



Clinical trial results:

A Phase 2, Randomized, Double-Blind, Vehicle-Controlled Study Evaluating the Safety, Efficacy and Pharmacokinetics of Single Dose EP-104IAR for 24 Weeks in Patients with Osteoarthritis of the Knee

Summary

EudraCT number	2021-000859-39
Trial protocol	DK
Global end of trial date	04 December 2023

Results information

Result version number	v1 (current)
This version publication date	10 October 2024
First version publication date	10 October 2024

Trial information

Trial identification

Sponsor protocol code	EP-104IAR-201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04120402
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eupraxia Pharmaceuticals
Sponsor organisation address	201-2067 Cadboro Bay Rd., Victoria, Canada, V8R 5G4
Public contact	Amanda Malone, PhD, Eupraxia Pharmaceuticals, +1 250-590-3968, amalone@eupraxiapharma.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 December 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of a single intra-articular (IA) injection of EP-104IAR in patients with osteoarthritis (OA) of the knee for up to 24 weeks

Protection of trial subjects:

The Index (treated) knee was prepared with chlorhexidine or betadine per the site's standard injection protocol. Lidocaine (also known as lignocaine) could be administered prior to the injection procedure to make the procedure more comfortable. Lidocaine could be injected into subcutaneous tissues along the needle pathway but was not injected into the suprapatellar bursal space.

Acetaminophen (paracetamol) 500 mg (up to a maximum of 3,000 mg per day) was permitted from the start of the Washout and Baseline Period until the end of the study, for the treatment of breakthrough OA pain in the Index knee. If required, the provided rescue medication could also be used to treat other painful events not related to the Index knee.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 August 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 74
Country: Number of subjects enrolled	Czechia: 75
Country: Number of subjects enrolled	Denmark: 170
Worldwide total number of subjects	319
EEA total number of subjects	319

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	164
From 65 to 84 years	154
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Between Sept 10, 2021, and Nov 16, 2022, 1294 people were screened for eligibility, at 12 research sites in Denmark, Poland, and Czech Republic.

Pre-assignment

Screening details:

On 1294 people screened for eligibility, and 319 were randomly assigned to EP-104IAR (n=164) or vehicle control (n=155).

Pre-assignment period milestones

Number of subjects started	319
Number of subjects completed	319

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

Subjects and assessors were blinded to treatment allocation. Due to the impossibility of obtaining identical presentations of study drug and vehicle, blinding at each site was achieved by appointing 1 unblinded individual responsible for administering treatments and 1 blinded assessor who performed all follow-up assessments. The blinded assessor was not present at the time of injection. Subjects were blinded to treatment by shielding the subject's view of the injection field.

Arms

Are arms mutually exclusive?	Yes
Arm title	EP-104IAR 25 mg

Arm description:

Single 5 mL intra-articular injection containing 25 mg of EP-104IAR

Arm type	Experimental
Investigational medicinal product name	EP-104IAR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use

Dosage and administration details:

A single 5 mL intra-articular injection containing 25 mg of EP-104IAR. Each single use vial of EP-104IAR Powder contains a sufficient quantity of powder to deliver a dose of 25 mg of FP. A small overage is included in each vial to account for losses to the vial and syringe during constitution prior to injection.

Arm title	Vehicle Control
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Arm description:

A single 5 mL intra-articular injection containing no active ingredients

Arm type	Placebo
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Investigational medicinal product name	Vehicle Control
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use

Dosage and administration details:

A single 5 mL intra-articular injection of the injection vehicle without the active ingredient, ie, a sterile liquid containing sterile water and excipients.

