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

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SIGNATURE PAGE

Declaration of Sponsor

Title: 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

Version / Date: Version 7.0 / 15 Aug 2022

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the International Conference on Harmonisation Guidelines on Good Clinical Practice.

SignNow e-signature ID: 06c4a72f55...
08/16/2022 16:59:10 UTC
Amanda Malone (Signer)

08/16/2022

Sponsor Representative
Amanda Malone, Chief Scientific Officer, Eupraxia Pharmaceuticals Inc.

Date (DD-MMM-YYYY)

[redacted]

INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

I have read the attached protocol entitled 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, Version 7.0, dated 15 Aug 2022, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Conference on Harmonisation Guidelines on Good Clinical Practice and applicable regulations and guidelines.

I agree to ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse (or legal partner) and dependent children)
- My sub-Investigators

before the start of the study and to report any changes that affect my financial disclosure status for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Eupraxia Pharmaceuticals.

Signature by the Investigator on this protocol signature page documents review, agreement and approval of the requirements contained within this protocol.

Signature of Principal Investigator	Date (DD-MMM-YYYY)

Principal Investigator Name & Title

Address

Telephone number

SYNOPSIS

Protocol Number EP-104IAR-201

Title	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
Short Title	OTZI
Study Product(s)	EP-104IAR: fluticasone propionate coated with a polyvinyl alcohol (PVA) membrane. Dose to be evaluated = 25 mg.
Indication	Osteoarthritis of the knee
Phase	2
Sponsor	Eupraxia Pharmaceuticals Inc. (Eupraxia)
Objectives	Primary Objective: • 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. Secondary Objectives: • To evaluate the safety of a single IA injection of EP-104IAR in patients with OA of the knee for up to 24 weeks (or 52 weeks for imaging sub-study only). • To evaluate the pharmacokinetics (PK) of a single IA injection of EP-104IAR for up to 24 weeks.
Design	A randomized, double-blind, vehicle-controlled parallel-group study. Qualified subjects will be administered a single IA dose of 25 mg EP-104IAR or vehicle and will be followed up for up to 24 weeks. The study involves 10 site visits. The maximum duration of participation per subject ≈32 weeks (up to 6 weeks Screening, 2 weeks Washout and Baseline and 24 weeks Follow-up). Participation in the optional imaging sub-study extends the maximum duration per subject to ≈60 weeks with additional magnetic resonance imaging (MRI) site visits. **Data Collection** The primary means of data collection will be via an electronic patient-reported outcome (ePRO) device. Subjects will be provided with a hand-held device programmed to prompt the subject to record data as required throughout the study as follows: **Daily:** • 11-point Numeric Pain Rating Scale (NPRS, 0-10 scale where 0 = no pain and 10 = worst pain imaginable), measured each **evening**, e.g., "How was your pain level in your (right/left) knee over the past 24 hours?". • Question on rescue medication use (24-hour recall), e.g., "Did you use any of the provided rescue medication over the past 24 hours?" (Yes/No). • If yes, question on whether rescue medication was used to treat pain in the Index knee, e.g., "Did you use the provided rescue medication to treat pain in your affected knee?" • Question on use of other pain medications, e.g., "Did you use any other pain medications over the past 24 hours for any reason?" (Yes/No).

	• Question on other non-drug rescue use, e.g., "Did you use any Physiotherapy or heat/cold compresses over the past 24 hours?" (Yes/No). • Question on activity level in prior 24 hours, e.g., "How would you describe your level of physical activity today?" (Low/Moderate/High). **Weekly:** • Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®) Pain Subscale (0-10 Numerical Rating Scale (NRS), 24-hour recall), preferably measured in the **morning**. • Subjects will be asked to refrain from using rescue medication in the 12 hours prior to completing the WOMAC questionnaire whenever possible. The ePRO device will provide a reminder and will ask if the subject complied, e.g., "Did you use any rescue medication in the last 12 hours?" (Yes/No). The questionnaire will be completed regardless of the subject's response. **Monthly (Every 4 Weeks):** • WOMAC Index (Pain, Physical Function and Stiffness subscales, 0-10 NRS, 24-hour recall) preferably measured in the **morning**. • Subjects will be asked to refrain from using rescue medication in the 12 hours prior to completing the WOMAC questionnaire whenever possible. The ePRO device will provide a reminder and will ask if the subject complied, e.g., "Did you use any rescue medication in the last 12 hours?" (Yes/No). The questionnaire will be completed regardless of the subject's response. During Washout and Baseline, daily NPRS and weekly WOMAC Pain questions will be asked separately for each knee. From Visit 2 onwards, pain questions will only be asked for the Index knee. ***Imaging Sub-study*:** Subjects will be invited to participate in an optional imaging sub-study, which will be performed in parallel to the main study data collection. MRI of the index knee will be obtained as part of this sub-study. These MRI analyses will include assessments of synovial inflammation (synovial thickness, synovial blood flow), cartilage volume, and articular cartilage status (cartilage morphology). Prior to each MRI, a macrocyclic gadolinium-based contrast agent will be administered intravenously to subjects. The main study will be unblinded and analyzed following the final subject's completion of the Week 24 assessments. The imaging sub-study will continue until the last participant completes the Week 52 (or early exit) assessment. All MRI central readers will be blinded to treatment allocation and study visit for the entirety of the imaging sub-study. Those subjects participating in the imaging study from Week 24-52 will be treated by standard of care from their physician if treatment is necessary.
Treatments	• EP-104IAR 25 mg • Vehicle control Details on randomization are provided in Section 6.1.
Inclusion Criteria	1. Males or females, aged ≥40 years. 2. Body mass index (BMI) ≤40.0 kg/m^2.

	3. Diagnosis of primary OA of the Index knee (as per American College of Rheumatology clinical and radiological criteria) with OA symptoms (as reported by the subject) that have been present for at least 6 months prior to Screening. 4. Index knee OA severity Grade 2 or 3 (based on Kellgren-Lawrence Grading Scale). • X-rays will be reviewed by a central reader. If a suitable x-ray performed within 6 months of the Screening Visit cannot be provided, an x-ray must be performed as part of the Screening assessments. 5. Subject has experienced unsatisfactory pain control from at least 2 prior standard OA treatments, or has used such medications before but chose to discontinue them due to intolerance or personal preference. • Standard pharmacological OA treatments include (but are not limited to): Topical or oral NSAIDs, topical capsaicin, IA corticosteroids, IA hyaluronic acid, acetaminophen / paracetamol, Duloxetine, tricyclic antidepressants for treatment of pain, tramadol and other opioids. • Subjects considered by the Investigator to be non-responsive to treatment with corticosteroids are not eligible. 6. At Screening Visit 1a, subject reports that their typical OA knee pain in one or both knees when not using medication is ≥ 4 out of 10. 7. The weekly WOMAC Pain subscale scores for the Index knee (collected at the end of each week of the Washout and Baseline Period) are both ≥4.0 and ≤9.0 out of 10 and must not differ (vary) by more than 3 points. 8. Demonstrated ability to comply with pain recording requirements during the Washout and Baseline Period (i.e., Subject must record daily NPRS scores (of any value) on at least 5 days in each week for both knees and both weekly WOMAC scores in both knees). 9. The weekly WOMAC Pain subscale scores for the non-Index knee (collected at the end of each week of the Washout and Baseline Period) are both ≤6.0. 10. Patient is ambulatory (without the need for a cane/other walking aide). 11. For females of child-bearing potential, willing to use a highly effective method of birth control between Baseline and End-of-Study Visits. 12. Willing and able to provide informed consent and comply with all study procedures and restrictions and the required visit schedule, etc.
Exclusion Criteria	1. OA of the Index knee due to acute injury or trauma that occurred within 12 months prior to Screening, or unstable joint (such as a torn anterior cruciate ligament) within 12 months of Screening. 2. X-ray evidence of chondrocalcinosis likely to affect the outcome of this study in the opinion of the investigator. 3. Diagnosed or suspected ipsilateral hip OA. 4. Knee pain that is not clinically attributable to OA of the knee (e.g., radicular low back pain or hip pain that is referred to the knee that could cause misclassification).

	5. Any other disorders that, in the Investigator's opinion, impact mobility, strength or sensation, or are a co-existent source of pain or inflammation that interferes with the subject's ability to assess their knee OA pain and function (e.g., fibromyalgia, painful diabetic neuropathy, low back pain, rheumatic disorders such as rheumatoid arthritis, other autoimmune diseases, ankylosing spondylitis, reactive arthritis (aka Reiter's syndrome), psoriatic arthritis, gout, etc.). 6. Presence of other symptoms or conditions in the Index knee that would confound evaluation of pain and other functional assessments of knee OA (e.g., a symptomatic popliteal cyst (Baker's cyst)). 7. History of infection in the Index knee within 9 months prior to Screening, or clinical signs and symptoms of an active infection in the Index knee at Screening or Baseline Visits. 8. Total/Partial Knee Replacement for the Index knee, or any other surgery (including arthroscopy) for the Index knee within 12 months prior to Screening, or planned surgery during the study. 9. Total/Partial Knee Replacement Surgery of the non-Index knee within 6 months prior to Screening, or planned surgery (in any location) during the study that would require use of a restricted medication during the study. 10. IA injection of corticosteroids in any joint within 3 months prior to Screening, or IA injection of extended-release corticosteroids in any joint within 6 months prior to Screening. 11. IA injection in the Index knee of platelet rich plasma or other prolotherapy (e.g., dextrose) within 3 months prior to Screening, or hyaluronic acid within 6 months prior to Screening. 12. Oral, intravenous (IV) or intramuscular corticosteroids for any indication within 30 days prior to Baseline; or planned used during the study. 13. Inhaled or intranasal corticosteroids, or expected need for these, for any indication from the start of the Washout and Baseline Period until at least 4 Weeks post-dose. 14. Any topical corticosteroids applied to the Index knee, or expected need for these, from the start of the Washout and Baseline Period until 24 Weeks post-dose, or planned use of restricted topical corticosteroids (on any location) during the study (restricted medications are listed in Section 8.1.2). Intravitreal corticosteroids are permitted with no restrictions. 15. Use of any long-acting opioids within 30 days prior to Screening, or use of any opioids (including tramadol and tapentadol) more than twice per week within 30 days prior to Screening and from which the subject is unwilling or unable to washout. 16. Presence or history of substance abuse, including but not limited to, opioids and marijuana. Current use of marijuana for any reason is also exclusionary. 17. Positive urine drug test at Screening or Baseline Visits that is not explained by the use of prescription medications permitted during the study. A positive urine drug test without a valid prescription that accounts for the result is automatically exclusionary and cannot be repeated. 18. Presence of alcohol abuse or dependence or drinking more than 21 units of alcohol per week (i.e., 3 drinks per day): 1 unit = 150 mL of wine, 360 mL of beer or 45 mL of 40% alcohol; or history of alcohol abuse judged by the Investigator as likely to recur during the study.

19. Current use of systemic immunosuppressive therapy; or use within 6 months prior to Screening.
20. Unwilling or unable to washout of any prohibited medications and not use them for the duration of the study (Washout and Baseline Period to End-of-Study Visit). Prohibited medications are listed in Protocol Section 8.1.
21. Use of another investigational drug or device within the 30 days prior to Screening, or an investigational biologic within the 60 days prior to Screening, or current/planned participation in another interventional trial during this study.
22. A history of sarcoidosis or amyloidosis.
23. A history of osteomyelitis.
24. A history of or active Cushing's syndrome.
25. Currently has or is receiving treatment for the following conditions: psychotic disorder, bipolar disorder, symptomatic depressive or anxiety disorders. Mild or well-controlled psychiatric disorders (e.g., mild depression) are permitted if the medication used is not prohibited by the protocol.(see Section 8.1).
26. At Screening, a baseline serum cortisol value ≤138 nmol/L (≤5 µg/dL) from the adrenocorticotropic hormone (ACTH) stimulation test, or an abnormal ACTH stimulation test result.
27. Currently has diagnosed insulin dependent diabetes mellitus or poorly controlled non-insulin dependent diabetes mellitus (defined as a Hemoglobin A1c (HbA1c) value of ≥8.0% (64 mmol/mol) at Screening.
    - Pre-diabetics (i.e., HbA1c levels between 5.7-6.4% (39-46 mmol/mol) at Screening) and well-controlled, non-insulin dependent diabetics (i.e., HbA1c levels ≤7.9% (63 mmol/mol)) at Screening) are permitted.
28. Diagnosed hepatic or renal disease, or the following laboratory values at Screening: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 x upper limit of normal (ULN); bilirubin >2 x ULN (unless isolated Gilbert's syndrome); serum creatinine >1.5 x ULN.
29. Current malignancy of any type, or history of a malignancy within 12 months prior to Screening (other than resected basal cell carcinoma, squamous skin cell carcinoma, or resected cervical atypia or carcinoma in situ).
30. Any infection requiring IV antibiotics within 4 weeks of the Baseline Visit, or oral antibiotics within 2 weeks of the Baseline Visit.
31. Known active or quiescent systemic fungal, bacterial (including tuberculosis) viral or parasitic infections, or ocular herpes simplex.
32. Known or clinically suspected infection with human immunodeficiency virus, hepatitis B or C viruses.
33. Skin breakdown on the Index knee where the injection will take place.
34. Females who are pregnant, lactating, or who have a positive pregnancy test result at Screening or Baseline Visits.
35. Known or suspected hypersensitivity or contraindication to any of the ingredients in the investigational medicinal product, including carboxymethyl cellulose and polysorbate 80, to fluticasone propionate or any other corticosteroids (for example cortisol-related endocrinopathy), or to lidocaine (if used during IA injection procedure).

	36. Known or pending disability or workers' compensation claims. 37. Previous randomization and treatment in this study. 38. Any other reason that, in the opinion of the Investigator, is likely to unfavorably alter subject risk-benefit, confound safety or efficacy results, or make it difficult for the subject to fully comply with study requirements. ***Imaging Sub-Study*** **Additional exclusion criteria for the optional Imaging Sub-Study** Subjects who are willing to participate in the imaging sub-study are also subject to the following exclusion criteria. If a subject meets any of these criteria it only invalidates their participation in the imaging sub-study: 39. Unwilling and/or unable to provide informed consent and comply with all imaging sub-study procedures and restrictions and the required visit schedule 40. Known allergy or a prior adverse reaction to gadolinium or to any of the excipients contained in the MRI contrast agent 41. History of severe allergy, drug reactions, or other hypersensitivity-like disorders and bronchial asthma 42. Any metal objects e.g., shrapnel, and any surgical clips, pacemakers, pins, plates, screws, metal sutures or wire mesh also including uterine coil, intra-ocular metal foreign bodies, new contact lens that allows for an automated recording of continuous intraocular pressures, the LINX reflux management system insulin pump, temporary external transvenous pacing leads, if considered contraindication for MRI scanning 43. Severe claustrophobia 44. Cochlear implants 45. Known renal conditions, for which contrast agents for MRI could add to risks, or moderate to severe renal dysfunction (defined as an estimated Glomerular Filtration Rate [eGFR] ≤ 40 mL/min/1.73m^2 by laboratory testing and the chronic kidney disease epidemiology collaboration [CKD-EPI] equation) 46. Females who are pregnant, lactating, or who have a positive pregnancy test result prior to any planned MRI procedure.
Primary and Secondary Endpoints	**Primary Efficacy Endpoint:** • Difference in change from baseline (CFB) between EP-104IAR and vehicle in WOMAC Pain at Week 12, in the intention-to-treat (ITT) population **Key Secondary Endpoints** • Difference in CFB between EP-104IAR and vehicle in WOMAC Function at Week 12 • Difference between EP-104IAR and vehicle in the area under the curve of WOMAC Pain at Week 12 • Difference in CFB between EP-104IAR and vehicle in WOMAC Pain at Week 24 • Difference between EP-104IAR and vehicle in OMERACT-OARSI strict responders at Week 12 (OMERACT-OARSI=Outcome Measures in Rheumatology-Osteoarthritis Research Society International)

	Additional secondary and exploratory safety, PK and imaging endpoints are discussed in detail in Section 11.
Procedures	See Schedule of Events for details of protocol required procedures and applicable visits (and timings). **Informed Consent** Informed consent will be obtained prior to performing any study related procedures or assessments. Site staff will be trained in methods of approaching and speaking to potential study subjects in a manner that conveys a neutral expectation of treatment effectiveness. ***Imaging Sub-Study*** All subjects will be asked if they would like to participate in the optional imaging sub-study. If they are agreeable, after a separate imaging consent process is performed, the subject will then sign an additional ICF specific to the imaging sub-study. **General Screening – Visit 1a and Visit 1b** Following provision of informed consent, the following eligibility assessments will be performed (assessments may be performed on different days): • Demographics, height, weight, BMI • OA history (to be confirmed by review of medical records if possible) • Medical and surgical history • Prior and concomitant medication (conmed) use, including the subject's reported response to prior OA treatments • In-clinic patient-reported score of typical OA knee pain when not using medication (in each knee) • Vital signs, physical examination including knee exam (both knees) • Blood samples for safety laboratory analysis (hematology, clinical chemistry, HbA1c and pregnancy testing) • ACTH stimulation test. This test can be performed at any time during Screening (including at Visit 1b). • Urine samples for safety and drugs of abuse testing • X-rays will be reviewed centrally to evaluate OA severity for eligibility purposes. - If a suitable x-ray from within the past 6 months is not available in the subject's medical records, a new one will be performed. - If both knees are potentially eligible at Screening, an x-ray of both knees should be performed to help identify the Index knee. • Potential subjects will also receive training and information about clinical trials, placebo/vehicle control and the importance of accurately reporting their pain and symptoms. The goal of this training is to minimise the placebo response. **Initiate Washout & Baseline Period - Visit 1b** Potentially eligible subjects will be instructed how to initiate the Washout and Baseline Period.

Subjects will be trained in the use of the ePRO device. Subjects will be provided with a bottle of rescue medication (acetaminophen/paracetamol) to be used (if needed) during the study and the rules around use and recording of rescue medication explained.

Washout and Baseline Period

Subjects will complete a 2-week period, in which their baseline (and qualifying) pain will be determined. Subjects taking disallowed pain medications will be required to washout during this period. Subjects will record their daily and weekly measurements using the ePRO device provided at the start of this period.

The daily and weekly measurements collected during this period will be used to determine eligibility (and if applicable, help identify the Index knee).

Baseline and Dosing – Visit 2 (Day 1)

Pre-Dose Activities

Subjects will return to the site once the Washout and Baseline Period is complete. Following review of the data on the ePRO device and confirmation of eligibility, qualified subjects will be randomized to receive a single injection of EP-104IAR or vehicle control in their Index knee.

If both knees are potentially eligible the Index knee will be selected based on the criteria in Section 9.1.3.2.

Baseline safety, PK and efficacy assessments will be performed prior to dosing, including the full WOMAC Index (for the Index knee), Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis and the Short Form 36 health survey.

Imaging Sub-Study

Subjects in the imaging sub-study will have a baseline MRI performed.

Once the Index knee is selected, subjects in the imaging study will receive a baseline MRI. The baseline MRI will be performed prior to all other pre-dose safety, PK and efficacy assessments. If the MRI is performed on a separate day to the other assessments, it should be scheduled to occur within 5 days of dosing. For women of childbearing potential, a urine pregnancy test must be performed prior to performing the MRI. The pregnancy test does not need to be repeated prior to dosing

Dosing Procedure

As EP-104IAR is visibly different from the vehicle control, an unblinded individual will administer the injection. Subjects will be blinded to treatment by shielding their view of the filled syringe and the injection field during the procedure. All other assessments will be performed by blinded site staff.

Unblinded site staff will prepare and administer the injection according to the instructions provided in the Investigational Medicinal Product Handling Manual. The injection procedure will be performed by a suitably qualified and experienced physician unless other suitably qualified and experienced personnel are permitted by local legislation (i.e., only applicable in Denmark). Lidocaine (also known as lignocaine) may be administered prior to the injection to make the procedure more comfortable for subjects. If used, lidocaine may be injected into subcutaneous tissues along the needle pathway but may not be injected into the suprapatella bursal space.

Prior to dose administration, the unblinded injector will aspirate the subject's knee. The volume of effusion (if any) will be recorded in the electronic case report form (eCRF).

The injection will be administered using ultrasound guidance. The needle will be inserted via the medial or lateral route with the subject's knee in an extended (non-flexed) position.

Post-dose Activities

Prior to discharge, safety and PK assessments will be performed and the subject will be reminded of the use of the ePRO device.

Follow-Up – Visits 3 – 9 (24 Weeks)

Subjects will attend up to 7 visits during the Follow-up Period. Visits should occur in the morning whenever possible (to ensure serum cortisol assessments occur at approximately the same time of day - between 7-11 a.m.) and ideally the same day of the week. The same blinded assessor should complete assessments at all visits whenever possible. Between visits, subjects will continue recording assessments at home using the ePRO device provided. If the subject requires additional rescue medication between scheduled visits, they may call the site to arrange to collect additional rescue medication.

If at any time during the study a subject independently reports symptoms of (or the scheduled knee examinations reveal findings that indicate) a potential infection in the Index knee (e.g., red and swollen with a moderate or large effusion, or hot and swollen with a moderate or large effusion), a blood sample will be collected for hematology testing and the subject should be referred for further specialist assessment as soon as possible.

Visit 3 (Day 3)

Subjects will attend the site approximately 48 hours following dosing for safety and PK assessments.

Visit 4 (Week 2)

Subjects will attend the site 2 weeks post-dose for safety and PK assessments.

Visits 5 – 8 (Weeks 4, 8, 12 and 18)

Subjects will attend the site for safety, PK and efficacy assessments.

Imaging Sub-Study

Subjects participating in the imaging sub-study will also undergo an MRI procedure on or immediately following Visit 7 (Week 12). All safety, PK and efficacy assessments will be performed prior to performing the MRI.

Visit 9 – Week 24 (End-of-Study or Early Exit Visit)

Subjects will attend the site for final safety, PK and efficacy assessments and will return any unused rescue medication, and their ePRO device.

Imaging Sub-Study

Subjects participating in the imaging sub-study will undergo an MRI procedure on or immediately following Visit 9 or the early exit visit. All safety, PK and efficacy assessments will be performed prior to undergoing MRI.

If a subject participating in the imaging sub-study exits the main study early, an early exit visit will be performed, and an early exit MRI acquired on or immediately following the visit. If the MRI is within 2 months of the previous MRI scan, then an MRI does not need to be performed, except in the case that the previous MRI was performed prior to dosing and the early exit MRI will be the only MRI collected post treatment administration. The early exit MRI will be conducted in this instance.

