. EP-104IAR consists of a thermally cured polyvinyl alcohol (PVA) membrane encapsulating a crystallised fluticasone propionate core. Fluticasone propionate was selected as the included corticosteroid on the basis of its structure–activity relationships, low aqueous solubility, and high first-pass metabolism, and because it has one of the highest affinities for the glucocorticoid receptor of widely used corticosteroids.[16] PVA has a 30-year safety record of use in human tissue in various applications including use in ocular and orthopaedic implants.[17] EP-104IAR uses controlled diffusion for delivery, allowing a prolonged and constant rate of drug administration, which lends itself to specificity of target drug release profiles and avoids the variability of release historically associated with degradable polymer formulations.

Preclinical research in dogs has shown a low peak fluticasone propionate concentration in the blood and joint after a single high-dose injection of EP-104IAR. No adverse effects were observed in cartilage or chondrocytes, and fluticasone propionate was released locally for more than 10 months with moderate exposure to plasma and a higher concentration in synovial fluid.[18] In the phase 1 trial,[19] a single 15 mg intra-articular dose of EP-104IAR was given to 24 patients with knee osteoarthritis with follow-up for up to 42 weeks post-treatment. EP-104IAR was well tolerated without serious treatment-related adverse events, and effects on systemic cortisol were short-term and transient. Predictable plasma pharmacokinetics were shown.[19] The aim of the phase 2 trial was to assess the clinical efficacy, pharmacokinetics, and safety of EP-104IAR in participants with knee osteoarthritis.

Methods

Study design

SPRINGBOARD was a multicentre, randomised, double-blind, vehicle-controlled, parallel-group, phase 2 clinical trial. Participants were evaluated following a single intra-articular dose of 25 mg EP-104IAR or vehicle control. The 24-week duration of the trial was anticipated to cover the period over which fluticasone propionate is released via diffusion from the EP-104IAR particles. The trial took place between Sept 10, 2021, and June 1, 2023, at ten research clinics, one hospital, and one private practice clinical setting (12 sites total, details provided in appendix 2 p 1). Sites were located in Denmark, Poland, and Czech Republic. Regulatory and ethical approval for the trial was obtained in each country (appendix 2 p 2). The study protocol and summary of amendments is provided in appendix 2 (pp 9–123). A person with lived experience of knee osteoarthritis was involved in study interpretation and writing of the report.

The trial was done according to the principles of the World Medical Association Declaration of Helsinki and Good Clinical Practice guidelines of the International Council for Harmonisation.[20] Written informed consent was provided by all trial participants, compliant with relevant guidelines and approved by the appropriate ethics committee. All personal data were protected by and compliant with the Personal Information Protection and Documents Act in Canada, and the General Data Protection Regulation in the European Union. This trial is registered with ClinicalTrials.gov, NCT04120402, and the EU Clinical Trials Register, EudraCT 2021-000859-39.

Participants

Participants were aged 40 years or older, with a diagnosis of primary knee osteoarthritis in the index knee as per ACR clinical and radiological criteria, with at least 6 months of reported symptoms before screening. Radiographic severity of index knee osteoarthritis assessed in the lateral and medial compartments was grade 2 or 3 as assessed by a central reader (Medical Metrics, Houston, TX, USA) using the Kellgren–Lawrence scale. Eligible participants had knee pain of at least 4 out of 10 on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain rating scale in one or both knees, after adequate washout of existing analgesic medication. WOMAC pain scores were collected at the end of each week of the 2-week screening and washout period. Both scores were required to be at least 4 and no more than 9 and to not differ by more than 3 points for the index knee; both scores were required to be no more than 6 for the non-index knee. Participants were excluded if they had any condition that would confound

evaluation of pain in the index knee, or surgery on the index knee within 12 months before screening. For safety reasons, clinical laboratory assessments included criteria for serum cortisol and adrenocorticotrophic hormone (ACTH); participants with a baseline serum cortisol concentration of less than or equal to 138 nmol/L (≤5 µg/dL) from the ACTH stimulation test were excluded. Initially, patients with diabetes were excluded; however, the protocol was amended to include those with well controlled non-insulin-dependent diabetes (glycated haemoglobin A_{1c} [HbA_{1c}] ≤63 mmol/mol) at screening. Paracetamol rescue medication (maximum of 3000 mg per day) was permitted from the start of the washout period until the end of the study. Full eligibility criteria can be found in the study protocol (appendix 2 pp 56–60).

Randomisation and masking

Participants were randomly assigned (1:1), stratified by clinical site, to the EP-104IAR or vehicle control group. The randomisation scheme was generated within a commercially available electronic data capture system (Zelta) by the unmasked trial supply team. Randomisation blocks of six were allocated by clinical site. Randomisation was performed directly via interactive web-based access to a central predefined computer-generated list by masked clinical site staff.

Participants and assessors were masked to treatment allocation. Because of visible differences between EP-104IAR and the vehicle, the individual who performed the injection was unmasked for treatment administration; however, treatment was masked to the participant by a screen. Assessors for patient outcomes were masked to treatment assignment. Additional details on randomisation and masking are given in the study protocol (appendix 2 pp 62–63).

Procedures

Participants attended a total of ten visits during the trial. The first visit occurred between 2 weeks and 8 weeks before receiving EP-104IAR or vehicle (day 1) and included information on the trial, the nature of the vehicle, accurate pain reporting using an electronic patient-reported outcome device, and laboratory assessments. At the second screening visit (2 weeks before day 1), participants began the 2-week washout and baseline period, were provided with the electronic patient-reported outcome device, and were issued pain medication (paracetamol oral tablets, up to 3000 mg per day) for breakthrough knee pain. During the washout and baseline period, baseline global assessments included demographic data (including sex with options male or female collected by self-report), medical and surgical history, patient-reported levels of index knee pain, safety analysis of ACTH concentrations, and x-rays. Participants were required to record weekly WOMAC pain scores for each knee and use of rescue medication via the electronic patient-reported outcome device, which informed the determination of eligibility for the trial.