Number of subjects in period 1	EP-104IAR 25 mg	Vehicle Control
Started	164	155
Received randomized treatment	163	155
Completed	163	155
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups

Reporting group title	EP-104IAR 25 mg
Reporting group description:	
Single 5 mL intra-articular injection containing 25 mg of EP-104IAR	
Reporting group title	Vehicle Control
Reporting group description:	
A single 5 mL intra-articular injection containing no active ingredients	

Reporting group values	EP-104IAR 25 mg	Vehicle Control	Total
Number of subjects	164	155	319
Age categorical			
Units: Subjects			
Adults (18-64 years)	82	82	164
From 65-84 years	81	73	154
85 years and over	1	0	1
Age continuous			
Units: years			
arithmetic mean	64.0	63.0	
standard deviation	± 9.29	± 9.52	-
Gender categorical			
Gender information was collected by self-report with options male or female.			
Units: Subjects			
Female	95	89	184
Male	69	66	135
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	162	152	314
Unknown or Not Reported	1	1	2
Race			
Units: Subjects			
Unknown or Not Reported	0	0	0
American Indian or Alaska Native	0	1	1
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	163	153	316
More than one race	0	0	0

End points

End points reporting groups

Reporting group title	EP-104IAR 25 mg
Reporting group description: Single 5 mL intra-articular injection containing 25 mg of EP-104IAR	
Reporting group title	Vehicle Control
Reporting group description: A single 5 mL intra-articular injection containing no active ingredients	

Primary: Difference in change from baseline between EP-104IAR and vehicle in WOMAC pain subscale (Week 12)

End point title	Difference in change from baseline between EP-104IAR and vehicle in WOMAC pain subscale (Week 12)
End point description: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (scores scaled 0-10, with 10 being the worst). Least squares mean from a mixed model for repeated measures (MMRM) for change from baseline with fixed effects for site, treatment, week, treatment-by-week interaction; random effect for subject; and covariate baseline WOMAC pain score.	
End point type	Primary
End point timeframe: Change from score at baseline to score at week 12 post-dose	

End point values	EP-104IAR 25 mg	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163 ^[1]	155		
Units: Change from baseline in WOMAC pain score				
least squares mean (standard deviation)	-2.89 (± 0.166)	-2.23 (± 0.171)		

Notes:

[1] - One participant was excluded from all analyses because treatment was not administered due to an AE

Statistical analyses

Statistical analysis title	Least squares mean difference in WOMAC pain
Statistical analysis description: From a mixed-effects model for repeated measures (MMRM) for change from baseline with fixed effects for site, treatment, week, treatment-by-week interaction; random effect for subject; and covariate baseline WOMAC pain score.	
Comparison groups	EP-104IAR 25 mg v Vehicle Control

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.108
upper limit	-0.206
Variability estimate	Standard error of the mean
Dispersion value	0.229

Secondary: Difference in change from baseline between EP-104IAR and vehicle in WOMAC function subscale (Week 12)

End point title	Difference in change from baseline between EP-104IAR and vehicle in WOMAC function subscale (Week 12)
End point description:	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function subscale (scores scaled 0-10, with 10 being the worst). Function subscale includes questions related to the physical functioning of osteoarthritis e.g. stair use, standing, walking etc. From a mixed model for repeated measures (MMRM) for change from baseline with fixed effects for site, treatment, week, treatment-by-week interaction; random effect for subject; and covariate baseline WOMAC function score.
End point type	Secondary
End point timeframe:	Change from score at baseline to score at week 12 post-dose

End point values	EP-104IAR 25 mg	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163 ^[2]	155		
Units: Score (0-10)				
least squares mean (standard deviation)	-2.59 (± 0.161)	-2.04 (± 0.166)		

Notes:

[2] - Change from score at baseline to score at week 12 post-dose

Statistical analyses

Statistical analysis title	Least squares mean difference in WOMAC function
Statistical analysis description:	Change from score at baseline to score at week 12 post-dose
Comparison groups	EP-104IAR 25 mg v Vehicle Control

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.978
upper limit	-0.113
Variability estimate	Standard error of the mean
Dispersion value	0.22

Secondary: Difference between EP-104IAR in vehicle in the area under the curve of WOMAC pain subscale (Week 12)

End point title	Difference between EP-104IAR in vehicle in the area under the curve of WOMAC pain subscale (Week 12)
End point description:	Area under the curve in change from baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (scores scaled 0-10, with 10 being the worst) from Week 0 to Week 12 was calculated on a per-individual basis using the linear trapezoidal rule. AUC was normalized to account for subjects whose actual days and nominal days at Week 12 differed. Treatments were compared using an ANCOVA model containing site; individual baseline WOMAC Pain; and treatment group as covariates.
End point type	Secondary
End point timeframe:	Area under the curve from Week 0 to Week 12 post-dose