	Visit 10 – Week 52 (for *Imaging Sub-Study Only*) Only subjects participating in the optional imaging sub-study will perform Visit 10. After Visit 9, no efficacy assessments, PK, or safety assessments apart from AE recording will be performed. Subjects will not be required to refrain from any medications/procedures after Visit 9. The subject will be treated as per standard of care by their physician during this time. At Visit 10 AEs and concomitant medications/procedures will be collected for the timeframe between Visit 9 and 10 to capture any changes in the subject's health status. Eligibility to conduct imaging will be reviewed based on MRI-sub-study exclusion criteria. If the subject remains eligible to undergo the final MRI based on these criteria and has a negative result on a urine pregnancy test (for females of childbearing potential) they may proceed to have the final MRI scan.
Sample Size	A sample size of approximately 240 completed subjects (120 per arm) is estimated to provide approximately 80% power (at a 2-sided, 5% significance level) to detect a 0.8-point difference in WOMAC Pain subscale score (on a 0-10 scale) between EP-104IAR and vehicle (assuming a standard deviation of 2.2). Assuming a 20% drop-out rate over the course of the study, approximately 300 subjects will be randomized and dosed. ***Imaging Sub-Study*** As this is an exploratory data collection, no power calculations have been considered.
Statistical Methods	**Efficacy Analyses** The primary efficacy endpoint is the difference in change from baseline between EP-104IAR and vehicle in WOMAC Pain at Week 12. The primary analysis will be performed in the ITT population. Change from individual pre-dose baseline WOMAC Pain will be fit to a mixed-effects for repeated measures model using all available data from the ITT population. This model will contain fixed effects terms for site; individual baseline WOMAC Pain; and the treatment-by-week interaction, where treatment and week are both treated as categorical variables; and a random per-patient intercept. An unstructured residual covariance matrix at the patient level will initially be fit; if this model fails to numerically converge, a compound symmetry structure will be used. No missing data imputation will be included in this model. Inferential results will be produced for the difference between EP-104IAR and vehicle at Week 12. Key secondary endpoints will be analyzed using analogous methods. A step-down hierarchical testing procedure will be used, at the 5% level, where each endpoint may only be formally assessed inferentially if all prior endpoints were statistically significant at the 5% level. Additional secondary and exploratory analyses, and covariate analyses, will also be conducted where appropriate (see Section 11.7.3). **Safety and Pharmacodynamic Analyses** • Safety data (safety labs, cortisol, physical exams, knee exams, vital signs, etc.) will be summarized by treatment using standard summary statistics for both raw data and change from baseline. • Treatment-emergent adverse events (TEAEs) will be summarized by treatment.

	• Impact on hypothalamic-pituitary-adrenal axis (ACTH stimulation test results) will be summarized by treatment using standard summary statistics. **Pharmacokinetic Analyses** • Plasma FP concentrations over time will be summarized/displayed graphically. Non-compartmental analysis will provide key PK parameters. • Residual EP-104IAR in used injection kits will be used to calculate actual doses received to allow dose-proportionality PK analyses. ***Imaging Sub-Study* Analyses** • Imaging analyses will include dynamic contrast enhanced (DCE)-MRI measurements related to synovial inflammation (synovial thickness, synovial blood flow, cartilage volume, and the status of the articular cartilage (cartilage morphology) assessments.

SCHEDULE OF EVENTS

Visit	1a Screening (Multiple days)	Visit 1b Initiate Washout /Baseline	Washout & Baseline Period	2 Baseline & Dosing	3	4	5	6	7	8	9 End-of-Study (or Early Exit Visit)
Study Week	**-8 to -3**	**-3 to -2**	**-2 & -1**	**1**	**1**	**2**	**4**	**8**	**12**	**18**	**24**
Study Day	-56 to -15	-15	-14 to -1	1	3	15	29	57	85	127	169
Visit Window		-2 days	-2 days		±1 day	±3 days	±3 days	±3 days	±3 days	±3 days	±7 days
Informed consent[1]	X										
Demographics	X										
Medical history incl. OA history	X										
Conmeds & procedures (& any changes)	X	X		X[2]		X	X	X	X	X	X
Height	X										
Weight	X			X[2]					X		X
Vital signs	X			X[3]		X	X	X	X	X	X
Physical examination	X			X[2]					X		X
Knee examination[4]	X			X[2]		X	X	X	X	X	X
In-clinic patient reported score of typical OA pain	X										
X-ray imaging – (if required)[5]	X										
Review inclusion/exclusion criteria	X	X		X[2]							
Selection of Index knee				X[2]							
Issue ePRO device & train Subject		X									
Check/collect device/re-train if required				X[2]		X	X	X	X	X	X
Initiate Washout and Baseline Period		X									
Issue/collect unused rescue medication		X		X		X	X	X	X	X	X
Drug accountability – rescue medication				X		X	X	X	X	X	X
Randomization				X[2]							

Visit	1a Screening (Multiple days)	Visit 1b Initiate Washout /Baseline	Washout & Baseline Period	2 Baseline & Dosing	3	4	5	6	7	8	9 End-of-Study (or Early Exit Visit)
Study Week	**-8 to -3**	**-3 to -2**	**-2 & -1**	**1**	**1**	**2**	**4**	**8**	**12**	**18**	**24**
Study Day	-56 to -15	-15	-14 to -1	1	3	15	29	57	85	127	169
Visit Window		-2 days	-2 days		±1 day	±3 days	±3 days	±3 days	±3 days	±3 days	±7 days
Administer investigational product[6]				X							
Record and assess AEs	X	X		X	X	X	X	X	X	X	X
Subject completes ePRO device[7]			Daily: NPRS, rescue use, physical activity levels, Weekly: WOMAC Pain subscale and pre-completion query on compliance with 12-hour rescue medication restriction								
Subject completes WOMAC Full Index using ePRO device (either at home or in clinic)[8]				X[2]			Monthly (every 4 weeks): WOMAC Full Index and pre-completion query on compliance with 12-hour rescue medication restriction				
SF-36 questionnaire[9]				X[2]					X		X
PtGA[9]				X[2]			X	X	X	X	X
MDGA[10]				X[2]			X	X	X	X	X
Urine sample for drugs of abuse test	X			X[2]					X		X
Urine sample for safety	X			X[2]			X		X		X
Blood/urine sample for pregnancy test[11]	X			X[2]							X
Blood sample for safety (hem, chem)	X[12]			X[2]	X	X	X		X		X[12]
Blood sample for cortisol[13]				X[2]	X	X	X	X	X	X	X
Blood sample for PK				X[15]	X	X	X	X	X	X	X
ACTH stimulation test	X[15]								X[16]		X[17,18]
Question on treatment received/administered											X

1 Must be obtained before performing any study related procedures.
2 Prior to dosing.
3 Prior to and one hour after dosing. (For the 1 hour post-dose assessment a -15 / +30-minute window is permitted.)
4 Both knees will be examined at Screening. Only the Index knee will be examined on all subsequent occasions.
5 A suitable x-ray must have been performed within 6 months prior to Screening. If not, refer patient for x-ray. If both knees are potentially eligible at Screening, an x-ray of both knees should be performed to help identify the Index knee. Kellgren-Lawrence evaluation of x-rays will be performed by a central reader.

6 IA injection must be performed using ultrasound guidance and by an unblinded suitably qualified and experienced individual after the patient has met all eligibility criteria and been randomized.
7 The ePRO device will be used to collect: Daily –NPRS, rescue use (acetaminophen/paracetamol and non-pharmacological), activity levels (at home); Weekly –WOMAC Pain (at home or while in clinic); Monthly (every 4 weeks)–WOMAC Full Index (either at home, or while in clinic). During the Washout & Baseline Period scores will be collected in both knees to ensure the Index knee is accurately identified. Once the Index knee has been selected (Visit 2 onwards) scores will only be collected in the Index knee.
8 At Visit 2 (pre-dose) the subject will complete the WOMAC Full Index while at the clinic using their ePRO device. After this visit, if WOMAC assessments occur on the same day as a scheduled visit, the subject will be advised to complete these assessments before arriving at the clinic. If that is not possible, then the subject should complete the WOMAC assessment on their device while at the clinic PRIOR to any other assessments that are performed at the site.
9 SF-36 and PtGA should be completed before other assessments performed at the site.
10 The same blinded physician should perform the MDGA at each study visit, whenever possible.
11 A serum pregnancy test will be performed on all women of childbearing potential at Screening. The sample collected for clinical chemistry analysis may be used for this purpose. A urine pregnancy test will be performed on all women of childbearing potential at Visit 2 and the End-of-Study (or Early Exit) visit. If the subject is participating in the optional imaging sub-study, the Visit 2 urine pregnancy test will be performed prior to performing the MRI. It does not need to be repeated prior to dosing.
12 HbA1c will be measured at Screening and End-of-Study (or Early Exit) visits.
13 To be collected at approximately the same time each visit, between 7-11 a.m. The clinical chemistry sample can be used for cortisol analysis, if being collected at the same visit.
14 Prior to and 2 hours after dosing. (For the 2 hour post-dose assessment a -15/+15-minute window is permitted.)
15 The ACTH stimulation test may be performed at any time of day and on any day during Screening, including at Visit 1b.
16 If the morning serum cortisol test result at Visit 6 (Week 8) is <350 nmol/L (<12.7 µg/dL) an ACTH stimulation test is to be performed at Visit 7 (Week 12). The site will be notified of this requirement in advance of the subject attending this visit.
17 For subjects whose ACTH stimulation test was abnormal at Visit 7, the test will be repeated at the End-of-Study (or Early Exit) Visit (the site will be notified of this requirement in advance of the subject attending this visit).
18 For those subjects not undergoing the ACTH stimulation test at Visit 9 (Week 24/Early Exit) if the result of the morning serum cortisol test at this visit is <350 nmol/L (<12.7 µg/dL), the site will be informed that an unscheduled visit is required to perform an ACTH stimulation test.

Notes: ACTH=Adrenocorticotropic hormone; AEs=Adverse events; Chem=Blood chemistry panel; Conmed=Concomitant medication; ePRO=Electronic patient-reported outcome; Hem=Blood hematology panel; MDGA=Physician's Global Assessment of Arthritis; MRI=Magnetic resonance imaging; NPRS=Numerical pain rating scale; OA=Osteoarthritis; PK=Pharmacokinetic; PtGA=Patient's Global Assessment of Arthritis; SF-36=Short Form 36 questionnaire; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

IMAGING SUB-STUDY ADDITIONAL SCHEDULE OF EVENTS

Visit	1a Screening (Multiple days)	2 Baseline & Dosing	7	9 End-of-Study (or Early Exit Visit)	10 Imaging Follow-up
Study Week	**-8 to -3**	**1**	**12**	**24**	**52**
Study Day	-56 to -15	1	85	169	365
MRI Specific Visit Window		Baseline MRI on a separate day. Within 5 days before IMP administration.	+14 days	+14 days	±14 days
Informed consent for Imaging Sub-Study[1]	X				
Medical history incl. OA history					X
Conmeds & procedures (& any changes)					X
MRI[2]		X	X	X	X
Review exclusion criteria for Imaging sub-study		X[3]	X[3]	X[3]	X[3]
Record and assess AEs					X
Urine sample for pregnancy test[4]		X	X	X	X

1 Must be obtained before performing any imaging related procedures.
2 MRI following the IV injection of a macrocyclic gadolinium-based contrast agent, as described in the MRI Imaging Charter. At visits after IMP injection, MRI must be completed after visit efficacy, safety, and PK procedures are performed. MRI may occur on the same day as these other assessments if the MRI scan is acquired as the final procedure.
3 Must be completed prior to imaging
4 A urine pregnancy test will be performed on all women of childbearing potential prior to imaging. For Visit 2, the pregnancy test does not need to be repeated prior to IMP administration.
Notes: AEs=Adverse events; IMP=Investigational medicinal product; IV=Intravenous; MRI=Magnetic resonance imaging; OA=Osteoarthritis.

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ACTH	Adrenocorticotropic hormone
ADR	Adverse drug reaction
AE	Adverse event
AI	Adrenal insufficiency
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
CFB	Change from baseline
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum concentration
Conmed	Concomitant medication
CRA	Clinical research associate (also referred to as a monitor/site monitor)
CRO	Contract Research Organization
Css	Average concentration at steady state
DCE-MRI	Dynamic Contrast Enhanced MRI
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated Glomerular Filtration Rate
ePRO	Electronic patient-reported outcome
EP-104IAR	Long-Acting Fluticasone Propionate for Intra-Articular Injection
FAS	Full analysis set
FP	Fluticasone propionate
GBCA	Gadolinium Based Contrast Agent
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HbA1c	Hemoglobin A1c
HPA	Hypothalamic pituitary adrenal axis
IA	Intra-articular
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product (also referred to as study-drug)
IP	Intraperitoneal
IRB	Institutional Review Board
IRT	Interactive response technology

ITT	Intention-to-treat
IV	Intravenous
MDGA	Physician's Global Assessment of Arthritis
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model for repeated measures
MRI	Magnetic resonance imaging
NIMP	Non-investigational medicinal product
NOAEL	No observed adverse effect level
NPRS	Numeric Pain Rating Scale
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OMERACT-OARSI	Outcome Measures in Rheumatology-Osteoarthritis Research Society International
PK	Pharmacokinetic(s)
PPS	Per-protocol analysis set
PtGA	Patient's Global Assessment of Arthritis
PtPain	Patient pain scores (11-point numerical rating scale)
PVA	Polyvinyl alcohol
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-36	Short Form 36 Health Survey
SRC	Safety Review Committee
SRM	Safety Review Meeting
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCA	Triamcinolone acetonide
TEAE	Treatment-emergent adverse event
TK	Toxicokinetic
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO-Drug	World Health Organization drug dictionary
WMA	World Medical Association
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

1. INTRODUCTION AND BACKGROUND

The investigational product EP-104IAR is a long-acting formulation of fluticasone propionate (FP) for intra-articular (IA) injection being developed by Eupraxia Pharmaceuticals Inc. (Eupraxia, the Sponsor) for the treatment of pain associated with osteoarthritis (OA) of the knee.

FP is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. Relative to other corticosteroids, FP has a high affinity for the glucocorticoid receptor, low solubility, a low rate of dissociation, and a comparatively long half-life (Johnson, 1998). These characteristics make FP an excellent candidate for prolonged anti-inflammatory effects. FP has a well-established systemic safety record in humans given its several decades of global market presence in the form of widely used inhaled and intranasal brands such as Flovent®, Flonase® and Advair®, as well as a topical agent under other brand names. In humans, FP has shown to be locally active with virtually no oral bioavailability (systemic exposure), and what little is absorbed, is rapidly metabolized (Harding, 1990).

EP-104IAR contains FP crystals that are coated with polyvinyl alcohol (PVA), and heat-treated to form particles that release FP slowly over several months. PVA is used extensively in the medical industry and has a 30-year safety record of use in various human tissues (Baker, et al., 2012). It has numerous biomedical applications and has been safely used as an implantable orthopedic medical device for meniscus/cartilage tissue replacement (Kobayashi, et al., 2003); (Kobayashi, et al., 2005); (Noguchi, et al., 1991); (Oka, et al., 2000); (Falez & Sciarretta, 2005).

The technology used for manufacturing EP-104IAR differs substantially from traditional coacervation technology. In microspheres produced by coacervation technologies, the drug is dispersed in the volume of biodegradable polymer. Such drug delivery systems rely on degradation of the polymer to release the drug from drug/polymer microspheres and consequently have a high polymer to drug ratio. In contrast, EP-104IAR relies on the diffusion of low solubility FP across a very thin (4 µm) crosslinked PVA membrane comprising approximately 6% of the drug product. The combination of a highly potent and low solubility corticosteroid with low levels of crosslinked polymer is expected to translate into prolonged and stable drug delivery, with substantially less polymer injected into the knee.

EP-104IAR has shown a favorable profile in non-clinical studies, suggesting it will be a safe and effective locally administered therapeutic in OA. The safety, pharmacokinetics (PK) and preliminary efficacy of EP-104IAR have also been studied in a Phase 1 randomized, double-blind, vehicle-controlled clinical study in 32 subjects with knee OA. A single IA injection of EP-104IAR 15 mg was found to be safe and well-tolerated. Although this small study was not powered to evaluate efficacy, pain relief onset was rapid and numerical separation from placebo was maintained for up to 12 weeks post-dose (as measured via patient pain scores (PtPain, 11-point numerical rating scale) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)) (Clinical Study Report EP-104IAR-101).

1.1 Background of the Disease and Treatment Options

Osteoarthritis is a progressive disease of synovial joints that most commonly occurs in the knees, hips, spine, fingers and toes, with the knee being the most commonly affected joint. In normal joints, cartilage acts as a cushion between bones and provides a smooth, gliding surface for movement. In joints with OA, the cartilage breaks down, causing pain, swelling and problems with movement. Inflammatory processes further damage the cartilage and over time cartilage wears away causing bone to rub directly against bone causing joint damage, severe pain and disability (Michael, et al., 2010).

OA of the knee is the most common joint disorder in the world and a leading cause of lower extremity disability in the developed world (Cross, et al., 2014); (Arden & Nevitt, 2006). Estimates of prevalence and incidence vary according to the definition of OA used (i.e., radiographic versus symptomatic) and the joints being assessed; however, it has been estimated that the lifetime risk of developing knee OA is approximately 40% in men and 47% in women, with prevalence increasing dramatically with age (Johnson & Hunter, 2014). As of 2018, it was estimated that approximately 14 million people have symptomatic knee OA in the United States (US) (Vina & Kwoh, 2018), where OA is one of the leading causes of work disability and accounts for more hospitalizations than rheumatoid arthritis (Arden & Nevitt, 2006). In the Nordic region, the prevalence of OA (defined as symptomatic, radiologically defined hip or knee OA) was more than 1.5 million in 2015. Globally, the prevalence of OA is expected to continually rise as populations age and obesity levels increase, leading to a substantial rise in the burden of OA on healthcare systems around the world (Kiadaliri, et al., 2018).

Diagnosis is based on clinical symptoms and radiological features. The most common clinical symptoms are pain and stiffness, usually in the morning; or after a period of inactivity a loss of joint function which limits daily activities. It is also often associated with depression and loss of sleep which can greatly affect patients' quality of life, causing further impact on the public health system (Vina & Kwoh, 2018).

Current treatment guidelines are aimed at managing signs and symptoms, with the goal of slowing progression if possible. There are several international evidence-based guidelines for OA management (Hochberg, et al., 2012); (McAlindon, et al., 2014); (Cutolo, et al., 2015). Standard approaches are typically stepwise in nature, ranging from general measures (e.g., lifestyle changes, weight loss, etc.) to physiotherapy, orthopedic aids and orthoses, followed by pharmacotherapy, and finally surgery and rehabilitation. Pharmacological interventions include acetaminophen (paracetamol), topical and oral non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and opioids. Other treatments include hyaluronic acid, D-glucosamine sulfate, chondroitin sulfate, and diacerein, collectively known as slow-acting drugs for osteoarthritis (Cutolo, et al., 2015).

Intra-articular injections of corticosteroids such as triamcinolone acetonide (TCA) are recommended for the management of symptoms associated with inflammation. The use of injectable corticosteroids in patients diagnosed with knee OA has shown to be safe and effective (Bellamy, et al., 2006). However, currently available injectable corticosteroids are

suboptimal in the treatment of OA due to their limited duration of activity and risk for systemic side effects (Juni, et al., 2015). Longer corticosteroid residence time should lead to increased clinical benefit because of anticipated improvements in duration of efficacy and a reduced frequency of injections. A recent article evaluating IA injections of TCA administered every 12 weeks over 2 years suggested that chronic exposure of TCA in patients with knee OA leads to increased cartilage loss (McAlindon, et al., 2017). In contrast, local safety data from a 10-month good laboratory practice (GLP) toxicology/toxicokinetic study of EP-104IAR in beagle dogs suggest it has less potential for cartilage loss (see Section 1.2.1 below). In addition, by decreasing the pharmacokinetic peak-to-trough ratio it is anticipated that greater efficacy will be achieved with fewer systemic side effects (e.g., flushing, glucose alterations and cortisol suppression). These aspects have been the focus of Eupraxia's efforts when developing EP-104IAR.

1.2 Summary of Non-clinical and Clinical Data

1.2.1 Non-clinical Summary

The active ingredient of EP-104IAR, FP, has known side effects when given as an inhaled product, see Investigator's Brochure and the current FDA-approved label for Flovent HFA (GlaxoSmithKline, 2019). EP-104IAR toxicology studies were performed to investigate whether new toxicities would occur related to IA administration into the knee and whether the cured PVA coating affects the toxicity profile. Pharmacokinetic studies were done to characterize the rate of release from the PVA-coated particles and extent of local (knee) and systemic exposure to FP.

To date, 17 in silico, in vitro and in vivo studies have been performed to characterize the PK, toxicokinetics (TK), systemic and local safety of EP-104IAR. Single doses of EP-104IAR have been evaluated in 4 species (dogs, rats, sheep and rabbits). Clinically relevant EP-104IAR lots identical, or closely related, to the clinical lots were characterized in several rat and dog studies whereas preliminary studies in rabbits and sheep used experimental and now discontinued lots of EP-104IAR.

No repeat-dose studies have been performed with EP-104IAR in any species.

Three PK/TK studies were conducted in Sprague-Dawley rats. Single doses of EP-104IAR were administered either via intra-peritoneal (IP) or subcutaneous (SC) injection. A single IP or SC injection of EP-104IAR at doses of 41.9 to 45.2 mg/animal was well-tolerated with no mortality nor test item-related clinical signs observed. In two feasibility studies to evaluate the potential to use IP injection in rats as a screening model for various experimental formulations, clinically significant morbidity consistent with an overdose of FP occurred in 7 Sprague-Dawley rats who were subsequently euthanized. These observations are considered inapplicable to the safety of the clinical formulation because:

- Rats were injected with EP-104IAR containing very high FP doses, as much as a Human Equivalent Dose of 333 mg, a 378-fold higher dose than the highest approved human dose of Flovent HFA of 0.88 mg/day.

- 6 of the 7 instances occurred in rats injected with test article employing discontinued experimental manufacturing processes, or uncoated FP.

- Drug was administered via a route that will not be used clinically (IP versus IA) and that is expected to have greater hepatotoxicity than IA administration.

Seven toxicology and toxicokinetic/PK studies have been conducted in beagle dogs, including 1 GLP study in 216 dogs. Single IA doses over a 100-fold range of dose levels from 0.6 mg to 55 mg were generally well-tolerated.

At the highest dose in a GLP dog study (55 mg), no adverse effects were documented for body weights, food consumption, ophthalmology or electrocardiography. Transient (<3 days) observations were made of knee discomfort and skin redness at the dosing site with no pain detectable at palpation recorded on, or after, Day 2; these findings were considered procedure-related and not test item-related. Slight increases of mean neutrophil counts, and slight decreases in mean lymphocyte and eosinophil counts, were observed in both sexes; both effects were reversible. Non-adverse minor but persistent decreases in creatinine and increases in cholesterol were also observed. In this dose there was also a trend for slightly lower adrenal gland weights and slightly higher liver weights; atrophy of the adrenal cortex; and hepatocellular vacuolation (consistent with glycogen deposition), albeit with no impact on liver function tests.

Dogs administered with EP-104IAR up to 55 mg (as well as FP alone and PVA alone at comparable high dose levels) had Mankin scores (a 14-point histologic/histochemical classification of cartilage health (Pritzker, et al., 2006)) equal to zero at all doses and time points. In dogs administered with 1.9 or 5.5 mg of EP-104IAR, there were only minimal, sporadic and transient local and systemic histopathology results. At the 55 mg dose, local effects consisted of granulomatous inflammation associated with the local presence of the test items in the synovial lining and occasionally in the synovial stroma; and degeneration/necrosis.

The key non-clinical PK and toxicological findings for EP-104IAR are:

- FP administered by the intravenous (IV) route is systemically cleared within a matter of days. In contrast, EP-104IAR has a t_{max} on the order of hours to days, then plasma levels decline approximately 6-fold over 60-90 days before entering a prolonged plateau phase for up to 10 months.

- Concentrations of FP in the synovial fluid equilibrate at approximately 2-orders of magnitude greater than in the plasma; measurable levels of FP in the synovial fluid can also be seen for at least 10 months.

- Plasma levels of FP appear to relate to dose in a sub-linear fashion, with a 2-fold increase in dose of EP-104IAR being associated with a 1.4-1.6-fold increase in exposure.

- The cured PVA coating on the crystallized FP core reduces peak exposures of plasma FP and prolongs the retention of FP at the IA injection site.

- EP-104IAR does not interact with the complement system and does not activate complement.

- EP-104IAR is generally well-tolerated systemically, at doses of up to 55 mg in dogs. Observed effects are consistent with the known impacts of glucocorticoid exposure.

- EP-104IAR impacts the adrenal cortex, and suppresses cortisol production, in a manner directly related to dose and systemic load of FP. However, these effects are reversible and, at higher doses (55 mg) of EP-104IAR, the PVA coating considerably attenuates the impact of FP when administered as EP-104IAR compared to uncoated crystalline FP.

- Low (1.9 and 5.5 mg) doses of EP-104IAR are associated with minimal and transient granulomatous inflammation, chondrocyte vacuolation and macrophage vacuolation. A 55 mg dose of EP-104IAR shows more substantial impact on these endpoints, and includes additional degeneration/necrosis.

- The No Observed Adverse Effect Level (NOAEL) in beagle dogs for a single IA injection of EP-104IAR is 5.5 mg FP; however, doses between 5.5 and 55 mg have not been explored, and it is plausible that the NOAEL is higher, particularly given the low level of toxicity observed at the 55 mg dose.

Further details of all non-clinical studies performed to date are included in the Investigator's Brochure.

1.2.2 Clinical Summary

A Phase 1 study has been conducted in Canada, in 32 subjects with knee OA. Subjects were randomized in a 3:1 ratio to receive either a single IA dose of 15 mg EP-104IAR or vehicle-control (24 subjects received EP-104IAR and 8 subjects received vehicle). Subjects were followed for up to 42 weeks post-dose with safety, efficacy and PK assessments (plasma and synovial fluid).

EP-104IAR was safe and well-tolerated. Treatment-emergent adverse events (TEAEs) occurred in 15 subjects (62%) in the EP-104IAR group (34 events) and in 4 subjects (50%) in the vehicle group (9 events). Subjects most frequently experienced TEAEs of Grade 1 (mild) severity (11 subjects, 46% in the EP-104IAR group versus 4 subjects, 50% in the vehicle group) and most TEAEs were observed within the first 12 weeks of the study (31 out of 43 TEAEs).

There were no deaths, no serious adverse events (SAEs) considered related to EP-104IAR and no TEAEs that led to withdrawal. There were no local safety findings (based on review of TEAEs, physical examination and gait assessments of the treated knee).

Average cortisol levels showed no clinically significant deviations compared to placebo and remained within the normal range of cortisol variation. There was a noticeable decrease in cortisol at 48 hours post-dose in some EP-104IAR subjects. Two subjects showed a transient decrease of >75% from baseline; one of which returned to baseline levels by one week and the other by three weeks.

Plasma PK was predictable, with concentrations within acceptable safety margins (based on marketed FP products). Synovial fluid FP levels were approximately 1- to 2-orders of magnitude higher than plasma levels and at theoretically efficacious concentrations for the majority of subjects.

The median dose of FP delivered in this study was 13.2 mg (approximately 88% of the intended dose).

Study EP-104IAR-101 was primarily a safety and PK study; however, a variety of pre-specified efficacy endpoints were included to permit a preliminary evaluation of the efficacy of EP-104IAR in comparison to vehicle. Pain and OA symptoms were measured using PtPain, WOMAC Index 3.1, and a Patient Global Assessment of Arthritis (PtGA). A Physician's Global Assessment of Arthritis (MDGA) and an evaluation of subjects' overall health status using the Short Form 36 health survey (SF-36) were also collected.

Pre-defined, exploratory inferential analyses demonstrated statistically significant improvements with EP-104IAR compared to vehicle at a few time points in the first 3 weeks post-dose (e.g., EP-104IAR showed 1.6-point (p=0.045) and 1.7-point (p=0.022) reductions in pain over vehicle at Weeks 1 and 3 respectively, and a 1.5-point (p=0.045) reduction over placebo for WOMAC Pain at Week 3). In addition, the time to first occurrence of lowest PtPain pain was faster for EP-104IAR compared to vehicle (2 weeks compared to 7.5 weeks for placebo, p=0.045). Graphical presentation of all the efficacy measures illustrates an immediate distributional shift in the EP-104IAR group relative to vehicle and a clear analgesic trend for EP-104IAR with distinct separation from vehicle between 8- and 12-weeks post-dose in PtPain, WOMAC Pain, stiffness, function and total scores, as well as PtGA, SF-36 and MDGA.

Further details on the safety, PK and efficacy of EP-104IAR are provided in the Investigator's Brochure.

2. RATIONALE

The use of injectable corticosteroids for the management of pain and stiffness associated with inflammation in patients diagnosed with OA of the knee has proven to be safe and effective (Bellamy, et al., 2006). However, currently available injectable corticosteroids are suboptimal in the treatment of OA of the knee due to their limited duration of activity and risk for systemic side effects (Juni, et al., 2015).

EP-104IAR has been developed to maximize local residency time in the knee joint and is expected to provide greater clinical benefit than currently approved injectable corticosteroids. In addition, by decreasing the peak-to-trough ratio of plasma concentrations it is anticipated that this greater duration of efficacy will be achieved with a reduced risk of systemic side effects.

Safety and efficacy data for EP-104IAR have been generated in a single clinical study in 32 subjects with knee OA (Study EP-104IAR-101). A dose of 15 mg EP-104IAR was safe and well-tolerated and all efficacy measures showed an immediate improvement that was sustained for between 8- and 12-weeks post-dose. A higher dose of EP-104IAR is anticipated to sustain efficacy for a longer duration.

***Imaging Sub-Study* Rationale**

This optional imaging sub-study is designed to provide early exploratory data to assess the effect of EP-104IAR on inflammation (McAlindon, et al., 2017). Additionally, magnetic resonance imaging (MRI) scans will allow to assess the quality and structure of the cartilage after the injection of EP-104IAR (Rodriguez-García, et al., 2021). It is not expected that these images will provide statistically significant data, but they are intended to provide exploratory data on the safety of EP-104IAR as a potential treatment for patients with OA (Van Spil, et al., 2019).

To minimize any potential impact on the main study outcome measures, MRIs acquired after IMP administration will be performed following completion of all efficacy, PK and safety measures required for the main study.

2.1 Dose Selection

This study will evaluate the safety, efficacy and PK of a single 25 mg dose of EP-104IAR compared to vehicle. This dose is 2-fold higher than the median dose of 13.2 mg delivered in the prior clinical study and, given the results in that study, is expected to be well-tolerated and extend the duration of efficacy beyond 12 weeks.

The 25 mg dose was selected based on careful consideration of both local and systemic safety factors. Full details are provided in the Investigator's Brochure.

2.1.1 Dose Justification Based on Local Exposure

Toxicity in the synovial joint was a major consideration when calculating safety margins between doses used in the GLP toxicology study in dogs to the dose proposed in this study.

The Food and Drug Administration guidance for industry on Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route (FDA, 2015) does not provide specific safety margins required to support human dosing for IA formulations. Consequently, several methods were compared to estimate human equivalent dosing.

Based on various animal to human conversions (using methods such as synovial fluid volume, cartilage surface area, cartilage volume, etc.) the 25 mg EP-104IAR dose in this study, corresponds to approximately 1.25 mg in dogs. The GLP toxicology study in beagle dogs evaluated 3 doses of EP-104IAR: 1.9, 5.5 and 55 mg. At the two lower clinically relevant doses of EP-104IAR, there were no local adverse effects. Where minimal effects were present, they were transient and occurred in a small number of animals. There was no evidence of histologic chondrocyte or cartilage effects at any doses or timepoints as determined based on Mankin scores. As such, the 5.5 mg EP-104IAR dose was considered the NOAEL, giving approximately at least a 4.4-fold margin of safety for local effects for the 25 mg dose to be evaluated in this study.

2.1.2 Dose Justification Based on Systemic Exposure

Data from the prior clinical study (EP-104IAR-101) showed clear and predictable systemic PK. The impact of systemic FP is well understood from knowledge of Flovent HFA (in addition to several other marketed formulations of FP). Established knowledge of systemic FP exposures was used to evaluate systemic safety of EP-104IAR at the 25 mg dose for use in this study.

A PK model was developed using data from Study EP-104IAR-101. Based on this model, average concentrations from a single administration of 25 mg EP-104IAR are expected to peak at around the maximum concentration (C_{max}) from a 440 µg b.i.d. Flovent HFA dose. They then fall below the C_{max} from a 220 µg b.i.d. Flovent HFA dose by 1 week post-dose; and below the average concentration at steady state (C_{ss}) from a 220 µg b.i.d. Flovent HFA dose by 2-3 weeks post-dose. The total exposure to FP over 24 weeks following a single 25 mg dose of EP-104IAR is expected to be the same as receiving an average of approximately 120 µg b.i.d. Flovent HFA over an equivalent period.

It is known that systemic levels of corticosteroids can impact the hypothalamic-pituitary-adrenal (HPA)-axis. Given the expected systemic PK of EP-104IAR, it is anticipated that some perturbation of endogenous cortisol may occur. Based on the modelled PK data, it is expected that peak cortisol suppression with a 25 mg dose of EP-104IAR will be similar to that seen with Zilretta® (an extended-release TCA product approved in the United States), and substantially better than immediate release TCA, but with faster return to baseline levels. In this study, subjects will be closely monitored for signs of adrenal insufficiency, see Section 2.2 below, for details.

2.2 Risks/Precautions

Commonly reported local adverse effects of IA corticosteroid injection include IA and periarticular calcifications, cutaneous atrophy, and cutaneous depigmentation (Habib, et al., 2010).

Reported systemic effects of IA corticosteroid injection include flushing, hypothalamic-pituitary-adrenal axis suppression, transient increase in blood glucose levels in diabetics, decrease in serum inflammatory markers and cytokines, decrease in blood mononuclear cells and an increase in polymorphonuclear leukocytes, decrease in plasma viscosity, anaphylaxis and allergic reactions, and infections (Habib, 2009). As a precaution, insulin-dependent and poorly controlled non-insulin-dependent diabetics, individuals with current or recent infections and individuals with abnormal laboratory test findings (as defined in the exclusion criteria, Section 5.3) will be excluded from this study.

EP-104IAR animal studies identified the adrenal glands and the liver as target organs for EP-104IAR toxicity, consistent with systemic FP exposure. As a precaution, individuals with impaired liver function (as defined in the exclusion criteria, Section 5.3) will be excluded from this study.

Animals with higher plasma levels of FP experienced reversible cortisol suppression. A similar finding was also observed in the Phase 1 clinical study. While the serum cortisol suppression observed in the Phase 1 study was transient and reversible, due to the higher dose of EP-104IAR being evaluated in this study, individuals with, or at greater risk of developing adrenal insufficiency (AI) will be excluded from participating in this study (see Section 5.3). During the study, serum cortisol will be monitored closely by the Medical Monitor and while the dose of EP-104IAR selected for evaluation in this study is not anticipated to have any adverse effects on adrenal function, as an additional precautionary step, adrenocorticotropic hormone (ACTH) stimulation testing will be performed, according to the criteria defined in Section 9.1.5.1.2. Subjects will be closely monitored for clinical signs and symptoms of AI and managed accordingly (see Section 10.2.5). Finally, subjects will also be instructed to carry a wallet card identifying the potential risk for AI as a result of participating in the clinical study, and the potential need for emergency glucocorticoid therapy in the setting of shock, surgery, etc.

In the GLP dog toxicology study, the primary local effects were synovial granulomatous inflammation and synovial degeneration and/or necrosis. The granulomatous inflammation appears to be due to the presence of particles in the synovium, while the degeneration appears to be due to high local levels of steroid. These effects were dose related. At clinically relevant doses, these effects were minimal to mild and considered not clinically significant. In the Phase 1 clinical study, there were no obvious local toxicity findings; however close attention should be paid to administration site adverse events (AEs), and examination of the knee. As a precaution, detailed knee examinations will be performed at all scheduled visits, with particular attention paid to any findings that could be indicative of a severe inflammatory response without another known cause, see Section 9.1.5.3.

It is expected that the frequency and severity of any AEs will be similar to those reported for other marketed IA corticosteroid injections.

Overall, it is believed that the known and unknown risks associated with EP-104IAR can be adequately monitored throughout the clinical study and are outweighed by its potential benefit in OA.

Imaging Sub-Study Risks

Side effects associated with the use of Gadolinium Based Contrast Agents (GBCA) are usually mild to moderate in intensity and transient in nature. The most frequently observed physiologic reactions are headache, nausea, paraesthesia, vomiting, dizziness, a sensation of heat, cold and/or pain at the injection site, and mild hypersensitivity reactions such as erythematous rash and pruritus (Fraum, et al., 2017).

More serious adverse reactions to GBCA are hypersensitivity (immediate and delayed up to 7 days), anaphylactic, and anaphylactoid reactions that may be very rarely severe, life-threatening or have a fatal outcome, particularly in patients with a history of allergy. Hypersensitivity reactions are also more common in patients with prior adverse reactions to GBCA (Fraum, et al., 2017). Patients with a history of allergy, or with a prior adverse reaction to a GBCA will be excluded from this sub-study.

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with gadolinium, most of which were in patients co-administered other gadolinium-containing contrast agents or in patients with acute or chronic severe renal impairment using the linear compounds (Khawaja , et al., 2015). Patients with renal impairment defined as an estimated glomerular filtration rate (eGFR) of ≤ 40 ml/min/1.73-m^2 and/or in whom GBCA's are contraindicated will be excluded from this sub-study. To further minimize risk, dynamic contrast enhanced (DCE)-MRI scans will be obtained for this study in accordance with the latest EMA recommended guidelines and using only approved macrocyclic gadolinium contrast agents e.g. gadobutrol, gadoteric acid, gadotexic acid and gadoteridol (EMA, 2017).

MRIs are generally considered safe during pregnancy, however, GBCAs have the potential to cause adverse effects on a developing fetus, or a breastfed infant (Fraum, et al., 2017). To minimize this risk, pregnant and lactating women will be excluded from the sub-study and women of child-bearing potential must provide a negative pregnancy test prior to each MRI. A positive pregnancy test result at any point will exclude further participation in the imaging sub-study.

A comprehensive description of the risks and undesirable effects of the specific contrast agent is available in the Package Insert of the specific GBCA used by the Imaging Centre. Investigators and patients can refer to the MRI site personnel for additional information.

Participants in the imaging sub-study will be also exposed to the discomfort associated with the scan procedure and some patients may experience a claustrophobic sensation

during the procedure. However, an MRI is a non-invasive, pain and radiation-free procedure (Menashe, et al., 2012) and every MRI facility will have comprehensive procedures that will be carefully followed to ensure that MRIs are conducted in a safe manner.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is:

- To evaluate the efficacy of a single IA injection of EP-104IAR in patients with OA of the knee for up to 24 weeks.

3.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety of a single IA injection of EP-104IAR in patients with OA of the knee for up to 24 weeks (or 52 weeks for imaging sub-study only).

- To evaluate the pharmacokinetics (PK) of a single IA injection of EP-104IAR for up to 24 weeks.

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a Phase 2, multi-center, randomized, double-blind, vehicle-controlled, parallel-group study.

Approximately 300 subjects with diagnosed knee OA will be randomized and followed for up to 24 weeks to evaluate the safety, efficacy and PK of a single IA dose of EP-104IAR compared to vehicle control.

Subjects may have unilateral or bilateral knee OA. In subjects where both knees are potentially eligible Index knee selection will be based on WOMAC Pain scores collected during the Washout and Baseline period and other eligibility criteria such as Kellgren-Lawrence grade, see Section 9.1.3.2 for details.

Safety assessments include AEs, vital signs, hematology and clinical chemistry assessments, and safety urinalysis testing. Local safety will be assessed via physical examinations of the treated knee. Evaluations of EP-104IAR's impact on the HPA-axis include morning serum cortisol collection (all subjects) and the ACTH stimulation test (selected subjects).

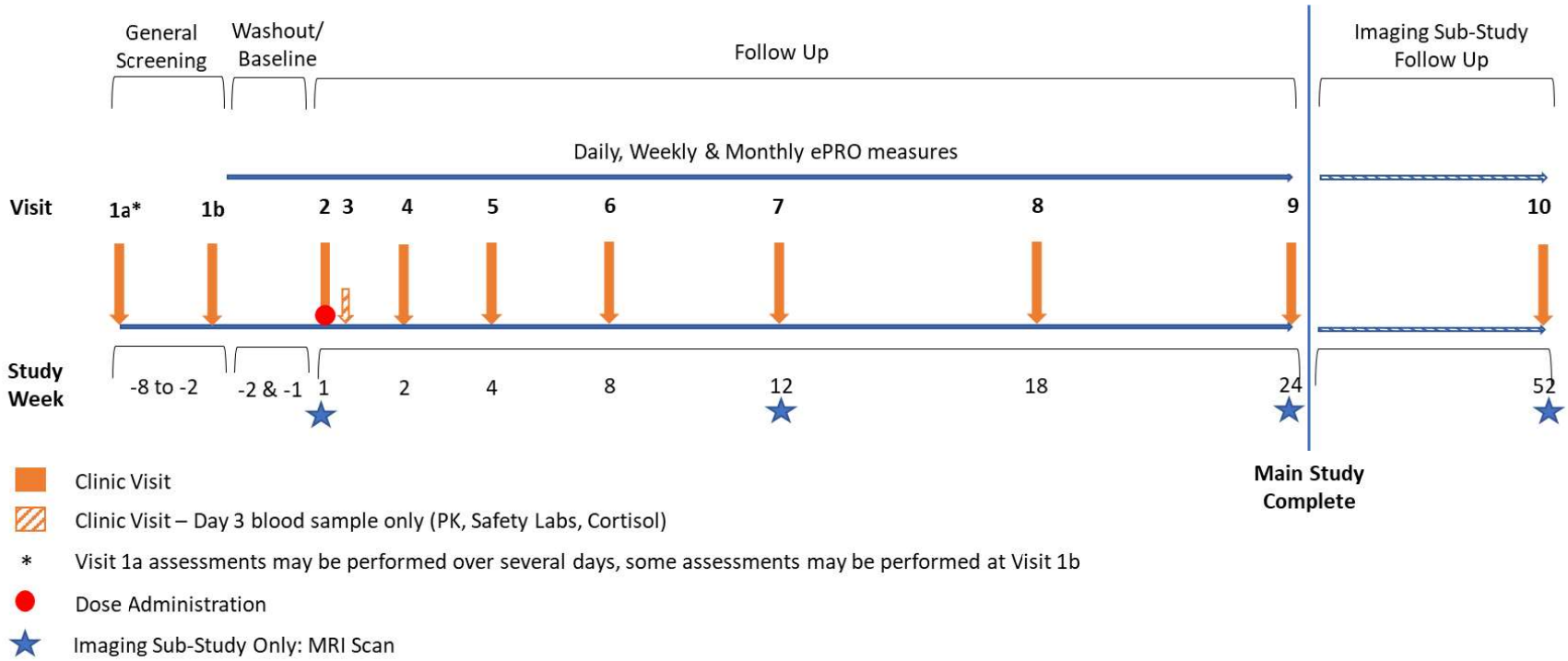
The primary means of efficacy data collection is via an electronic patient-reported outcome (ePRO) device which will be used throughout the study to collect daily assessments of pain using the Numeric Pain Rating Scale (NPRS), rescue medication and non-drug rescue therapy use, and activity levels; weekly WOMAC Pain subscale measurements; and monthly WOMAC Pain, Function and Stiffness. The MDGA, PtGA and SF-36 health survey will also be collected at site visits.

The main study involves 10 site visits, as illustrated in Figure 1, below.

Imaging Sub-Study

For those participating in the imaging sub-study, there will be between 1 and 4 additional site visits depending on whether the MRIs can be acquired on the same day as the main study assessments.

Figure 1 Visit Overview



Note: ePRO=Electronic patient-reported outcome; MRI=Magnetic resonance imaging; PK=Pharmacokinetic.

Visit 1a and 1b: General Screening (multiple days)

The study includes a general screening period of up to 6 weeks. During this period subjects will be evaluated for eligibility. Screening assessments may take place over several days to permit collection and assessment of x-rays for Kellgren-Lawrence grading and laboratory tests.

Visit 1b: Initiate Washout & Baseline

Potentially eligible subjects will be instructed how to initiate the Washout and Baseline Period. Subjects will be instructed to begin washout of their current pain medications and will be provided with an ePRO device used to record daily and weekly measurements to determine if they have qualifying knee pain to enter the study.

Rescue medication (acetaminophen/paracetamol, up to 3,000 mg per day (i.e., 3 g)) will be issued at this visit to treat the subject's breakthrough knee OA pain. Subjects will be required to record if they use rescue medication using the ePRO device.

Visit 2: Randomization and Dose Administration

Following completion of the Washout and Baseline Period, subjects will return to the site for a final review of their eligibility criteria and selection of their Index knee.

Imaging Sub-Study:

Subjects who participate in the imaging sub-study will have a baseline MRI performed on their index knee. MRI scans will be conducted as described in the MRI Imaging Charter.

The baseline MRI will be performed prior to all other pre-dose safety, PK and efficacy assessments. If the MRI is performed on a separate day to the other assessments, it should be scheduled to occur within 5 days of dosing.

For women of childbearing potential, a urine pregnancy test must be performed prior to performing the baseline MRI. The pregnancy test does not need to be repeated prior to dosing.

Following completion of all pre-dose safety, PK and efficacy assessments, eligible subjects will be randomized to EP-104IAR or vehicle control and baseline assessments will be performed.

A single dose of EP-104IAR or vehicle control will be administered into the Index knee. The injection procedure will be performed at the study site by an unblinded and appropriately qualified/experienced individual using ultrasound guidance.

Following completion of post-dose safety assessments, subjects will be provided with a bottle of rescue medication (acetaminophen/paracetamol) for use during the Follow-up Period and reminded of their next visit date.

Visits 3 – 9: Follow-Up

Subjects will be followed up for 24 weeks following dose administration. During this period, subjects will attend up to 7 visits. Visits should occur in the morning whenever possible (to ensure serum cortisol assessments occur at approximately the same time of day - between 7-11 a.m.) and ideally the same day of the week. The same blinded assessor should complete assessments at all visits whenever possible.

Between visits, subjects will continue to record their daily, weekly and monthly (every 4 weeks) assessments at home using the ePRO device provided.

Imaging Sub-study:

Subjects participating in the imaging sub-study will also undergo an MRI procedure at or immediately following Visit 7 and at or immediately following Visit 9 (or the early exit visit).

All safety, PK and efficacy assessments will be performed prior to receiving the MRI. The MRI may be performed on a separate day to these assessments.

To ensure the subject is safe to proceed with imaging procedures, a urine pregnancy test will be performed and eGFR will be calculated based on the most recent creatinine value.

Visit 10 – Week 52 (*Imaging Sub-Study Only*)

Only subjects participating in the optional imaging sub-study will perform Visit 10.

After Visit 9 , no efficacy, PK, or safety assessments (apart from AE recording) will be performed. Subjects will not be required to refrain from any medications/procedures after Visit 9. The subject will be treated as per standard of care by their physician during this time.

At Visit 10 AEs and concomitant medications/procedures will be collected for the timeframe between Visit 9 and 10 to capture any changes in the subject's health status.

Eligibility to conduct imaging will be reviewed based on imaging-sub-study exclusion criteria, where the eGFR calculation will be based on the Visit 9 creatinine value, unless more recent results are available. If the subject remains eligible to undergo the MRI based on these criteria and provided a negative result on a urine pregnancy test (for females of childbearing potential) they may proceed to have the final MRI scan. The detailed schedule of assessments is provided in Section 9.2 and the Schedule of Events.

4.2 Duration of Subject Participation

The maximum duration of subject participation is approximately 32 weeks: Screening duration is up to 6 weeks; Washout and Baseline Period is approximately 2 weeks; and the Treatment and Follow-up Period duration is approximately 24 weeks.

Imaging Sub-Study

The maximum duration for a subject participating in the imaging sub-study is approximately 60 weeks, which includes the 32 weeks described above, and an additional 28 weeks for the one additional imaging follow-up visit after the main study has concluded.

4.3 Safety Oversight

In addition to the Medical Monitor's continual safety oversight, a safety review committee (SRC) will also be constituted to further protect the safety of study participants.

To ensure the Sponsor remains blinded to treatment allocations, the SRC will comprise 3 voting members independent of the sponsor company: the chairperson and 2 medically qualified individuals. An unblinded statistician or data manager, not otherwise involved in the data analysis, may also attend if needed to provide support with data navigation.

A formal SRC charter will be developed, detailing SRC remit, composition, responsibilities, safety review meeting (SRM) structure/timing, data provision and review, blinding and unblinding procedures and documentation of SRC recommendations, etc.

The SRC will meet on at least 2 scheduled occasions:

1. when the first 48 randomised subjects (approximately 24 EP-104IAR and 24 placebo) have reached their 4-week follow-up visit

2. when the first 48 randomised subjects have reached their 12-week follow-up visit

Safety data for any additional randomised subjects who have reached an earlier follow-up visit will be included in the data review package at each meeting. Enrollment will continue in parallel to the SRMs unless a pre-defined stopping rule has been met.

Safety data will include AEs, vital signs, safety laboratory data (including cortisol and ACTH stimulation test results for any subjects who have completed this test) and local safety findings (e.g., knee examination data) and will be presented in summary form for each treatment group and as individual blinded subject listings.

PK data will include plasma PK summaries.

Efficacy data will only be provided if it is necessary for the SRC to apply a potential risk versus potential benefit evaluation to any observed safety signals; however, no formal interim efficacy analyses will be performed. Efficacy data will include NPRS and WOMAC subscale scores.

Based on any observed safety findings reviewed at the SRMs, the SRC will make recommendations to the Sponsor concerning continuation, termination or modifications of the trial. Blinded safety and PK data will be made available to the Sponsor prior to making any modifications to the trial.

In addition to the scheduled SRMs, safety data will be continuously reviewed by the Medical Monitor for trends or findings of concern. The Medical Monitor may request the SRC be reconvened at any time to review new safety findings and determine if the study should continue to enrol subjects.

Examples of reasons to reconvene the SRC include (but are not limited to):

- An AE of severe, persistent pain in the Index knee in an EP-104IAR-treated subject that is out of proportion with the subject's degree of OA and not otherwise explained by any other cause (e.g., injury or infection)

- Increased Index knee pain out of proportion with the subject's degree of OA, in combination with all of the following: redness, warmth, extensive swelling, 2+ effusion (upon stroke test), that are not explained by any other cause, in an EP-104IAR-treated subject

- The occurrence of an infection in the Index knee without another known cause

- The occurrence of a suspected unexpected serious adverse reaction (SUSAR) in an EP-104IAR-treated subject

- The occurrence of confirmed symptomatic adrenal insufficiency in >1 EP-104IAR-treated subject

Recommendations following review of new safety data by either the Medical Monitor or the SRC may include (but are not limited to): pausing enrollment to permit further evaluation of data; scheduling an additional planned review of data once further subjects have been dosed; amending the protocol to exclude subjects at potentially greater risk; or stopping enrollment (terminating the study early).

4.4 Pre-Defined Study Stopping Rules

The study will be stopped if 2 or more EP-104IAR-treated subjects experience a severe local inflammatory response in their Index knee that is considered (by the SRC) to be potentially caused by EP-104IAR.

A local inflammatory response may be considered to have occurred in the following situations:

- An AE of severe, persistent pain in the Index knee that is out of proportion with the subject's degree of OA and not otherwise explained by any other cause (e.g., injury or infection)

- Increased Index knee pain out of proportion with the subject's degree of OA, in combination with all of the following: redness, warmth, extensive swelling, 2+ effusion (upon stroke test), that are not explained by any other cause

As symptoms of OA are often inflammatory in nature and increased pain in the Index knee could be caused by the subject's underlying OA, thorough investigations will be carried out to rule out other causes of symptoms to ensure the study is not inadvertently stopped prematurely.

Further investigations of Index knee examination findings that indicate a potential infection will include: a blood sample for hematology testing and referral to a specialist who may perform a joint aspiration and analysis of effusion to rule out local infection via culture (white blood cell count; differential counts and viscosity; presence of crystals; etc).

If the symptoms are not explained by a local infection, or other known cause and the subject received EP-104IAR treatment the finding will be considered a severe local inflammatory response potentially caused by EP-104IAR.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects

Approximately 300 subjects will be randomized and dosed. For detailed justification of the sample size refer to Section 11.2.

5.2 Inclusion Criteria

Investigators must maintain a screening log of all potential study candidates that includes limited information about the potential candidate, date, and outcome of the screening process (e.g., randomised, reason for ineligibility, or refused to participate).

The following inclusion criteria must be met for each subject:

1. Males or females, aged ≥40 years.
2. Body mass index (BMI) ≤40.0 kg/m^2.
3. Diagnosis of primary OA of the Index knee (as per American College of Rheumatology (ACR) clinical and radiological criteria) with OA symptoms (as reported by the subject) that have been present for at least 6 months prior to Screening.
4. Index knee OA severity Grade 2 or 3 (based on Kellgren-Lawrence Grading Scale).
   - X-rays will be reviewed by a central reader. If a suitable x-ray performed within 6 months of the Screening Visit cannot be provided, an x-ray must be performed as part of the Screening assessments.
5. Subject has experienced unsatisfactory pain control from at least 2 prior standard OA treatments, or has used such medications before but chose to discontinue them due to intolerance or personal preference.
   - Standard pharmacological OA treatments include (but are not limited to): Topical or oral NSAIDs, topical capsaicin, IA corticosteroids, IA hyaluronic acid, acetaminophen / paracetamol, Duloxetine, tricyclic antidepressants for treatment of pain, tramadol and other opioids.
   - Subjects considered by the Investigator to be non-responsive to treatment with corticosteroids are not eligible.
6. At Screening Visit 1a, subject reports that their typical OA knee pain in one or both knees when not using medication is ≥4 out of 10.
7. The weekly WOMAC Pain subscale scores for the Index knee (collected at the end of each week of the Washout and Baseline Period) are both ≥4.0 and ≤9.0 and must not differ (vary) by more than 3 points.
8. Demonstrated ability to comply with pain recording requirements during the Washout and Baseline Period (i.e., Subject must record daily NPRS scores (of any value) on at least 5 days in each week for both knees and both weekly WOMAC scores in both knees).

9. The weekly WOMAC Pain subscale scores for the non-Index knee (collected at the end of each week of the Washout and Baseline Period) are both ≤6.0.

10. Patient is ambulatory (without the need for a cane/other walking aide).

11. For females of child-bearing potential, willing to use a highly effective method of birth control between Baseline and End-of-Study Visits.

12. Willing and able to provide informed consent and comply with all study procedures and restrictions and the required visit schedule, etc.

5.3 Exclusion Criteria

1. OA of the Index knee due to acute injury or trauma that occurred within 12 months prior to Screening, or unstable joint (such as a torn anterior cruciate ligament) within 12 months of Screening.

2. X-ray evidence of chondrocalcinosis likely to affect the outcome of this study in the opinion of the investigator.

3. Diagnosed or suspected ipsilateral hip OA.

4. Knee pain that is not clinically attributable to OA of the knee (e.g., radicular low back pain or hip pain that is referred to the knee that could cause misclassification).

5. Any other disorders that, in the Investigator's opinion, impact mobility, strength or sensation, or are a co-existent source of pain or inflammation that interferes with the subject's ability to assess their knee OA pain and function (e.g., fibromyalgia, painful diabetic neuropathy, low back pain, rheumatic disorders such as rheumatoid arthritis, other autoimmune diseases, ankylosing spondylitis, reactive arthritis (aka Reiter's syndrome), psoriatic arthritis, gout, etc.).

6. Presence of other symptoms or conditions in the Index knee that would confound evaluation of pain and other functional assessments of knee OA (e.g., a symptomatic popliteal cyst (Baker's cyst)).

7. History of infection in the Index knee within 9 months prior to Screening, or clinical signs and symptoms of an active infection in the Index knee at Screening or Baseline Visits.

8. Total/Partial Knee Replacement for the Index knee, or any other surgery (including arthroscopy) for the Index knee within 12 months prior to Screening, or planned surgery during the study.

9. Total/Partial Knee Replacement Surgery of the non-Index knee within 6 months prior to Screening, or planned surgery (in any location) during the study that would require use of a restricted medication during the study.

10. IA injection of corticosteroids in any joint within 3 months prior to Screening, or IA injection of extended-release corticosteroids in any joint within 6 months prior to Screening.

11. IA injection in the Index knee of platelet rich plasma or other prolotherapy (e.g., dextrose) within 3 months prior to Screening, or hyaluronic acid within 6 months prior to Screening.

12. Oral, IV or intramuscular corticosteroids for any indication within 30 days prior to Baseline; or planned used during the study.

13. Inhaled or intranasal corticosteroids, or expected need for these, for any indication from the start of the Washout and Baseline Period until at least 4 Weeks post-dose.

14. Any topical corticosteroids applied to the Index knee, or expected need for these, from the start of the Washout and Baseline Period until 24 Weeks post-dose, or planned use of restricted topical corticosteroids (on any location) during the study (restricted medications are listed in Protocol Section 8.1.2). Intravitreal corticosteroids are permitted with no restrictions.

15. Use of any long-acting opioids within 30 days prior to Screening, or use of any opioids (including tramadol and tapentadol) more than twice per week within 30 days prior to Screening and from which the subject is unwilling or unable to washout.

16. Presence or history of substance abuse, including but not limited to, opioids and marijuana. Current use of marijuana for any reason is also exclusionary.

17. Positive urine drug test at Screening or Baseline Visits that is not explained by the use of prescription medications permitted during the study. A positive urine drug test without a valid prescription that accounts for the result is automatically exclusionary and cannot be repeated.

18. Presence of alcohol abuse or dependence or drinking more than 21 units of alcohol per week (i.e., 3 drinks per day): 1 unit = 150 mL of wine, 360 mL of beer or 45 mL of 40% alcohol); or history of alcohol abuse judged by the Investigator as likely to recur during the study.

19. Current use of systemic immunosuppressive therapy; or use within 6 months prior to Screening.

20. Unwilling or unable to washout of any prohibited medications and not use them for the duration of the study (Washout and Baseline Period to End-of-Study Visit). Prohibited medications are listed in Section 8.1.

21. Use of another investigational drug or device within the 30 days prior to Screening, or an investigational biologic within the 60 days prior to Screening, or current/planned participation in another interventional trial during this study.

22. A history of sarcoidosis or amyloidosis.

23. A history of osteomyelitis.

24. A history of or active Cushing's syndrome.

25. Currently has or is receiving treatment for the following conditions: psychotic disorder, bipolar disorder, symptomatic depressive or anxiety disorders. Mild or well-controlled psychiatric disorders (e.g., mild depression) are permitted if the medication used is not prohibited by the protocol (see Section 8.1).

26. At Screening, a baseline serum cortisol value ≤138 nmol/L (≤5 µg/dL) from the ACTH stimulation test, or an abnormal ACTH stimulation test result.

27. Currently has diagnosed insulin-dependent diabetes mellitus or poorly controlled non-insulin dependent diabetes mellitus (defined as a hemoglobin A1c (HbA1c) value of ≥8.0% (64 mmol/mol) at Screening.

    - Pre-diabetics (i.e., HbA1c levels between 5.7-6.4% (39-46 mmol/mol) at Screening) and well-controlled non-insulin dependent diabetics (i.e., HbA1c levels ≤7.9% (63 nmol/mol) at Screening) are permitted.

28. Diagnosed hepatic or renal disease, or the following laboratory values at Screening: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 x upper limit of normal (ULN); bilirubin >2 x ULN (unless isolated Gilbert's syndrome); serum creatinine >1.5 x ULN.

29. Current malignancy of any type, or history of a malignancy within 12 months prior to Screening (other than resected basal cell carcinoma, squamous skin cell carcinoma, or resected cervical atypia or carcinoma in situ).

30. Any infection requiring IV antibiotics within 4 weeks of the Baseline Visit, or oral antibiotics within 2 weeks of the Baseline Visit.

31. Known active or quiescent systemic fungal, bacterial (including tuberculosis), viral or parasitic infections, or ocular herpes simplex.

32. Known or clinically suspected infection with human immunodeficiency virus, hepatitis B or C viruses.

33. Skin breakdown on the Index knee where the injection will take place.

34. Females who are pregnant, lactating, or who have a positive pregnancy test result at Screening or Baseline Visits.

35. Known or suspected hypersensitivity or contraindication to any of the ingredients in the investigational medicinal product, including carboxymethyl cellulose and polysorbate 80, to fluticasone propionate or any other corticosteroids (for example cortisol-related endocrinopathy), or to lidocaine (if used during IA injection procedure).

36. Known or pending disability or workers' compensation claims.

37. Previous randomization and treatment in this study.

38. Any other reason that, in the opinion of the Investigator, is likely to unfavorably alter subject risk-benefit, confound safety or efficacy results, or make it difficult for the subject to fully comply with study requirements.

Imaging Sub-Study

Additional exclusion criteria for the *Imaging Sub-study*

Subjects who are willing to participate in the imaging sub-study are also subject to the following exclusion criteria. If a subject meets any of these criteria it only invalidates their participation in the imaging sub-study:

39. Unwilling and/or unable to provide informed consent and comply with all imaging sub-study procedures and restrictions and the required visit schedule
40. Known allergy or a prior adverse reaction to gadolinium or to any of the excipients contained in the MRI contrast agent
41. History of severe allergy, drug reactions, or other hypersensitivity-like disorders and bronchial asthma
42. Any metal objects e.g., shrapnel, and any surgical clips, pacemakers, pins, plates, screws, metal sutures or wire mesh also including uterine coil, intra-ocular metal foreign bodies, new contact lens that allows for an automated recording of continuous intraocular pressures, the LINX reflux management system insulin pump, temporary external transvenous pacing leads, if considered contraindication for MRI scanning
43. Severe claustrophobia
44. Cochlear implants
45. Known renal conditions, for which contrast agents for MRI could add to risks, or moderate to severe renal dysfunction (defined as an eGFR $\leq$ 40 mL/min/1.73m^2 by laboratory testing and the chronic kidney disease epidemiology collaboration [CKD-EPI] equation).
46. Females who are pregnant, lactating, or who have a positive pregnancy test result prior to any planned MRI procedure.

5.4 Withdrawal of Subjects

Subjects may withdraw their consent, or voluntarily withdraw from the study at any time without having to provide a reason and without prejudice to further treatment.

The Investigator and Sponsor have the right to withdraw subjects from the study. However, as this is a single dose study, the Sponsor's preference is that subjects remain in the study for as much of the 24-week follow-up period as possible, to maximize the amount of safety and efficacy information collected on EP-104IAR.

Reasons for withdrawing a subject may include:

- Lack of compliance with the protocol or study restrictions
- Occurrence of an AE (serious or non-serious), at the discretion of the Investigator
- At the Investigator's discretion if it is in the subject's best interest

- At the request of the Sponsor, whether for administrative or other reasons
- Sponsor discontinues the study, or a specific site

The reason(s) for withdrawal must be recorded on the subject's electronic case report form (eCRF) and source documentation. If the subject withdraws from the study without providing a reason, the reason for discontinuation should be documented as "withdrawal of consent".

Subjects who are withdrawn from the study prematurely should undergo all End--of--Study (Visit 9) assessments, if possible.

If a subject is discontinued due to an AE/SAE, the event should be followed by the Investigator through contact with the subject until resolution or stabilization has occurred, or the subject is lost to follow-up and cannot be contacted.

Subjects who withdraw or who are removed from the study for any reason after being randomized (whether they received their dose of investigational medicinal product (IMP) or not), will not be replaced.

Imaging Sub-Study

In addition to the reasons for withdrawing a subject from the main study listed above, if a subject participating in the imaging sub-study has an adverse reaction to the contrast agent, becomes pregnant, or develops moderate to severe renal dysfunction (i.e., an eGFR $\leq$ 40 mL/min/1.73 m^2) they should be withdrawn from the imaging sub-study and undergo no further MRI assessments.

Withdrawal from the imaging sub-study does not impact the subject's participation in the main study. However, if a subject participating in the imaging sub-study exits the main study early, they will also be withdrawn from the imaging sub-study. An early exit visit will be performed, and an early exit MRI acquired on or immediately following the visit. If the early exit MRI is within 2 months of the previous MRI scan, then an MRI does not need to be performed, except in the case that the previous MRI was performed prior to dosing and the early exit MRI will be the only MRI collected post IMP administration. The early exit MRI will be conducted in this instance.

6. RANDOMIZATION, BLINDING AND UNBLINDING

6.1 Randomization

At Screening Visit 1a subjects will be assigned a unique subject identification (ID) number that will be used throughout the study. The Investigator will maintain a list of subject ID numbers and names to enable records to be found at a later date.

Randomization will take place at Visit 2, before IMP administration. Randomization will be performed centrally, based on a pre-defined computer-generated randomization list accessed via an interactive response technology (IRT) system. The IRT system will ensure random allocation of eligible subjects in a 1:1 ratio to EP-104IAR 25 mg or vehicle treatment groups.

A statistician otherwise not involved in the trial will generate the randomization scheme. The randomization list will not be available to any person involved in the conduct and evaluation of the trial until the trial database is declared clean and locked.

6.2 Blinding

This is a double-blind study where subjects and assessors will be blinded to treatment allocation. Due to the impossibility of obtaining identical presentations of EP-104IAR and vehicle control, blinding at each site will be achieved by appointing 1 unblinded individual responsible for administering treatments and 1 blinded assessor who will perform all follow-up assessments. The blinded assessor should not be present at the time of injection.

Subjects will be blinded to treatment by shielding the subject's view of the IMP and the injection field.

The following laboratory test results could potentially enable blinded site staff to ascertain treatment allocation: morning serum cortisol and serum cortisol values following the ACTH stimulation test. Following randomization, these test results will not be included in the laboratory safety reports provided to the site, but instead will be sent separately to the Medical Monitor for review. The Medical Monitor will contact the Investigator to discuss appropriate steps for confirmatory testing and/or appropriate medical management of the subject if required. As the cortisol values selected to trigger ACTH stimulation testing in this study are deliberately conservative, a large proportion of both EP-104IAR and vehicle subjects will require this test simply due to their natural fluctuations in serum cortisol levels. Therefore, the requirement to perform an ACTH stimulation test does not indicate that a subject received EP-104IAR and vice versa.

6.3 Unblinding

Users assigned unblinded roles within the IRT system will have access to randomization details for all randomized subjects at their site. In the event of an emergency (e.g., an SAE that requires knowledge of treatment, or a pregnancy), the PI may access the IRT system to unblind a single subject. The PI should make every effort to contact the Sponsor or the Medical Monitor before the blind is broken; otherwise, the Medical Monitor will be notified

as soon as possible. In addition, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will also be notified of any emergency unblinding during the study. Emergency unblinding will be documented in the IRT system. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

If breaking the blind is considered necessary for other safety reasons, for example due to signals of alerting adverse drug reactions (ADRs) and regulatory reporting of SUSARs, unblinding can be performed by the Sponsor without compromising blinded members of the trial team, and the reason for unblinding should be documented.

Imaging Sub-Study

Details concerning data management in the imaging sub-study will be described in the Data Management Plan and other appropriate study specific documents. The planned unblinding and analysis of the main study will not be impacted by the ongoing imaging sub-study. All MRI central readers will be blinded to treatment allocation and study visit for the entirety of the imaging sub-study.

7. STUDY TREATMENTS

Detailed instructions on the storage, preparation, administration and accountability requirements for the IMP and non-investigational medicinal products (NIMPs) will be provided in the IMP Handling Manual.

7.1 IMP Dosage Forms/Formulation

All IMP used in this study have been manufactured in accordance with current Good Manufacturing Practice.

7.1.1 EP-104IAR

The EP-104IAR investigational medicinal product is a two-vial system (see Parts A and B in Table 1):

- **Part A**: (EP-104IAR Powder) a sterile powder containing cured PVA-coated FP crystals.
  - FP crystals are coated with biocompatible polymer, PVA, and then heat-treated to crosslink the polymer and form long-acting particles designed to release FP over several months. The PVA membrane represents less than 10% of the drug product composition.
  - 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.
- **Part B**: (vehicle) a sterile liquid containing sterile water and excipients necessary to prepare a uniform suspension of the powder.
  - Each single use vehicle vial includes a 1 mL overage to account for losses during the vehicle transfer and powder suspension constitution process.

The EP-104IAR Powder is suspended in the sterile vehicle immediately prior to IA injection. Instructions for the constitution procedure are provided in the IMP Handling Manual.

7.1.2 Vehicle Control

The placebo control used in this study is 5 mL of vehicle (Part B in Table 1). Vehicle is provided as bulk supplies of single use bottles, containing 6 mL of vehicle and labeled for use in this study.

Table 1 Composition of EP-104IAR

PART A. EP-104IAR Powder		
Component	**Function**	**mg Label Claim (mg Including Overage)[1]**
Fluticasone Propionate, USP	API	25.0 (30.0)
Polyvinyl Alcohol, USP	Release modifier	1.6 (1.9)
PART B. Vehicle		
Component	**Function**	**mg**
Carboxymethyl Cellulose, USP	Viscosity builder	37.5
Polysorbate 80, NF	Suspending agent	0.75
Sodium Chloride, USP	Isotonicity	41.0
Sodium Phosphate Dibasic Heptahydrate, USP	Buffer	10.90
Sodium Phosphate Monobasic, USP	Buffer	1.30
Water for Irrigation, USP	Solvent	QS to 5.00 mL
Total Volume		**5 mL[2]**

1 A small overage is included in each vial to account for losses during constitution prior to injection.
2 Vials are filled with 6 mL to ensure 5 mL can be withdrawn and used to constitute the powder prior to injection.
Notes: API=Active pharmaceutical ingredient; NF=National Formulary; QS=Quantum Sufficit (a sufficient quantity); USP=United States Pharmacopeia.

7.2 Dosage and Administration

7.2.1 Treatment Arms

- EP-104IAR 25 mg constituted in 5 mL of vehicle
- Vehicle control (5 mL)

7.2.2 Dosing and Administration Guidelines

Following randomization, unblinded site staff will prepare and administer the injection according to the instructions provided in the IMP Handling Manual. The injection procedure will be performed by a suitably qualified and experienced physician, except in Denmark, where other study personnel with documented training and long-term experience in IA injections may also perform the injection. Wherever possible the same unblinded injector should administer the drug to all subjects at the site.

To maintain subject blinding to treatment assignment, the subject's view must be shielded to ensure they cannot see the dosing procedure or the filled syringe.

The syringe containing the constituted EP-104IAR or vehicle control should be labeled with the subject number, date and time of dosing.

Knee Preparation

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

Joint Aspiration

Prior to dose administration the unblinded injector will aspirate the subject's knee. The volume of effusion (if any) will be recorded in the eCRF. If it is not possible to extract any synovial fluid this should be noted in the eCRF.

Ultrasound Guidance

Sites are required to administer the injection using ultrasound guidance.

Knee Position

The needle will be inserted via the medial or lateral route with the subject's knee in an extended (non-flexed) position and the entire contents of the syringe (5 mL) should be administered into the synovial space using a 21-gauge 1.5-inch needle (provided by the Sponsor).

Post Administration

A sterile dressing will be applied after the injection is completed, and the subject will be observed for 5 minutes to ensure that they tolerated the injection.

Empty used vials of drug and vehicle and the syringe used for injection will be placed into a residual drug kit container (provided by the Sponsor). The used needles should be discarded according to usual practice. This container will be stored as described in the IMP Handling Manual until drug accountability has been performed by the unblinded Monitor.

7.3 Packaging and Labeling

Packaging and labelling of the IMP and NIMP supplies (including rescue medication) is the responsibility of the Sponsor.

All IMPs and NIMPs will be labelled with a trial-specific labels prior to supply to the site.

All NIMPs (including rescue medication) are commercially available and will be purchased centrally. No modification from the usual commercial state of the NIMPs will be made, except for study-specific labelling.

7.3.1 EP-104IAR Labeling

Study-specific labelling of EP-104IAR will be performed in accordance with the European Union Guidelines for Good Manufacturing Practice, and will comply with Annex 13:

Investigational Medicinal Products, and other applicable local regulatory requirements. For further details, see the IMP Handling Manual.

7.3.2 Vehicle Labeling

Trial-specific labelling of vehicle will be performed in accordance with the European Union Guidelines to Good Manufacturing Practice, and will comply with Annex 13: Investigational Medicinal Products, and other applicable local regulatory requirements. For further details, see the IMP Handling Manual.

7.4 Site Supply, Storage, Accountability

7.4.1 Site Supply

Once a site has been approved to receive IMP, the site will be provided with an initial supply of EP-104IAR vials, vehicle vials, and rescue medication (acetaminophen/ paracetamol). Syringes, labels and needles used for preparation and injections will also be provided. The need for resupply will be assessed on a regular basis considering the number of subjects randomised, and the number of subjects in Screening at the site.

7.4.2 Storage

The IMP supplies should be stored at the trial site (or at the site pharmacy) as required by local regulations and laws for the participating sites. The investigator will ensure that the EP-104IAR and vehicle is stored in secure location under appropriate conditions (controlled room temperature at 20-25°C (68-77°F), with excursions permitted from 15-30°C (59-86°F)). Each site should have a thermometer that records minimum and maximum temperatures daily. Maintenance of a temperature log is mandatory. The log should be updated daily by site personnel. This log must be available for review by the monitor during on-site monitoring visits.

Any deviations in storage temperature must be reported to the Sponsor without delay as instructed in the IMP Handling Manual. In case of temperature deviation or damaged supply upon receipt or during storage at trial site, the affected supplies must not be used until acceptance from the sponsor. The sponsor will decide if the affected supplies may be released back into inventory, returned to the supply vendor, or destroyed locally. The affected supplies should be kept segregated in quarantine of evaluation results in the decision that the supplies cannot be used. Site staff should immediately document the supply status in the IRT system and contact their clinical research associate (CRA) for further guidance.

7.4.3 Accountability

The Investigator is responsible for IMP supplies received from the Sponsor. The Investigator (or delegated person) will ensure that adequate records of the receipt, preparation, administration and return of the IMPs are kept and that the IMP is used only for qualified subjects randomised in the study. All data regarding the IMP must be recorded on the relevant forms provided.

Each site will maintain an IMP inventory/dispensing record for all drugs dispensed and returned. At the end of the study, a copy of the IMP inventory/dispensing record should be sent to the Sponsor for the trial master file. The original will be kept in the site files. These forms are subject to regulatory inspection at any time.

After drug accountability has been completed and verified by the CRA, all unused IMP will be either sent for destruction or returned to the Sponsor. Processes for destruction or returns will be described further in the IMP Handling Manual.

7.5 Rescue Medication

Acetaminophen (paracetamol) 500 mg (up to a maximum of 3,000 mg (i.e., 3 g) per day) is 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 may also be used to treat other painful events not related to the Index knee.

Rescue medication will be dispensed at Visit 1b, with additional supplies dispensed at subsequent visits. Subjects will be required to bring their bottles of used and unopened acetaminophen (paracetamol) to the site at indicated visits to permit the number of pills remaining to be counted and new supplies to be issued.

Subjects will be required to record if they have used rescue medication each day on the ePRO device, see Section 9.1.7.5. Subjects will be asked to refrain from using rescue medication in the 12 hours prior to completing the WOMAC questionnaire, See Section 9.1.7.1.

7.6 IMP Dose Modification

No dose modifications are permitted.

7.6.1 Procedures for Overdose

Overdose should not be possible as each vial of EP-104IAR only contains a small overage to account for residual suspension remaining in the vial and syringe. However, if the intended dose results in extreme local or systemic symptoms, the Investigator should lavage the Index knee with saline and aspirate to remove as much EP-104IAR as possible.

Overdosage of corticosteroids may result in signs/symptoms of hypercorticism. Subjects should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing subjects postoperatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, accepted procedures for the management of symptoms should be followed (e.g., treatment with physiologic hydrocortisone, etc.).

Subjects will be instructed to carry a wallet card identifying the potential risk for AI as a result of participating in the clinical study, and the potential need for emergency glucocorticoid therapy in the setting of shock, surgery, etc.

8. STUDY RESTRICTIONS

8.1 Prohibited Therapy and Concomitant Treatment

Subjects will be advised that unless it is emergency treatment, all new prescriptions must be checked by the study team prior to taking the first dose. Any concomitant treatment given for any reason during the study must be recorded on the eCRF and in the subject's medical records, including dosage, start and stop dates and reason for use.

If a subject uses a prohibited or restricted therapy prior to receiving their dose of IMP they are no longer eligible for randomization and should be withdrawn from the study.

If a subject uses a prohibited or restricted therapy after receiving their dose of IMP they will be asked to remain in the study and complete all safety, efficacy and PK assessments according to the protocol; however, their data might not be used in all analyses. Further details of circumstances that will exclude data from specific analyses will be included in the Statistical Analysis Plan (SAP).

Imaging Sub-Study

For subjects participating in the imaging sub-study, the following restrictions only apply up to Visit 9. After Visit 9 (i.e., from weeks 24-52), there are no restrictions for any therapies.

8.1.1 Permitted Therapies for Index Knee OA Pain

The following are permitted to treat OA pain in the Index knee:

- Acetaminophen (paracetamol) up to 3,000 mg/day (i.e., 3 g)
- Heating and cooling pads
- Physiotherapy

8.1.2 Restricted Therapies

Selected corticosteroids are **permitted with the following restrictions**:

- High-potency topical corticosteroids (Table 2) may be used when necessary, for up to 5 consecutive days in any location except for the Index knee. Subjects should avoid using topical corticosteroids on more than 5% of their body surface area if possible (e.g., 10 x 10 inches or 25 x 25 cm, half an arm).
- Mid- to low-potency topical steroids (Table 2) may be used in any location except for the Index knee. Subjects should avoid using topical corticosteroids on more than 5% of their body surface area if possible (e.g., 10 x 10 inches or 25 x 25 cm, half an arm).
- Inhaled and intranasal corticosteroids are not permitted from the start of the Washout period until at least 4 weeks post-dose but may be used after this time.

- Intravitreal corticosteroids are permitted (with no restrictions).

Table 2 Topical Corticosteroid Potency Chart

Class	Examples of Generic Drug Names, Strengths and Formulations
1-2 (High Potency)	Amcinomide (0.1% cream, lotion, ointment)
	Betamethasone dipropionate (0.05% cream, gel, ointment)
	Betamethasone valerate (0.1% ointment)
	Clobetasol propionate (0.05% cream, foam, lotion, ointment, shampoo, solution)
	Desoximetasone (0.05% gel, 0.25% cream, ointment)
	Diflorasone diacetate (0.05% cream, ointment)
	Fluocinonide (0.1% cream, 0.05% cream, gel, ointment)
	Fluocinonide acetonide (0.2% cream, ointment)
	Halcinonide (0.1% cream, ointment)
	Halobetasol propionate (0.05% cream, ointment)
	Mometasone furoate (0.1% ointment)
	Triamcinolone acetonide (0.5% cream, ointment)
3-7 (Mid-Low Potency)	Alclometasone dipropionate (0.05% cream, ointment)
	Betamethasone benzoate (0.025% cream, gel, lotion)
	Betamethasone dipropionate (0.05% lotion)
	Betamethasone valerate (0.1% cream, lotion, 0.12% foam)
	Clorcortolone pivalate (0.1% cream)
	Desonide (0.05% cream, gel, lotion, ointment)
	Desoximetasone (0.05% cream)
	Dexamethasone (any strength/formulation)
	Fluocinolone (0.01% cream, solution)
	Fluocinolone acetonide (0.01% cream, oil, solution, 0.025% cream, ointment)
	Flurandrenolide (0.5% cream, ointment, 0.25% cream, ointment, 0.05% cream, lotion, ointment, tape, 4mcg/cm^2 tape)
	Fluticasone propionate (0.05% ointment, 0.05% cream 0.005% ointment)
	Hydrocortisone (any strength/formulation)
	Hydrocortisone butyrate (0.1% ointment, solution)
	Hydrocortisone valerate (0.2% cream, ointment)
	Methylprednisolone (any strength/formulation)
	Mometasone furoate (0.1% cream, lotion)
	Prednicarbate (0.1% cream)
	Prednisolone (any strength/formulation)
	Triamcinolone acetonide (0.1% cream, lotion, ointment, spray, 0.025% cream, lotion, ointment)

Source: https://line.17qq.com/articles/esrucrarx.html. (Accessed 16 April 2021.)

Table 3 lists medications that are **permitted in subjects who are using stable doses at the Screening Visit** (i.e., no dosage changes ≥25% in the 3 months prior to the Screening Visit) **and who do not plan any dose changes during the study**.

Subjects are **not** permitted to begin taking a **new** prescription drug from this list after the Screening Visit (unless specifically stated otherwise in the table below).

Table 3 Medications Permitted at Stable Doses

Category	Examples and Clarifications
Antidiabetic drugs for treatment of non-insulin dependent diabetes mellitus	Alpha-glucosidase inhibitors, such as: acarbose, miglitol, Biguanides, such as: metformin and metformin combination drugs, Dopamine agonists, such as bromocriptine, Dipeptidyl peptidase-4 inhibitors, such as: alogliptin, linagliptin, saxagliptin, sitagliptin etc. Glucagon-like peptide-1 receptor agonists, such as: albiglutide, dulaglutide, exenatide, liraglutide, semaglutide etc. Meglitinides, such as: nateglinide, repaglinide, etc. Sodium-glucose transporter 2 inhibitors, such as: dapagliflozin, canagliflozin, empagliflozin, ertugliflozin etc. Sulfonylureas, such as: glimepiride, gliclazide, glyburide, chlorpropamide, tolazamide, tolbutamide etc. Thiazolidinediones, such as: rosiglitazone, pioglitazone, etc.
Antidepressants	SSRIs, such as citalopram, escitalopram, fluoxetine, paroxetine, sertraline, etc. SNRIs, such as: desvenlafaxine, duloxetine, levomilnacipran, venlafaxine, etc. Tricyclic antidepressants, such as: amitriptyline, desipramine, doxepin, imipramine, nortriptyline, etc. MAOIs such as: isocarboxazid, phenelzine, tranylcypromine, etc. Atypical antidepressants, such as: bupropion, mirtazapine, trazodone, vilazodone, vortioxetine, etc.
Antiplatelet drugs	e.g., clopidogrel, dipyridamole, dipyridamole/aspirin, eptifibatide, prasugrel, ticagrelor, ticlodipine, etc. Use of a new antiplatelet drug is permitted from 2-weeks post-dose onwards. Low dose aspirin (≤325 mg per day) is permitted
Benzodiazepines	e.g., alprazolam, clonazepam, diazepam, lorazepam, midazolam, oxazepam, temazepam, etc.
Non-benzodiazepine hypnotics	e.g., eszopiclone, zaleplon, zolpidem, zopiclone, etc.

Notes: MAOIs=Monoamine oxidase inhibitors; SNRIs=Serotonin and norepinephrine reuptake inhibitors; SSRIs=Selective serotonin reuptake inhibitors.

8.1.3 Prohibited Therapies

Table 4 lists drugs and non-drug therapies that are **not permitted at any time** during the study.

Table 4 Prohibited Drugs and Therapies

Category	Clarifications and Examples (Not Exhaustive)
Acupuncture	For the Index knee
Analgesics	Acetaminophen (paracetamol) >3,000 mg/day (i.e., 3 g)
Analgesics – oral NSAIDs	Includes prescription and over-the-counter products Includes cox-2 selective inhibitors Low dose aspirin (≤325 mg per day) is permitted

Table 4 Prohibited Drugs and Therapies (Cont'd)

Category	Clarifications and Examples (Not Exhaustive)
Analgesics – topical NSAIDs and capsaicin	Not permitted for use on the Index knee. For pain in other locations, avoid using on more than 5% of body surface area (e.g., 10 x 10 inches or 25 x 25 cm, half an arm) e.g., capsaicin, diclofenac, ibuprofen, ketoprofen, piroxicam, indomethacin, etc.
Analgesics - opioids	Includes tramadol and tapentadol e.g., codeine, fentanyl, hydrocodone, hydrocodone/acetaminophen (paracetamol), hydromorphone, meperidine (pethidine), methadone, morphine, oxycodone, oxycodone and acetaminophen (paracetamol), oxycodone and naloxone, etc.
Anesthetic medications injected into the Index knee	Except for Lidocaine (lignocaine) used during dose administration
Anticoagulants	e.g., apixaban, dabigatran, edoxaban, enoxaparin, fondaparinux, heparin, rivaroxaban, warfarin, etc.
Anticonvulsants and mood stabilizers	e.g., carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine, topiramate, valproic acid, and valpromide, etc.
Antidiabetic drugs	e.g. insulin (short to long-acting) and combination therapies containing insulin).
Antipsychotics (typical or atypical)	e.g., aripiprazole, aripiprazole lauroxil, asenapine, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone, lurasidone, olanzapine, paliperidone, paliperidone palmitate, perphenazine, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, ziprasidone, etc.
Corticosteroids	All oral corticosteroids. Topical corticosteroids applied to the Index knee. IA, intravenous, intramuscular, and soft-tissue injection of any other corticosteroid in any location
CNS stimulants/depressives	e.g., amphetamines, barbiturates, cocaine, opiates, marijuana or THC, etc.
Immunosuppressive therapies	e.g., corticosteroids, tofacitinib, cyclosporine, sirolimus (rapamycin), everolimus, azathioprine, leflunomide, abatacept, adalimumab, anakinra, etanercept, infliximab, vedolizumab, basiliximab, daclizumab, etc.
Lithium or lithium salts	
Natural health or non-prescription products that claim to be effective for pain or OA	e.g., glucosamine sulfate, chondroitin sulfate, MSM, etc.
Non-drug IA injections in the Index knee	e.g., hyaluronic acid, prolotherapy (e.g. dextrose), platelet rich plasma, etc.
Osteoporosis treatments	e.g., abaloparatide (Tymlos), alendronate (Fosamax), denosumab (Prolia, Xgeva), ibandronate (Boniva), risedronate (Actonel), Teriparatide (Forteo), zoledronic acid (Reclast), etc.
Strong CYP3A4 inhibitors	e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, etc. FP (the active ingredient of EP-104IAR) is a substrate of CYP3A4. The use of strong CYP3A4 inhibitors with FP is not recommended as increased systemic corticosteroid adverse effects may occur.

Notes: CNS=Central nervous system; CYP3A4=Cytochrome P450 3A4 enzyme; FP=Fluticasone propionate; IA=Intra-articular; MSM=Methylsulfonylmethane; NSAIDS=Non-steroidal anti-inflammatory drugs; OA=Osteoarthritis; THC=Tetrahydrocannabinol.

8.2 Permitted Methods of Birth Control

Female subjects of childbearing potential must practice a highly effective method of birth control throughout the study. Contraceptive measures will be reviewed with patients during the informed consent process.

The following methods of birth control are considered highly effective:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral, intravaginal, or transdermal.
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral, injectable, or implantable.
- intrauterine device (IUD).
- intrauterine hormone-releasing system (IUS).
- bilateral tubal occlusion.
- vasectomised partner.
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire study and consistent with the usual lifestyle of the subject).

9. STUDY PROCEDURES

If a site has sub-Investigators participating in the study, follow-up assessments should be made by the same Investigator/sub-Investigator (blinded assessor) for a specific subject, to the extent possible, for consistency of evaluations over time.

Timings for all assessments are provided in the Schedule of Events.

Whenever possible any subject reported outcome measures should be completed prior to any invasive procedures at the site (e.g., prior to blood draws etc.).

9.1 Description of Study Assessments

9.1.1 Demographics

Date of birth (month/year), age, sex, ethnicity and race, height, weight and BMI will be collected.

9.1.2 Medical and OA History

A full medical history and detailed OA history will be collected, including documentation of prior OA medications and all concomitant medications and therapies.

Diagnosis of OA will be confirmed using the ACR clinical and radiographic classification criteria for OA of the knee (Altman, et al., 1986):

		At least 1 of:		
Knee Pain	+	Age >50 years Morning stiffness <30 minutes Crepitus	+	Osteophytes

9.1.3 Imaging Assessments

9.1.3.1 X-ray Imaging/Kellgren-Lawrence Grading

X-rays will be sent to a central imaging laboratory for standardized Kellgren-Lawrence grading according to the criteria in Table 5 below.

If the subject presents with two potentially eligible knees at Screening, an x-ray of both knees should be provided to help identify the Index knee. If subjects have only one affected knee (or only one knee is potentially eligible), then only an x-ray of the affected/potentially eligible knee is required.

X-rays must be performed according to the Imaging Protocol provided. If suitable x-rays for the evaluation of the subject's knee OA were performed within the 6 months prior to the Screening Visit 1a, they may be transferred to the central reader laboratory for review. If no suitable x-ray has been performed the subject should be sent for a new x-ray. The central reader laboratory will provide a report containing the subject's Kellgren-Lawrence grade to the site to aid with assessment of subject eligibility.

Table 5 Kellgren-Lawrence Grading Scale Criteria

Grade	Description
Grade 0	No radiological findings of osteoarthritis
Grade 1	Doubtful narrowing of joint space and possible osteophytic lipping.
Grade 2	Definite osteophytes, possible narrowing of joint space.
Grade 3	Moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone contour.
Grade 4	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour.

9.1.3.2 Magnetic Resonance Imaging

Imaging Sub-Study Only

The imaging sites will be qualified to ensure research conversance and suitability of facilities. The imaging site personnel will be trained by imaging experts prior to initiation of the study. Imaging data will be redacted to ensure that subject identifiers are removed, and the image will be transmitted to a core imaging laboratory, stored in a central imaging database for the study and assessed by central expert reader(s).

All images (MRI) will be read centrally by a blinded radiologist appointed by the central imaging lab, who is not directly involved in the treatment or clinical evaluation of the subject. The blinded radiologist will remain blinded for the Week 52 MRI scans.

DCE-MRI of the index knee will be used to perform analyses that will potentially inform on the duration and local safety of EP-104IAR. These analyses will include measurements related to synovial inflammation (synovial thickness, synovial blood flow), cartilage volume and the status of the articular cartilage (cartilage morphology) assessments. A macrocyclic GBCA will be administered intravenously to subjects, prior to the MRI at baseline, and Weeks 12, 24, and 52, in accordance with the instructions provided in the MRI Imaging Charter which will also detail the exact imaging protocol and MRI sequences.

If feasible, the reader of the images should remain the same for the duration of the study, to minimise the risk of inter-reader variability.

DCE-MRIs will be performed using a validated protocol at the time points specified in the Schedule of Events. The minimum requirement will be for the MRI provider to use a 1.5 or 3 Tesla scanner. The MRI protocol and scanner settings will be calibrated between the imaging sites and maintained for all sites for the duration of the study.

9.1.4 Selection of the Index knee

For subjects who present with two potentially eligible knees at Screening it will be necessary to identify which knee is the Index knee (the Index knee is the knee in which IMP/vehicle control is to be administered and all efficacy and safety assessments are performed from Visit 2 onwards).

Selection of the Index knee will occur prior to randomisation at Visit 2, following final review of all eligibility criteria. To aid the sites in their review of eligibility criteria and selection of the Index knee, the ePRO devices will provide a summary of the Washout and Baseline diary entries for each knee, including (at minimum) the number of daily and weekly pain recordings and the Weekly WOMAC Pain scores. The criteria in Table 6 below will be used to help select the Index knee.

If both knees meet all the criteria for the Index knee and do not exceed the maximum permitted WOMAC Pain subscale scores for the non-Index knee, then the worst knee is selected as the Index knee. If the WOMAC Pain scores are the same in both knees, the Investigator may select either knee as the Index knee in consultation with the Subject.

Table 6 Criteria for Selecting the Index knee in Subjects with a Diagnosis (or Symptoms) of Bilateral Knee OA at Screening

Criteria	Index Knee	Non-Index Knee
Diagnosis of primary OA of the knee (per ACR clinical and radiological criteria)	Required	Not required
	AND	**AND**
Subject reports OA symptoms present at least 6 months prior to Screening	Required	Not required
	AND	**AND**
Kellgren- Lawrence Grade	2 or 3	Not required
	AND	**AND**
Both WOMAC Pain subscale scores in the Washout & Baseline Period	≥ 4.0 to ≤9.0 (out of 10) and do not vary by >3 points	≤6.0 (out of 10)

Notes: ACR=American College of Rheumatology; OA=osteoarthritis; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

9.1.5 Safety Assessments

Safety will be assessed through AE reporting, vital signs, clinical laboratory evaluations, and physical/knee examinations.

During the study, all clinical events spontaneously reported by the subject, observed by site staff or elicited by general questioning will be reported in the eCRF. Subjects will be questioned on their health status at each visit. Open-ended questions will be asked to elicit information about AEs (see Section 10 for details).

The Investigator will receive and review the laboratory results for all subjects at their site and will review the data for all other assessed safety variables.

9.1.5.1 Clinical Laboratory Assessments

Detailed instructions on the collection, processing, handling and shipping of laboratory samples will be provided in the Laboratory Manual.

Blood samples will be analyzed for the following:

- Hemoglobin, hematocrit, erythrocytes (RBC), leukocytes (WBC), WBC differential (including total lymphocyte count and absolute neutrophil count), platelets
- HbA1c at Screening and Week 24 (End-of-Study/Early Exit Visit) only
- Alkaline phosphatase (ALP), ALT, AST, bicarbonate, bilirubin (total), blood urea nitrogen (BUN), chloride, creatinine, glucose (non-fasting), potassium, protein (total), sodium, uric acid
- Serum cortisol (see Section 9.1.5.1.1 below)

Urine samples will be analyzed for the following:

- pH, specific gravity, protein, glucose, ketones, bilirubin, hemoglobin, leukocytes, nitrite

Imaging Sub-Study

For subjects participating in the imaging sub-study, the most recent creatinine result will be used to calculate eGFR to confirm eligibility for MRI, e.g.:

- Visit 2: eGFR is calculated using the Screening Visit creatinine value.
- Visit 7: eGFR is calculated using either the Visit 6 or Visit 7 creatinine value.
- Visit 9: eGFR is calculated using either the Visit 8 or Visit 9 creatinine value.
- Visit 10: eGFR is calculated using the Visit 9 creatinine value

Estimated GFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey, et al., 2009).

The clinical significance of out-of-range clinical laboratory findings will be determined and documented by the Investigator (or sub-Investigator).

9.1.5.1.1 Serum Cortisol

Blood samples for serum cortisol must be collected in the morning between 7 a.m. and 11 a.m. (exception: the ACTH stimulation test performed during Screening may be performed at any time of day).

During Screening, serum cortisol results from the samples collected during the ACTH stimulation test will be reported directly to the site for eligibility evaluation purposes.

Following randomization (Visit 2 onwards), serum cortisol results and ACTH stimulation test results will not be reported to the sites. Results will be reported separately to the Medical Monitor for review. See Section 6.2.

9.1.5.1.2 ACTH Stimulation Test

The ACTH stimulation test measures the ability of the adrenal cortex to respond to ACTH by appropriately producing cortisol. It is used to help diagnose adrenal insufficiency (AI).

The ACTH stimulation test involves the following steps (full details will be provided in the Laboratory Manual). Subjects are not required to be fasting for this test. The ACTH stimulation test may be performed at any time of day.

The procedure for the ACTH test is as follows:

- A baseline blood sample will be collected to measure serum cortisol and ACTH
  - If the ACTH stimulation test occurs on a scheduled visit where a morning serum cortisol sample is already being collected between 7 and 11 a.m., only a baseline blood sample for the measurement of ACTH is required.
- Inject the provided cosyntropin into the subject's shoulder muscle
- 30 minutes (±5 minutes) post-injection, collect a blood sample to measure serum cortisol
- 60 minutes (±5 minutes) post-injection, collect a blood sample to measure serum cortisol

The test will be performed in the following circumstances:

- **Visit 1a – Visit 1b** (Screening) in all subjects
  - This is to identify subjects with existing, undiagnosed AI, so they can be excluded from the study.
- If the subject's **Visit 6** (Week 8) serum cortisol is <350 nmol/L (<12.7 µg/dL), perform the ACTH stimulation test at **Visit 7** (Week 12)
  - This is intended to identify if a subject with serum cortisol levels at the lower end of the normal range has developed asymptomatic AI in response to peak exposures of EP-104IAR.
  - If the subject's **Visit 7** (Week 12) ACTH stimulation test is abnormal, repeat the ACTH stimulation test at **Visit 9** (Week 24/End-of-Study/Early Exit Visit).
- If the subject's **Visit 9** (Week 24/End--of--Study/ Early Exit Visit) serum cortisol is <350 nmol/L (<12.7 µg/dL), perform the ACTH stimulation test at an **Unscheduled Visit**
  - This is intended to identify if a subject with serum cortisol levels at the lower end of the normal range has developed slow developing asymptomatic AI in response to EP-104IAR administration, as it can take several weeks for AI to develop following adrenal atrophy.

  - Not required if the subject has already completed an ACTH test at Visit 9 due to an earlier abnormal ACTH result.

- If the subject's serum cortisol is ≤138 nmol/L (≤5 µg/dL) at **any visit** after dose administration **AND** they experience signs and symptoms of AI (see Section 10.2.5), perform the ACTH stimulation test at the **next scheduled visit**.

See Figure 2 below.

During Screening, sites will receive serum cortisol results from the ACTH stimulation test directly from the central safety laboratory to determine subject eligibility. At all later timepoints serum cortisol results will be received by the unblinded Medical Monitor, who will inform the site which subjects should undergo the ACTH stimulation test. ACTH stimulation test results will be reported to the unblinded Medical Monitor for review.

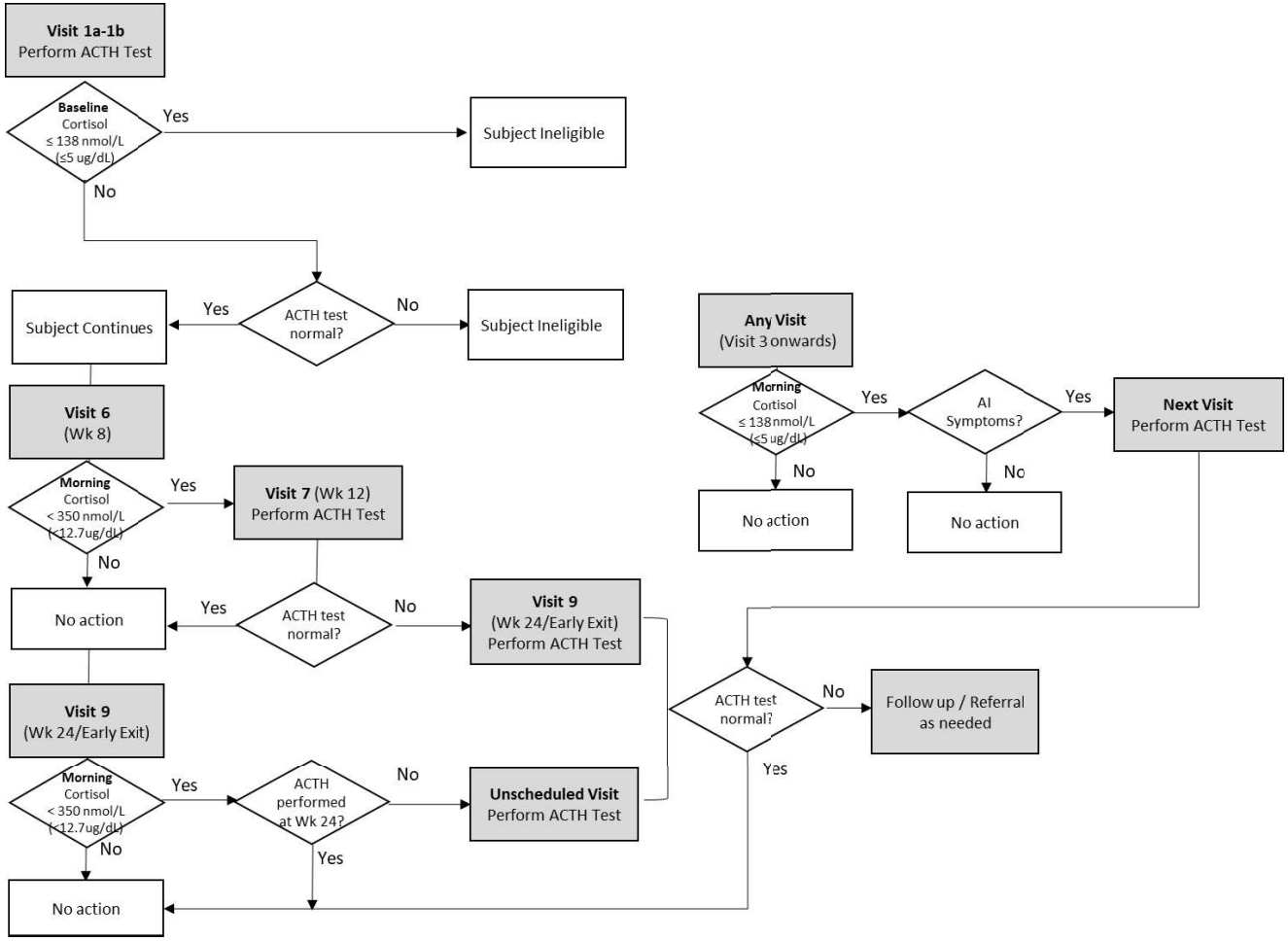
Criteria for evaluating if the ACTH stimulation test response is normal or abnormal are provided in the Laboratory Manual.

If the results of the ACTH stimulation test are considered to be abnormal and the subject also displays symptoms of adrenal suppression, they should be managed accordingly and may require glucocorticoid replacement therapy (e.g., with physiologic hydrocortisone). If appropriate, such subjects should be referred to an Endocrinologist (or other appropriate specialist) for further evaluation and treatment.

The ACTH stimulation test is extremely sensitive (95% sensitivity and 97% specificity); however, this translates to a false positive result in approximately 1 out of every 20 tests. The ACTH stimulation test will be repeated at the End-of-Study Visit in any subjects with an abnormal test result at Week 12.

Subjects who are diagnosed with AI following dose administration should be managed by their Endocrinologist (or other appropriate specialist) until resolution. If the subject's AI is ongoing at their final scheduled study visit, the Investigator should follow-up with the subject approximately 3 months later, with at least 1 additional contact during that 3-month period.

Figure 2 Triggers for ACTH Stimulation Testing



Note: ACTH=Adrenocorticotropic hormone Wk=Week.

9.1.5.1.3 Pregnancy Testing

Blood samples collected at Screening Visit 1a will be used to measure human chorionic gonadotropin (hCG) in female subjects of childbearing potential.

Urine samples collected at Visit 2 (pre-dose) and End-of-Study Visit (or Early Exit Visit) will be used for pregnancy testing in female subjects of childbearing potential.

Imaging Sub-Study

Urine samples for pregnancy testing will be acquired before each MRI for female subjects of childbearing potential. At Visit 2, the pregnancy test performed prior to the MRI does not need to be repeated prior to IMP administration.

9.1.5.1.4 Drugs of Abuse Test

Urine will be analyzed for drugs of abuse using the provided urine testing kit.

9.1.5.2 Physical Examination

Physical examinations include assessments of general appearance, skin, HEENT (head, ears, eyes, nose and throat), chest and lungs, cardiovascular, abdomen, musculoskeletal and extremities, neurological, psychiatric and mental status.

9.1.5.3 Knee Examination

At Visit 1a both knees will be examined. From Visit 2 onwards, only the Index knee will be examined.

The subject's knee will be examined for:

- Range of motion (0-45 degrees, 46-90 degrees, 91-135 degrees)
- Presence of an effusion (Stroke Test: zero, trace, 1+, 2+, 3+)
  - Zero: No wave produced on downstroke
  - Trace: Small wave on medial side with downstroke
  - 1+: Large bulge on medial side with downstroke
  - 2+: Effusion spontaneously returns to medial side after upstroke
  - 3+: So much fluid it is not possible to move the effusion out of the medial aspect of the knee
- Crepitus on palpation with range of motion (yes/no)
- Stability of collateral ligaments (stable, mild instability, moderate instability, unstable)
- Stability of cruciate ligaments (stable, mild instability, moderate instability, unstable)

- Warmth and tenderness on palpation of the joint (yes/no)
- Skin appearance (scars, redness, bruising, swelling; all as yes/no)
- Gait (normal, mild antalgia, moderate antalgia, severe antalgia)

If the examination reveals findings that indicate a possible infection in the Index knee (e.g., the knee is red and swollen with a moderate or large effusion, or is hot and swollen with a moderate or large effusion), a blood sample will be collected for hematology testing and the subject should be referred for further specialist assessment as soon as possible. If an Index knee joint infection is suspected, this should be reported as an SAE (see Section 10.1.4 for details), and every effort should be made to retrieve documentation of the diagnosis and diagnostic procedures performed. If an Index knee finding appears to meet the criteria for further investigation and/or review by the SRC, contact the Medical Monitor (see Sections 4.3 and 4.4 for details).

9.1.5.4 Vital Signs

Vital signs include seated blood pressure (BP), heart rate (HR), respiration rate (RR) and body temperature.

Vital signs will be measured and recorded at every visit (except Visits 1b and 3). When vital signs are scheduled for the same visit as a blood sample, vital signs will be taken before the blood sample. At Visit 2, vital signs will be obtained prior to and approximately 1 hour after dosing.

Vital signs will be collected after the subject has been in a seated position for at least 5 minutes with both feet flat on the floor and the measurement arm supported so that the mid-point of the manometer cuff is at heart level. At each visit BP should be obtained using the same cuff size and the same arm. BP should be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

9.1.6 Pharmacokinetic Assessments

9.1.6.1 Plasma

The PK of EP-104IAR will be assessed by analysis of plasma levels of FP. A validated method will be used for measuring FP in the blood. Detailed instructions on the collection, processing, handling and shipping of plasma samples will be provided in the Laboratory Manual.

9.1.6.2 Used Injection Kits

Empty vials and syringes used to administer EP-104IAR will be retained after administration and stored at the site according to the instructions in the IMP Handling Manual until drug accountability has been completed. After this time, they will be shipped to the bioanalytical laboratory for residual drug analysis to calculate the delivered dose for each subject. The timing of drug accountability visits will be detailed in the Clinical Monitoring Plan.

9.1.7 Efficacy Assessments

Efficacy will be assessed using several patient-reported outcome measures and the MDGA. The following patient-reported measures will be collected using the ePRO device: WOMAC Index, NPRS, rescue medication / non-drug therapy, and physical activity levels.

The PtGA and SF-36 measures will be collected using an ePRO module in the site eCRF.

9.1.7.1 WOMAC® Index

The WOMAC® Index (Version 3.1, 11-point numeric rating scale (NRS), 24-hour recall) is a disease-specific, self-reported measure to assess pain, stiffness and physical function in subjects with knee OA. It consists of 24 items divided amongst 3 subscales to evaluate pain, stiffness and physical function (Bellamy, 2005).

- The Pain subscale evaluates pain associated with OA of the Index knee during walking, using stairs, in bed, sitting or lying, and standing.

- The Stiffness subscale evaluates stiffness associated with OA of the Index knee after first walking and later in the day.

- The Physical Function subscale evaluates physical function related to stair use, rising from sitting, standing, bending, walking, getting in/out of a car, shopping, putting on/taking off socks, rising from bed, lying in bed, getting in/out of bath, sitting, getting on/off toilet, heavy household duties, and light household duties.

The WOMAC Index is a reliable, valid and sensitive measure of disability associated with OA of the knee. An electronic version of the questionnaire will be completed by the subject using the ePRO device.

- The WOMAC Pain subscale, will be completed **weekly**, preferably in the **morning**.
  - During the Washout and Baseline period WOMAC Pain will be recorded for both knees
  - From Visit 2 onwards WOMAC Pain will be recorded for the Index knee

- The full WOMAC Index (Pain, Physical Function and Stiffness subscales) will be completed at Visit 2 (pre-dose) and then **monthly** (every 4 weeks), preferably in the **morning** for the Index knee.

Subjects will be asked to refrain from using rescue medication in the 12 hours prior to completing the WOMAC questionnaire whenever possible. The ePRO device will provide a reminder and will ask if the subject complied e.g. “Did you use any rescue medication in the last 12 hours?” (Yes/No). The WOMAC questionnaire will be completed regardless of the subject’s response.

9.1.7.2 NPRS – Numerical Pain Rating Scale

Subjects will rate their daily Index knee pain throughout the study using the NPRS. During the Washout and Baseline Period this question will be asked separately for each knee. From Visit 2 onwards NPRS scores will only be collected for the Index knee. Subjects will enter scores each **evening** directly into the ePRO device provided.

The question for the subject is: "How was your pain level in your (right/left) knee over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
None	Mild			Moderate			Severe			Worst Pain Imaginable

9.1.7.3 PtGA – Patient Global Assessment of Arthritis

The subject will assess his/her current disease activity using the PtGA NRS (0-10), where 0 equals "Very Good" and 10 equals "Very Poor".

The question for the subject is: "Considering all of the ways your arthritis in your left/right knee affects you and your life, how are you doing today?"

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Very Good	Good			Fair			Poor			Very Poor

Scores will be completed by the subject in the eCRF at the site.

9.1.7.4 SF-36 Health Survey

The SF-36 Health Survey Version 2 (Acute, 1-week recall) is a widely used patient-based generic quality-of-life questionnaire containing 36 items measuring health in 8 domains (Ware & Sherbourne, 1992). These include physical functioning, role limitations due to physical health problems, role limitations due to emotional problems, social functioning, vitality, mental health, bodily pain and general health perceptions. The questionnaire will be completed by the subject using the eCRF at the site.

9.1.7.5 Rescue Medication/Non-Drug Therapy

Subjects will be required to record their use of rescue medication using the ePRO device. A daily question "Did you use any of the provided rescue medication over the past 24 hours?" (Yes/No) will be asked each **evening**.

If yes, a follow-up question on whether rescue medication was used to treat pain in the Index knee will also be asked. E.g., "Did you use the provided rescue medication to treat pain in your affected knee?" (Yes/No)

Subjects will not be required to record the number of pills used each day. Instead, the site's accountability/pill counts will be entered into the eCRF and will be used to calculate an approximate average number of pills used per day and/or per week, over the study period. Subjects will be asked to refrain from using rescue medication in the 12 hours prior to completing the WOMAC questionnaire whenever possible.

Using the ePRO device, subjects will also be asked to record:

- the use of other pain medications. A daily question "Did you use any other pain medications over the past 24 hours for any reason?" (Yes/No) will be asked each **evening**.

- the use of any non-drug rescue therapies. A daily question "Did you use any Physiotherapy or heat/cold compresses over the past 24 hours?" (Yes/No) will be asked each **evening**.

9.1.7.6 Physical Activity Levels

Subjects will be asked to evaluate their level of physical activity using the ePRO device. A daily question "How would you describe your level of physical activity today?" (Low/ Moderate/High) will be recorded each **evening**.

9.1.7.7 MDGA-Physician's Global Assessment of Arthritis

This measurement is intended to capture the Investigator/blinded assessor's clinical opinion based on the entirety of information available at each visit. e.g., the Investigator/blinded assessor can consider the subject's reported OA symptoms by asking "How is your knee pain and stiffness today?" or "How is your knee feeling today?", review the PtGA, and review any AEs or knee examination findings that might indicate a change in disease activity/severity.

The Investigator/blinded assessor will assess the subject's current disease activity using the NRS (0-10), where 0 equals "None" and 10 equals "Very Severe".

The question is: "How would you describe the patient's disease activity today?"

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
None	Mild			Moderate			Severe			Very Severe

9.1.8 Exploratory Assessments

9.1.8.1 Question on Treatment Received

Following completion of all other safety, PK and efficacy assessments at Visit 9 (End of study/Early-Exit Visit) the subject and the blinded assessor will each be asked the following question:

"Do you think (you/the subject) received the test medication or the placebo?" (Test medication / Placebo)

Why do you think this (check all that apply)?

- ☐ Knee pain
- ☐ Knee function
- ☐ Knee stiffness
- ☐ Quality of life
- ☐ Adverse effects
- ☐ Other (specify) _____

The responses to this question may be useful when interpreting any unusual or unexpected physician or patient-reported outcome measures.

9.2 Schedule of Assessments

For a detailed schedule of assessments (including all protocol required assessments, visits and visit windows) please refer to the Schedule of Events.

9.2.1 Visit 1a and Visit 1b: General Screening (Day -56 to -15)

Informed consent will be obtained prior to performing any study related procedures or assessments.

Site staff will be trained in methods of approaching and speaking to potential study subjects in a manner that conveys a neutral expectation of treatment effectiveness.

After signing the informed consent, the following data will be collected and study procedures will be performed per Schedule of Events, to assess subject eligibility for the study:

- Demographics (birthdate (month/year), age, sex, race, ethnicity, height, weight, BMI).
- OA history (to be confirmed by review of medical records if possible).
- Medical and surgical history.
- Prior and concomitant medication (conmed) use, including the subject's reported response to prior OA treatments.
- Vital signs.
- Physical examination including knee exam in both knees.
- In-clinic patient-reported score of typical OA knee pain when not using medication.

- Subjects will be asked separately for each knee: "What is your typical level of knee OA pain in your left/right knee when you do not use pain medication?

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
None	Mild			Moderate			Severe			Worst Pain Imaginable

- Blood samples for safety laboratory analysis (hematology, clinical chemistry, pregnancy testing and HbA1c).
- An ACTH stimulation test. This test may be performed at any time during Screening, including at Visit 1b.
- Urine samples for safety urinalysis and drugs of abuse testing.
- X-rays will be collected and reviewed centrally to evaluate OA severity for eligibility purposes using the Kellgren-Lawrence grading scale.
  - If an x-ray from within the past 6 months is not available in the subject's medical records, a new one will be performed.
  - If both knees are potentially eligible at Screening, an x-ray of both knees should be performed to help identify the Index knee.
- During Screening (Visit 1a or 1b) potential subjects will receive training and information about clinical trials, placebo/vehicle control, the placebo response and the importance of accurately reporting their pain and symptoms.

9.2.2 Visit 1b: Initiate Washout & Baseline (Day -15, window -2 days)

Subjects will be instructed how to begin washout of their current pain medications and will be trained in the use of the ePRO device.

Subjects will be provided with a bottle of rescue medication (acetaminophen/paracetamol) to be used (if needed) during the study and the rules around use and recording of rescue medication will be explained.

9.2.3 Washout and Baseline Period (Day -14 to -1, window -2 days)

Following Visit 1b, subjects will begin a 2-week Washout and Baseline Period, from which their baseline and qualifying pain will be determined. Subjects taking disallowed pain medications will be required to washout during this period. Subjects will be instructed to begin recording their daily and weekly measurements using the ePRO device provided at the start of this period and will continue recordings until the end of the study.

Daily and weekly measurements will be collected during this entire period and will be used to determine eligibility, as described below.

Daily pain scores in each knee will be recorded using the 11-point NPRS. **Daily** questions on rescue medication usage, non-drug rescue therapies and physical activity levels will also be completed. Subjects will be reminded to answer these questions at approximately the same time each day, in the **evening** before retiring.

Weekly scores in each knee will be recorded preferably in the **morning** using the WOMAC Pain subscale.

Eligibility for randomization at Visit 2 will be calculated based on:

- Number of daily pain recordings (each knee).
  - Subjects must complete at least 5 out of 7 of the daily NPRS scores in each week of the Washout and Baseline Period.
- The two WOMAC Pain subscale scores in the Index knee (collected at the end of each week of the Washout and Baseline Period).
  - Subjects must complete both weekly WOMAC Pain subscales for the Index knee.
  - The WOMAC Pain subscale comprises 5 questions each scored 0-10. The 5 scores are added together and divided by 5 to give a composite score out of 10.
    - The 2 composite scores must each be ≥4.0 and ≤9.0.
    - The 2 composite scores must not differ (vary) by more than 3 points.
- The two WOMAC Pain subscale scores in the non-Index knee (collected at the end of each week of the Washout and Baseline Period).
  - The 2 composite scores are both ≤6.0.

If a Subject fails to complete scheduled assessments during the Washout and Baseline Period for reasons outside their control (e.g., technical issues or a misplaced, lost, or broken ePRO device) and is willing to continue in the study, the Sponsor may agree (at their discretion) to the subject re-starting the 2-week Washout and Baseline Period if it can be completed within the 8-week Screening period.

9.2.4 Visit 2: Baseline and Dosing (Day 1)

9.2.4.1 Pre-Dose Procedures

Subjects will return to the site once the Washout and Baseline Period is complete. Subjects will be required to bring their ePRO device and any unused rescue medication to the site.

Following review of eligibility and Index knee selection, qualified subjects will be randomized to receive a single IA injection of EP-104IAR or vehicle control in their Index knee.

In addition to confirming eligibility, **pre-dose activities** include:

- Blood samples for hematology, clinical chemistry, cortisol and PK analyses.
- Urine collection for safety urinalysis, pregnancy test and drugs of abuse.
- Vital signs.
- Physical exam.
- Exam of Index knee.
- Weight.
- PtGA.
- MDGA.
- WOMAC Index.
- Health status (SF-36).
- Recording changes in procedures or conmed use.

Imaging Sub-Study

Subjects who volunteer to participate in the imaging sub-study will have a separate visit for baseline MRI to be performed prior to all pre-dose activities listed above.

The baseline MRI can occur on a separate day but must be within 5 days before dosing.

For women of childbearing potential, the pre-dose urine sample for pregnancy testing will be collected prior to the baseline MRI to confirm eligibility for the MRI scan. This does not need to be repeated prior to dosing

9.2.4.2 Dosing Procedures

The dosing procedure is outlined in Section 7.2.2.

9.2.4.3 Post-Dose Procedures

The following activities will be completed after dosing:

- Recording of any AEs.
- Vital signs 1 hour post-dose (a -15 /+30-minute window is permitted).
- Plasma PK sample 2 hours post-dose (a -15/+15-minute window is permitted).
- Rescue medication accountability will be performed (returned pills will be counted) and additional rescue medication provided if necessary.
- Reminder on the use of the ePRO device will provided.

9.2.5 Visits 3–9: Follow-up (Weeks 1–24)

Following dose administration, subjects enter the Follow-up Period and should complete all assessments per the Schedule of Events. The majority of data will be collected by the subject at home using an ePRO device.

Daily:

- NPRS for the Index knee, measured in the **evening**.
- Question on rescue medication use, measured in the **evening**.
- Question on other non-drug rescue use, measured in the **evening**.
- Question on activity level, measured in the **evening**.

Weekly:

- WOMAC Pain subscale for the Index knee, measured preferably in the **morning**.
- Subjects will be asked to refrain from using rescue medication in the 12 hours prior to completing the WOMAC questionnaire whenever possible. The ePRO device will provide a reminder and will ask if the subject complied, e.g., "Did you use any rescue medication in the last 12 hours?" (Yes/No). The questionnaire will be completed regardless of the subject's response.

Monthly (Every 4 weeks)

- WOMAC Index (Pain, Function and Stiffness subscales) for the Index knee, preferably measured in the **morning**.
- Subjects will be asked to refrain from using rescue medication in the 12 hours prior to completing the WOMAC questionnaire whenever possible. The ePRO device will provide a reminder and will ask if the subject complied, e.g., "Did you use any rescue medication in the last 12 hours?" (Yes/No). The questionnaire will be completed regardless of the subject's response.

Subjects will attend 7 scheduled visits during the Follow-up Period. Visits should occur in the morning whenever possible (to ensure serum cortisol assessments occur at approximately the same time of day - between 7-11 a.m.) and ideally the same day of the week. The same blinded assessor should complete assessments at all visits whenever possible. Between visits, subjects will continue recording daily, weekly and monthly (every 4 weeks) assessments at home using the ePRO device provided.

9.2.5.1 Visit 3 (Day 3 ±1 day)

Subjects will attend the site approximately 48 hours following dosing to provide blood samples for hematology, clinical chemistry, cortisol and PK assessments only. Any AEs reported by the subject will be recorded.

9.2.5.2 Visit 4 (Week 2, Day 15 ±3 days)

The following assessments will be performed at this visit:

- Blood samples for hematology, clinical chemistry, cortisol and PK.
- Vital signs.
- Exam of Index knee.
- Recording of AEs and changes in conmed use.
- Rescue medication accountability will be performed and additional rescue medication provided if necessary.
- Check ePRO device and provide re-training if necessary.

9.2.5.3 Visit 5 (Week 4, Day 29 ±3 days)

The following assessments will be performed at this visit:

- Blood samples for hematology, clinical chemistry, cortisol and PK analyses.
- Urine collection for safety urinalysis.
- Vital signs.
- Exam of Index knee.
- PtGA.
- MDGA.
- WOMAC Index.
- Recording of AEs and changes in conmed use.
- Rescue medication accountability will be performed and additional rescue medication provided if necessary.
- Check ePRO device and provide re-training if necessary.

9.2.5.4 Visit 6 (Week 8, Day 57 ±3 days)

The following assessments will be performed at this visit:

- Blood samples for cortisol and PK.
- Vital signs.
- Exam of Index knee.

- PtGA.
- MDGA.
- WOMAC Index.
- Recording of AEs and changes in conmed use.
- Rescue medication accountability will be performed and additional rescue medication provided if necessary.
- Check ePRO device and provide re-training if necessary.

9.2.5.5 Visit 7 (Week 12, Day 85 ±3 days)

The following assessments will be performed at this visit:

- Blood samples for hematology, clinical chemistry, cortisol and PK analyses.
- **Selected subjects only -** ACTH stimulation test.
- Urine collection for safety urinalysis and drugs of abuse.
- Vital signs.
- Physical exam.
- Exam of Index knee.
- Weight.
- PtGA.
- MDGA.
- WOMAC Index.
- Health status (SF-36).
- Recording of AEs and changes in conmed use.
- Rescue medication accountability will be performed and additional rescue medication provided if necessary.
- Check ePRO device and provide re-training if necessary.

Imaging Sub-Study (Week 12, Day 85 +14 days)

- Review MRI eligibility criteria

- Urine collection for pregnancy test (if applicable)
- MRI

9.2.5.6 Visit 8 (Week 18, Day 127 ±3 days)

The following assessments will be performed at this visit:

- Blood samples for cortisol and PK.
- Vital signs.
- Exam of Index knee.
- PtGA.
- MDGA.
- Recording of AEs and changes in conmed use.
- Rescue medication accountability will be performed and additional rescue medication provided if necessary.
- Check ePRO device and provide re-training if necessary.

9.2.5.7 Visit 9 (Week 24, Day 169 ±7 days) End-of-Study/Early Exit Visit

The following assessments will be performed at this visit:

- Blood samples for hematology, clinical chemistry, HbA1c, cortisol and PK analyses.
- Urine collection for safety urinalysis, pregnancy test and drugs of abuse.
- **Selected subjects only -** ACTH stimulation test.
- Vital signs.
- Physical exam.
- Exam of Index knee.
- Weight.
- PtGA.
- MDGA.
- WOMAC Index.
- Heath status (SF-36).

- Recording of AEs and changes in conmed use.
- Rescue medication accountability will be performed and unused medication collected.
- Check and collect ePRO device.
- The subject and the blinded Assessor will each be asked which treatment they believe was administered.

Imaging Sub-study (Week 24, Day 169 +14 days)

- Review MRI eligibility criteria
- Urine collection for pregnancy test (if applicable)
- MRI

9.2.5.8 Visit 10 (Week 52 Day 356 ±14 days)

Imaging Sub-Study Only

- Review MRI eligibility criteria
- Urine collection for pregnancy test (if applicable)
- MRI
- Recording of AEs and changes in conmed use since Visit 9.
- Recording of medical and OA history since Visit 9

9.2.6 Early Discontinuation Procedures

If the subject is discontinued/withdrawn early from the main study, all assessments for Visit 9/End-of-Study/Early Exit Visit per Schedule of Events should be performed.

Imaging Sub-Study

If a subject participating in the imaging sub-study is discontinued/withdrawn from the main study, an early exit visit will be performed as described above. In addition, an early exit MRI will be acquired on or immediately following the visit.

- If the early exit MRI is within 2 months of the previous MRI scan, then an MRI does not need to be performed, except in the case that the previous MRI was performed prior to dosing and the early exit MRI will be the only MRI collected post treatment administration. The early exit MRI will be conducted in this instance.

If a subject is discontinued/withdrawn early from the imaging sub-study, they may continue participating in the main study at the Investigator's discretion if none of the main study withdrawal criteria apply (see Section 5.4).

9.2.7 Unscheduled Visits

Unscheduled visits may be performed at the Investigator's discretion if there are safety findings of concern at scheduled visit assessments or reported by subjects between visits.

An unscheduled visit should also be performed in the following circumstances:

- **All subjects -** If the subject requires additional rescue medication between scheduled visits, they may call the site to obtain an additional bottle of rescue medication.

- **All subjects -** If at any time during the study a subject independently reports symptoms indicative of an infection in the Index knee (e.g., a red and swollen knee with moderate or large effusion, or a hot and swollen knee with a moderate or large effusion), a blood sample will be collected for hematology testing and the subject should be referred for further specialist assessment as soon as possible.

- **Subjects with abnormal ACTH stimulation test results -** If the ACTH stimulation test performed at Visit 9 (Week 24/End-of-Study/Early Exit) is abnormal (as per the unblinded Medical Monitor's assessment), the subject should be asked to return to the site for a repeat test to confirm the initial result and additional safety evaluations, as required.

- **Subjects with abnormal serum cortisol test results –** If the serum cortisol test at Visit 9 (Week 24/End-of-Study/Early Exit) is abnormal as per the unblinded Medical Monitor's assessment (and the subject did not already complete an ACTH stimulation test at that visit), the subject should be asked to return to the site to complete an ACTH stimulation test.

- **Subjects who withdraw early –** If a subject withdraws early from the study and their most recent visit serum cortisol was <350 nmol/L (<12.7 µg/dL) (as per the unblinded Medical Monitor's review) the subject should be asked to return to the site for an ACTH stimulation test and additional safety evaluations, as required.

10. EVALUATING, RECORDING & REPORTING AEs & SAEs

10.1 Definitions

10.1.1 Adverse Event

Any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

10.1.2 Adverse Drug Reaction

In the pre-approval clinical experience with a new medical product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADR). Adverse events for which causal relationship is assessed as "possible", "probable" or "definite" will therefore be considered ADRs.

10.1.3 Unexpected AE/ADR

An AE/ADR, the nature (i.e., specificity/seriousness/outcome/frequency) or severity of which is not consistent with the applicable reference safety information (Investigator's Brochure).

10.1.4 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (the term life-threatening in the definition of serious refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe).
- Requires in-patient hospitalization or prolongation of existing hospitalization, unless for an elective procedure (a planned, non-emergency medical intervention) for conditions which have not appreciably worsened during the study.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is one that may jeopardize the subject or require intervention to prevent any of the other outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the

subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events should also be considered as serious.

Conversely, some hospitalizations, particularly those which are the result of elective or previously scheduled surgery for pre-existing conditions which have not worsened during the study should not automatically be classed as SAEs. Any worsening of a pre-existing medical condition or any new medical condition that meets the above SAE criteria should be considered as an SAE.

Any suspected joint infection in the Index knee should be considered an important medical event and documented as an SAE.

The Investigator is encouraged to discuss with the Medical Monitor any AEs for which the issue of seriousness is unclear or questionable.

10.1.5 Suspected Unexpected Serious Adverse Reaction

Any ADR that is both serious and unexpected that, based on the opinion of the Sponsor, is felt to have a reasonable suspected causal relationship to a medicinal product.

The reference safety information used to assess the unexpectedness of an event will be the version of the Investigator's Brochure valid at the time of the event.

10.2 Adverse Event Descriptors

10.2.1 Severity/Intensity Categorization

The term severe is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction), as shown in Table 7, below. This designation is not the same as "serious" which is based on patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

In general, the intensity of a particular AE to be recorded is the worst intensity experienced by the subject during the event. A new event with different severity will be entered only if the initial AE is considered completely resolved, and the subject then experiences a subsequent occurrence of this AE. The medical assessment of severity/intensity will be determined using the criteria in Table 7.

Table 7 AE Severity/Intensity Criteria

Intensity	Description
Mild	The AE is easily tolerated and does not interfere with usual activity
Moderate	The AE interferes with daily activity, but the subject is still able to function
Severe	The AE is incapacitating and the subject is unable to work or complete usual activity

Note: AE=Adverse event.

10.2.2 Causal Relationship Categorization

An Investigator who is qualified in medicine must make the determination of relationship to investigational product or the administration procedure for each AE and SAE based on the criteria in Table 8. For classification purposes, relationship to investigational product or the administration procedure is considered "unrelated" for assessments of "unrelated" and "unlikely related"; and "related" for those of "possible", "probable" or "definite."

Table 8 AE Causal Relationship Categorization

Term	Relationship	Definition
Definite	Yes	• Event or laboratory test abnormality, with plausible time relationship to drug administration or the administration procedure • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)
Probable/ Likely	Yes	• Event or laboratory test abnormality, with reasonable time relationship to drug administration or the administration procedure • Unlikely to be attributed to disease or other drugs
Possible	Yes	• Event or laboratory test abnormality, with reasonable time relationship to drug administration or the administration procedure • Could also be explained by disease or other drugs
Unlikely	No	• Event or laboratory test abnormality, with a time to drug administration or the administration procedure that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unrelated	No	• Event or laboratory test abnormality clearly related to circumstances not connected with the drug or the administration procedure

Note: AE=Adverse event.

For SAEs, in addition to the Investigator's assessment of causality, the Sponsor and Medical Monitor will evaluate causality to determine the need for expedited regulatory reporting. The SRC may also be consulted if necessary.

If the causal relationship between an SAE and the investigational product is determined by the Sponsor/Medical Monitor to be "definitely, probably/likely, or possibly related", the event will be considered to be related to the investigational product for the purposes of regulatory reporting. Expedited regulatory reporting is required for related SAEs which are also unexpected.

10.2.3 Outcome Categorization

Outcome may be classified as: recovered without sequelae; recovered with sequelae; ongoing; resolving; fatal; or unknown (if follow-up is not possible).

If the outcome of an SAE is reported as recovered with sequelae, the Investigator should specify the kind of sequelae on the SAE form. If the outcome of an SAE is reported as

unknown, the Investigator should specify (on the SAE form) the rationale why unknown was selected.

10.2.4 Symptoms and Signs of Knee Osteoarthritis

Signs and symptoms of knee OA should not be considered AEs unless they appear to be a clinically significant worsening of the underlying disease. If so, the verbatim term should clearly be recorded as worsening signs and symptoms. (e.g., “worsening OA”, “worsening stiffness in Index knee”, etc.)

10.2.5 Symptoms and Signs of Adrenal Insufficiency

Subjects will be closely monitored for clinical signs and symptoms of AI. These can include:

- Extreme fatigue or weakness.
- Weight loss and decreased appetite.
- Nausea, diarrhea or vomiting.
- Low blood pressure, dizziness, or syncope.
- Abdominal pain.
- Unusual muscle or joint pain.
- Unusual changes in thinking, including irritability, confusion.
- Depression (or depressive symptoms).
- Electrolyte abnormalities e.g.,
  - Sodium <133 mEq/L (<133 mmol/L).
  - Potassium >5.5 mEq/L (>5.5 mmol/L).

Monitoring of clinical signs and symptoms will be performed by the Investigator. In addition, the Medical Monitor will review safety data (which also includes morning serum cortisol values and cortisol values following ACTH stimulation).

If AI is suspected, a cortisol sample should be collected and a subsequent ACTH stimulation test performed if indicated.

If AI is confirmed the Investigator may consider prescribing glucocorticoid replacement therapy if warranted. Subjects with confirmed AI should be referred to an Endocrinologist (or other appropriate specialist) for management until resolution of AI. If the Subject’s AI is ongoing at their final scheduled study visit, the Investigator should follow up with the subject approximately 3 months later, with at least 1 additional contact within that 3-month period.

10.2.6 Symptoms and Signs of COVID-19

In December 2019, a novel strain of coronavirus (SARS-CoV-2), which causes the disease COVID-19, was reported in China and has since become a global pandemic. Knowledge about COVID-19 symptoms, treatments and patient outcomes continues to rapidly evolve and may change during the course of this clinical study.

Sites should take every precaution necessary and follow the guidance of their government's public health officials to minimise risk to staff and study subjects. The European Medicine Agency's most up to date guidance on the "Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic" should be followed where necessary.

If a subject shows or reports any of the known symptoms of COVID-19 prior to randomization they should not be enrolled into the study. The subject should be immediately referred for COVID-19 testing and all necessary precautions should be taken at the site to minimise potential risk of infection to staff and other subjects. If the subject's test is negative then study assessments may be resumed. If the test is positive, the subject may be re-screened for eligibility at a later date once recovered.

If a subject shows or reports any of the known symptoms of COVID-19 at any time following dose administration, they should be immediately referred for COVID-19 testing and all necessary precautions should be taken at the site to minimise potential risk of infection. If possible, the subject should be followed up by the Investigator until the end of the planned follow-up period to document any new/ongoing AEs or safety findings. If the subject recovers and wishes to continue in the study, they may continue with planned visits and assessments at the Investigator's discretion.

Inclusion or exclusion of affected subjects' data in various analysis populations and handling of missing data due to COVID-19 will be determined during blinded data review and documented in the SAP.

10.2.7 Clinical Laboratory Evaluations

A change in the value of a safety laboratory investigation can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to a pathological value, or a further worsening of an already pathological value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a laboratory parameter is clinically significant and therefore represents an AE. If the Investigator considers such an AE as serious (e.g., medically significant event fulfilling criteria per Section 10.1.4), it must be reported as an SAE.

If, at the end of the study, there are clinically significant laboratory abnormalities which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to non-clinically significant values or until a plausible explanation (e.g., concomitant disease) is found for the clinically significant laboratory values.

At the end of the study period, all pathological laboratory findings/values diagnosed throughout the treatment period should be reviewed by the Investigator to provide a final clinical assessment in view of the dynamic of laboratory changes/abnormalities.

10.2.8 Overdose and Medication Error

All special events such as IMP overdose and medication errors including constitution and dose administration errors must be documented in the subject's eCRF and source documents. If any overdose, or medication errors lead to an SAE (see Section 10.1.4), the event must be reported per standard guidelines.

10.3 Reporting Procedure for AEs, SAEs and Pregnancy

10.3.1 Adverse Events

The AE reporting period begins when the subject signs the informed consent form and ends at Visit 9 (Week 24/End-of-Study/Early Exit Visit). All AEs either observed by the Investigator or one of his/her site team, or reported by the subject spontaneously, or in response to a direct question, will be noted in the eCRF and source documentation. This applies to all AEs regardless of the presumed relationship to the study treatment.

To avoid bias in eliciting AEs, subjects should be asked a non-leading question, such as **"How are you feeling?"**

It is important to question the subject in a non-leading way about changes in their health or concomitant medication usage since their last visit. This information should be collected prior to completion of assessments at all study visits. In addition, any symptoms/conditions reported during assessments and deemed to be clinically significant by the Investigator will be assessed as AEs.

The Investigator must acquire sufficient information in order to assess causality. This may require additional laboratory testing, physical examinations, telephone contacts, etc.

Where possible, the Investigator should report a diagnosis rather than signs and symptoms or abnormal laboratory values.

The date of onset, intensity/severity, relationship to IMP, any action taken, date of resolution (or the fact that it is still continuing), outcome, and whether the AE is serious or not will be recorded in the eCRF.

10.3.2 Serious Adverse Events

An SAE must be immediately reported to the Sponsor within 24 hours of awareness.

The Investigator must complete the SAE form and verify the accuracy of the information recorded with the corresponding AE, concomitant medication, and medical history eCRF page(s).

Where possible, the Investigator should report a diagnosis rather than signs and symptoms. In case of a fatal outcome, the Investigator should provide a working diagnosis (event which caused outcome, e.g., fatal myocardial infarction) instead of reporting only death; and an autopsy report with death certificate should be provided where possible.

The Investigator will report all SAEs (related or not related) from the time the informed consent is signed until 24 weeks after IMP administration. SAEs starting before dose administration must be identified as such.

If a subject dies during their study participation, or if the Investigator becomes aware of the death of a discontinued subject within 24 weeks after dose administration, the death must be reported to the Sponsor, whether considered treatment-related or not.

Imaging Sub-Study

For subjects participating in the imaging sub-study, the Investigator will continue to report any SAEs (related or unrelated) or deaths (related or unrelated) until the subject completes their final imaging visit (i.e., Visit 10), or withdraws from the sub-study.

The onset date of the AE is defined as the onset of signs and symptoms or a change from baseline. The onset date of the SAE is defined as the date the signs and symptoms/diagnosis became serious, i.e., met at least 1 of the criteria for seriousness listed in Section 10.1.4. The resolution date of the SAE is defined as when the symptoms resolve, or the event is considered chronic (e.g., sequelae) or stable, and/or if the seriousness criteria are no longer applicable. Serious adverse events that are ongoing at the time of death are considered unresolved.

All recorded SAEs, regardless of relationship to investigational product, will be followed up until resolution, stabilization, or the subject is lost to follow-up and cannot be contacted. In circumstances where the Investigator is unable to contact the subject (or his/her relatives), the Investigator must provide a written statement (recorded in the subject's source documents), confirming that the subject is lost to follow-up. At a minimum, the following should be provided at the time of the initial SAE report:

- Subject number, age, and gender/sex.
- Event description (including onset date of the event and reason for it being considered serious).
- Relationship to investigational product (i.e., causality).

- Name of the investigational product (including drug dose and administration dates).
- Investigator name and address.
- Name of the reporter (including site name or number and country).
- Dated signature of the Investigator or sub-Investigator.

Additional follow-up information, if required or available, must be provided immediately (within 24 hours of awareness) following Investigator (or site) awareness of the information.

Preliminary reports will be followed by detailed descriptions which will include information from hospital case reports, autopsy reports/certificates (in case of death) and other documents when requested and applicable.

The Sponsor, or its delegate, is responsible for expedited reporting to the relevant Regulatory Authorities, to Investigators and to local and central IRB/IEC as per local regulations.

Any SAE considered to have a causal relationship (i.e., related) to the investigational product and discovered by the Investigator at any time after the study is completed should be reported to the Sponsor. A rationale for the assessment of a causal relationship must be provided by the Investigator together with the SAE form. Any safety information that is obtained after database lock of the clinical database will be documented only in the safety database and, if applicable, will undergo expedited reporting.

Additional detail regarding SAE reporting will be provided in the study documentation.

10.3.2.1 Elective Surgery/Routine Examination

Elective surgery (a non-emergency medical procedure that was planned prior to enrolment in this study) or an in-patient routine examination for a pre-existing condition does not qualify as an SAE. However, AEs which occur during the elective hospitalization will need to be collected and reported.

10.3.3 Pregnancy

Pregnancy alone is not considered an AE/SAE. However, if a subject becomes pregnant within 24 weeks after dose administration and EP-104IAR was administered, the outcome of the pregnancy (including normal births) must be followed up and documented, even if the subject was withdrawn from the study.

A female subject must immediately inform the Investigator if she becomes pregnant during the study. The Medical Monitor must be contacted immediately to break the blind. The Investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. If appropriate, the Investigator may aspirate the knee to remove as much remaining EP-104IAR as possible (see Section 7.6.1).

The Investigator/Sponsor is responsible for monitoring the subject and pregnancy outcome. Every effort should be made to gather information regarding the pregnancy outcome until 90 days postpartum (or otherwise as appropriate). It will be the responsibility of the Sponsor, together with the appropriate support of the Investigator, to obtain this information.

Any report of pregnancy recorded for any female subject should be reported to the Sponsor within the same timelines as an SAE, i.e., within 24 hours of awareness. The Investigator should complete a Pregnancy Report Form. Complications of pregnancy such as abortion (spontaneous or induced for medical reasons), premature birth (occurring before the start of the 37th week of pregnancy) or congenital abnormality are considered SAEs and should be reported using the SAE form.

All pregnancies occurring within 24 weeks of administration of the IMP in a withdrawn female subject should be reported to the Sponsor within the same timelines as an SAE.

Imaging Sub-Study

If a subject participating in the imaging sub-study becomes pregnant any time after Visit 9 (Week 24) there is no requirement to report the pregnancy to the Sponsor. However, the subject must be withdrawn from the imaging sub-study and no further MRIs should be collected.

11. STATISTICAL ANALYSIS

11.1 Statistical Methods

Key reporting and statistical methodologies are listed in this study protocol. In addition, a complete detailing of data presentation and analysis details will be documented in a separate SAP; that document will provide full detail of all analyses and reporting of the study data allowing for data idiosyncrasies identified on an ongoing (blinded) basis. The SAP will be finalized prior to formal study unblinding. Data presentations may be both tabular or graphical, as appropriate.

Primary presentations of data will be provided by treatment arm and then by suitable strata for the data type (e.g., planned time of assessment).

Inferential testing, where performed, will be two-sided and made at the 5% significance level.

11.2 Sample Size and Power Calculations

This study has been sized making the following assumptions:

- Inferential testing is at the (two-sided) 5% level, and with a desired power of 80%.
- The primary endpoint is the difference between treatment groups in change from baseline WOMAC Pain (average of 5 pain items) at 12 weeks post-dose, as measured using a 0-10 scale.
- The standard deviation of the endpoint is 2.2, as assessed from review of similar studies from clinicaltrials.gov.
- The desired difference to detect is 0.8.

Based on these assumptions, a sample size of approximately 120 subjects per treatment group is required. Assuming a drop-out rate of approximately 20%, 150 subjects will be randomized and dosed in each treatment arm.

11.3 Populations

11.3.1 Intention-to-Treat Population

The intention-to-treat (ITT) population consists of all subjects who are randomized to treatment. Analysis will be conducted allocating subjects to the treatment to which they were randomized, irrespective of what was actually received.

11.3.2 Full Analysis Set Population

The full analysis set (FAS) population consists of all subjects who satisfy the following criteria:

- Randomized to treatment.
- Received a dose of randomized treatment.
- Had at least 1 post-baseline assessment.

11.3.3 Per-protocol Set Population

The per-protocol analysis set (PPS) population consists of all subjects who, in addition to the FAS criteria, had no major protocol violations (as defined in the SAP).

11.3.4 Safety Population

The safety population consists of all randomized subjects who were administered a dose of IMP/vehicle control. The subjects in this group will be analyzed based on the treatment they received.

11.4 Background and Demographic Characteristics

Demographic data will be summarized using standard summary statistics, by treatment group and in totality. No hypothesis testing will be performed on demographic data.

11.5 Study Medication

The total amount of drug given will be calculated for each subject and will be compared to the amount expected to be given for each subject and will be summarized by treatment group.

11.6 Concomitant Therapy

Concomitant medications will be categorized according to a standard dictionary (World Health Organization Drug dictionary (WHO-Drug) classification). Counts and percentages of subject use for each medication will be computed and summarized by treatment group.

11.7 Efficacy Evaluations

11.7.1 Primary

The primary efficacy endpoint is the difference in change from baseline between EP-104IAR and vehicle in WOMAC Pain at Week 12, in the ITT population.

Baseline WOMAC Pain will be calculated at the individual level and is defined as the average of three measurements; 2 measurements during the Washout and Baseline Period and 1 at Visit 2 (pre-dose). Change from individual pre-dose baseline will then be calculated for each post-dosing weekly assessment from Week 1 through Week 24. A mixed-effects model for repeated measures (MMRM) model will then be fit to the change from baseline data for all subjects in the ITT population, including fixed effects terms for:

site (potentially grouped, a classification that will be made as part of the blind review process and documented in the SAP prior to formal study unblinding); individual baseline WOMAC Pain; and the treatment-by-week interaction, where treatment and week are both defined as categorical variables. A random per-patient intercept will also be included. An unstructured covariance matrix at the patient level will initially be fit; if this model fails to converge numerically, a compound symmetry structure will be used.

No imputation of missing data will be performed for this analysis; the MMRM model allows handling of missing data under a suitable set of missing data assumptions. If blinded data review indicates that those assumptions appear not to be met, or there is a non-negligible degree of missingness, suitable alternative modeling approaches will be detailed in the SAP prior to formal study unblinding.

In addition, if the PPS population markedly differs from the ITT population, identical analyses for the PPS population will be performed.

Inferential results will be presented comparing EP-104IAR versus vehicle.

11.7.2 Key Secondary Endpoints

The following secondary endpoints will be assessed in a hierarchical manner, comparing EP-104IAR versus vehicle. If the primary endpoint is statistically significant at the 5% level, then the first secondary endpoint may be formally assessed for statistical significance. If the first secondary endpoint is statistically significant at the 5% level, then the second secondary endpoint may be formally tested, and so forth. Upon failure of any inferential test at the 5% level, no subsequent secondary endpoints may be declared to be statistically significant.

The endpoints are as follows:

- Difference in change from baseline between EP-104IAR and vehicle in WOMAC Function at Week 12.
  - Analysis will be identical to that described for the primary endpoint.
- Difference between EP-104IAR and vehicle in the area under the WOMAC Pain-time curve to 12 weeks post-dose.
  - Area under the curve in change from baseline WOMAC Pain from Week 0 to Week 12 will be calculated on a per-individual basis using the linear trapezoidal rule. Subjects discontinued prior to Week 12 will have their missing data imputed using an appropriate method, documented in the SAP prior to formal study unblinding. Treatments will be compared using a linear model containing fixed effects terms for site (possibly grouped, as described earlier); individual baseline WOMAC Pain; and treatment group.

- Difference in change from baseline between EP-104IAR and vehicle in WOMAC Pain at Week 24.

  – Analysis will be identical to that described for the primary endpoint, but will extract the estimate at Week 24 instead of Week 12.

- Difference between EP-104IAR and vehicle in Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) strict responders (Pham, et al., 2004) at Week 12.

  – The proportion of patients meeting the strict responder definition at Week 12 will be compared (EP-104IAR versus placebo) using Fisher's exact test. Patients who discontinue prior to Week 12 will be considered to be non-responders.

Full analysis details will be provided in the SAP.

11.7.3 Other Efficacy Measures (Secondary and Exploratory)

All other efficacy data (WOMAC subscales, total WOMAC, NPRS, PtGA, MDGA, SF-36) will be summarized using standard summary statistics by treatment group. Exploratory analyses will be performed to identify key features of the efficacy profile. Full details of the summarizations, graphical presentations and exploratory analyses will be presented in the SAP.

11.7.3.1 Additional Secondary Endpoints

- Difference in change from baseline between treatment groups in WOMAC Pain at Weeks 1-11 and 13–23

- Difference in change from baseline between treatment groups in WOMAC Pain Q1 (pain on walking) at Weeks 1-24

- Difference in change from baseline between treatment groups in average daily NPRS at Weeks 1-24

- Difference in change from baseline between treatment groups in WOMAC Function at Weeks 4, 8, 16, 20 and 24

- Difference in change from baseline between treatment groups in WOMAC Stiffness scores at Weeks 4, 8, 12, 16, 20 and 24

- Difference in change from baseline between treatment groups in WOMAC Total scores at Weeks 4, 8, 12, 16, 20 and 24

- Difference between treatment groups in time to return to baseline WOMAC Pain

- Difference between treatment groups in area under the curve (AUC) of WOMAC Pain at Weeks 1–24

- Difference between treatment groups in AUC of average daily NPRS at Weeks 1-24
- Difference between treatment groups in AUC of WOMAC Function, Stiffness and Total scores at Weeks 4, 8, 12, 16, 20 and 24
- Difference between treatment groups in OMERACT-OARSI strict responders at Weeks 4, 8, 16, 20 and 24
- Difference between treatment groups in PtGA at Weeks 4, 8, 12, 18 and 24
- Difference between treatment groups in MDGA at Weeks 4, 8, 12, 18 and 24
- Difference between treatment groups in SF-36 at Weeks 12 and 24
- Difference between treatment groups in average rescue medication usage at Weeks 1-24
- Difference between treatment groups in average activity levels at Weeks 1-24

11.7.3.2 Exploratory Efficacy Analyses

Covariate efficacy analyses will be conducted, where appropriate. Full details of planned exploratory analyses will appear in the SAP.

11.8 Safety Evaluations

Safety data (safety labs, cortisol, physical exam, knee exams, vital signs, ACTH stimulation test results, etc.) will be summarized for the safety population using standard summary statistics, by treatment group. Both raw data and change from baseline, where appropriate, will be assessed. Where appropriate, graphical display will be used to highlight key features of the data. No prospective hypothesis testing will be performed on safety parameters.

Medical histories and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be summarized in a similar manner to other safety data.

11.8.1.1 Exploratory Imaging Analyses

Imaging Sub-Study Only

For subjects participating in the optional imaging sub-study, changes in cartilage volume, structure morphology and inflammatory activity (synovial thickness and synovial blood flow) in the knee joint based on DCE-MRI assessment at Weeks 12, 24 and 52 will be reported and summarised using standard summary statistics, by treatment group.

- Changes in cartilage structure and morphology will be compared to values at baseline.
- Changes in inflammatory activity in the knee joint will be compared to values at baseline.

Where appropriate, graphical representations will be used to highlight key features of the data.

11.9 Other Evaluations

11.9.1 Pharmacokinetics

Plasma PK concentration data will be summarized using standard summary statistics and displayed graphically. Non-compartmental analysis will be used to summarize key characteristics of the PK curve.

12. ETHICAL CONSIDERATIONS

The study will be conducted according to the principles of the World Medical Association's (WMA) Declaration of Helsinki (as amended by the 64th WMA General Assembly, Brazil, October 2013) and current International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP).

The Sponsor will ensure that the study complies with all local, federal or country regulatory requirements.

12.1 Institutional Review Board or EC/IEC

The protocol, any protocol amendments, ICF and any other documents required by the IRB/IEC must be submitted by the Investigator for review and approval to the IRB/IEC. The Investigator must also ensure that the IRB/IEC reviews the progress of the study regularly and, if necessary, renews its approval of the study on an annual basis.

A copy of the approval letter must be forwarded to the Sponsor before the study is implemented.

12.2 Informed Consent

The ICF must comply with the Declaration of Helsinki, federal regulations, and ICH guidelines, and must be approved by the appropriate IRB/IEC prior to use.

The Investigator or an authorized associate must explain orally and in writing the nature of the study and the treatment in such a manner that the subject is aware of potential benefits and risks. Subjects must also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects must be provided sufficient time to consider participation, including discussion with family members prior to signing the ICF.

Documentation of the discussion and the date of informed consent must be recorded in the source documentation. Subjects must give informed consent in writing.

If an amended or revised ICF is introduced during the study, further consent from each subject still in the study will be required.

During Screening, potential subjects will receive training about participating in a clinical trial. They will be shown a brief video explaining about clinical trials, placebo controls and the importance of accurately recording their patient-reported outcome measures. The video will include a short comprehension quiz. These training materials will be approved by the IRB/IEC prior to their use at any sites.

Imaging Sub-Study

All subjects will be asked if they would like to participate in the optional imaging sub-study. If they are agreeable, after the informed consent process for the main study is

performed (see above), the subject will then sign an additional ICF specific to the imaging sub-study.

12.3 Confidentiality

The Investigator must ensure the anonymity of all subjects participating in the study.

Each subject will be assigned a unique subject number and this should be used on all forms associated with the subject's documents or samples that will be supplied to the Sponsor or any party completing testing on behalf of the Sponsor (e.g., blood for central laboratory assessments).

The Sponsor will ensure that the use and disclosure of personal health information obtained during this clinical study complies with the applicable legislation related to the privacy and protection of personal information (e.g., Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada, and the General Data Protection Regulation (GDPR) in the European Union).

All anonymous data remain the property of the Sponsor (Eupraxia Pharmaceuticals Inc.).

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Record Keeping

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

The Investigator must ensure that all study related site source data, study related documents and reports will be available, and that the provision of direct access for monitoring and auditing by the Sponsor or its designees will be permitted. In addition, the Investigator must ensure that all study related site source data, study related documents and reports will be made available for inspection by the appropriate Regulatory Authority and review by the IRB/IEC.

The Investigator or designee will enter all required study data into eCRFs in an electronic data capture (EDC) system. Training on the system will be provided to all sites, including instructions on how to address missing data, corrections, query procedures and electronic signatures. Only individuals who are identified on the authorized signature page may enter/correct data in the eCRF. The Investigator or designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

Completed eCRFs should be ready for review by the Sponsor's Monitor within 5 business days of each visit for a given subject. Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the study monitor (source document verification), and the maintenance of a drug dispensing log by the Investigator.

For those subjects who withdraw before completion of the study, all available efficacy and safety data must be entered in the eCRF. Incomplete or inconsistent data on the eCRF will result in data queries addressed to the Investigator for resolution.

13.1.1 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which case reports for each subject are based. They are to be separate and distinct from eCRFs. These records should include detailed notes on:

- Medical history prior to participation in the study.
- Basic identifying information, such as demographics, that link the subject's source documents with the eCRFs.
- Results of all diagnostic tests performed, diagnoses made, therapy provided and any other data on the condition of the subject.
- Subject's exposure to study treatment.

- All AEs.
- Subject's exposure to concomitant procedures or therapy (including date and quantity).
- All relevant observations and data on the condition of the subject throughout the study.
- Oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). The date of informed consent must be recorded in the source documentation.

For the following assessments, direct entry into the ePRO device or into pages of the eCRF is acceptable without other source documents: WOMAC, NPRS, SF-36, subject-reported daily questions on rescue medication use, non-drug therapy use, daily activity levels and PtGA scores. For these data, the ePRO/eCRFs will be considered the source document.

13.2 Study Monitoring

A combination of centralized and on-site monitoring will be utilised on this study. All study specific processes will be documented in a detailed Monitoring Plan. The study will be monitored by representatives of the Sponsor from a contract research organization (CRO). The Monitor will contact the Investigator regularly and will be allowed, on request, to inspect the various records of the study (eCRFs and other pertinent data) provided that subject confidentiality is maintained in accordance with local requirements.

It will be the Monitor's responsibility to inspect the eCRFs at frequent regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The Monitor must have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The Investigator (or delegate) agrees to co-operate with the Monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.3 Data Management

Data collected via the ePRO devices will be transferred electronically from the device to Data Management at regular pre-defined intervals during the study. Laboratory test results will be transferred electronically from the Central Laboratory to Data Management at regular pre-defined intervals during the study.

Data management will be conducted in accordance with the CRO's standard operating procedures. All study-specific processes and definitions will be documented in a Data Management Plan. Coding of medical terms and medications will be performed using the MedDRA and WHO-Drug dictionaries. Dictionary versions will be specified in the Data Management Plan.

A comprehensive validation check program will verify the data and queries will be generated for resolution by the site. Throughout the study, the Sponsor or its designates may review data as deemed necessary.

14. GENERAL ADMINISTRATIVE PROCEDURES

14.1 Supplies

Sites will be provided supplies required to manage this study. These include but are not limited to:

- Investigator file(s) (for filing of all study related documentation).
- EP-104IAR and vehicle, including dose administration supplies (needles, syringes, etc.).
- Rescue medication.
- Cosyntropin for the ACTH stimulation test.
- Kits for collection, storage and transportation of blood samples required for central and bioanalytical laboratories. This will also include all applicable manuals/guidelines and contact details.
- Contact list of all relevant study personnel.
- Documentation and directions for the use of relevant study questionnaires.
- eCRF completion guidelines.
- Site Operations Manual (includes IMP Handling Manual, Laboratory Manual, etc.).
- All study forms (e.g., SAE, pregnancy, drug accountability, etc.).

14.2 Insurance

The Sponsor confirms it has in place an appropriate insurance policy. Applicable information on compensation, insurance, and indemnity will be included in the Agreement between the Site and the Sponsor (or Sponsor's delegate).

14.3 Investigator Training

All Investigators and their study personnel will receive training regarding study procedures and GCP/regulations specific to the conduct of clinical studies. A training session aimed at reducing the placebo/vehicle response will also be provided. Training will take place prior to screening of the first subject at the study site.

Imaging Sub-Study

MRI training will be provided to each participating site either via a teleconference or a self-training platform to provide an overview of the sub-study, MRI eligibility, images required for data assessment, information on subject positioning and the collection and transfer of data. Emphasis will be placed on standardization of image acquisition across subjects and timepoints.

14.4 Archiving

The Investigator will retain all study documentation for the duration specified in their respective site agreement or as specified by the applicable Regulatory Authority, whichever is longer. No records will be destroyed without prior written instruction from the Sponsor. Archived data may be held on microfiche or electronic record, provided that a back-up copy exists and that a hard copy can be generated if required.

The Investigator must inform the Sponsor immediately if any documents are lost, to be transferred to a different facility, or to be transferred to a different owner.

14.5 Publication Policy

The Sponsor is committed to the timely communication of data from clinical research studies. If a publication is generated, it will be a multi-center publication. Authors will be selected in adherence with the International Committee of Medical Journal Editors criteria (available from: http://www.icmje.org).

Investigators may not present or publish partial or complete study results individually without the Sponsor's agreement.

Any manuscript or abstract proposed by the Investigators must be reviewed and approved in writing by the Sponsor before submission for publication. Names of all Investigators participating in the study will be included in the publication.

15. MODIFICATION OF PROTOCOL OR STUDY TERMINATION

Excluding an emergency situation in which proper treatment is required for the protection, safety and wellbeing of subjects, the study will be conducted as described in the approved protocol.

15.1 Protocol Waivers, Deviations and Violations

Protocol waivers are not permitted except where necessary to eliminate an immediate hazard to subjects.

Any deviation from the protocol will be recorded and explained. Deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria.
- Received the wrong treatment.
- Received excluded concomitant treatment.

The Investigator will also ensure that deviations meeting IRB/IEC criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC will be provided to the Sponsor and maintained within the Trial Master File.

Criteria describing deviations and how they will be documented and handled will be specified in the Protocol Deviations Handling Plan, Data Management Plan and the SAP.

15.2 Protocol Amendments

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must only be made with the prior approval of the Sponsor.

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments. The applicable Regulatory Authority and the IRB/IEC will review and approve protocol amendments prior to their implementation.

Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted for information, if required by local regulations.

If there are changes to the ICF as a result of a protocol amendment, written IRB/IEC approval and the new approved ICF must be forwarded to the Sponsor.

15.3 Study Termination

Sections 4.3 and 4.4 describe the pre-defined study stopping rule and the role of the SRC in making decisions on study progression.

In addition to those processes, the Sponsor reserves the right to terminate the study in its entirety or terminate the study at an individual site at any time.

Reasons for site termination may include (but are not limited to) unsatisfactory subject enrollment with respect to quality and/or quantity, site is unable to comply with the requirements of the protocol or GCP, or data recording is inaccurate and/or incomplete.

In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subject's interests. Both parties will arrange the procedures on an individual basis after review and consultation and in accordance with the study contract.

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