On day 1, the index knee was selected for treatment and participants were assessed for eligibility. Eligible participants were randomly assigned to either the EP-104IAR or vehicle control group. Pre-dose safety, pharmacokinetic, and efficacy analyses were performed. Before administration, 25 mg of EP-104IAR was reconstituted in 5 mL of vehicle, which was designed with enough viscosity to ensure that the particles remained in suspension during the injection procedure and consisted of water for irrigation and excipients. Injection supplies containing the residual drug were retained post-dose for fluticasone propionate concentration analysis. Ultrasound was used (for guidance only) to insert the needle into the index knee, which was aspirated and any effusion volume recorded. A syringe connected to the same needle delivered either EP-104IAR 25 mg or vehicle into the synovial space using a medial or lateral approach. Aspiration and injection procedures were performed by an unmasked, suitably qualified and experienced physician or other suitable study personnel at the research clinic. Participants were observed for 5 min post-injection to ensure that the procedure was well tolerated. Safety and pharmacokinetic assessments were performed within 2 h following the injection, and again at 48 h post-dose (day 3) and 2 weeks post-dose (week 2). Subsequent visits took place at weeks 4, 8, 12, and 18 for assessment of safety, pharmacokinetics, and efficacy. The final visit occurred on week 24 for final assessments and return of electronic patient-reported outcome devices. Details of all scheduling and relevant procedures are in the study protocol (appendix 2 pp 75–96).

Fluticasone propionate was quantified in residual drug by liquid chromatography with tandem mass spectrometry and in peripheral blood collected pre-dose, 2 h post-dose, and during weeks 1, 2, 4, 8, 12, 18, and 24.

The EP-104IAR dose of 25 mg (escalated from 15 mg in the phase 1 study) was anticipated to extend the duration of efficacy while still being below the no observed effect level in dogs when scaled up to humans by 4·4-fold.

An independent, unmasked, safety review committee consisted of three medically qualified professionals with pertinent experience. Safety assessment of the first 48 randomly assigned participants occurred after their 4-week follow-up visit and following their 12-week visit. Both meetings concluded that the study should continue without modification. No formal interim efficacy analyses were performed. The Medical Monitor (ARB) could request the safety review committee be reconvened at any time to review new safety findings; however, no additional meetings were requested.

Outcomes

The primary outcome measure for this trial was the difference between the EP-104IAR and vehicle control groups in change in WOMAC pain score from baseline to week 12, analysed in all participants who were randomly assigned and received treatment.

The four key secondary outcome measures were the difference between the EP-104IAR and vehicle control groups in change in WOMAC function score from baseline to week 12, the difference between the EP-104IAR and vehicle control groups in the area under the curve (AUC) for change in WOMAC pain score from baseline to week 12, the difference between the EP-104IAR and vehicle control groups in change in WOMAC pain score from baseline to week 24, and the difference between the EP-104IAR and vehicle control groups in frequency of response at week 12 defined according to the Outcome Measures for Arthritis Clinical Trials–Osteoarthritis Research Society International (OMERACT–OARSI) criteria. The OMERACT–OARSI response criteria have two options for response; the more stringent of the two was used in this analysis and required a 50% or greater improvement in WOMAC pain or function score and an absolute change of 2 or more in the respective score (scores scaled 0–10).[21] Participants meeting these criteria are referred to here as responders. WOMAC stiffness score and total WOMAC score were assessed as additional secondary outcomes. Additional outcomes of the Patient Global Assessment of Arthritis and Short Form 36 Health Survey (SF-36) were collected in accordance with the OMERACT–OARSI Core Domain Set for knee osteoarthritis trials.[22] For a full list of secondary endpoints see appendix 2 (pp 108–110).

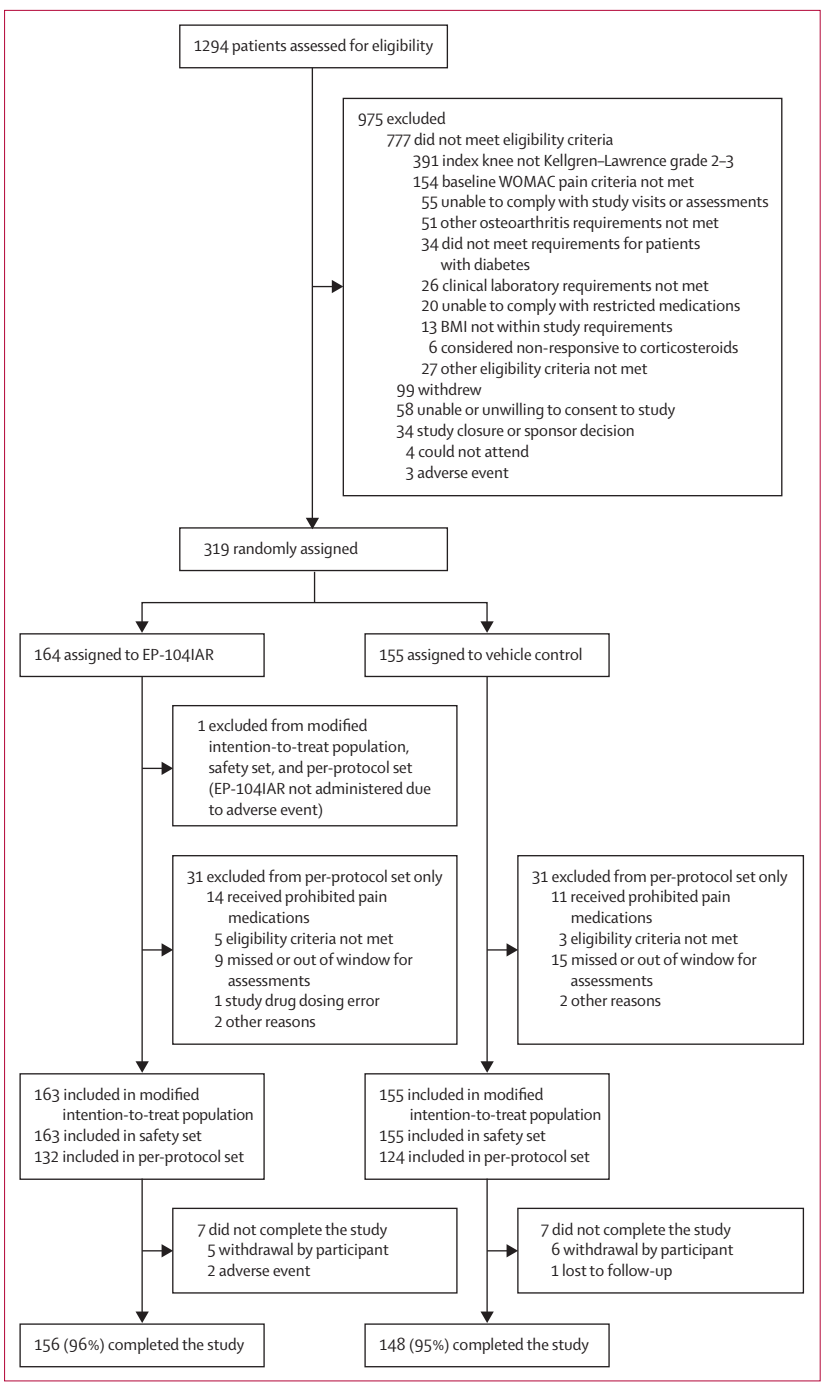

Figure 1: **Trial profile**
WOMAC=Western Ontario and McMaster Universities Arthritis Index.

Exploratory post-hoc analyses included analysis of the per-protocol set, defined as all participants who received a dose of randomly assigned treatment, had at least one post-baseline assessment, and had no major protocol violations potentially impactful of efficacy data. The subset of participants with moderate WOMAC pain scores of 3·5–6·5 at baseline was also analysed post-hoc. In this study, WOMAC function scores were collected every 4 weeks whereas WOMAC pain scores were collected weekly. To evaluate duration of response in this study on a weekly basis, a post-hoc analysis calculated the frequency of pain responders at each week based on the OMERACT–OARSI criteria but only the weekly pain score assessment. Pain response was defined as a decrease of 50% or more in WOMAC pain score from baseline with an absolute change of 2 or more points.

Safety was assessed throughout the trial via monitoring of treatment-emergent adverse events, vital signs, physical examinations, and laboratory analyses (including serum cortisol and glucose, which may be affected by corticosteroid exposure) at each study visit, and ACTH stimulation tests. The relationship of treatment-emergent adverse events to study treatment was assessed by the investigator.

Statistical analysis

The trial was sized with the assumption that interferential testing was at the (two-sided) 5% level with a desired power of 80% to detect the target difference of 0·8. The assumed SD of the primary endpoint was 2·2, as assessed from review of similar studies. On the basis of these assumptions, a sample size of approximately 120 participants per treatment group was required. On the assumption of a dropout rate of approximately 20%, 150 participants were planned in each treatment group.

For the primary endpoint, change from individual pre-dose baseline was calculated for each post-dosing weekly assessment to week 24. A mixed-effects model for

repeated measures (MMRM) was fit to these data, including fixed effects terms for site, individual baseline WOMAC pain score, and the treatment-by-week interaction, where treatment and week were both defined as categorical variables. A random per-patient intercept was also included. No imputation of missing data was performed for this analysis; the MMRM model allows handling of missing data under the assumption that data are missing at random. A multiple imputation approach using the SAS multiple imputation procedure was used to assess the robustness of the assumption that data were missing at random, whereby data missing due to lack of efficacy were imputed in 100 datasets as if participants received vehicle control and data missing due to other reasons were imputed in another 100 datasets as if participants received EP-104IAR.

Key secondary endpoints were assessed in a hierarchical manner, comparing EP-104IAR versus vehicle control. If the primary endpoint was statistically significant at the 5% level, then the first secondary endpoint (listed in order in the Outcomes section) would be formally assessed for statistical significance. If the first secondary endpoint was statistically significant at the 5% level, then the second secondary endpoint was to be formally tested, and so forth. Upon failure of any inferential test at the 5% level, no subsequent secondary endpoints could be declared statistically significant. There was no allowance for multiple comparisons for secondary endpoints not included in the hierarchy (other secondary endpoints) or for exploratory endpoints.

Analysis of primary and key secondary endpoints was done in all participants who were both randomly assigned and received treatment, defined in the statistical analysis plan as the intention-to-treat population and referred to as the modified intention-to-treat population hereafter because it excludes one randomly assigned participant who did not receive treatment because of an adverse event. Responder analyses were done in the population of patients with data at the specified timepoint. Between-group difference was analysed either by an MMRM for change from baseline with fixed effects for site, treatment, week, treatment-by-week interaction; random effect for subject; and covariate baseline of the patient-reported outcome score or component being assessed; or by an ANCOVA model with fixed effect terms for treatment, site, and covariate baseline of the patient-reported outcome score or component being assessed. Safety data were summarised for all participants who were randomly assigned and received a dose of randomly assigned treatment using standard summary statistics, by treatment group. For the frequency of treatment-emergent adverse events, the risk difference between EP-104GI and vehicle control groups was calculated with Wilson CIs.

AUC was calculated for WOMAC pain change from baseline for each timepoint on a per-participant basis using the linear trapezoidal rule. Per-day normalisation was used to account for instances where the actual and nominal number of days within an interval differ.

Pharmacokinetic parameters were estimated from a linear model fit to the log-transformed fluticasone propionate plasma concentration data at a dose of 27·2 mg. The model contained terms for log-transformed dose and a polynomial function of log-transformed day-post-dose. The degree of this polynomial was explored using

	EP-104IAR 25 mg (n=163)	Vehicle control (n=155)
Age, years	64·0 (9·31)	63·2 (9·37)
Sex		
Male	69 (42%)	66 (43%)
Female	94 (58%)	89 (57%)
Race		
American Indian or Alaska Native	0	1 (1%)
Asian	0	1 (1%)
Black or African American	1 (1%)	0
White	162 (99%)	153 (99%)
Ethnicity		
Hispanic or Latino	1 (1%)	2 (1%)
Not Hispanic or Latino	161 (99%)	152 (98%)
Not reported	1 (1%)	1 (1%)
Country		
Denmark	85 (52%)	84 (54%)
Poland	38 (23%)	36 (23%)
Czech Republic	40 (25%)	35 (23%)
BMI, kg/m²	29·9 (4·61)	29·9 (4·16)
Non-insulin dependent diabetes	13 (8%)	13 (8%)
Diagnosis of osteoarthritis in non-index knee*	107 (66%)	84 (54%)
Duration of symptoms in the index knee, years	6·6 (2·9–12·0)	5·8 (3·0–11·3)
Time since diagnosis in the index knee, years	3·3 (0·9–9·2)	3·8 (1·3–8·6)
Index knee Kellgren–Lawrence grade†		
Grade 2	77 (47%)	76 (49%)
Grade 3	86 (53%)	78 (50%)
Grade 4	0	1 (1%)†
Baseline WOMAC scores of the index knee		
Pain	6·00 (1·16)	5·74 (1·11)
Function	5·66 (1·52)	5·37 (1·49)
Previous surgeries or procedures related to knee osteoarthritis for index knee		
Anterior cruciate ligament repair	0	4 (3%)
Meniscus repair	5 (3%)	8 (5%)
Debridement	9 (6%)	12 (8%)
Other	7 (4%)	10 (6%)

Data are mean (SD), n (%), or median (IQR). WOMAC=Western Ontario and McMaster Universities Arthritis Index. *Per investigator report. †One participant with Kellgren–Lawrence grade 4 of the index knee was enrolled in error as the study eligibility criteria required grade 2–3; this participant was included in all analyses.