End point values	EP-104IAR 25 mg	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163 ^[3]	155		
Units: Area under the score (0-10)-time curve				
least squares mean (standard error)	-235.67 (± 11.769)	-166.78 (± 12.169)		

Notes:

[3] - One participant was excluded from all analyses because treatment was not administered due to an AE

Statistical analyses

Statistical analysis title	Least squares mean difference in WOMAC pain AUC
Statistical analysis description:	From an ANCOVA model with treatment, site, and baseline WOMAC Pain as covariates.
Comparison groups	EP-104IAR 25 mg v Vehicle Control

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-68.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-100.092
upper limit	-37.689
Variability estimate	Standard error of the mean
Dispersion value	15.853

Secondary: Difference in change from baseline between EP-104IAR and vehicle in WOMAC pain subscale (Week 24)

End point title	Difference in change from baseline between EP-104IAR and vehicle in WOMAC pain subscale (Week 24)
End point description:	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (scores scaled 0-10, with 10 being the worst). Least squares mean from a mixed model for repeated measures (MMRM) for change from baseline with fixed effects for site, treatment, week, treatment-by-week interaction; random effect for subject; and covariate baseline WOMAC pain score.
End point type	Secondary
End point timeframe:	
Change from score at baseline to score at week 24 post-dose	

End point values	EP-104IAR 25 mg	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163 ^[4]	155		
Units: Score (0-10)				
least squares mean (standard error)	-2.26 (± 0.171)	-2.11 (± 0.175)		

Notes:

[4] - One participant was excluded from all analyses because treatment was not administered due to an AE

Statistical analyses

Statistical analysis title	Least squares mean difference in WOMAC pain
Comparison groups	EP-104IAR 25 mg v Vehicle Control

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.518
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.613
upper limit	0.309
Variability estimate	Standard error of the mean
Dispersion value	0.234

Secondary: Difference between EP-104IAR in vehicle in OMERACT-OARSI strict responders (Week 12)

End point title	Difference between EP-104IAR in vehicle in OMERACT-OARSI strict responders (Week 12)
End point description:	Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) strict responders are defined as at least 50% improvement (decrease from baseline) in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain or function subscales (scores scaled 0-10, with 10 being the worst) and an absolute change of at least 2 in the respective score. Patients who discontinued prior to Week 12 were considered non-responders.
End point type	Secondary
End point timeframe:	
Proportion of strict responders at week 12 post-dose	

End point values	EP-104IAR 25 mg	Vehicle Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163 ^[5]	155		
Units: Responders	87	61		

Notes:

[5] - One participant was excluded from all analyses because treatment was not administered due to an AE

Statistical analyses

Statistical analysis title	Difference in proportion of strict responders
Comparison groups	EP-104IAR 25 mg v Vehicle Control
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.028
Method	Fisher exact

Notes:

[6] - From Fisher's exact test comparing the proportion of OMERACT-OARSI responders between treatment and vehicle.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were summarized and analyzed for safety evaluations i.e, events which occurred from the time of the EP-104IAR or vehicle injection procedure until the Week 24/End-of-Study/Early Exit Visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Safety population - Vehicle control arm
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Reporting group description:

The safety population consisted of all randomized subjects who were administered a dose of study drug. The subjects in this group were analysed based on the treatment they received.