Table 1: **Baseline demographics and disease characteristics (modified intention-to-treat population)**

	EP-104IAR (n=163)	Vehicle control (n=155)	Between-group difference (EP-104IAR *vs* vehicle control)	p value
Primary endpoint				
Change in WOMAC pain score from baseline to week 12	−2·89 (−3·22 to −2·56)	−2·23 (−2·56 to −1·89)	−0·66 (−1·11 to −0·21)*	0·0044
Change in WOMAC pain score from baseline to week 12, multiple imputation	−2·91 (−3·23 to −2·60)	−2·27 (−2·60 to −1·94)	−0·64 (−1·09 to 0·19)†	0·0050
Key secondary endpoints (in order of hierarchical analysis)				
Change in WOMAC function score from baseline to week 12	−2·59 (−2·91 to 2·27)	−2·04 (−2·37 to −1·71)	−0·55 (−0·98 to −0·12)‡	0·014§
Change in AUC for WOMAC pain score from baseline to week 12	−235·67 (−258·74 to −212·60)	−166·78 (−190·63 to −142·93)	−68·89 (−99·96 to −37·82)†	<0·0001†§
Change in WOMAC pain score from baseline to week 24	−2·26 (−2·06 to −1·92)	−2·11 (−2·44 to −1·78)	−0·15 (−0·61 to 0·31)*	..
Frequency of OMERACT–OARSI responders (week 12)	87/156 (56%)	61/143 (43%)	..	..
Additional secondary endpoints				
Change in total WOMAC score from baseline to week 12	−2·72 (−3·04 to −2·40)	−2·11 (−2·44 to −1·78)	−0·61 (−1·04 to −0·18)‡	..
Change in WOMAC stiffness score from baseline to week 12	−2·80 (−3·13 to −2·47)	−2·08 (−2·42 to −1·74)	−0·71 (−1·17 to −0·25)‡	..
WOMAC pain 30% responders (week 12)¶	112/156 (72%)	86/143 (60%)	..	..
WOMAC pain 70% responders by timepoint (week 18)‖	46/152 (30%)	22/137 (16%)	..	..
Change in average daily NPRS scores from baseline to week 14	−2·81 (−3·15 to −2·47)	−2·26 (−2·61 to −1·91)	−0·55 (−1·02 to −0·08)‡	..
Change in PtGA scores from baseline to week 12	−1·97 (−2·29 to −1·65)	−1·71 (−2·05 to −1·38)	−0·25 (−0·70 to 0·19)‡	..
Change in SF-36 mental component scores from baseline to week 12	−0·81 (−1·88 to 0·26)	−0·22 (−1·33 to 0·89)	−0·59 (−2·05 to 0·87)**	..
Change in SF-36 physical component scores from baseline to week 12	5·66 (4·53 to 6·78)	4·40 (3·22 to 5·59)	1·25 (−0·29 to 2·80)**	..

Data are least squares mean (95% CI) or n/N (%), unless otherwise stated. AUC=area under the curve. MMRM=mixed model for repeated measures. NPRS=numerical pain rating scale. OMERACT–OARSI=Outcome Measures for Arthritis Clinical Trials–Osteoarthritis Research Society International. PtGA=Patient Global Assessment of Arthritis. SF-36=Short Form 36 Health Survey. WOMAC=Western Ontario and McMaster Universities Arthritis Index. *From an MMRM for change from baseline with fixed effects for site, treatment, week, treatment-by-week interaction; random effect for participant; and covariate baseline WOMAC pain score. †From an ANCOVA model with treatment, site, and baseline WOMAC pain as covariates. ‡From an MMRM for change from baseline with fixed effects for site, treatment, week, treatment-by-week interaction; random effect for participant; and covariate baseline of the patient-reported outcome score or component being assessed. §Indicates significance based on the stepdown procedure described for key secondary endpoints. ¶Pain 30% responders defined as having at least 30% decrease from baseline in WOMAC pain. ‖Pain 70% responders defined as having at least 70% decrease from baseline in WOMAC pain. **From an ANCOVA model with fixed effect terms for treatment, site, and covariate baseline SF-36 domain score.

Table 2: **Summary of primary and secondary endpoints (modified intention-to-treat population)**

iterative model fitting. Covariate analyses were performed to explore demographic factors of sex, age, and BMI on fluticasone propionate plasma concentration over time.

Data were analysed by an external team of statisticians not involved in the study conduct using SAS version 9.4 (or higher) or Phoenix WinNonlin version 8.3 (or higher; Certara USA, Princeton, NJ, USA).

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Following screening of 1294 potential participants who provided consent between Sept 10, 2021, and Nov 16, 2022, 319 were randomly assigned to EP-104IAR (n=164) or vehicle control (n=155). 318 participants (135 [42%] male and 183 [58%] female, 315 [99%] White) received randomly assigned treatment and were included in the modified intention-to-treat population (figure 1). The demographic and disease characteristics of the participants are shown in table 1. Follow-up was completed on June 1, 2023. Enrolment by country and clinical site is shown in appendix 2 (p 1).

At week 12, the reduction in WOMAC pain score from baseline was greater in the EP-104IAR group than in the vehicle control group (least squares mean change from baseline −2·89 [95% CI −3·22 to −2·56] in the EP-104IAR group *vs* −2·23 [−2·56 to −1·89] in the vehicle control group, between-group difference −0·66 [−1·11 to −0·21]; p=0·0044; table 2); this difference was significant through to week 14 (figure 2A). As a result, the primary endpoint of the trial was met. A prespecified multiple imputation robustness analysis of the MMRM model showed there was a very low missing data rate of 6%, and the primary outcome had a similar result with and without multiple imputation (table 2).

The four key secondary endpoints are shown in table 2 and figure 2, in order of hierarchical analysis. For the first and second key secondary endpoints analysed, the difference between the EP-104IAR and vehicle control groups in change in WOMAC function score from baseline to week 12 and difference between the groups in AUC for change in WOMAC pain from baseline to week 12, the EP-104IAR group showed significant improvements over 12 weeks compared with the vehicle control group (figure 2B–C). A significant between-group difference for AUC in WOMAC pain score was sustained until the end of the trial at week 24.

The third key secondary endpoint analysed, the difference between the EP-104IAR and vehicle control groups in change in WOMAC pain score from baseline to week 24, showed a greater numerical improvement in the EP-104IAR group than in the vehicle control group (figure 2A); however, this difference was not significant (table 2).

The final key secondary endpoint analysed showed a greater proportion of OMERACT–OARSI responders in the EP-104IAR group at all timepoints up to week 24 compared with the vehicle control group (figure 2D). However, as a consequence of the preceding endpoint not reaching significance, this endpoint was not met.

Exploratory post-hoc analysis of the frequency of pain responders at each week for EP-104IAR versus vehicle control was done in the modified intention-to-treat population and in the subset of participants with moderate

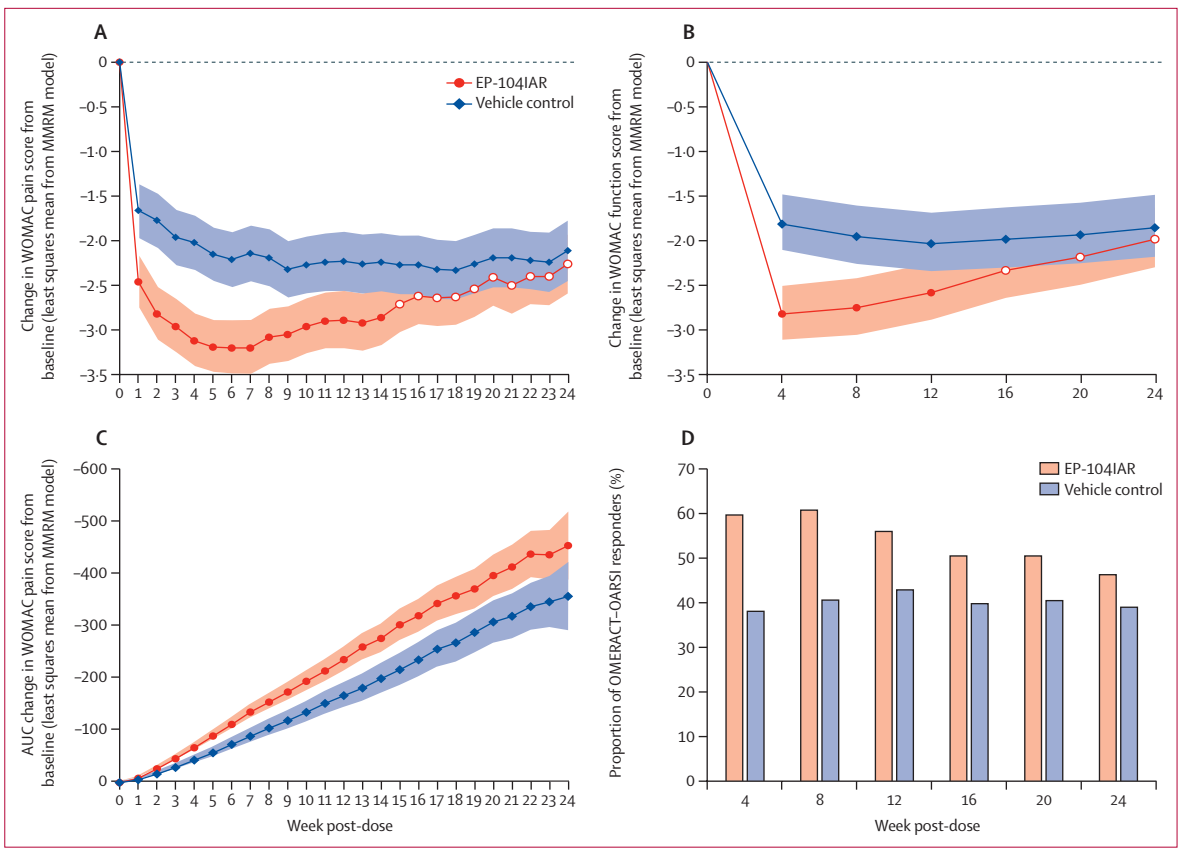

Figure 2: **Primary and key secondary outcomes**
Change in WOMAC pain (A) and function (B) scores from baseline, AUC for change in WOMAC pain score from baseline (C), and proportion of OMERACT–OARSI responders (D) following a single injection of EP-104IAR 25 mg or vehicle control (modified intention-to-treat population). Solid dots indicate p<0·05 and open dots indicate p≥0·05 from an MMRM for change from baseline with fixed effects for site, treatment, week, treatment-by-week interaction; random effect for participant; and covariate baseline WOMAC pain score. Shaded areas indicate 95% CI. AUC=area under the curve. MMRM=mixed model for repeated measures. OMERACT–OARSI=Outcome Measures for Arthritis Clinical Trials–Osteoarthritis Research Society International. WOMAC=Western Ontario and McMaster Universities Arthritis Index.

baseline pain scores (214 participants; EP-104IAR, n=105; vehicle control, n=109). A higher frequency of pain responders was seen in the EP-104IAR group compared with the vehicle control group, with a 15% or greater difference between treatment groups seen up to week 14 in the modified intention-to-treat population and up to week 22 in the moderate pain population (appendix 2 p 3).

Exploratory analysis of the per-protocol set of 256 participants (EP-104IAR, n=132; vehicle control, n=124; figure 1) excluded 31 participants from each treatment group including 14 from the EP-104IAR group and 11 from the vehicle control group who received prohibited pain medications (including NSAIDs and paracetamol >3000 mg per day) during the trial and therefore had confounded efficacy assessments. As would be expected for this population, the EP-104IAR group showed better improvement in measured outcomes versus the vehicle control group, with differences between groups being similar or greater than those in the modified intention-to-treat analysis (data not shown). The proportion of participants with 70% reduction in WOMAC pain score was also consistently greater for EP-104IAR versus vehicle control for the per-protocol set compared with the modified intention-to-treat population (data not shown). A forest plot showing standardised mean differences between EP-104IAR and vehicle control in key efficacy endpoints is shown in appendix 2 (p 8).

The actual dose of fluticasone propionate administered in the EP-104IAR group was determined from residual drug and ranged from 11·5 mg to 30·0 mg with a median of 27·2 mg (IQR 25·2–28·2). Iterative model fitting resulted in a polynomial of degree 5 (appendix 2 p 4). Terminal phase half-life was estimated at approximately 18–20 weeks. The geometric mean maximum concentration (C_{max}) in plasma was estimated as 90·1 pg/mL (percentage of coefficient of variation 126) at a median time to maximum observed concentration (t_{max}) of 22·3 h (IQR 2·00–48·4). Concentrations were maintained at 66% to 33% of peak, for weeks 2–24 at near constant levels. Because of the long residence time, many pharmacokinetic parameters were poorly estimable. Increase in fluticasone propionate concentrations was largely linear

	EP-104IA 25 mg (n=163)		Vehicle control (n=155)		Risk difference between groups (95% CI)*
	Participants, n (%)	Events, n	Participants, n (%)	Events, n	
Deaths	0	0	0	0	..
Serious treatment-emergent adverse events	4 (2%)	4	1 (1%)	1	1·81 (–9·23 to 12·79)
Serious treatment-related adverse events	0	0	0	0	..
Discontinuations due to serious treatment-emergent adverse events	2 (1%)	2	0	0	1·23 (–9·81 to 12·23)
Treatment-emergent adverse event of special interest	0	0	0	0	..
Participants with treatment-emergent adverse event related to study treatment†‡	15 (9%)	17	11 (7%)	12	2·11 (–8·89 to 13·10)
Arthralgia	9 (6%)	9	9 (6%)	9	–0·28 (–11·3 to 10·71)
Participants with any treatment-emergent adverse event†	106 (65%)	210	89 (57%)	174	7·61 (–3·42 to 18·54)
Arthralgia	38 (23%)	38	23 (15%)	26	8·47 (–2·58 to 19·38)
COVID-19	14 (9%)	14	14 (9%)	14	–0·44 (–11·4 to 10·58)
Nasopharyngitis	14 (9%)	16	12 (8%)	15	0·85 (–10·1 to 11·86)
Influenza	6 (4%)	6	9 (6%)	9	–2·13 (–13·1 to 8·87)
Influenza-like illness	4 (2%)	5	10 (6%)	10	–4·00 (–15·0 to 7·01)
Hypertension	7 (4%)	7	4 (3%)	4	1·71 (–9·33 to 12·66)
Back pain	5 (3%)	5	4 (3%)	5	0·49 (–10·5 to 11·46)
Bronchitis	4 (2%)	4	4 (3%)	4	–0·13 (–11·2 to 10·86)
Toothache	4 (2%)	4	3 (2%)	3	0·52 (–10·5 to 11·50)
Cough	3 (2%)	3	3 (2%)	3	–0·09 (–11·1 to 10·90)
Upper respiratory tract infection	4 (2%)	4	2 (1%)	3	1·16 (–9·88 to 12·15)
Headache	3 (2%)	3	2 (1%)	3	0·55 (–10·5 to 11·54)
Ligament sprain	2 (1%)	2	3 (2%)	3	–0·71 (–11·7 to 10·30)
Pain in extremity	3 (2%)	3	2 (1%)	2	0·55 (–10·5 to 11·54)
Respiratory tract infection	4 (2%)	4	1 (1%)	1	1·81 (–9·23 to 12·79)
Spinal pain	4 (2%)	6	1 (1%)	1	1·81 (–9·23 to 12·79)

*For risk difference between groups, Wilson CI is shown. †Individual event terms are shown which occurred in at least five participants overall. Participants are counted once for each event term. ‡For list of all treatment-emergent adverse events related to study treatment see appendix 2 (p 184).

Table 3: **Treatment-emergent adverse events occurring up to 24 weeks after a single dose of EP-104IAR 25 mg or vehicle control (safety set)**

with age; 24% for each 10 years of age. Increasing BMI from 25 kg/m² to 30 kg/m² decreased exposure by 22%, with minimal decrease for BMI above approximately 30 kg/m² (appendix 2 pp 5–6). These effects did not appear to differ between male and female participants.

In the EP-104IAR group, 106 (65%) of 163 participants had one or more treatment-emergent adverse event compared with 89 (57%) of 155 in the vehicle control group. In the EP-104IAR group, 15 (9%) participants had treatment-emergent adverse events related to study treatment compared with 11 (7%) in the vehicle control group (table 3, appendix 2 p 184). Arthralgia occurred more frequently in the EP-104IAR group (38 [23%] participants) than in the vehicle control group (23 [15%] participants). However, the frequency of study treatment-related arthralgia was almost identical for EP-104IAR (nine [6%] participants) and vehicle control (nine [6%] participants).

Five participants had serious treatment-emergent adverse events, four (2%) in the EP-104IAR group (cerebrovascular accident, accidental overdose [of oral pain medication], loss of consciousness, and acute vestibular syndrome) and one (1%) in the vehicle control group (prostate cancer). None were classed as related to EP-104IAR. Two participants discontinued the trial because of adverse events, both in the EP-104IAR group: coccyx injury or spinal column injury and worsening of pain left knee or arthralgia (non-index or untreated knee). Neither were deemed related to EP-104IAR.

Glucose concentrations on day 3 post-dose were similar between treatment groups with a mean of 5·6 mmol/L (SD 0·9) in the EP-104IAR group versus 5·6 mmol/L (1·2) in the vehicle control group (appendix 2 p 7). The mean change in glucose concentration from baseline to day 3 post-dose was small (–0·5 mmol/L [SD 1·0]) in participants with non-insulin-dependent diabetes in the EP-104IAR group (compared with –0·1 mmol/L [1·4] in the vehicle control group; appendix 2 p 7). Mean change in serum cortisol from baseline to day 3 in the EP-104IAR group was –62·3 nmol/L (SD 188·3), which returned to near baseline (–2·7 nmol/L [99·3]) by week 2. Mean change in serum cortisol from baseline to day 3 in the vehicle control group was 21·7 nmol/L (SD 102·8; appendix 2 p 7). No participants developed adrenal insufficiency.

Discussion

This randomised, double-blind trial of EP-104IAR achieved its primary endpoint and showed a significant reduction in WOMAC pain score from baseline to week 12 compared with vehicle control in participants with knee osteoarthritis with a least squares mean difference between groups of –0·66 (95% CI –1·11 to –0·21).

Several different indicators have been suggested as relevant when understanding potential clinical meaningfulness, including between-group difference in WOMAC pain score and the frequency of OMERACT–OARSI responders.[23] A moderately clinically meaningful change

in WOMAC pain score has been defined as an approximate 30% reduction using an external anchor measure as recommended by the US Food and Drug Administration; in this case, Patient Global Assessment of Arthritis.[24,25] In this study, 72% of participants in the EP-104IAR group had a 30% or greater reduction in WOMAC pain score at week 12 versus 60% in the vehicle control group. Furthermore, 30% of participants in the EP-104IAR group had a reduction in WOMAC pain score of 70% or more at week 12 versus 16% in the vehicle control group. Also, the proportion of OMERACT–OARSI responders at week 12 was greater in the EP-104IAR group than in the vehicle control group (56% *vs* 43%). Taken together, these data suggest a clinically meaningful benefit of EP-104IAR.

Between-study comparisons are challenged by differences in patient populations, trial designs, and study conduct. However, in terms of previous intra-articular corticosteroid studies, the clinical benefits of EP-104IAR appear more sustained compared with regular-release corticosteroids.[26] In terms of other slow-release products, the randomised phase 3 study of triamcinolone acetonide extended-release injectable suspension microspheres (FX006) showed a least squares mean difference in WOMAC pain score at week 12 of –0·37 (95% CI –0·55 to –0·20) between the FX006 and saline placebo groups.[27] The current study data suggest that the reduction in pain provided by EP-104IAR compared with control might be greater, although care should be taken when comparing across trials. The difference in WOMAC pain relief between EP-104IAR and vehicle control was significant up to week 14; FX006, the only currently approved extended-release intra-articular corticosteroid, is reported to achieve the same measure to 12 weeks.[27] In participants with moderate knee osteoarthritis at baseline, EP-104IAR showed a greater improvement in WOMAC pain score compared with vehicle control than the difference between groups shown in the modified intention-to-treat population, and the pain responder analysis showed at least 15% more pain responders in the EP-104IAR group than in the vehicle control group at week 22. This is a promising finding for this group of patients with moderate knee osteoarthritis, who are the largest demographic and who have decreased satisfaction with limited available treatments as their disease progresses beyond mild symptoms.[15]

Pharmacokinetic analyses showed that by contrast with traditional degradation-based extended-release products, EP-104IAR's release of fluticasone propionate via diffusion is stable and long-lasting. Concentrations of fluticasone propionate were maintained at 33–66% of peak for weeks 2–24 at near-constant levels. Comparing the pharmacokinetics of fluticasone propionate inhalation 440 µg twice a day with EP-104IAR, the C_{max} of inhaled fluticasone propionate is similar to EP-104IAR (87 pg/mL *vs* 90 pg/mL). Shortly after EP-104IAR injection, average concentrations of fluticasone propionate were similar to the steady state concentration of approximately 30 pg/mL observed with 220 µg twice-daily inhaled fluticasone propionate.[28] The blunting of C_{max} with EP-104IAR was associated with modest effects on serum cortisol, which normalised by week 2, with no effect on glucose concentration observed in either the EP-104IAR group or specifically in participants with non-insulin-dependent diabetes. By comparison, FX006 has been shown to increase blood glucose concentration over days 1–3 post-dose in patients with diabetes, resulting in glucose concentrations above the target glycaemic range for more than 30% of that 3-day period.[29] No events of hyperglycaemia were reported during this trial of EP-104IAR.

Safety findings in this study showed a greater proportion of treatment-emergent adverse events related to study treatment in the EP-104IAR group than in the vehicle control group (9% *vs* 7%); however, there were no serious adverse events or discontinuations due to adverse events related to EP-104IAR. Although adverse events of arthralgia were more frequent in the EP-104IAR group, frequency of treatment-related arthralgia was similar between groups. Reduction in cartilage thickness with immediate-release formulation corticosteroids is concerning. Although we did not perform comprehensive MRI cartilage assessments, EP-104IAR is designed to produce a prolonged exposure to fluticasone propionate in the joint, and the initial peak concentration is much lower than that for immediate-release corticosteroids, which might mitigate potential effects on cartilage, but this would need to be studied. Also, effects on serum glucose and cortisol via interaction of fluticasone propionate with the hypothalamic-pituitary-adrenal axis were observed to be small and not of clinical concern.

This study had several limitations. Greater ethnic diversity within the patient population would have allowed for improved generalisability. We did not evaluate the success of masking. The study treatment was administered by an unmasked injector, although assessors of patient outcomes were masked to treatment assignment. Efficacy outcomes were patient reported; no objective measurement of knee function was made. By excluding patients considered previously non-responsive to corticosteroids to avoid risk in those with a lower chance of benefit, we might have introduced potential bias; only six of 1294 patients screened were excluded for this reason. Also, information on previous intra-articular corticosteroid use, which might have biased patient expectations, was collected only for the period of 6 months before screening. Adequate and well controlled phase 3 trials to further evaluate the safety and efficacy of EP-104IAR are needed.

In conclusion, the results of this trial show that EP-104IAR has the potential for clinically meaningful benefit in reducing knee osteoarthritis pain, addressing a substantial unmet medical need. Additionally, the stable delivery of fluticasone propionate over an extended period with fewer systemic and local side effects than other corticosteroid treatments for knee osteoarthritis support the possibility of bilateral and repeat dosing.

Contributors

JH, PGC, MW, and LSS were involved in trial conception, design, and data interpretation. AM was involved in trial conception, design, conduct, and data interpretation. MMK was involved in trial conduct and data interpretation. HR, SLB, and KM were clinical site principal investigators. ARB, CPM, ACM, YL, CD, and VP were involved in trial conduct, oversight, and collection of trial data. CD, AM, and PGC directly accessed and verified the underlying data. All authors had full access to all data in the study, were involved in drafting the article or revising it critically for important intellectual content, and had final responsibility for the decision to submit for publication.

Declaration of interests

JH, AM, MMK, CD, and VP are employees of Eupraxia Pharmaceuticals. SLB, HR, and KM are or were employees of Sanos Clinics who were contracted by Eupraxia Pharmaceuticals to perform the clinical research. ACM, YL, CPM, and ARB are employees of NBCD, a contract research organisation contracted by Eupraxia Pharmaceuticals to perform data management and trial management. PGC has performed speakers' bureaus or consultancies for AbbVie, AstraZeneca, Eli Lilly, Eupraxia, Galapagos, Genascence, GSK, Grunenthal, Janssen, Levicept, Medipost, Merck, Moebius, Novartis, Sandoz, Stryker, TrialSpark, and UCB. MW is on the Board of Directors for Eupraxia Pharmaceuticals and received royalties from NextStep Arthropedix. LSS declares no competing interests.

Data sharing

The sponsor will consider requests for clinical trial data from qualified researchers with an appropriate and clearly defined scientific objective, following the publication of the primary results of the trial. Data considered for sharing can include anonymised aggregate clinical trial data not covered by relevant privacy legislation, clinical study reports, statistical analysis plan, informed consent forms, and protocol. Researchers will be required to sign a Data Use Agreement before receiving study documents. Data requests can be submitted to amalone@eupraxiapharma.com.

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References

1 GBD 2021 Osteoarthritis Collaborators. Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Rheumatol* 2023; **215:** e508–22.

2 Li E, Tan J, Xu K, Pan Y, Xu P. Global burden and socioeconomic impact of knee osteoarthritis: a comprehensive analysis. *Front Med (Lausanne)* 2024; **11:** 1323091.

3 March L, Cross M, Lo C, et al. Osteoarthritis: a serious disease: submitted to the US Food and Drug Administration. 2016. https://oarsi.org/sites/oarsi/files/docs/2016/oarsi_white_paper_oa_serious_disease_121416_1.pdf (accessed Dec 29, 2023).

4 Schwartz AM, Farley KX, Guild GN, Bradbury Jr TL. Projections and epidemiology of revision hip and knee arthroplasty in the United States to 2030. *J Arthroplasty* 2020; **35**: S79–85.

5 Brophy RH, Fillingham YA. AAOS clinical practice guideline summary: management of osteoarthritis of the knee (nonarthroplasty), third edition. *J Am Acad Orthop Surg* 2022; **30:** e721–29.

6 Sharma A, Kudesia P, Shi Q, Gandhi R. Anxiety and depression in patients with osteoarthritis: impact and management challenges. *Open Access Rheumatol* 2016; **8:** 103–13.

7 Chow YY, Chin KY. The role of inflammation in the pathogenesis of osteoarthritis. *Mediators Inflamm* 2020; **2020:** 8293921.

8 Michael JW, Schlüter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. *Dtsch Arztebl Int* 2010; **107:** 152–62.

9 Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019; **27:** 1578–89.

10 DeMik DE, Bedard NA, Dowdle SB, Burnett RA, McHugh MA, Callaghan JJ. Are we still prescribing opioids for osteoarthritis? *J Arthroplasty* 2017; **32:** 3578–82.e1.

11 Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol* 2020; **72:** 220–33.

12 Jüni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. *Cochrane Database Syst Rev* 2015; **10:** CD005328.

13 Meurota C, Jacques C, Martin C, et al. Targeting the GLP-1/GLP-1R axis to treat osteoarthritis: a new opportunity? *J Orthop Translat* 2022; **32:** 121–29.

14 Lo K, Au M, Ni J, Wen C. Association between hypertension and osteoarthritis: a systematic review and meta-analysis of observational studies. *J Orthop Translat* 2022; **32:** 12–20.

15 Schepman P, Thakkar S, Robinson R, Malhotra D, Emir B, Beck C. Moderate to severe osteoarthritis pain and its impact on patients in the United States: a national survey. *J Pain Res* 2021; **14:** 2313–26.

16 Johnson M. Development of fluticasone propionate and comparison with other inhaled corticosteroids. *J Allergy Clin Immunol* 1998; **101:** S434–39.

17 Baker MI, Walsh SP, Schwartz Z, Boyan BD. A review of polyvinyl alcohol and its uses in cartilage and orthopedic applications. *J Biomed Mater Res B Appl Biomater* 2012; **100:** 1451–57.

18 Getgood A, Dhollander A, Malone A, Price J, Helliwell J. Pharmacokinetic profile of intra-articular fluticasone propionate microparticles in beagle dog knees. *Cartilage* 2019; **10:** 139–47.

19 Malone A, Price J, Price N, et al. Safety and pharmacokinetics of EP-104IAR (sustained-release fluticasone propionate) in knee osteoarthritis: a randomized, double-blind, vehicle-controlled phase 1 trial. *Osteoarthritis Cartilage* 2021; **3:** 100213.

20 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310:** 2191–94.

21 Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage* 2004; **12:** 389–99.

22 Smith TO, Hawker GA, Hunter DJ, et al. The OMERACT-OARSI core domain set for measurement in clinical trials of hip and/or knee osteoarthritis. *J Rheum* 2019; **46:** 981–89.

23 Dworkin RH, Turk DC, McDermott MP, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *PAIN* 2009; **146:** 238–44.

24 Conaghan PG, Dworkin RH, Schnitzer TJ, et al. WOMAC meaningful within-patient change: results from 3 studies of tanezumab in patients with moderate-to-severe osteoarthritis of the hip or knee. *J Rheumatol* 2022; **49:** 615–21.

25 US Food and Drug Administration. FDA patient-focused drug development guidance series for enhancing the incorporation of the patient's voice in medical product development and regulatory decision making. 2024. https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical (accessed Sept 9, 2024).

26 Bellamy N, Campbell J, Welch V, Gee TL, Bourne R, Wells GA. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006; **2:** CD005328.

27 Conaghan PG, Hunter DJ, Cohen SB, et al. Effects of a single intra-articular injection of a microsphere formulation of triamcinolone acetonide on knee osteoarthritis pain: a double-blinded, randomized, placebo-controlled, multinational study. *J Bone Joint Surg Am* 2018; **100:** 666–77.

28 GlaxoSmithKline. Flovent HFA [package insert]. Research Triangle Park, NC: GlaxoSmithKline; August, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021433Orig1s040ReplacementLbl.pdf (accessed Sept 10, 2024).

29 Russell SJ, Sala R, Conaghan PG, et al. Triamcinolone acetonide extended-release in patients with osteoarthritis and type 2 diabetes: a randomized, phase 2 study. *Rheumatology (Oxford)* 2018; **57:** 2235–41.