Reporting group title	Safety population - EP-104IAR arm
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Reporting group description: -

Serious adverse events	Safety population - Vehicle control arm	Safety population - EP-104IAR arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 155 (0.65%)	4 / 163 (2.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 155 (0.65%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 155 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 155 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Loss of consciousness			
subjects affected / exposed	0 / 155 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Acute vestibular syndrome			
subjects affected / exposed	0 / 155 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety population - Vehicle control arm	Safety population - EP-104IAR arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 155 (43.87%)	76 / 163 (46.63%)	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	10 / 155 (6.45%)	4 / 163 (2.45%)	
occurrences (all)	10	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	23 / 155 (14.84%)	38 / 163 (23.31%)	
occurrences (all)	26	38	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 155 (7.74%)	14 / 163 (8.59%)	
occurrences (all)	15	16	
COVID-19			
subjects affected / exposed	14 / 155 (9.03%)	14 / 163 (8.59%)	
occurrences (all)	14	14	
Influenza			
subjects affected / exposed	9 / 155 (5.81%)	6 / 163 (3.68%)	
occurrences (all)	9	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2019	Following regulatory agency input, the following changes were made: Change to single dose level (25 mg), previously dose escalation up to 50 mg was included. Inclusion criteria revised to require unsatisfactory pain control from, or intolerance of, at least 2 prior standard osteoarthritis (OA) treatments. Exclusion of participants considered by the investigator to be non-responsive to corticosteroids. Increase in sample size from 76 to 95 per arm. Requirement for ultrasound guidance of the injection (previously optional).
28 April 2021	Change of study location from the United States based to Denmark. Added recording of rescue pain medication use. Requirement added for typical knee pain at Screening to be ≥ 4.0 out of 10. Requirement for average daily index knee numeric pain rating scale (NPRS) score in the second week of the Washout and Baseline Period changed from ≥ 5.0 / ≤ 9.0 to ≥ 4.0 / ≤ 10.0 . Requirement for non-index knee pain scores at Screening changed from a single NPRS score ≤ 4 to both weekly Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain scores and the average daily NPRS scores in the second week of Washout and Baseline Period ≤ 4.0 . Exclusion of chondrocalcinosis relaxed to only exclude chondrocalcinosis likely to affect the outcome of this study in the opinion of the investigator. Removal synovial fluid collection for pharmacokinetic (PK) and biomarker analyses. Added precautions in the event of symptoms and signs of COVID-19.
06 July 2021	Changes to align protocol language with that appearing on the electronic Patient Reported Outcomes (ePRO) device, in other study documents, and in typical site procedures. Requirement updated for the injection to be performed by suitably qualified and experienced physician, previously this may have been a suitably qualified and experienced physician's assistant/nurse practitioner.
15 October 2021	Number of sites and countries increased. Removed requirements for average daily index knee NPRS score in the second week of the Washout and Baseline Period ≥ 4.0 and ≤ 10.0 and individual daily index knee NPRS scores to not vary by more than 4 points. Requirement for non-index knee pain scores at screening changed from both weekly WOMAC pain scores and the average daily NPRS scores in the second week of Washout and Baseline Period ≤ 4.0 , to only WOMAC pain scores at the end each week both ≤ 6.0 . Morning serum cortisol no longer required at Screening, instead the adrenocorticotrophic hormone (ACTH) stimulation test was to be performed in all participants during Screening. Criteria added for selection index knee, covering the event both knees were potentially eligible.
10 November 2021	Requirement for weekly WOMAC pain subscale scores for the index knee (end of each week of the Washout and Baseline Period) from both ≥ 5.0 and ≤ 9.0 to both ≥ 4.0 and ≤ 9.0 (and not vary by >3 points).

13 April 2022	Allowed inclusion of well-controlled, non-insulin dependent diabetics (i.e., HbA1c levels $\leq 7.9\%$ (63 mmol/mol). Previously, patients with diabetes mellitus defined as a haemoglobin A1c (HbA1c) value of $\geq 6.5\%$ (47 mmol/mol) were excluded. Allowance for re-starting the Washout and Baseline Period (within the 8-week screening period) if baseline WOMAC pain scores were not completed due to reasons beyond the participant's control eg, technical issues with the ePRO device. Statistical methods revised such that they were to be described in detail in the Statistical Analysis Plan (SAP) which will be finalised prior to unblinding of the study.
17 August 2022	Addition of an optional imaging sub-study extending the maximum duration per participant to approximately 60 weeks with additional magnetic resonance imaging (MRI) site visits.
24 March 2023	Addition of an optional extended PK sub-study to detect the amount of corticosteroid FP in subjects following Week 24/End of study visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported