Official Title: A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ACP-044 in Subjects With Pain Associated With Osteoarthritis of the Knee

NCT Number: NCT05008835

Document Date: 16 February 2022

CLINICAL STUDY PROTOCOL

UNMASKED PROTOCOL

A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ACP-044 in Subjects With Pain Associated With Osteoarthritis of the Knee

Protocol Number: ACP-044-005

Amendment 4

Original Protocol Date: 04 March 2021

Protocol Amendment 1 Date: 10 May 2021

Protocol Amendment 2 Date: 21 May 2021

Protocol Amendment 3 Date: 03 August 2021

Protocol Amendment 4 Date: 16 February 2022

SPONSOR SIGNATURE PAGE

Title: A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ACP-044 in Subjects With Pain Associated With Osteoarthritis of the Knee

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Signature Date

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Approve	[redacted] 17-Feb-2022 19:13:35 GMT+0000

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DECLARATION OF INVESTIGATOR

I confirm that I have read the above protocol. I understand it, and I will work according to the moral, ethical, and scientific principles governing clinical research as set out in the principles of Good Clinical Practice, as required by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E6 and as described in the United States (US) Code of Federal Regulations (CFR) 21 CFR parts 50, 54, 56, 312, and according to applicable local requirements.

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator or Consultant for review by you, your staff, and the applicable institutional review board/ethics committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

Investigator

Signature	Date
Name (printed)	

PROTOCOL SYNOPSIS

Protocol Number	ACP-044-005
EudraCT Number	Not applicable
Protocol Title	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ACP-044 in Subjects With Pain Associated With Osteoarthritis of the Knee
Name of Investigational Product	ACP-044
Indication	Treatment of osteoarthritis pain
Phase of Development	2
Sponsor	Acadia Pharmaceuticals Inc. [redacted]
Study Hypothesis	ACP-044 is more effective at treating osteoarthritis pain than placebo and is safe and well tolerated

Primary Objective To evaluate the efficacy of ACP-044 compared with placebo in the treatment of pain associated with osteoarthritis (OA) of the knee	**Primary Endpoint** Change from Baseline to Week 4 in the weekly average of the daily average Numeric Rating Scale (NRS) pain intensity scores
Secondary Objective To evaluate the efficacy of ACP-044 compared with placebo in the treatment of pain associated with OA of the knee	**Key Secondary Endpoints** • Patient Global Impression of Change (PGIC) at Week 4 with reference to baseline status • Change from Baseline to Week 4 in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score and individual subscale scores for pain, stiffness, and physical function • Proportion of subjects who are responders as defined by 30% and 50% reduction from Baseline to Week 4 in the weekly average of the daily average NRS pain intensity scores

	Additional Secondary Endpoints Change from Baseline to Week 4 in: • Weekly average of the daily worst NRS pain intensity scores • Brief Pain Inventory–Short Form (BPI-sf) • 12-item Short Form Survey (SF-12)
Exploratory Objective To evaluate the use of rescue medication in subjects with pain associated with OA of the knee treated with ACP-044 compared with placebo	**Exploratory Endpoints** • Comparison of average daily rescue medication use • Hospital Anxiety and Depression Scale (HADS)
Safety Objective To evaluate the safety and tolerability of ACP-044 compared with placebo in the treatment of pain associated with OA of the knee	**Safety Endpoints** • Treatment-emergent adverse events (TEAEs) • Vital signs • Electrocardiograms (ECGs) • Physical examination results • Clinical laboratory tests • Columbia–Suicide Severity Rating Scale (C-SSRS)
Pharmacokinetic Objective To characterize the pharmacokinetic (PK) profile of ACP-044 in subjects with pain associated with OA of the knee	**Pharmacokinetic Endpoints** • Plasma concentrations of ACP-044 using sparse sampling on the following study days: Baseline (Week 0), Week 1, Week 2, and Week 4 (EOT)/ET • ACP-044 PK parameters determined using a population PK approach
Pharmacokinetic/Pharmacodynamic Objective To characterize the exposure-response relationship using appropriate modelling and simulation methods	**Pharmacokinetic/Pharmacodynamic Endpoints** • Guided by exploratory analyses, appropriate ACP-044 exposure-response relationship: o for efficacy using the primary endpoint o for safety using the most frequent and other relevant TEAEs
Number of Study Sites	Up to approximately 50 US sites will participate in this study.

Number of Subjects Planned	Approximately 480 subjects will be screened and approximately 240 subjects are planned for randomization. Each treatment arm (ACP-044 800 mg BID dose, ACP-044 400 mg QID dose, and placebo) will randomize approximately 80 subjects, assuming a screen failure rate of 50%.
Test Product, Dose, and Administration	The investigational products are ACP-044 400 mg tablets, or matching placebo (size- and color-matched) tablets. Study drug doses are to be administered orally for 4 weeks. Doses to be studied are: • ACP-044 800 mg dose delivered two times a day (provided as 2×400 mg ACP-044 tablets) • ACP-044 400 mg dose delivered four times a day (provided as 1×400 mg ACP-044 tablet) • Placebo, size- and color-matched to ACP-044 tablets Blinded drug will be provided in blister cards. All subjects will take the same number of tablets per day in order to maintain the blinded study design. Dosing is to occur in the morning (2 tablets), noon (1 tablet), evening (2 tablets), and night (1 tablet) and should occur at the same time each day over the duration of the study.
Study Design	This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ACP-044 in subjects with pain associated with radiographically confirmed OA of the knee. The study will compare active treatment groups, receiving either 800 mg ACP-044 BID or 400 mg ACP-044 QID, with a placebo group. The Sponsor, subjects, and Investigators will be blinded to treatment assignment. This unmasked protocol version provides details of certain study design elements, procedures, and statistical methods that are intended for use only by the unmasked Sponsor and restricted clinical service providers and their designated agents. The study periods are: • Screening: up to 4 weeks • Baseline Pain Assessment: a 7-day period during which baseline pain assessments will be recorded for 7 days. Additional 3-day window may be added, if needed. • Double-blind treatment: 4 weeks

	• Safety follow-up: approximately 7 days after end of treatment (EOT)/early termination (ET) and approximately 30 days after the last dose of study drug **Screening Period (Up to 4 weeks)** During the Screening period, subjects will be assessed for study eligibility. All subjects must have radiographically confirmed OA of the knee, including review of imaging and confirmation of a Kellgren-Lawrence (K-L) score of 2 or 3. Subjects who have had an X-ray of the index knee within 12 weeks of Screening may provide a historical image for central reading to confirm eligibility, or imaging can be done during Screening at protocol-trained radiological sites. Randomization visits cannot occur until there is confirmation from the central reader that there are no exclusionary findings on the knee joint images. The index knee is defined as the most painful knee at Screening. Prohibited analgesic medications must be discontinued during the Screening period. Investigators must not withdraw a subject's prohibited medication other than analgesics solely for the purpose of enrolling them into the study. Medications will be discontinued only if it is deemed clinically appropriate to do so and in consultation with the prescribing physician. All pain medication, except for the rescue medication (acetaminophen), will be discontinued 7 days or 5 half-lives, whichever is longer, prior to the Baseline Pain Assessment Period. In the event of inadequate pain relief, acetaminophen may be taken with a maximum daily dose of 2500 mg. Rescreening of a subject will be allowed, with the approval of the Medical Monitor. **Baseline Pain Assessment Period (1 Week)** Following eligibility at screening, subjects will complete a Baseline Pain Assessment Period that will occur approximately 7 days before randomization; an additional 3-day window may be added, if needed. During the Baseline Pain Assessment Period, subjects will be instructed in the use of a handheld device (electronic diary [eDiary]) to record their daily pain scores and rescue medication use. Compliance with recording of pain score and use of rescue medication will be assessed for continued subject eligibility. Subjects must discontinue taking study-provided rescue medication during the Baseline Pain Assessment Period and for at least 24 hours prior to the start of study visits. Rescue medication use during the Baseline Pain Assessment Period through Visit 3 and within

	24 hours of the study visits (Visits 5, 6, and 8) will be documented in the electronic data capture (EDC). Subjects who enter the Baseline Pain Assessment Period will not be allowed to rescreen. Subjects who experience technical issues with the device and their pain scores were not assessed may be rescreened and the Baseline Pain Assessment Period may be extended, if needed and with permission of the Sponsor. **Treatment Period (4 Weeks)** At Baseline (Week 0), eligible subjects will be randomly assigned in a 1:1:1 ratio to receive ACP-044 800 mg BID, ACP-044 400 mg QID, or placebo, according to a randomization schedule. Randomization will be stratified by sex and baseline K-L score (2 or 3). All efficacy assessments will be completed and a PK blood sample will be taken at the Baseline visit prior to administration of the first dose of study drug (Table S–1). Subjects will continue daily entry into the eDiary of pain scores, compliance with ingestion of study medication, and rescue medication use from Week 0 through to Week 4/EOT/ET. Subjects will receive their first dose at the study site after all Baseline assessments have been completed and a PK blood sample will be taken approximately 1 hour after dosing. Dosing is four times a day. During the treatment period (Week 0 through Week 4), subjects will be permitted to use only acetaminophen as rescue medication. Subjects will record their use of acetaminophen in their eDiary. Subjects must discontinue acetaminophen use for at least 24 hours prior to the start of study visits in order to minimize the confounding effects of the rescue medication on efficacy measurements. A PK sample will be taken at each study visit according to the schedule described in the Pharmacokinetic Assessments section. At the Week 4 visit, end of treatment (EOT) procedures will be completed. **Safety Follow-up Period (30 Days)** Safety will be further assessed during a follow-up visit to occur in the clinic approximately 7 (±3) days after EOT/ET procedures. During this in-clinic visit, pain intensity, adverse events (AEs), and concomitant medications will be assessed, since the EOT/ET. Then, a follow-up telephone call will occur approximately 30 (+4) days after the last dose of study drug to assess AEs and concomitant medications.

	The study design schematic is presented in Figure S–1. The schedule of assessments is provided in Table S–1.
Study Duration	The duration of participation for individual study subjects will be approximately 13 weeks, consisting of a screening period of up to 4 weeks, a 7-day baseline pain assessment period, a 4-week double-blind treatment period, and a safety follow-up period of approximately 30 (+4) days (Figure S–1). The study start date is defined as the date the first subject is enrolled, which is the date the first subject is randomized. The primary completion date is the last date that subject data was collected for the primary outcome measure. The study completion date is defined as the last date that subject data was collected for the primary outcome measure, secondary outcome measure(s), and adverse events, which includes the safety follow-up telephone call visit.
Main Criteria for Inclusion and Exclusion	To be eligible for this study, subjects must meet all of the inclusion criteria and none of the exclusion criteria. **Inclusion Criteria:** 1. Male or female subjects ≥18 and <65 years of age at the time of Screening 2. Able to understand and provide signed informed consent 3. Has a body mass index (BMI) ≤39 kg/m^2 at Screening 4. Confirmed history of pain associated with OA in the index knee 5. Clinical diagnosis of OA in at least one knee joint (i.e., the index knee) based on the American College of Rheumatology Criteria with radiographic evidence of OA (K-L score of 2 or 3) at Screening Note: K-L scores of 1 or 4 are exclusionary 6. Willing to maintain current activity and exercise levels throughout the study 7. Willing and able to comply with clinic visits and study-related procedures 8. Consent to allow all radiographs and medical/surgical/hospitalization records of care received elsewhere to be shared with the Investigator and third parties who will examine the images (i.e., central x-ray reader) 9. Negative urine drug screen result at Screening, Baseline Pain Assessment Period, and Baseline. A positive urine drug test

	for a prescribed medication that is permitted at Screening, but not in the study, is acceptable if it has been prescribed. The subject will need to washout from this medication, if appropriate, and have a negative screen for this medication prior to randomization. Investigators must not withdraw a subject's prohibited medication other than analgesics solely for the purpose of enrolling them into the study. Medications will be discontinued only if it is deemed clinically appropriate to do so and in consultation with the prescribing physician. 10. Must have a negative COVID-19 diagnostic polymerase chain reaction (PCR) test at Screening. Not planning to receive a COVID-19 vaccine during Screening through 30 days of the last dose of study drug. If the subject has received a COVID-19 vaccine, they must be fully vaccinated at least 1 week before the Screening visit and be symptom free. If subjects have received a COVID-19 booster shot, they will need to have completed the shot at least one week before Screening and have no residual symptoms. Note: subjects are considered fully vaccinated 2 weeks after their second dose in a 2-dose series or 2 weeks after a single-dose vaccine. 11. If the subject is male, the subject and his partner must use a highly effective form of contraception (i.e., double-barrier method which includes a condom plus diaphragm with spermicide or condom plus spermicide) at the time of Screening and for at least 30 days after the last dose of study drug. If subjects have had a vasectomy, they must still use a condom. Subjects must also agree to not donate sperm for the duration of the study and for at least 30 days after the last dose of study drug 12. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) OR must agree to use TWO clinically acceptable methods of contraception for at least 30 days prior to Day -1, throughout the entire study, and for at least 30 days following completion of the study. Acceptable methods of contraception include the following: a. A barrier method (condom, diaphragm, or cervical cap) with spermicide

	b. Hormonal contraception, including oral, injectable, transdermal, or implantable methods c. Intrauterine device (IUD) Only one of the two clinically acceptable methods can be a hormonal method. All female subjects of childbearing potential must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative urine pregnancy test at Baseline. ***Inclusion Criteria Specific to Baseline Pain Assessment Period*** 13. Baseline Pain Assessment Period weekly average daily pain score ≥4 14. Has no more than 1 day with a pain score of 10 during the Baseline Pain Assessment Period 15. Has a standard deviation of <1.6 for average daily pain score diary entries during the Baseline Pain Assessment Period 16. Able to complete logging of pain scores for at least 6 of the last 7 days of the Baseline Pain Assessment Period **Exclusion Criteria:** ***Medical Conditions*** 1. Pain anywhere else in the body which is greater than or equal to OA pain in the index knee, or likely to interfere with subject's assessment of pain throughout the study, as judged by the Investigator 2. History or presence on imaging of knee arthropathy (osteonecrosis, subchondral insufficiency fracture, rapidly progressive OA type 1 or type 2), recent fall, injury, or trauma affecting the index knee, ligament tear, neuropathic joint arthropathy, knee dislocation (patella dislocation is eligible), extensive subchondral cysts, Baker's cyst, evidence of bone fragmentation or collapse, or primary metastatic tumor with the exception of chondromas, or pathological fractures during the Screening Period 3. History or presence at Screening of non-OA inflammatory joint disease (e.g., rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, pseudo-gout, gout, spondyloarthropathy, joint infections within the past 5 years, Paget's disease of the spine, pelvis, or femur, neuropathic disorders, multiple sclerosis, fibromyalgia, tumors or infections of the spinal

	cord, or renal osteodystrophy) or any condition that would interfere with the rating of OA pain 4. Recent arthroscopic surgery within 1 month of Screening; or has any planned surgery or procedure during the study ***Concomitant Treatments*** 5. Use of monoamine reuptake inhibitors, tricyclic antidepressants, anticonvulsants, and/or serotonin norepinephrine reuptake inhibitors within 4 weeks prior to Screening. 6. Unwilling to discontinue current use of analgesic medication following Screening and to adhere to study requirements for rescue treatments (acetaminophen to be taken as needed with a maximum daily dose of 2500 mg), including, but not limited to, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, selective cyclooxygenase 2 inhibitors, or combinations thereof, within 7 days or five half-lives of the drug prior to the Baseline Pain Assessment Period, whichever is longer Note: only the rescue medication, i.e., acetaminophen, is allowed for OA pain in the knee; aspirin, at a dose of up to 81 mg per day, is allowed for prophylaxis of coronary and cerebrovascular events if stable for 30 days prior to Screening and the dose is expected to remain the same throughout the duration of the study. 7. Use of immediate- or extended-release or controlled-release opioids (e.g., oxycontin), transdermal fentanyl, or methadone within 3 months prior to Screening 8. Use of opioids, for the treatment of pain other than OA of the knee, with a morphine equivalent dose of ≥30 mg per day for more than 2 days per week within 1 month prior to Screening 9. Use of systemic (i.e., oral) corticosteroids or intra-articular corticosteroids in any joint within 30 days prior to the screening visit (topical, intranasal, and inhaled corticosteroids are permitted) 10. Intra-articular injection of any approved (i.e., hyaluronic acid and corticosteroids) or unapproved treatments (e.g., platelet-rich plasma, capsaicin) into the index knee within 3 months of Screening 11. Physical/occupational/chiropractic therapy for the lower extremities or acupuncture for the lower extremities within

	30 days of Screening, or the need for such therapy during the study ***Medical History, Laboratory Studies, Vital Signs, and Electrocardiograms*** 12. Has current evidence, or history within the previous 12 weeks prior to Screening, of a serious and/or unstable psychiatric, neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, endocrinologic, or other medical disorder, that in the judgment of the Investigator and/or Medical Monitor would jeopardize the safe participation of the subject in the study 13. Had a malignancy in the last year, with the exception of nonmetastatic basal cell of the skin or localized carcinoma in situ of the cervix 14. Has any clinically significant laboratory abnormalities at Screening that in the judgment of the Investigator or Medical Monitor would jeopardize the safe participation of the subject in the study. Has one or more clinical laboratory test values outside the range specified below at Screening or Baseline: a. aspartate aminotransferase (AST) ≥1.5 × the upper limit of normal range (ULN) b. alanine aminotransferase (ALT) ≥1.5 × ULN c. total bilirubin (TBL) >ULN range or has a known condition that is associated with hyperbilirubinemia (e.g. Gilbert's syndrome) 15. Has moderate or severe renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 from screening clinical laboratory tests) 16. Has an ECG QTcF result >480 ms at Screening or Baseline 17. Has a history of uncontrolled hypertension, as defined by: a. Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg at Screening or Baseline b. Systolic blood pressure of 160-179 mmHg or diastolic blood pressure of 100-109 mmHg at Screening or Baseline, AND a history of end-organ damage (including history of left ventricular hypertrophy, heart failure, angina, myocardial infraction, stroke, transient ischemic attack, renal failure, peripheral arterial disease and moderate to advanced retinopathy [hemorrhages or exudates, papilledema])

	c. Known clinical diagnosis of orthostatic hypotension d. Evidence of orthostatic hypotension at Baseline, defined as a decrease in systolic blood pressure ≥20 mmHg or diastolic blood pressure ≥10 mmHg after transitioning from the supine position (after resting for 5 minutes) to standing at 1 or 3 minutes. Subjects unable to stand may be assessed while sitting upright. 18. Congestive heart failure with New York Heart Classification of stage III or IV (Appendix A) 19. Transient ischemic attack or cerebrovascular accident within the past 12 months prior to Screening, or myocardial infarction, or acute coronary syndromes within the past 6 months prior to Screening 20. Is suicidal at Screening or Day -1 as defined below: a. An answer of "yes" to C-SSRS questions 4 or 5 (current or over the last 6 months); OR b. Has attempted suicide within 1 year prior to Screening; OR c. Is actively suicidal in the Investigator's judgment 21. Beck Depression Inventory–II (BDI-II) score ≥29 at Screening 22. Has a history of uncontrolled diabetes mellitus (DM), Type 1 or Type 2 DM, or glycosylated hemoglobin (HbA_{1c}) >8.0% at Screening 23. Known history of human immunodeficiency virus (HIV) infection 24. Known history of infection with hepatitis B virus. Subjects with a history of hepatitis B are eligible if there is documentation of a negative test for hepatitis B surface antigen and a positive test for antibodies to the hepatitis B virus surface antigen 25. Known history of infection with the hepatitis C virus. Subjects with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test 26. Has a known or suspected history of drug abuse or a recent (within the last 5 years) history of alcohol abuse. 27. Use of medicinal or recreational marijuana or cannabidiol (CBD) within 1 month prior to Screening. The use of these substances are not allowed throughout the study.

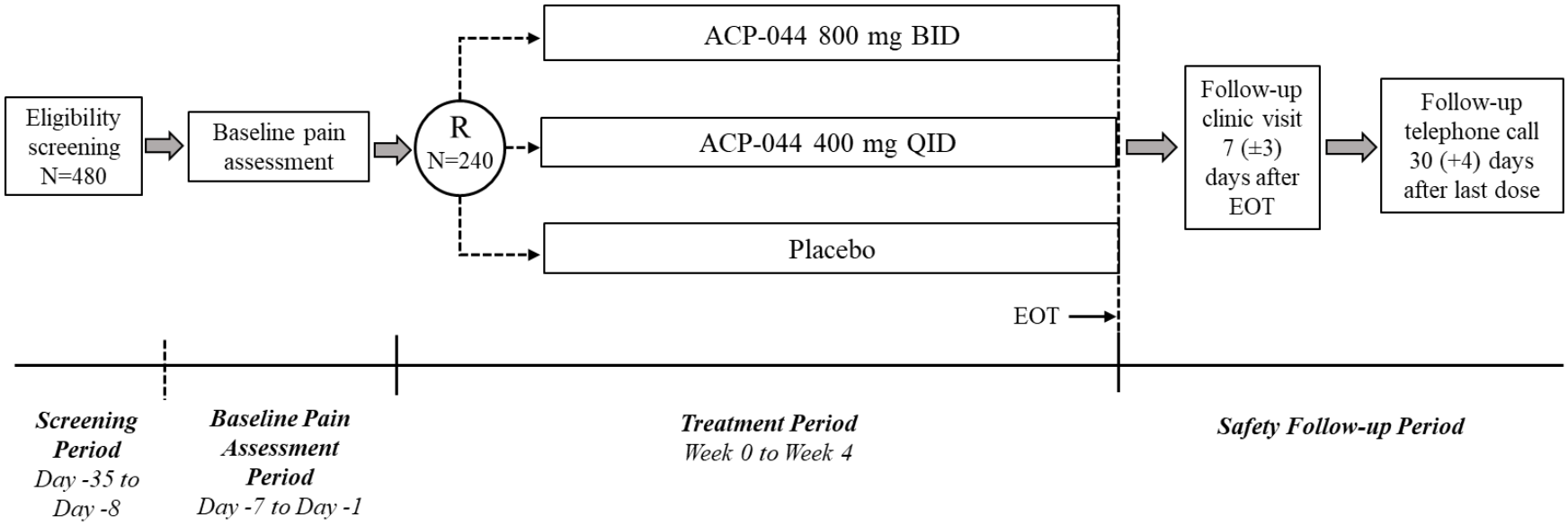
	Other Criteria 28. Subject is unlikely to be able to swallow double-blind study drug (i.e., swallowing tablets 4 times per day, including two tablets at the first and third dosing) 29. Subject is unwilling or unable to comply with the use of the handheld devices 30. Has a significant sensitivity or allergic reaction to ACP-044 or its excipients, or rescue medication 31. Has participated in or is participating in a clinical research study evaluating ACP-044 or has received another investigational product within 30 days or 5 half-lives, whichever is longer, prior to Screening 32. Is an employee or is a family member of an employee of Acadia Pharmaceuticals Inc. or the clinical research site or the CRO administering this study
Pharmacokinetic Assessments	At each predefined timepoint, PK samples will be obtained for measurement of concentrations of ACP-044-at the following visits: • Baseline (Week 0) visit (Visit 3; both before dosing and approximately 1 hour after dosing) • Visit 5 • Visit 6 • Visit 8/or upon early termination (ET) PK blood samples taken at Visits 5, 6, and 8 should be collected at <u>one</u> of the following time intervals: • 2-5 hours after morning dosing • 6-9 hours after morning dosing • 10-12 hours after morning dosing Every effort should be made to collect PK samples at distinct time intervals during Visits 5, 6, and 8. However, if the interval is the same across these visits, then the collection time should vary within that interval. The following scenario is <u>only for illustrative purposes</u>, a number of other scenarios are possible. • For example, if the time interval of 6-9 hours after morning dosing is used for Visits 5, 6, and 8, then every effort should be made to collect PK samples at 6, 7, and 8 hours after morning dosing at each of these visits, respectively. When possible, an additional PK sample (approximately 4 mL) will be collected from subjects who experience a serious adverse event

	(SAE) or an adverse event (AE) leading to discontinuation, as soon as possible after the occurrence of that event. For all PK samples (scheduled and unscheduled), with the exception of those taken following an AE or SAE, the dates and times of administration of the last three doses of the study drug should be recorded. For samples collected from subjects who experience an SAE or an AE leading to discontinuation, the date and time of the last dose prior to the SAE or AE should also be recorded. ACP-044 plasma concentration data will remain blinded until the unblinding of the clinical database at the end of the study.
Sample Size Calculations	Approximately 240 subjects will be randomized in a 1:1:1 ratio to ACP-044 800 mg BID dose, ACP-044 400 mg QID dose, or placebo. Assuming a treatment difference of 0.85 and a common standard deviation of 1.7 between an ACP-044 dose arm and placebo, 64 subjects per arm is needed to provide approximately 80% power to detect this treatment difference using a 2 sample t-test at 2-sided alpha level of 0.05. Assuming a discontinuation rate of 20%, 80 subjects per treatment group will be randomized.
Statistical Methods	**<u>Population Analysis Sets</u>** The **Safety Analysis Set** includes all randomized subjects who received at least one dose of study drug (ACP-044 or placebo). Subjects will be analyzed based on the treatment that they actually received. The Safety Analysis Set will be used for all safety analyses. The **Full Analysis Set** (FAS) includes all randomized subjects who received at least one dose of study drug and with baseline pain assessments and at least one post-baseline pain assessment. Subjects will be analyzed based on the treatment to which they are assigned. The Full Analysis Set will be used for the analysis of all efficacy endpoints. For ACP-044 plasma concentration summaries, the **Pharmacokinetics Analysis Set** will consist of subjects with at least one measurable ACP-044 plasma concentration. **<u>General Statistical Approach</u>** For continuous variables, descriptive statistics will include the following information: the number of subjects with data values (n), mean, standard error of the mean, median, standard deviation, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category. All statistical hypotheses will be tested at the 0.05 significance level.

	Demographic and baseline characteristics, including medical history and exposure to study drug will be summarized descriptively by treatment group and by all subjects combined. **Primary Analysis** The primary efficacy variable will be analyzed using an analysis of covariance model (ANCOVA) based on the FAS with treatment, sex, and baseline K-L score (randomization strata) as factors and baseline weekly average of daily average pain score as a covariate in the model. The primary comparison will be between each ACP-044 dose group versus the placebo group. The comparison between the average of the means of the two ACP-044 dose groups versus the mean of the placebo group will also be conducted. Missing data will be imputed using multiple imputation based on missing at random assumption (MAR) with an exception of missing data from subjects who are treated with ACP-044 and discontinue the study due to lack of efficacy or adverse events. Their missing data will be imputed using the data from placebo group. Sensitivity analysis using pattern mixture model and tipping point approach with multiple imputation to impute missing data will be performed to assess the robustness of the results due to treatment discontinuation and other intercurrent events. **Secondary Analyses** For analysis of continuous secondary endpoints, the analysis method will be the same as that used for the primary variables except for PGIC which will be analyzed using analysis of variance (ANOVA) with treatment, sex, and baseline K-L score as factors. For analysis of categorical variables in secondary endpoints, e.g., proportions of subjects with ≥30% reduction from baseline to Week 4 in the weekly average of the daily average NRS score; the Cochran Mantel Haenszel approach stratified by the randomization strata will be used for subjects with missing data considered as non-responders. **Safety Analyses** Safety data will be summarized by treatment group using descriptive statistics. No formal statistical testing will be performed for any of the safety endpoints. Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, fatal TEAEs, SAEs, SAEs related to study drug, and TEAEs of special interest (AESI) will all be summarized. Descriptive statistics for ECGs, vital signs and weight, and clinical laboratory parameters, including changes from Baseline (prior to first dose), will be tabulated by timepoint and by treatment group.

	The incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with International Council for Harmonisation (ICH) guidelines will also be summarized by treatment group. Additional safety analysis details will be specified in the SAP. **Pharmacokinetic (PK) Analyses** Plasma concentration data for ACP-044 will be listed and summarized using descriptive statistics. Results will be used for other analyses (e.g., population PK modelling), which will be presented in a separate report. **Pharmacokinetic/Pharmacodynamic (PK/PD) Analyses** Guided by exploratory analyses, PK/PD models to describe the exposure-response relationship between ACP-044 exposure parameters and the relevant efficacy and safety endpoints will be developed using appropriate PK/PD methods. Results will be presented in a separate report per a prespecified data analysis plan.
Date	16 February 2022

Figure S–1 Schematic of Study Design for ACP-044-005



Abbreviations: BID=twice daily; EOT=end of treatment; QID=four times daily; R=randomization

Table S–1 Schedule of Events and Assessments for ACP-044-005

	Screening Period	Baseline Pain Assessment Period	Double-Blind Treatment Period							Safety Follow-up Period	
										Clinic visit	Telephone call
Visit Day/Week	Days -35 to -8	Days -7 to -1	Baseline Week 0	Day 3	Week 1	Week 2	Week 3	Week 4	Unscheduled Visit[r]	7 days after EOT	30 days after last dose
Visit Number	1	2	3	4	5	6	7	8 (EOT/ET)			
Visit window (# days)		+3	0	±1	±3	±3	±3	±3		±3	+4
Informed consent	X										
Inclusion/exclusion criteria	X	X	X								
Medical, medication, and surgical history and demographics	X										
Physical examination	X		X					X			
Vital signs (including orthostatic changes)[a]	X	X	X		X	X		X	X		
Height, weight, and BMI calculation[b]	X		X					X			
12-lead ECG[c]	X		X[c]		X	X		X			
Clinical laboratory tests	X		X	X[d]	X	X	X[d]	X			
Pregnancy test[e]	X		X					X			
Urine drug screen	X	X	X[f]					X			
COVID-19 test[g]	X										
C-SSRS	X	X	X		X	X		X	X		
Beck Depression Inventory–II	X										
Verified Clinical Trials Subject Registry	X										
Central Imaging[h]	X										
Issue eDiary and train on use[i]		X									
Collect eDiary								X			
Randomization			X								

Table S-1 Schedule of Events and Assessments for ACP-044-005 (Continued)

	Screening Period	Baseline Pain Assessment Period	Double-Blind Treatment Period							Safety Follow-up Period	
										Clinic visit	Telephone call
Visit Day/Week	**Days -35 to -8**	**Days -7 to -1**	**Baseline Week 0**	**Day 3**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Unscheduled Visit[r]**	**7 days after EOT**	**30 days after last dose**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 (EOT/ET)**			
Visit window (# days)		**+3**	**0**	**±1**	**±3**	**±3**	**±3**	**±3**		**±3**	**+4**
PK blood sample collection[j]			X[k]		X[l]	X[l]		X[l]			
eDiary completion: Numeric Rating Scale Daily Pain Score (Average and Worst)[m]		X	X	X	X	X	X	X		X	
PGIC[n]					X	X		X			
WOMAC[n]			X		X	X		X			
BPI-sf[n]			X		X	X		X			
SF-12			X					X			
HADS	X		X					X			
Participant Scorecard[o]					X	X		X			
Accurate Symptom Reporting (ASR) Training – subject facing	X		X		X[p]	X[p]		X[p]			
Placebo Response Reduction (PRR) Training – subject facing	X		X		X[p]	X[p]		X[p]			
Study drug dispensing/accountability			X		X	X		X			
eDiary completion: Rescue medication dispensing/accountability[q]		X	X	X	X	X	X	X			
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Assessment of adverse events	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ASR=accurate symptom reporting; BMI=body mass index; BPI-sf=Brief Pain Inventory–Short Form; COVID-19=coronavirus disease 2019; C-SSRS=Columbia–Suicide Severity Rating Scale; ECG=electrocardiogram; eDiary=electronic diary; EOT=end of treatment; ET=early termination; HADS=Hospital Anxiety and Depression Scale; PGIC=Patient Global Impression of Change; PK=pharmacokinetic; PRR=placebo response reduction; SF-12=12-item Short Form Survey; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

[a] Vital signs will include body temperature, resting respiration rate, supine and standing systolic and diastolic blood pressure, and pulse rate. Blood pressure and pulse rate will be measured after the subject rests for 5 minutes in the supine position. The subject will then be asked to stand and blood pressure and pulse rate will be taken after standing for 1 minute and then again after 3 minutes. Subjects unable to stand may be assessed while sitting upright. The same position and arm should be used each time vital signs are measured for a given subject.

[b] Height will only be measured at the Screening visit, and BMI will be calculated based on height and weight measurements at Screening. Weight will also be measured at any unscheduled visit.

[c] A single 12-lead ECG will be performed at Screening, at Baseline (Week 0) both predose and at 1 hour postdose (the first dose of the day), Week 1, Week 2, and EOT/ET. A 1-hour window is permitted for the predose ECG and a 20-minute window is permitted for the postdose ECGs. Electrocardiograms should be performed before blood sampling or at least 30 minutes after blood sampling.

[d] A full chemistry (CHEM) panel of clinical laboratory tests will be completed, excluding glucose and the CHEM tests noted in Section 6.5.5 to only be performed at Screening.

[e] Applicable to women of childbearing potential. A serum pregnancy test should be performed at Screening and a urine test must be performed at all other designated visits.

[f] At Baseline, urine drug screen will be performed using a dipstick test which must be negative for any non-permitted medications or drugs in order for the subject to continue in the study.

[g] COVID-19 diagnostic PCR test at Screening.

[h] Randomization visit cannot occur until there is confirmation from the central reader that there are no exclusionary findings.

[i] Subjects will be instructed on the use of and will complete electronic clinical outcome assessments using handheld devices during the study. An eDiary, will be used to record pain scores, compliance with ingestion of study medication, and use of rescue medication.

[j] A PK sample (approximately 4 mL) should also be taken from subjects who experience SAEs or AEs leading to discontinuation, as soon as possible after the occurrence of the event.

[k] A predose PK blood sample must be collected before administration of study drug. A postdose PK blood sample will be collected at the end of ECG assessment approximately 1 hour after study drug administration.

[l] PK samples at Visits 5, 6, and 8 will be collected at one of the following time intervals: 1) 2-5 hours after morning dosing OR 2) 6-9 hours after morning dosing OR 3) 10-12 hours after morning dosing. Every effort should be made to collect the PK samples at distinct time intervals during Visits 5, 6, and 8. However, if the interval is the same across these visits, then the collection time should vary within that interval.

[m] Pain intensity assessments are to be recorded in the evening during the Baseline Assessment Period and prior to their 4th dose of the day during the Double-blind period. Subjects will be rating both the average daily pain as well as their worst daily pain. At the Safety Follow-up Clinic Visit (7 days after EOT), subjects will rate both the average daily pain as well as their worst daily pain over the past week and the data will be entered into EDC.

[n] At study visits, PGIC, WOMAC, and BPI-sf should be performed before blood sample collection, ECG, and other procedures.

[o] Participant Scorecard is viewed by the subject and reviewed by the Investigator at the designated study visits. The Investigator or designee, will acknowledge the scorecard review on the training platform, aLearn.

[p] ASR and PPR training at Visits 5, 6, and/or 8 is on an as needed basis and the need for training will be determined by Participant Scorecard intervention recommendations.

[q] Record rescue medication use in eDiary.

[r] The Investigator may perform any additional evaluations deemed to be clinically indicated. If an unscheduled visit is required for safety reasons, a 12-lead ECG and all appropriate clinical laboratory tests are to be performed.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE	adverse event
BID	twice daily
BMI	body mass index
BPI-sf	Brief Pain Inventory–Short Form
CL/F	apparent systemic clearance following nonintravenous (e.g., oral) administration
COVID-19	coronavirus disease 2019
CRO	contract research organization
C-SSRS	Columbia–Suicide Severity Rating Scale
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOT	end of treatment
ET	early termination
FAS	Full Analysis Set
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HbA_{1c}	glycosylated hemoglobin
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
K-L	Kellgren-Lawrence score
NRS	Numeric Rating Scale
OA	osteoarthritis
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PP	Per-protocol
PR	PR interval of ECG
QID	four times daily
QRS interval	QRS interval of ECG
QT interval	QT interval for heart rate of ECG
QTc	corrected QT interval of ECG for heart rate

Term	Definition
QTcB	corrected QT interval using Bazett's correction method
QTcF	corrected QT interval using Fridericia's correction method
RNA	riboxynucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SF-12	12-item Short Form Survey
$t_{½}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
UDS	urine drug screen
US	United States
VCT	Verified Clinical Trials
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

1 INTRODUCTION

This document is a research protocol and the described study will be conducted in compliance with the protocol, the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline, and applicable regulatory requirements.

1.1 Background Information

Chronic musculoskeletal pain affects a large proportion of the global population. A significant cause of chronic musculoskeletal pain is due to osteoarthritis (OA). Osteoarthritis is a progressive, chronic disease caused by the breakdown and loss of cartilage of the joints, which leads to pain in the hips, knees, hands, feet, and spine. Symptoms and disability increase with increasing age. The prevalence of OA in patients aged 65 and older is 60% in men and 70% in women, and is continually rising (Sarzi-Puttini et al. 2005).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment in patients with mild-to-moderate OA. The efficacy of NSAIDs is well documented, albeit modest, while their use is associated with a number of well recognized risks (Bjordal et al. 2004). The risks associated with long-term therapy with NSAIDs have been well characterized and include gastrointestinal bleeding and increased risk of cardiovascular events (Lanas 2011; Trelle et al. 2011). Those with advanced OA pain typically try several NSAIDs and must often escalate to other therapies including opioids as well as a variety of transiently effective intra-articular therapies.

As a chronically progressive disease, many patients progress until their last option is a joint replacement. However, even with surgery, the complete relief of pain or disability is not guaranteed. For the majority of patients worldwide the inadequate pain relief and disability due to OA has a profound impact on the quality of life with an associated loss of productivity, (Dibonaventura et al. 2011), and substantial cost to society, including healthcare cost (Salmon et al. 2016).

1.2 Investigational Product

ACP-044 is a non-metal based, orally bioavailable, small molecule reactive species decomposition accelerant (RSDAx) with minimal brain distribution that works by accelerating the degradation of peroxynitrite (PN) and peroxide. Peroxynitrite and peroxide are powerful oxidants produced under conditions of injury (e.g., surgical incision) and disease (e.g., diabetes and osteoarthritis pain) that cause untoward effects via protein nitration, release of pro-inflammatory mediators, and modification of sensory ion channels leading to neuronal sensitization and pain (Aubdool et al. 2016; Muscoli et al. 2007; Pacher et al. 2007; Salvemini and Neumann 2009; Stavniichuk et al. 2014;

Sugiyama et al. 2017; Trevisan et al. 2014; Virag et al. 2002). By removing PN, ACP-044 may prevent or reverse neuronal sensitization that underlies acute and persistent pain.

1.3 Nonclinical Data

In vivo, ACP-044 is efficacious in acute animal models of hyperalgesia and allodynia including the chronic pain condition such as OA pain. In a rat OA pain model (mono-iodoacetate [MIA]-induced), ACP-044 significantly reduced mechanical hyperalgesia for at least 24 hours postdose.

1.4 Previous Clinical Experience

1.4.1 Clinical Pharmacology

Three Phase 1 studies have been clinically completed to date in healthy subjects up to 55 years of age. A total of 54 subjects have received ACP-044 (maximum of 2000 mg administered as a single oral dose) and 14 subjects received placebo. In the single ascending dose study, 32 subjects were enrolled in four dose cohorts (150, 450, 1100, and 2000 mg ACP-044; subjects were randomized to 6 active and 2 placebo for each dose cohort). In the food effect study, 12 subjects received two single oral doses of 600 mg ACP-044 according to fed or fasting conditions. In the multiple ascending dose study, 24 subjects were enrolled in three dose cohorts (200, 400, and 600 mg dosed orally three times each day for 7 days; subjects were randomized to 6 active and 2 placebo for each dose cohort). The single and multiple ACP-044 doses were safe and well tolerated in healthy subjects.

ACP-044 exhibits linear kinetics with no time- or dose-dependent effect on pharmacokinetic (PK) parameters. Systemic exposure to ACP-044 was dose-proportional across the studied dose range. Decline from peak is characterized by a relatively quick elimination phase with a mean half-life of 1.6 to 3.2 hours.

Minimal to no accumulation was observed following multiple-dose administration, and as such, the single-dose PK profile is considered representative of the steady-state profile. The PK profile of ACP-044 following oral administration is best described by a one-compartment model with first-order absorption and first-order elimination. Following oral administration, ACP-044 is rapidly absorbed with a median time to maximum drug concentration (T_{max}) of approximately 1-2 hours. Ingestion of a high-fat meal had a small effect on the rate of absorption (approximately 23% reduction in maximum observed [peak] drug concentration (C_{max}) and 1 hour delay in T_{max}) and had no effect on the extent (area under the plasma concentration-time curve [AUC]) of ACP-044 absorption. Since the relative extent of absorption was unaffected by the presence of a high fat meal, it is anticipated that the slight reduction in C_{max} and prolongation of T_{max} will be of no clinical significance.

In vitro, ACP-044 has shown moderate protein binding in human plasma. At concentrations of 10 μM, binding was 88%.

Consistent with the nonclinical data, ACP-044 volume of distribution in studied subjects was <30 L, which suggests that ACP-044 does not reach beyond the extracellular fluid with limited to no distribution into tissues (intracellularly).

ACP-044 is primarily metabolized in the liver and the major metabolite is a sulfate conjugate. Consistent with preclinical data, following oral administration in healthy subjects, approximately 35% of ACP-044 was excreted unchanged in urine indicating that hepatic metabolism and renal excretion contribute to ACP-044 elimination. Following oral administration in healthy subjects, decline from peak is mono-exponential and is characterized by a rapid elimination phase with rapid clearance (mean CL/F=6.04 to 11.3 L/h) and a short half-life (mean $t_{½}$=1.6 to 3.2 hours).

According to nonclinical assessments ACP-044 did not directly inhibit (IC_{50} values >100 μM) the cytochrome (CYP) isozymes tested (1A2, 2C8, 2C19, 2D6, and 3A4) or transporters (IC_{50} >600 μM for P-gp, OATP1B1, OATP1B3, OAT1, OCT1, MATE1 and MATE2-K; IC_{50}=174 μM for OAT3; IC_{50} >30 μM for breast cancer resistant protein [BCRP]). Future studies are planned to investigate the full panel of CYPs and transporters and their drug-drug interaction (DDI) potential.

Always refer to the latest version of the ACP-044 Investigator's brochure for the overall benefit/risk assessment and the most accurate and current information regarding nonclinical data, drug metabolism, pharmacokinetics, efficacy, and safety.

1.5 Study Rationale

ACP-044 has demonstrated efficacy in acute and chronic nociceptive models in rodents and has been shown to be safe and well tolerated in single and multiple ascending dose studies in healthy subjects. The present study is a proof-of-concept study to evaluate the efficacy of ACP-044 as an analgesic for the management of pain associated with OA of the knee and to evaluate the safety, tolerability, and PK profile of ACP-044.

1.5.1 Rationale for Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study in subjects with pain who have radiographically confirmed OA of the knee. The study will assess the efficacy of ACP-044 by comparing active treatment groups receiving either 800 mg ACP-044 BID or 400 mg ACP-044 QID, with a placebo group. In a rat model of OA pain (mono-iodoacetate [MIA] model), a significant reduction in mechanical hyperalgesia was observed for at least 24 hours postdose in ACP-044 treated animals. Guided by the nonclinical MIA animal model,

the present study is designed to ascertain the efficacy of ACP-044 in treating pain in a clinical setting.

1.5.2 Rationale for Dose Selection

In a nonclinical MIA rodent model of OA pain, ACP-044 at 100 and 300 mg/kg significantly increased joint compression thresholds, to approximately the same degree as celecoxib. It is unknown, however, whether the response is driven by C_{max} or AUC. In the present proof of concept study, the maximum tolerated dose of ACP-044 is being evaluated by testing two dosing regimens (i.e., 800 mg BID or 400 mg QID) to allow the selection of the optimal dosing regimen and better characterization of the exposure-response relationship.

1.6 Potential Risks and Benefits

Nonclinical studies in animal models of acute and chronic nociception have demonstrated efficacy (i.e., analgesia) with ACP-044 and that it is safe and well tolerated. This study will help identify whether ACP-044 is efficacious as an analgesic treatment in humans. If the study shows treatment with ACP-044 is effective, this could lead to further clinical development of this treatment for pain associated with OA.

A detailed summary of the potential risks and benefits is available in the ACP-044 Investigator's Brochure.

1.6.1 Known Potential Risks

In the Phase 1 clinical studies in healthy subjects, the side effects that occurred in more than 1 subject treated with ACP-044 were indigestion and headache.

In the nonclinical studies, side effects seen in animals that were given ACP-044 were vomiting, stomach acid reflux, loose stools, and changes in some organ weights. Although these side effects have not been seen in human studies, they may be potential risks.

There may be unforeseeable risks or side effects that are related to the study drug and that are unknown at this time. The study drug, when taken alone or in combination with other medications, may have risks that are unknown. Rare or unknown side effects may occur. It is not possible to predict the chances of such problems or how bad they could be.

All drugs have a potential risk of an allergic reaction which, if not treated promptly, could become life threatening. Some symptoms of allergic reaction are: rash, difficulty breathing, wheezing, swelling around the mouth, throat or eyes, a fast pulse, and sweating. Each research center is expected to have qualified staff, equipment, and drugs to be able to manage an acute allergic reaction.

1.6.2 Known Potential Benefits

ACP-044 is being assessed for the management of pain associated with OA of the knee. As the present study is a proof-of-concept study, there have been no clinical benefits demonstrated to date.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of ACP-044 compared with placebo in the treatment of pain associated with osteoarthritis (OA) of the knee.

2.1.1 Primary Endpoint

The primary endpoint is change from Baseline to Week 4 in the weekly average of the daily average Numeric Rating Scale (NRS) pain intensity scores.

2.2 Secondary Objective

The secondary objective of the study is to evaluate the efficacy of ACP-044 compared with placebo in the treatment of pain associated with OA of the knee.

2.2.1 Secondary Endpoints

The key secondary endpoints are:

- Patient Global Impression of Change (PGIC) at Week 4 with reference to baseline status
- Change from Baseline to Week 4 in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score and individual subscale scores for pain, stiffness, and physical function
- Proportion of subjects who are responders as defined by 30% and 50% reduction from Baseline to Week 4 in the weekly average of the daily average NRS pain intensity scores

Additional secondary endpoints are:

- Change from Baseline to Week 4 in:
    - Weekly average of the daily worst NRS pain intensity scores
    - Brief Pain Inventory–Short Form (BPI-sf)
    - 12-item Short Form Survey (SF-12)

2.3 Exploratory Objective

The exploratory objective of the study is to evaluate the use of rescue medication in subjects with pain associated with OA of the knee treated with ACP-044 compared with placebo.

2.3.1 Exploratory Endpoints

The exploratory endpoints are:

- Comparison of average daily rescue medication use
- Hospital Anxiety and Depression Scale (HADS)

2.4 Safety Objective

The safety objective of the study is to evaluate the safety and tolerability of ACP-044 compared with placebo in the treatment of pain associated with OA of the knee.

2.4.1 Safety Endpoints

Safety will be evaluated by analyses of the following:

- Treatment-emergent adverse events (TEAEs)
- Vital signs
- Electrocardiograms (ECGs)
- Physical examination results
- Clinical laboratory tests
- Columbia–Suicide Severity Rating Scale (C-SSRS)

2.5 Pharmacokinetic Objectives

The PK objective of the study is to characterize the PK profile of ACP-044 in subjects with pain associated with OA of the knee.

2.5.1 Pharmacokinetic Endpoints

The PK endpoints of the study are:

- Plasma concentrations of ACP-044 using sparse sampling on the following study days: Baseline (Week 0), Week 1, Week 2, and Week 4 (EOT)/ET
- ACP-044 PK parameters determined using a population PK approach

2.6 Pharmacokinetic/Pharmacodynamic Objective

The pharmacokinetic/pharmacodynamic (PK/PD) objective of the study is to characterize the exposure-response relationship using appropriate modelling and simulation methods.

2.6.1 Pharmacokinetic/Pharmacodynamic Endpoints

- Guided by exploratory analyses, appropriate ACP-044 exposure-response relationship:
    - for efficacy using the primary endpoint
    - for safety using the most frequent and other relevant TEAEs

3 STUDY DESCRIPTION

3.1 Overview of Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ACP-044 in subjects with pain associated with radiographically confirmed OA of the knee. The study will compare active treatment groups, receiving either 800 mg ACP-044 BID or 400 mg ACP-044 QID, with a placebo group. The Sponsor, subjects, and Investigators will be blinded to treatment assignment.

Up to approximately 50 sites in the United States (US) will screen approximately 480 subjects and approximately 240 subjects are planned for randomization (80 subjects per treatment group).

The duration of participation for individual study subjects will be approximately 13 weeks, consisting of a screening period of up to 4 weeks, a 7-day baseline pain assessment period, a 4-week double-blind treatment period, and a safety follow-up period of approximately 30 (+4) days.

The study periods are:

- Screening: up to 4 weeks
- Baseline Pain Assessment: a 7-day period during which baseline pain assessments will be recorded for 7 days. Additional 3-day window may be added, if needed.
- Double-blind treatment: 4 weeks
- Safety follow-up: approximately 7 days after end of treatment (EOT)/early termination (ET) and approximately 30 days after the last dose of study drug

The study start date is defined as the date the first subject is enrolled, which is the date the first subject is randomized.

The primary completion date is the last date that subject data was collected for the primary outcome measure.

The study completion date is defined as the last date that subject data was collected for the primary outcome measure, secondary outcome measure(s), and adverse events, which includes the safety follow-up telephone call visit.

Procedures for when a subject is lost to follow-up are provided in Section 4.6.

The study schematic is presented in Figure S–1 and the schedule of assessments is provided in Table S–1.

3.1.1 Screening Period (Up to 4 Weeks)

During the Screening period, subjects will be assessed for study eligibility. All subjects must have radiographically confirmed OA of the knee, including review of imaging and confirmation of a Kellgren-Lawrence (K-L) score of 2 or 3. Subjects who have had an X-ray of the index knee within 12 weeks of Screening may provide a historical image for central reading to confirm eligibility, or imaging can be done during Screening at protocol-trained radiological sites. Randomization visits cannot occur until there is confirmation from the central reader that there are no exclusionary findings on the knee joint images. The index knee is defined as the most painful knee at Screening.

Prohibited analgesic medications must be discontinued during the Screening period. Investigators must not withdraw a subject's prohibited medication other than analgesics solely for the purpose of enrolling them into the study. Medications will be discontinued only if it is deemed clinically appropriate to do so and in consultation with the prescribing physician.

All pain medication, except for the rescue medication (acetaminophen), will be discontinued 7 days or 5 half-lives, whichever is longer, prior to the Baseline Pain Assessment Period. In the event of inadequate pain relief, acetaminophen may be taken with a maximum daily dose of 2500 mg.

Rescreening of a subject will be allowed, with the approval of the Medical Monitor.

3.1.2 Baseline Pain Assessment Period (1 Week)

Following eligibility at screening, subjects will complete a Baseline Pain Assessment Period that will occur approximately 7 days before randomization; an additional 3-day window may be added, if needed. During the Baseline Pain Assessment Period, subjects will be instructed in the use of a handheld device (electronic diary [eDiary]) to record their daily pain scores and rescue medication use. Compliance with recording of pain score and use of rescue medication will be assessed for continued study eligibility.

Subjects must discontinue taking study-provided rescue medication during the Baseline Pain Assessment Period and for at least 24 hours prior to the start of study visits. Rescue

medication use during the Baseline Pain Assessment Period through Visit 3 and within 24 hours of the study visits (Visits 5, 6, and 8) will be documented in the electronic data capture (EDC).

Subjects who enter the Baseline Pain Assessment Period will not be allowed to rescreen. Subjects who experience technical issues with the device and their pain scores were not assessed may be rescreened and the Baseline Pain Assessment Period may be extended, if needed and with permission of the Sponsor.

3.1.3 Treatment Period (4 Weeks)

At Baseline (Week 0), eligible subjects will be randomly assigned in a 1:1:1 ratio to receive ACP-044 800 mg BID, ACP-044 400 mg QID, or placebo, according to a randomization schedule. Randomization will be stratified by sex and baseline K-L score (2 or 3).

All efficacy assessments will be completed and a PK blood sample will be taken at the Baseline visit prior to administration of the first dose of study drug (Table S–1). Subjects will continue daily entry into the eDiary of pain scores, compliance with ingestion of study medication, and rescue medication use from Week 0 through to Week 4/EOT/ET.

Subjects will receive their first dose at the study site after all Baseline assessments have been completed and a PK blood sample will be taken approximately 1 hour after dosing. Dosing is four times a day.

During the treatment period (Week 0 through Week 4), subjects will be permitted to use only acetaminophen as rescue medication. Subjects will record their use of acetaminophen in their eDiary. Subjects must discontinue acetaminophen use for at least 24 hours prior to the start of study visits in order to minimize the confounding effects of the rescue medication on efficacy measurements.

A PK sample will be taken at each study visit according to the schedule described in the Section 6.7.

At the Week 4 visit, end of treatment (EOT) procedures will be completed.

See Section 4.5 for subjects who discontinue early from the study.

3.1.4 Safety Follow-up Period (30 Days)

Safety will be further assessed during a follow-up visit to occur in the clinic approximately 7 (±3) days after EOT/ET procedures. During this in-clinic visit, pain intensity, adverse events (AEs), and concomitant medications will be assessed, since the EOT/ET. Then, a follow-up telephone call will occur approximately 30 (+4) days after the last dose of study drug to assess AEs and concomitant medications.

The study schematic is presented in Figure S–1.

4 SUBJECT ELIGIBILITY AND WITHDRAWAL CRITERIA

To be eligible for this study, subjects must meet all of the inclusion criteria and none of the exclusion criteria.

4.1 Inclusion Criteria

A subject must meet all of the following inclusion criteria to be eligible for participation in the study:

1. Male or female subjects ≥18 and <65 years of age at the time of Screening
2. Able to understand and provide signed informed consent
3. Has a body mass index (BMI) ≤39 kg/m^2 at Screening
4. Confirmed history of pain associated with OA in the index knee
5. Clinical diagnosis of OA in at least one knee joint (i.e., the index knee) based on the American College of Rheumatology Criteria with radiographic evidence of OA (K-L score of 2 or 3) at Screening

   Note: K-L scores of 1 or 4 are exclusionary
6. Willing to maintain current activity and exercise levels throughout the study
7. Willing and able to comply with clinic visits and study-related procedures
8. Consent to allow all radiographs and medical/surgical/hospitalization records of care received elsewhere to be shared with the Investigator and third parties who will examine the images (i.e., central x-ray reader)
9. Negative urine drug screen result at Screening, Baseline Pain Assessment Period, and Baseline. A positive urine drug test for a prescribed medication that is permitted at Screening, but not in the study, is acceptable if it has been prescribed. The subject will need to washout from this medication, if appropriate, and have a negative screen for this medication prior to randomization. Investigators must not withdraw a subject's prohibited medication other than analgesics solely for the purpose of enrolling them into the study. Medications will be discontinued only if it is deemed clinically appropriate to do so and in consultation with the prescribing physician.
10. Must have a negative COVID-19 diagnostic polymerase chain reaction (PCR) test at Screening. Not planning to receive a COVID-19 vaccine during Screening through 30 days of the last dose of study drug. If the subject has received a COVID-19 vaccine, they must be fully vaccinated at least 1 week before the Screening visit and be symptom free. If subjects have received a COVID-19 booster shot, they will need to have completed the shot at least one week before Screening and have no residual symptoms.

Note: subjects are considered fully vaccinated 2 weeks after their second dose in a 2-dose series or 2 weeks after a single-dose vaccine.

11. If the subject is male, the subject and his partner must use a highly effective form of contraception (i.e., double-barrier method which includes a condom plus diaphragm with spermicide or condom plus spermicide) at the time of Screening and for at least 30 days after the last dose of study drug. If subjects have had a vasectomy, they must still use a condom.

    Subjects must also agree to not donate sperm for the duration of the study and for at least 30 days after the last dose of study drug

12. If the subject is female, she must not be pregnant or breastfeeding. She must also be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) OR must agree to use TWO clinically acceptable methods of contraception for at least 30 days prior to Day -1, throughout the entire study, and for at least 30 days following completion of the study.

    Acceptable methods of contraception include the following:

    a. A barrier method (condom, diaphragm, or cervical cap) with spermicide
    b. Hormonal contraception, including oral, injectable, transdermal, or implantable methods
    c. Intrauterine device (IUD)

    Only one of the two clinically acceptable methods can be a hormonal method.

    All female subjects of childbearing potential must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative urine pregnancy test at Baseline.

Inclusion Criteria Specific to Baseline Pain Assessment Period

13. Baseline Pain Assessment Period weekly average daily pain score ≥4
14. Has no more than 1 day with a pain score of 10 during the Baseline Pain Assessment Period
15. Has a standard deviation of <1.6 for average daily pain score diary entries during the Baseline Pain Assessment Period
16. Able to complete logging of pain scores for at least 6 of the last 7 days of the Baseline Pain Assessment Period

4.2 Exclusion Criteria

A subject must meet none of the following exclusion criteria to be eligible for the study:

Medical Conditions

1. Pain anywhere else in the body which is greater than or equal to OA pain in the index knee, or likely to interfere with subject's assessment of pain throughout the study, as judged by the Investigator
2. History or presence on imaging of knee arthropathy (osteonecrosis, subchondral insufficiency fracture, rapidly progressive OA type 1 or type 2), recent fall, injury, or trauma affecting the index knee, ligament tear, neuropathic joint arthropathy, knee dislocation (patella dislocation is eligible), extensive subchondral cysts, Baker's cyst, evidence of bone fragmentation or collapse, or primary metastatic tumor with the exception of chondromas, or pathological fractures during the Screening Period
3. History or presence at Screening of non-OA inflammatory joint disease (e.g., rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, pseudo-gout, gout, spondyloarthropathy, joint infections within the past 5 years, Paget's disease of the spine, pelvis, or femur, neuropathic disorders, multiple sclerosis, fibromyalgia, tumors or infections of the spinal cord, or renal osteodystrophy) or any condition that would interfere with the rating of OA pain
4. Recent arthroscopic surgery within 1 month of Screening; or has any planned surgery or procedure during the study

Concomitant Treatments

5. Use of monoamine reuptake inhibitors, tricyclic antidepressants, anticonvulsants, and/or serotonin norepinephrine reuptake inhibitors within 4 weeks prior to Screening.
6. Unwilling to discontinue current use of analgesic medication following Screening and to adhere to study requirements for rescue treatments (acetaminophen to be taken as needed with a maximum daily dose of 2500 mg), including, but not limited to, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, selective cyclooxygenase 2 inhibitors, or combinations thereof, within 7 days or five half-lives of the drug prior to the Baseline Pain Assessment Period, whichever is longer

   Note: only the rescue medication, i.e., acetaminophen, is allowed for OA pain in the knee; aspirin, at a dose of up to 81 mg per day, is allowed for prophylaxis of coronary and cerebrovascular events if stable for 30 days prior to Screening and the dose is expected to remain the same throughout the duration of the study
7. Use of immediate- or extended-release or controlled-release opioids (e.g., oxycontin), transdermal fentanyl, or methadone within 3 months prior to Screening

8. Use of opioids, for the treatment of pain other than OA of the knee, with a morphine equivalent dose of ≥30 mg per day for more than 2 days per week within 1 month prior to Screening
9. Use of systemic (i.e., oral) corticosteroids or intra-articular corticosteroids in any joint within 30 days prior to the screening visit (topical, intranasal, and inhaled corticosteroids are permitted)
10. Intra-articular injection of any approved (i.e., hyaluronic acid and corticosteroids) or unapproved treatments (e.g., platelet-rich plasma, capsaicin) into the index knee within 3 months of Screening
11. Physical/occupational/chiropractic therapy for the lower extremities or acupuncture for the lower extremities within 30 days of Screening, or the need for such therapy during the study

Medical History, Laboratory Studies, Vital Signs, and Electrocardiograms

12. Has current evidence, or history within the previous 12 weeks prior to Screening, of a serious and/or unstable psychiatric, neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, endocrinologic, or other medical disorder, that in the judgment of the Investigator and/or Medical Monitor would jeopardize the safe participation of the subject in the study
13. Had a malignancy in the last year, with the exception of nonmetastatic basal cell of the skin or localized carcinoma in situ of the cervix
14. Has any clinically significant laboratory abnormalities at Screening that in the judgment of the Investigator or Medical Monitor would jeopardize the safe participation of the subject in the study. Has one or more clinical laboratory test values outside the range specified below at Screening or Baseline:
    a. aspartate aminotransferase (AST) ≥1.5 × the upper limit of normal range (ULN)
    b. alanine aminotransferase (ALT) ≥1.5 × ULN
    c. total bilirubin (TBL) >ULN range or has a known condition that is associated with hyperbilirubinemia (e.g., Gilbert's syndrome)
15. Has moderate or severe renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 from screening clinical laboratory tests)
16. Has an ECG QTcF result >480 ms at Screening or Baseline
17. Has a history of uncontrolled hypertension, as defined by:
    a. Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg at Screening or Baseline

b. Systolic blood pressure of 160-179 mmHg or diastolic blood pressure of 100-109 mmHg at Screening or Baseline, AND a history of end-organ damage (including history of left ventricular hypertrophy, heart failure, angina, myocardial infraction, stroke, transient ischemic attack, renal failure, peripheral arterial disease and moderate to advanced retinopathy [hemorrhages or exudates, papilledema])

c. Known clinical diagnosis of orthostatic hypotension

d. Evidence of orthostatic hypotension at Baseline, defined as a decrease in systolic blood pressure ≥20 mmHg or diastolic blood pressure ≥10 mmHg after transitioning from the supine position (after resting for 5 minutes) to standing at 1 or 3 minutes. Subjects unable to stand may be assessed while sitting upright.

18. Congestive heart failure with New York Heart Classification of stage III or IV (Appendix A)
19. Transient ischemic attack or cerebrovascular accident within the past 12 months prior to Screening, or myocardial infarction, or acute coronary syndromes within the past 6 months prior to Screening
20. Is suicidal at Screening or Day -1 as defined below:
    a. An answer of "yes" to C-SSRS questions 4 or 5 (current or over the last 6 months); OR
    b. Has attempted suicide within 1 year prior to Screening; OR
    c. Is actively suicidal in the Investigator's judgment
21. Beck Depression Inventory–II (BDI-II) score ≥29 at Screening
22. Has a history of uncontrolled diabetes mellitus (DM), Type 1 or Type 2 DM, or glycosylated hemoglobin (HbA_{1c}) >8.0% at Screening
23. Known history of human immunodeficiency virus (HIV) infection
24. Known history of infection with hepatitis B virus. Subjects with a history of hepatitis B are eligible if there is documentation of a negative test for hepatitis B surface antigen and a positive test for antibodies to the hepatitis B virus surface antigen
25. Known history of infection with the hepatitis C virus. Subjects with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test
26. Has a known or suspected history of drug abuse or a recent (within the last 5 years) history of alcohol abuse

27. Use of medicinal or recreational marijuana or cannabidiol (CBD) within 1 month prior to Screening. The use of these substances are not allowed throughout the study

Other Criteria

28. Subject is unlikely to be able to swallow double-blind study drug (i.e., swallowing tablets 4 times per day, including two tablets at the first and third dosing)
29. Subject is unwilling or unable to comply with the use of the handheld devices
30. Has a significant sensitivity or allergic reaction to ACP-044 or its excipients, or rescue medication
31. Has participated in or is participating in a clinical research study evaluating ACP-044 or has received another investigational product within 30 days or 5 half-lives, whichever is longer, prior to Screening
32. Is an employee or is a family member of an employee of Acadia Pharmaceuticals Inc. or the clinical research site or the CRO administering this study

4.3 Screen Failures

Rescreening of a subject will be allowed, with the approval of the Medical Monitor.

Subjects may be rescreened following a COVID-19 infection as long as they have no sequelae from COVID-19 infection, per Exclusion Criterion 12.

Subjects who enter the Baseline Pain Assessment Period will not be allowed to rescreen. Subjects who experience technical issues with the device and their pain scores were not assessed, may be rescreened and the Baseline Pain Assessment Period may be extended, if needed and with permission of the Sponsor.

The minimum information that will be captured for screen failures includes date informed consent is signed, demography, screen failure details, and any adverse event (AE)/serious adverse event (SAE).

4.4 Subject Withdrawal of Consent

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time, and for any reason, without prejudice to his or her future medical care.

If the subject decides to withdraw consent from all components in the study, this must be documented and no additional assessments will be performed. If the subject wants to discontinue treatment and agrees to the evaluations specified at the EOT/ET visit and/or at safety follow-up (whichever is applicable), as outlined in Table S–1, the agreed assessments should be conducted. The subject's reason for wanting to discontinue treatment and the

agreement to continue with the applicable assessments for study termination must be documented.

4.5 Subject or Study Discontinuation

Subjects may be discontinued from the study for a number of reasons, including, but not limited to, those listed below:

- AE
- Death
- Lack of efficacy
- Lost to follow-up (Section 4.6)
- Non-compliance with study drug
- Investigator decision
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- Use of prohibited medication
- Withdrawal of consent by subject
- Other

If at any time the C-SSRS results for a given subject reveal potential suicidality, then the Investigator should assess the clinical significance of such results. If a clinically significant risk of suicidality is identified for a subject, then the Investigator should discontinue the subject and implement appropriate treatment (Section 6.5.4).

Individual subject and aggregate safety data will be reviewed regularly throughout the study to determine whether the study should be stopped, modified, or continued based on the review of cumulative data. This review will include analysis of similar clinically significant laboratory findings/abnormalities, ECG abnormalities, vital sign abnormalities and AE's among subjects in order to assess all potential risks from blinded investigational product.

The Sponsor reserves the right to discontinue the study at any time for any reason. Such reasons may be any of, but not limited to, the following:

- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected incidence of known AEs

- Frequently-occurring, similar serious adverse events that increases risk for all subjects from continued participation in the study
- Frequently-occurring, similar clinically significant laboratory findings/abnormalities, ECG abnormalities, and/or vital sign abnormalities that increases risk for all subjects from continued participation in the study
- Medical, ethical, or business reasons affecting the continued conduct of the study

Regulatory authorities also have the right to terminate the conduct of the study in their region for any reason.

If the study is terminated for any reason, subjects remaining in the study will return to standard of care.

4.5.1 Discontinuation of Study Drug for Individual Subjects

The Investigator and Medical Monitor will review all laboratory, ECG, and related safety data regularly throughout the study for all individual subjects in order to determine whether any individual subject may continue to safely participate in the study. In general, either the Investigator or the Medical Monitor may discontinue the subject from the study at any time when any specific laboratory or ECG data change from Baseline indicates that the subject is placed at increased risk from continued participation in the study.

In rare instances, it may be necessary for a subject to permanently discontinue study drug. Study drug stopping criteria are described below. If a subject experiences any of the below events, it must be documented as an AE.

See Section 4.5.2 for handling of subjects who discontinue and for any further evaluations that need to be completed.

4.5.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study drug for abnormal liver tests is required by the Investigator when a subject meets one of the conditions outlined below. The Investigator can discontinue study drug in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if they believe that it is in best interest of the subject.

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 × upper limit of normal (ULN)
    - if there is an elevation of >2 x ULN, the laboratory assessment should be repeated
    - If ALT or AST is ≥3 × ULN, international normalized ratio (INR) should be tested

- If a subject is discontinued from the study because of ALT or AST ≥3 × ULN, every reasonable attempt should be made to follow the subject until the value(s) normalize or until the Investigator deems it to be chronic or stable.

- Total bilirubin (TBL) ≥1.5 × ULN
- Creatine kinase (CK)/creatine phosphokinase (CPK) ≥5 × ULN for more than 1 week

4.5.1.2 Cardiovascular-Related Stopping Criteria

If a clinically significant finding of orthostatic hypotension, bradycardia, or change in QTcF, as defined below, is identified after enrollment, the Investigator or qualified designee and Medical Monitor will determine if the subject can continue in the study and if any change in subject management is needed.

- Orthostatic hypotension – decrease in systolic blood pressure (SBP) ≥20 mmHg or diastolic BP (DBP) ≥10 mmHg after transitioning from the supine position (after resting for 5 minutes) to standing at 1 or 3 minutes with or without symptoms such as light headedness or dizziness and not explained by dehydration, illness, or medications
- Significant bradycardia, defined as heart rate of ≤45 beats per minute (BPM) on an ECG, or pulse decrease of ≥25% from Baseline with resulting heart rate <60 BPM
- QTcF result >470 ms for males and >480 ms for females or QTcF increases ≥60 ms from Baseline

4.5.1.3 Adverse Event Stopping Criteria

If a clinically significant finding of any below-mentioned or any other medically-concerning AE that is considered by the Investigator and Sponsor to be causally related to study drug is identified after enrollment, the Investigator or qualified designee and Medical Monitor will determine if the subject can continue in the study and if any change in subject management is needed.

- life-threatening event
- immediate drug reaction (e.g., Stevens-Johnson syndrome)
- QT prolongation
- acute renal insufficiency
- cardiopulmonary arrest

4.5.2 Handling of Subject Discontinuation During the Treatment Period

Unless the subject has withdrawn consent from all components of the study, every reasonable effort should be made to complete Week 4 (EOT)/ET and all safety follow-up assessments (as outlined in Table S–1) for all subjects who discontinue prematurely during the treatment period of the study. All information will be reported on the applicable pages of the electronic case report form (eCRF).

If a subject is discontinued from the study because of an AE, every reasonable attempt should be made to follow and appropriately treat (or refer for treatment) the subject until the AE resolves or until the Investigator deems the AE to be chronic or stable. For subjects who continue to be followed for safety, SAEs should continue to be reported as described in Section 7.4.2. All SAEs will continue to be followed and appropriately treated until such events have resolved or the Investigator deems them to be chronic or stable.

4.6 Subject Lost to Follow-up

A subject will be considered lost to follow-up if they fail to attend a scheduled visit and are unable to be contacted by the study site.

Every reasonable effort should be made to contact the subject and will include a minimum of three documented phone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods. All contact attempts are to be documented in the source documents.

4.7 Prior and Concomitant Therapy

All medications used from study screening until completion of the second safety follow-up telephone call contact are to be recorded.

4.7.1 Prior Medication

Prior medication is defined as any medication with stop dates prior to the date of the first dose of study drug.

4.7.2 Concomitant Medication

Concomitant medication is defined as any medications taken after the date of the first dose of study drug through to the second follow-up telephone call.

In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medication without prior consultation with the Investigator (unless the subject is receiving treatment for a medical emergency).

The Investigator may prescribe appropriate medication to treat AEs.

Drugs that confound the potential analgesic response and are prohibited (Appendix B) include:

- monoamine reuptake inhibitors, antidepressants, anticonvulsants, and/or serotonin norepinephrine reuptake inhibitors
- Analgesics (other than rescue medication, i.e., acetaminophen), including NSAIDs, opioids, selective cyclooxygenase 2 inhibitors, or combinations thereof

  Note: only the rescue medication, i.e., acetaminophen, is allowed for OA pain in the knee (not combinations including acetaminophen); aspirin, at a dose of up to 81 mg per day, is allowed for prophylaxis of coronary and cerebrovascular events if stable for 30 days prior to Screening and the dose is expected to remain the same throughout the duration of the study. Aspirin should not be used with an anticoagulant.
- systemic corticosteroids or intra-articular corticosteroids
- intra-articular injection of any approved (i.e., hyaluronic acid) or unapproved treatments (e.g., platelet-rich plasma, capsaicin)

Additional restriction (Appendix B) includes:

- HMG-CoA reductase inhibitors (statins) are restricted and cannot be initiated after Screening and throughout the study. Subjects who are on a stable dose of a statin at Screening may be eligible for enrollment.

4.8 Permitted, Restricted, and Prohibited Medications

Prohibitions and restrictions for concomitant medications should be followed between the initial screening visit and Week 4 (EOT)/ET as specified in Appendix B.

Permitted concomitant medications should remain at a stable dose throughout the study.

Subjects who require current treatment with a prohibited medication will be withdrawn from the study.

Subjects who have taken a prohibited medication during the study will be withdrawn from the study unless:

- the prohibited medication has been discontinued, AND
- withdrawal from the study presents an unacceptable medical risk to the subject

The justification to allow the subject who has taken a prohibited medication to continue in the trial will be made by the Sponsor/Medical Monitor, with medical input from the Investigator, and will be documented. If a subject is allowed to remain in the trial, this will be reported as a major protocol deviation and not a waiver.

4.8.1 Rescue Medications, Treatments, and Procedures

Subjects are encouraged to limit the amount of rescue medication (i.e., acetaminophen) taken during the study. Subjects must discontinue taking study-provided rescue medication during the Baseline Pain Assessment Period and for at least 24 hours prior to the start of study visits in order to minimize the confounding effects of the rescue medication on efficacy measurements. Rescue medication use during the Baseline Pain Assessment Period through Visit 3 and within 24 hours of the study visits (Visits 5, 6, and 8) will be documented in the EDC. The total daily dose of acetaminophen should not exceed 2500 mg (5 tablets).

4.9 Lifestyle Considerations

4.9.1 Activity

Subjects should maintain the same activity level throughout the study duration.

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Description

The investigational products are ACP-044 400 mg tablets or matching placebo. Placebo tablets will be size- and color-matched to the ACP-044 tablets.

In order to maintain the double-blind design of the study, tablets will be administered orally four times per day for 4 weeks.

Doses to be studied are:

- ACP-044 800 mg total dose delivered two times a day (provided as 2×400 mg ACP-044 tablets)
- ACP-044 400 mg total dose delivered four times a day (provided as 1×400 mg ACP-044 tablet)
- Placebo, size- and color-matched to ACP-044 tablets

5.1.1 Formulation, Appearance, Packaging, and Labeling

The Sponsor will supply ACP-044 400 mg tablets and matching placebo tablets provided in blister cards.

ACP-044 is a white to off-white powder. ACP-044 400 mg tablets include the active compound (ACP-044) and the following excipients: [redacted]. The drug product is formulated with standard pharmaceutical excipients at 400 mg strength (454.5 mg of ACP-044).

Placebo tablets contain all of the same excipients as ACP-044 400 mg tablets but do not contain any ACP-044.

ACP-044 tablets and placebo tablets are manufactured under Good Manufacturing Practice.

5.1.2 Product Storage and Stability

Investigational product must be stored between 20°C to 25°C (68°F and 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP controlled conditions] in a secure area with restricted access and according to local and national regulations.

5.1.3 Rescue Medication

The sponsor will provide acetaminophen 500 mg tablets for the Baseline Pain Assessment Period and the Double-blind Period. The bottles of acetaminophen will be labeled with a protocol-specific label regarding the maximum allowable daily dose for the study. All rescue medication will be stored per commercially labeled conditions.

5.1.4 Dosing and Administration

At Baseline (Week 0), eligible subjects will be randomly assigned in a 1:1:1 ratio to receive ACP-044 800 mg BID, ACP-044 400 mg QID, or placebo (Table 5-1). In order to maintain the double-blind design of the study, all subjects will take the same number of tablets per day. Dosing is to occur in the morning (2 tablets), noon (1 tablet), evening (2 tablets), and night (1 tablet) and should occur at the same time each day over the duration of the study.

The first dose of study drug will be administered in the clinic, subjects will be instructed on administration of study drug, and subjects will be sent home with blinded study drug in blister cards.

Table 5-1 Blinded Daily Dosing Regimen

	First Daily Dose	Second Daily Dose	Third Daily Dose	Fourth Daily Dose
Placebo	PP	P	PP	P
ACP-044 400 mg (four times a day)	XP	X	XP	X
ACP-044 800 mg (twice a day)	XX	P	XX	P

Abbreviations: P=ACP-044 placebo tablet; X=ACP-044 400 mg tablet

5.1.5 Method of Assigning Subjects to Treatment Groups

At Baseline (Week 0), eligible subjects who meet inclusion and do not meet exclusion criteria will be randomized in a 1:1:1 ratio to receive ACP-044 800 mg BID, ACP-044 400 mg QID, or placebo, according to a randomization schedule.

5.1.6 Blinding

Treatment assignments will be blinded to all study subjects, Investigators, site personnel, and Sponsor personnel. In the event of a potential SUSAR, in accordance with current health authority guidance, treatment assignments for the affected subject may be unblinded to a controlled group of the Sponsor's Safety and/or Regulatory personnel for reporting purposes; the site personnel, Investigators, and monitors will remain blinded in this situation.

Details regarding medical emergency unblinding procedures are provided in Section 9.8.

5.1.7 Study Drug Compliance

The Investigator or designated study center personnel will maintain a log of all study drug dispensed and returned during the study. Study drug supplies for each subject will be inventoried and accounted for throughout the study to verify the subject's compliance with the dosage regimen. Subjects will be counseled regarding compliance at every visit. Subjects who have <80% or >120% compliance may be discontinued from the study. If a subject shows significant undercompliance (<80%) between any two scheduled visits, the Medical Monitor should be notified to determine if the subject remains eligible for the study and whether the incident should be considered a protocol deviation.

If a subject misses a dose, they should not take an extra dose.

5.1.8 Overdose

An overdose is a deliberate or inadvertent administration of a treatment (i.e., study drug or rescue medication) at a dose higher than the maximum recommended dose per protocol. It must be reported, irrespective of outcome, even if toxic effects were not observed (Section 7.4.4). All events of overdose are to be captured as protocol deviations.

5.2 Investigational Product and Rescue Medication Accountability Procedures

The Investigator or designee will keep current and accurate records of the study drug product dispensed, used and returned for each subject to assure the regulatory authority and the Sponsor that the study drug is being handled appropriately. Any study drug and rescue medication supplied is for use in this study only and should not be used for any other purpose. A clinical research associate (CRA) will be responsible for monitoring product accountability procedures and tablet counts by the site staff.

Site staff will keep current records of rescue medication dispensed, used, and returned for each subject to assure the regulatory authority and the Sponsor that the rescue medication is being handled appropriately.

At the conclusion of the study, final study drug reconciliation will be conducted at the site. Final study drug accountability documentation will be maintained at both the site and at the Sponsor. Any remaining unused study drug and rescue medication and all used and unused packaging will be sent back to the Sponsor's designee for destruction. Documentation of study drug destruction will be recorded and maintained by both the Sponsor and the Sponsor's designee.

6 STUDY PROCEDURES

Study specific procedures are detailed below. All assessments will be completed according to the schedule described in Table S–1. Every effort should be made to complete the required procedures and evaluations at the designated visits and times.

6.1 Remote Assessments or Visits

Circumstances may arise (e.g., pandemic, natural disaster, or political upheaval) when a study visit at the clinic may not be possible. In those cases, study visit assessments may be performed at a location other than the research site, either in person, or via video technology or telephone where possible. The Investigator must contact the Medical Monitor in advance for approval with the plan. Sites must keep a log to identify details of all visits that are performed remotely. The location of the collected assessments should be captured in the source documents.

6.2 Screening Assessments

All screening assessments must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

6.2.1 Medical and Medication History

A complete medical, medication (including past OA treatments), and surgical history will be obtained from each potential subject at the Screening visit. Demographic information, including date of birth, sex, race, and ethnicity will be recorded as well.

Any new medical condition reported with a start date after the ICF has been signed will be captured as an AE. Subjects may be asked to provide pharmacy or medical records to substantiate the medication history.

Any medication reported as taken on or after Baseline (Week 0) will be captured as concomitant medication.

6.2.2 Beck Depression Inventory–II

The BDI is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression (Beck et al. 1961). Like the BDI, the BDI-II also contains 21 questions, each answer being scored on a scale value of 0 to 3. Higher total scores indicate more severe depressive symptoms. The standardized cutoffs used differ from the original:

- 0-13: minimal depression
- 14-19: mild depression
- 20-28: moderate depression
- 29-63: severe depression

The BDI-II will be completed at Screening.

6.2.3 Verified Clinical Trials Registry

The Verified Clinical Trials LLC (VCT) Research Subject Database (VCT Registry) is used at study sites to help determine whether a subject is already participating in or has recently participated in another clinical trial. Subjects will be given detailed information about the processing of their personal data through the VCT Registry in a separate patient information and consent form (Verified Clinical Trials LLC Research Subject Database Declaration of Consent for the Processing of Personal Data) and will be asked to give explicit consent by signing this separate patient information and consent form. Where allowed under local laws and regulations, such consent from subjects is a precondition for being able to participate in this clinical study. No personal data will be entered into or processed through the VCT Registry, unless the relevant subject has given explicit consent.

The VCT Registry is used to help prevent dual enrollment at the time of screening and throughout the duration of the study.

6.3 Baseline Pain Assessment Period

Approximately 7 (+3) days prior to randomization, subjects will complete a Baseline Pain Assessment Period. During this period, subjects will be instructed in the use of a handheld device (eDiary) to record their daily pain scores and use of rescue medication.

Prior to beginning the Baseline Pain Assessment Period, to ensure accurate reporting of OA knee pain, subjects will receive Accurate Symptom Response Training (ASR) and Placebo Response Reduction (PRR) Training.

Compliance with recording of pain score and use of rescue medication will be assessed for continued study eligibility.

6.3.1 Accurate Symptom Reporting Training

The Accurate Symptom Reporting (ASR) training instructs subjects how to report pain scores accurately and reliably, and on the proper use of pain scales, with the aim of increasing the reporting accuracy of subject pain.

Subjects will receive training via eDiary at Visit 1 and Visit 3; additional training may be performed at Visits 5, 6, and/or 8 on an as needed basis and the need will be determined by Participant Scorecard recommendations.

6.3.2 Placebo Response Reduction Training

The Placebo Response Reduction (PRR) training teaches the subject about the appropriate expectations of personal benefit while participating in a clinical trial. The purpose is to provide subjects with truthful information that will neutralize the typically excessive expectations that drive high placebo responses in clinical studies.

Subjects will receive training via eDiary at Visit 1 and Visit 3; additional training may be performed at Visits 5, 6, and/or 8 on an as needed basis and the need will be determined by Participant Scorecard recommendations.

6.4 Efficacy Assessments

6.4.1 Numeric Rating Scale of Pain Intensity

A 0 to 10 NRS will be used to assess the subject's pain throughout the study. Subjects will be required to assess and record daily in the eDiary their knee pain intensity and daily use of rescue medication. Subjects will be rating both the average daily pain as well as their worst daily pain.

Knee pain intensity will be assessed by describing their knee pain at the present time from 0 to 10 where "0" means "no pain at all" and "10" means "the worst pain imaginable".

Pain intensity assessments are to be recorded in the evening prior to their 4th dose of the day.

Subjects must discontinue acetaminophen use for at least 24 hours prior to the start of study visits in order to minimize the confounding effects of the rescue medication on efficacy measurements.

6.4.2 Patient Global Impression of Change

The self-report measure Patient Global Impression of Change (PGIC) reflects a subject's belief about how their pain has changed since start of study treatment. PGIC is a 7-point scale

depicting a subject's rating of overall improvement. Subjects rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse".

The PGIC will be completed at Week 1, Week 2, and Week 4 (EOT)/ET. At study visits, the PGIC should be performed before blood sample collection, ECG, and other procedures.

6.4.3 Western Ontario and McMaster Universities Osteoarthritis Index

The WOMAC is widely used in the evaluation of hip and knee osteoarthritis (Collins et al. 2011) and rates pain during the last 48 hours. It is a self-administered questionnaire consisting of 24 items divided into three subscales:

- Pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing upright
- Stiffness (2 items): after first waking and later in the day
- Physical Function (17 items): using stairs, 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 domestic duties, light domestic duties

The test questions are scored on a scale of 0-4, which correspond to: None (0), Mild (1), Moderate (2), Severe (3), and Extreme (4). The scores for each subscale are summed up, with a possible score range of 0-20 for Pain, 0-8 for Stiffness, and 0-68 for Physical Function. The sum of the scores for all three subscales provides the total WOMAC score. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

The WOMAC will be completed at Baseline (Week 0), Week 1, Week 2, and Week 4 (EOT)/ET. At study visits, the WOMAC should be performed before blood sample collection, ECG, and other procedures.

6.4.4 Brief Pain Inventory–Short Form

The BPI is a self-report measure used to assess the severity of pain and its impact on functioning in patients with chronic diseases (Cleeland and Ryan 1994). The short form version uses a 24-hour recall period (i.e., assesses pain and its impact over the previous 24 hours).

The BPI uses a 0 (no pain) to 10 (pain as bad as you can imagine) numeric rating scale to measure how much pain has interfered with seven daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep.

The BPI will be completed at Baseline (Week 0), Week 1, Week 2, and Week 4 (EOT)/ET. At study visits, the BPI should be performed before blood sample collection, ECG, and other procedures.

6.4.5 12-Item Short Form Survey

The SF-12 survey, version 2 (SF-12v2), is a shortened form (12 items) of the SF-36 Health Survey (Ware et al. 1996). It is a self-reported general assessment of health-related quality of life from the subject's perspective. The SF-12 has eight domains including physical health summary measures: physical functioning, role–physical, bodily pain, and general health and mental health summary measures: vitality, social functioning, role–emotional, and mental health. From the evaluation of these domains, algorithms are used to generate physical and mental health composite summary scores, PCS and MCS, respectively, for comparison to normative data. In normative data, the mean score is set to 50; thus, scores >50 indicate better physical or mental health than the mean scores and scores <50 indicate worse health. The timeframe for this scale is the past 4 weeks.

The SF-12 will be completed at Baseline (Week 0) and Week 4 (EOT)/ET.

6.4.6 Hospital Anxiety and Depression Scale

The HADS was developed to detect states of anxiety or depression (Zigmond and Snaith 1993). The questionnaire focuses on non-physical symptoms so that it can be used to diagnose depression in people with significant physical ill-health. The questionnaire comprises seven questions for anxiety and seven questions for depression, which are each scored separately. Each item on the questionnaire is scored from 0 (No, not at all) to 3 (Yes definitely), for a total score between 0 to 21 for either anxiety or depression. The timeframe for this scale is the past week.

The HADS will be completed at Screening, Baseline (Week 0), and Week 4 (EOT)/ET.

6.4.7 Participant Scorecard

The Participant Scorecard presents subjects with data on key tasks reflecting their own performance in the study, plus automated and customized tips for how to improve their performance. Scores are assigned for study metrics that serve as markers of data quality and accurate symptom reporting, and have been shown to affect accuracy of study endpoints. Scores are typically shown for medication adherence, eDiary compliance, and accuracy of symptom reporting, although other domains may be included. Although study staff are urged to be present with the subject during the scorecard review, human intervention is not required but may be needed. For instance, scorecard scores that are within the limits of the signal analysis are displayed in green and require no human intervention. The scores that are outside

of signal thresholds are shown in yellow or red and require human intervention. Reviewing scorecards in this manner improves efficiency and timeliness of recommendations, while decreasing the biases and burdens introduced by filtering re-training through site staff. For-cause re-training on Accurate Symptom Reporting (Section 6.3.1) may be triggered on the platform in response to subject scores. The scorecard and as-needed re-training must be viewed by the subject prior to the completion of visit assessments, and reviewed by the Investigator during the subject's visit.

The scorecard is viewed by the subject and reviewed by the Investigator at Visits 5, 6, and 8/EOT/ET.

6.5 Safety Assessments

6.5.1 Physical Examination

A complete, general physical examination will be conducted at Screening and a brief physical exam will be conducted at Baseline (Week 0) and Week 4 (EOT)/ET. Height will only be measured and reported at Screening and weight will be measured and recorded at Screening, Baseline (Week 0), and Week 4 (EOT)/ET.

The full examination should include a review of body systems and should include a neurological examination (e.g., level of consciousness, speech, cranial nerves [including pupil equality and reactivity], motor assessment, sensory assessment, coordination, gait, reflexes, and Romberg test). Height and weight will be measured and reported as described above.

The brief physical exam will include the following: evaluation of general appearance, respiratory, cardiovascular, and gastrointestinal systems. A general physical examination will be conducted.

6.5.2 Vital Signs

Vital signs will include body temperature, resting respiration rate, supine and standing systolic and diastolic blood pressure, and pulse rate. Blood pressure and pulse rate measurements will be taken after the subject rests for 5 minutes in the supine position. The subject will then be asked to stand and blood pressure and pulse rate will be taken after the subject stands for 1 minute and then again after 3 minutes. Subjects unable to stand may be assessed while sitting upright. A drop in SBP of ≥20 mmHg or in DBP of ≥10 mmHg or if the subject is experiencing lightheadedness or dizziness is considered abnormal and orthostasis should be considered (further detail is provided in Section 4.5.1.2).

Vital signs will be evaluated at all designated study visits. A 15-minute window is permitted for vital sign measurements.

Vital signs should be measured prior to (PK and laboratory) blood draws.

6.5.3 Electrocardiograms

All 12-lead electrocardiograms (ECGs) will be complete, standardized recordings. A single 12-lead ECG will be performed at Screening, at Baseline (Week 0) both predose and 1 hour postdose (the first dose of the day), Week 1, Week 2, and Week 4 (EOT)/ET. A 1-hour window is permitted for the predose ECG; a 20-minute window is permitted for the postdose ECGs. Electrocardiograms should be performed prior to blood sampling (or at least 30 minutes after blood sampling) and vital signs but after pain assessments are completed.

The subject must rest in a supine position for 5 minutes before the ECG is obtained. ECG tracings (paper or electronic) will be reviewed and interpreted by a qualified clinician. All ECG tracings and results (ventricular rate, PR, QRS, QT, QTcF, and QTcB intervals) will be included in the subject's record.

At Screening, if the ECGs have a prolonged QTcF due to an identifiable cause, and it is medically appropriate to address that cause, a repeat ECG may be performed during Screening at the discretion of the Medical Monitor.

At Baseline (Week 0), a subject may be enrolled based on the review and interpretation of the ECG by a qualified physician. If the interpretation of the ECG indicates a QTcF outside of the allowable range, the subject will be discontinued from the study, but this will not be considered a protocol deviation.

6.5.4 Columbia-Suicide Severity Rating Scale

The C-SSRS monitors changes in suicidal thinking and behavior over time, in order to determine risk (Posner et al. 2011). The following four constructs are measured: the severity of ideation, the intensity of ideation, behavior, and lethality.

The Baseline/Screening version will be administered at Screening, and the Since Last Visit version will be administered at all subsequent visits. The C-SSRS results for each subject should be reviewed by the Investigator after completion. If at any time the C-SSRS results for a given subject reveal potential suicidality, then the Investigator should assess the clinical significance of such results. If a clinically significant risk of suicidality is identified for a subject, then the Investigator should discontinue the subject and implement appropriate treatment (Section 4.5).

C-SSRS will be completed at all designated study visits.

6.5.5 Laboratory Evaluations

Clinical laboratory sample collection (including HbA_{1c} at Screening only) is encouraged, but not required to be completed under fasting conditions. The laboratory evaluations will include, but are not limited to, the following:

- Clinical chemistry serum tests (CHEM)
  - Sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca),carbon dioxide (CO_2), blood urea nitrogen (BUN), creatinine (CR), uric acid,
  - Estimated glomerular filtration rate (eGFR) should only be performed at Visit 1 (Screening)
  - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
    - INR to be evaluated, as needed (described in Section 4.5.1.1)
  - Creatine kinase (CK)/creatine phosphokinase (CPK)
  - Lipid panel should only be performed at Visit 1 (Screening):
    - Total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, cholesterol/HDL ratio, non-HDL cholesterol; should only be performed at Visit 1 (Screening)
  - HbA_{1c} should only be performed at Visit 1 (Screening)
  - Glucose
  - Albumin (ALB) should only be performed at Visit 1 (Screening)
  - Total protein should only be performed at Visit 1 (Screening)
- Hematology tests
  - Complete blood count (CBC) including:
    - White blood cell (WBC) count
    - Complete differential (relative and absolute)
    - Hematocrit (Hct), hemoglobin, red blood cells (RBC), platelets
    - Reticulocyte count
- Endocrinology
  - Thyroid stimulating hormone (TSH) and free T4 (Screening)
- Pregnancy test

  - A serum pregnancy test should only be performed at screening (Table 6–1) for women of childbearing potential
  - A urine pregnancy test should be performed at Baseline (Week 0) and Week 4 (EOT)/ET (Table 6–1) for women of child-bearing potential
    - If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place

- COVID-19 test:
  - COVID-19 diagnostic PCR test at Screening
- Urinalysis (UA)
  - Blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH, nitrates
- Urine drug screen (UDS) with reflex testing
  - A urine drug screen will test for controlled substances at Screening, Baseline Pain Assessment Period, and at Week 4/EOT/ET. A dipstick urine drug screen will be performed at Baseline (Week 0) for rapid detection of controlled substances and for certain prescription medications in order to determine if the subject continues to meet subject eligibility. The following controlled substances will be tested for with a urine drug screen and/or urine dipstick according to the schedule presented in Table 6–1: amphetamine, barbiturates, benzodiazepines, buprenorphine, cocaine, ecstasy (MDMA), methadone, morphine/opiates, methamphetamine, marijuana (THC), phencyclidine (PCP), propoxyphene, tricyclic antidepressants. Negative drug screens are required for study eligibility.
    - If there is a positive urine drug screen for an analgesic medication that is not allowed per protocol, the subject must washout of medication, if appropriate, prior to the Baseline Pain Assessment Period.
    - If there is a positive urine drug screen for a medication that is allowed per protocol (e.g., metformin leading to a false positive for amphetamine), the subject must have a valid prescription for such medication, and if the subject denies use of the positive prohibited medication (e.g., amphetamine), they can be included in the study and it will not be considered a protocol deviation.

Laboratory evaluations will be completed according to the schedule presented in Table 6–1 and procedures detailed in the study laboratory manual. Additional safety testing may be performed at the discretion of the Investigator or designee.

Table 6–1 Safety Laboratory Evaluations

Visit	Tests
Screening	CHEM, CBC, UA, COVID-19[a], serum pregnancy, and urine drug screen
Baseline Pain Assessment Period	Urine drug screen
Baseline (Week 0) predose	CHEM, CBC, UA, urine pregnancy, and urine dipstick test[b]
Day 3	CHEM[c]
Week 1	CHEM, CBC, UA
Week 2	CHEM, CBC, UA
Week 3	CHEM[c]
Week 4 (EOT/ET)	CHEM, CBC, UA, urine pregnancy, and urine drug screen

Abbreviations: CBC=complete blood count; CHEM=clinical chemistry serum tests; COVID-19=coronavirus disease 2019; EOT=end of treatment; ET=early termination; UA=urinalysis

[a] COVID-19 diagnostic PCR test at Screening

[b] Urine dipstick test will be administered which must be negative for any non-permitted medications or drugs in order for the subject to continue in the study

[c] Full chemistry (CHEM) panel of clinical laboratory tests will be completed, excluding glucose and the CHEM tests noted in Section 6.5.5 to only be performed at Screening

6.6 Electronic Clinical Outcome Assessments

The electronic Clinical Outcome Assessment (eCOA) devices will be used during the Baseline Pain Assessment Period and throughout the Double-blind study period. Subjects will complete electronic-based assessments using handheld devices during the study, specifically, a tablet device will be used during clinic visits and an eDiary will be provided for subjects to take home. The eDiary, will be provided to all subjects to record pain scores, compliance with ingestion of study medication, and use of rescue medication.

During the Baseline Pain Assessment Period, subjects will record their daily pain scores and rescue medication use. Compliance with recording of pain score and use of rescue medication will be assessed for continued study eligibility.

Subjects will continue daily entry into the eDiary of pain scores, rescue medication use, and compliance with ingestion of study medication from Baseline (Week 0) through to Week 4 (EOT)/ET.

6.7 Pharmacokinetic Assessments

Pharmacokinetic blood samples will be collected for measurement of plasma concentrations of ACP-044. ACP-044 plasma concentration data will remain blinded until the unblinding of the clinical database at the end of the study.

At each predefined timepoint, PK samples will be obtained for measurement of concentrations of ACP-044 at the following visits:

- Baseline (Week 0) visit (Visit 3; both before dosing and approximately 1 hour after dosing)
- Visit 5
- Visit 6
- Visit 8/or upon early termination (ET)

Pharmacokinetic blood samples taken at Visits 5, 6, and 8 should be collected at one of the following time intervals:

- 2-5 hours after morning dosing
- 6-9 hours after morning dosing
- 10-12 hours after morning dosing

Every effort should be made to collect PK samples at distinct time intervals during Visits 5, 6, and 8. However, if the interval is the same across these visits, then the collection time should vary within that interval. The following scenario is only for illustrative purposes, a number of other scenarios are possible.

- For example, if the time interval of 6-9 hours after morning dosing is used for Visits 5, 6, and 8, then every effort should be made to collect PK samples at 6, 7, and 8 hours after morning dosing at each of these visits, respectively.

When possible, an additional PK sample (approximately 4 mL sample) will be collected from subjects who experience a serious adverse event (SAE) or an adverse event (AE) leading to discontinuation, as soon as possible after the occurrence of that event.

For all PK samples (scheduled and unscheduled), with the exception of those taken following an AE or SAE, the dates and times of administration of the last three doses of the study drug should be recorded. For samples collected from subjects who experience an SAE or an AE leading to discontinuation, the date and time of the last dose prior to the SAE or AE should also be recorded.

6.7.1 Blood Sampling

Five (5) approximately 4 mL venous blood samples will be collected from each subject for measurement of plasma ACP-044 concentrations.

In addition, a blood sample (approximately 4 mL sample) for determination of concentrations of ACP-044 will be collected in the event of an SAE or an AE leading to discontinuation.

6.7.2 Specimen Preparation, Handling, Storage, and Shipment

Pharmacokinetic blood samples may be collected from a cannula port or via venipuncture. Pre-prepared PK sampling tubes will be provided to each site within the lab visit kits for collection and storage of PK samples. At each timepoint, blood will be collected, processed as appropriate, and samples will be shipped to the central laboratory for storage and to the bioanalytical laboratory for analysis.

For samples collected from subjects who experience any SAE or experience an AE leading to discontinuation, the date and time of the last dose of study drug prior to the SAE or AE leading to discontinuation will also be recorded.

A laboratory manual will be provided for sample processing, storage, and shipping procedures.

6.8 Safety Follow-up

Safety will be further assessed during the follow-up period regardless of whether a subject completes the study or withdraws (or when they withdraw; see also Section 4.4 for limitations in case of withdrawal of consent). The assessments to be conducted are outlined below and in Table S–1.

Safety will be further assessed during a follow-up visit to occur in the clinic approximately 7 (±3) days after EOT/ET procedures. During this in-clinic visit, pain intensity (i.e., subjects will rate both the average daily pain as well as their worst daily pain over the past week and the data will be entered into EDC), adverse events (AEs), and concomitant medications will be assessed, since the EOT/ET. Then, a follow-up telephone call will occur approximately 30 (+4) days after the last dose of study drug to assess AEs and concomitant medications.

6.9 Unscheduled Visits

Unscheduled visits may occur as determined by the Investigator. The following safety assessments generally should be recorded at each unscheduled visit: assessment of AEs, concomitant medications/treatments, C-SSRS, and measurement of vital signs. If an unscheduled visit is required for safety reasons, a 12-lead ECG and all appropriate clinical

laboratory tests are also to be performed. The Investigator may perform any additional safety evaluations deemed by the Investigator to be clinically indicated.

7 ADVERSE EVENTS

7.1 Specification of Safety Parameters

7.1.1 Definition of Adverse Event

An AE is defined as "any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study drug, whether or not considered related to study drug".

An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality or seriousness. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE.

AEs do not include the following:

- Stable or intermittent chronic conditions (such as myopia requiring eyeglasses) that are present prior to Baseline and do not worsen during the study
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if not present at time of consent, or scheduled surgery/procedure.
- Overdose of concomitant medication without any signs or symptoms will not be considered an AE, but if subject is hospitalized or has other serious criteria, the overdose shall be reported on the Sponsor's Overdose Reporting form
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred)
- Pregnancy will not be considered an AE, but if it occurs, it will be reported on a pregnancy form

For subjects who discontinue from the study, AEs will be recorded from the time informed consent is obtained until 30 (+4) days after the last dose of study drug.

7.1.2 Definition of Serious Adverse Event

In addition to the severity rating, each AE will be classified by the Investigator as "serious" or "not serious." The seriousness of an event will be defined according to the applicable regulations and generally refers to the outcome of an event. An SAE is one that meets one or more of the following:

- Is fatal
- Is life threatening
- Results in disability or permanent damage
- Requires hospitalization (initial or prolonged)
- Results in congenital anomaly or birth defect
- Other serious event (medically significant/important medical event)

Definition of Life Threatening

A life threatening event places the subject at immediate risk of death from the event as it occurred. This does not include an AE, which, had it occurred in a more severe form, might have caused death.

Definition of Hospitalization

Hospitalization is defined by the Sponsor as a full admission to the hospital for diagnosis and treatment. This includes prolongation of an existing inpatient hospitalization.

Examples of visits to a hospital facility that do **not** meet the serious criteria for hospitalization include:

- Emergency room visits (that do not result in a full hospital admission)
- Outpatient surgery
- Preplanned or elective procedures
- Protocol procedures
- Social hospitalization, defined as admission to the hospital as a result of inadequate family support or care at the subject's primary residence

Definition of Disability or Permanent Damage

Disability is defined as a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

Definition of Medically Significant

Important medical events (medically significant events) that may not result in death, be life threatening, or require hospitalization may be considered to be an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

An SAE may also include any other event that the Investigator or Medical Monitor judges to be serious or that suggests a significant hazard, contraindication, side effect, or precaution.

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

The severity of each AE will be assessed as described below and reported in detail as indicated on the eCRF:

- **Mild**: awareness of sign or symptom but easily tolerated, causing minimal discomfort, and not interfering with normal everyday activities
- **Moderate**: sufficiently discomforting to interfere with normal everyday activities
- **Severe**: incapacitating and/or preventing normal everyday activities

7.2.2 Relationship to Study Drug

The causality of each AE should be assessed and classified by the Investigator as “related” or “not related.” An event is considered related if there is a reasonable possibility that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).

Consider the following when assessing causality:

- Temporal associations between the agent and the event
- Response to drug cessation (de-challenge) or re-challenge
- Compatibility with known class effect
- Known effects of concomitant medications
- Pre-existing risk factors
- A plausible mechanism
- Concurrent illnesses

- Past medical history

7.2.3 Duration

The start and stop dates for AEs will be recorded using the following criteria:

- **Start:** Date of the first episode of the AE or date of worsening in severity
- **Stop:** Date when AE ceased permanently, worsened in severity, or resolved with or without sequelae

7.2.4 Frequency

The frequency of the AE should be indicated according to the following definitions:

- **Single:** Experienced once, without recurrence at same severity
- **Recurrent:** More than one discrete episode with the same severity

7.2.5 Action Taken with Study Drug

- **Dose not changed:** No change in study drug
- **Drug interrupted:** Study drug temporarily stopped
- **Drug withdrawn:** Study drug discontinued permanently
- **Not applicable**
- **Unknown**

7.2.6 Therapy

- **None:** No new treatment instituted
- **Medication:** New treatment initiated as a direct result of AE
- **Other:** Other action required

7.2.7 Outcome

- **Recovered/resolved:** Recovered or resolved
- **Recovered/resolved with sequelae:** Recovered or resolved with sequelae
- **Not recovered/not resolved:** Not recovered or not resolved
- **Fatal:** Death due to an AE
- **Unknown:** Unknown

7.2.8 Seriousness

- **Not serious**
- **Serious** (see Section 7.1.2)

7.2.9 Definition of Unexpectedness

An AE, the nature or severity of which is not consistent with the information provided in the Reference Safety Information section of the current ACP-044 Investigator's brochure.

7.3 Time Period and Frequency for Event Assessment and Follow-up

Adverse events will be recorded from the time informed consent is obtained through the study safety follow-up period. If an AE is ongoing at the end of the study safety follow-up period, every reasonable attempt should be made to follow and appropriately treat the subject until the AE resolves or until the Investigator deems the AE to be chronic or stable.

In the event that a subject discontinues and has an ongoing AE at the time of discontinuation (Section 4.5.2) or is withdrawn from the study because of an AE, the subject should be followed and appropriately treated until the AE resolves or until the Investigator deems the AE to be chronic or stable.

7.4 Reporting Procedures

7.4.1 Adverse Event Reporting

The Investigator must record all observed AEs and all reported AEs. At each visit, the Investigator should ask the subject a nonspecific question (e.g., "Have you noticed anything different since your last visit?") to assess whether any AEs have been experienced since the last report or visit.

Note that any use of medication (and specifically any newly prescribed medication) during the course of a study may indicate the occurrence of an AE that may need to be recorded on both the AE and the concomitant medication page.

All AEs, serious and not serious, will be recorded on the AE eCRF page using appropriate medical terminology. Severity and relationship to study drug will be assessed by the Investigator.

When possible, clinical AEs should be described by diagnosis and not by symptoms (e.g., "cold" or "seasonal allergies" instead of "runny nose").

All AEs, *whether or not related to the study drug*, must be fully and completely documented on the AE eCRF and in the subject's notes.

7.4.2 Serious Adverse Event Reporting

The reporting of SAEs by the Sponsor or designee to the regulatory authorities is a regulatory requirement. Each regulatory authority has established a timetable for reporting SAEs based upon established criteria.

Serious AEs must be reported within 24 hours of discovery to the Sponsor or its designee; use the appropriate form for initial and/or follow-up reporting.

At a minimum, events identified by the Sponsor to require expedited reporting as serious, unexpected, and related to study drug must be brought to the attention of the responsible institutional review board/ethics committee (IRB/EC), as per applicable regulations. These will be provided by the Sponsor after their assessment. For European Union member states, the Sponsor or its designee will provide reports of suspected unexpected serious adverse reactions (SUSARs) directly to the ECs, as required by local legislation. In all other countries, it is the Investigator's responsibility to provide these expedited reports to the responsible IRB/EC. It is also the Investigator's responsibility to notify the responsible IRB/EC regarding any new and significant safety information.

When an SAE occurs, Investigators will review all documentation related to the event and will complete the paper SAE form with all required information (for initial and/or follow-up information) and fax or email (within 24 hours of discovery) to the contact information provided on the SAE form.

Subjects will be followed through the safety follow-up period (i.e., 30 [+4] days after last dose of study drug) for any SAEs and/or other reportable information until such events have resolved or the Investigator deems them to be chronic or stable.

In the event of any SAE (other than death), the study subject will be instructed to contact the Investigator (or designee) using the telephone number provided in the ICF. All subjects experiencing an SAE will be seen by the Investigator or designee as soon as is feasible following the report of the SAE.

Serious AEs occurring after the safety follow-up period (i.e., 30 [+4] days after last dose of study drug) should be reported if in the judgment of the Investigator there is "a reasonable possibility" that the event may have been caused by the product.

SAEs should also be reported to the IRB/EC according to local regulations.

7.4.3 Reporting of Pregnancy

Any female subject who becomes pregnant during the study (with or without AEs) must be withdrawn from the study and the pregnancy must be reported on the Pregnancy form within

24 hours of discovery to the Sponsor or its designee. Any female subject who becomes pregnant during the study will be followed through the pregnancy outcome.

If pregnancy occurs during the study, the pregnant subject should be unblinded so that counseling may be offered based on whether the fetus was exposed to the active drug or placebo.

Any AEs that are the consequence of pregnancy and which meet the criteria for serious should also be reported via the SAE form.

7.4.3.1 Reporting Paternal Drug Exposure

Paternal drug exposure is defined as a father's exposure to a medicinal product before or during his partner's pregnancy. Any paternal drug exposure cases must be reported to the Sponsor within 24 hours of discovery via the Pregnancy form. Any AEs that are the consequence of paternal drug exposure and which meet the criteria for serious must also be reported to the Sponsor within 24 hours of discovery via the SAE form.

7.4.4 Reporting of Overdose

An overdose is a deliberate or inadvertent administration of a treatment (i.e., study drug or rescue medication) at a dose higher than the maximum recommended dose per protocol. It must be reported to the Sponsor or designee on the Sponsor Overdose Reporting form within 24 hours of discovery. In addition, all events of overdose are to be captured as protocol deviations (see Section 5.1.8).

8 CLINICAL MONITORING

Routine monitoring of study sites is described in Section 11.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol and amendment(s) as applicable, with GCP, and with applicable regulatory requirements. Details of the study site monitoring process are described in a separate clinical monitoring plan document.

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 Statistical and Analytical Plans

Statistical methods will be documented in detail in a statistical analysis plan (SAP) to be approved by the Sponsor prior to database lock. Deviations from the approved SAP will be described and justified in the final clinical study report.

9.2 Statistical Hypotheses

Let Δ_i ($\boldsymbol{\mu}_{Act\_i} - \boldsymbol{\mu}_{PBO}$) be the difference in the mean change from Baseline to Week 4 in the weekly average of the daily average pain between each of the ACP-044 ($\boldsymbol{\mu}_{Act\_i}$) dose groups and placebo ($\boldsymbol{\mu}_{PBO}$) group.

The null hypothesis is: $\Delta_i = 0$;

The alternative hypothesis is: $\Delta_i \neq 0; i = 1, 2$.

9.3 Sample Size Determination

Approximately 240 subjects will be randomized in a 1:1:1 ratio to ACP-044 800 mg BID dose, ACP-044 400 mg QID dose, or placebo. Assuming a treatment difference of 0.85 and a common standard deviation of 1.7 between an ACP-044 dose arm and placebo, 64 subjects per arm is needed to provide approximately 80% power to detect this treatment difference using a 2 sample t-test at 2-sided alpha level of 0.05. Assuming a discontinuation rate of 20%, 80 subjects per treatment group will be randomized.

9.4 Subject Populations for Analysis

The **Safety Analysis Set** includes all randomized subjects who received at least one dose of study drug (ACP-044 or placebo). Subjects will be analyzed based on the treatment that they actually received. The Safety Analysis Set will be used for all safety analyses.

The **Full Analysis Set** (FAS) includes all randomized subjects who received at least one dose of study drug and with baseline pain assessments and at least one post-baseline pain assessment. Subjects will be analyzed based on the treatment to which they are assigned. The Full Analysis Set will be used for the analysis of all efficacy endpoints.

For ACP-044 plasma concentration summaries, the **Pharmacokinetics Analysis Set** will consist of subjects with at least one measurable ACP-044 plasma concentration.

9.5 Statistical Analyses

9.5.1 General Statistical Approach

For continuous variables, descriptive statistics will include the following information: the number of subjects with data values (n), mean, standard error of the mean, median, standard deviation, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category. All statistical hypotheses will be tested at the 0.05 significance level.

Demographic and baseline characteristics, including medical history and exposure to study drug will be summarized descriptively by treatment group and by all subjects combined.

9.5.2 Primary Analyses

The primary efficacy variable will be analyzed using an analysis of covariance model (ANCOVA) based on the FAS with treatment, sex, and baseline K-L score (randomization strata) as factors and baseline weekly average of daily average pain score as a covariate in the model. The primary comparison will be between each ACP-044 dose group versus the placebo group. The comparison between the average of the means of the two ACP-044 dose groups versus the mean of placebo group will also be conducted. Missing data will be imputed using multiple imputation based on missing at random assumption (MAR) with an exception of missing data from subjects who are treated with ACP-044 and discontinue the study due to lack of efficacy or adverse events. Their missing data will be imputed using the data from placebo group. The details of missing data imputation and multiplicity adjustment will be described in the SAP.

Sensitivity analysis using pattern mixture model and tipping point approach with multiple imputation to impute missing data will be performed to assess the robustness of the results due to treatment discontinuation and other intercurrent events.

9.5.3 Secondary Analyses

For analysis of continuous secondary endpoints, the analysis method will be the same as that used for the primary variables except for PGIC which will be analyzed using analysis of variance (ANOVA) with treatment, sex, and baseline K-L score as factors. For analysis of categorical variables in secondary endpoints, e.g., proportions of subjects with ≥30% reduction from baseline to Week 4 in the weekly average of the daily average NRS score; the Cochran Mantel Haenszel approach stratified by the randomization strata will be used for subjects with missing data considered as non-responders.

9.5.4 Exploratory Analyses

The analysis of the exploratory variables will be described in the SAP.

9.5.5 Safety Analyses

Safety data will be summarized by treatment group using descriptive statistics. No formal statistical testing will be performed for any of the safety endpoints. Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, fatal TEAEs, SAEs, SAEs related to study drug, and TEAEs of special interest (AESI) will all be summarized.

Descriptive statistics for ECGs, vital signs and weight, and clinical laboratory parameters, including changes from Baseline (prior to first dose), will be tabulated by timepoint and by

treatment group. The incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines will also be summarized by treatment group.

Additional safety analysis details will be specified in the SAP.

9.5.6 Pharmacokinetic Analyses

Plasma concentration data for ACP-044 will be listed and summarized using descriptive statistics. Results will be used for other analyses (e.g., population PK modelling), which will be presented in a separate report.

9.5.7 Pharmacokinetic/Pharmacodynamic Analyses

Guided by exploratory analyses, PK/PD models to describe the exposure-response relationship between ACP-044 exposure parameters and the relevant efficacy and safety endpoints will be developed using appropriate PK/PD methods. Results will be presented in a separate report per a prespecified data analysis plan.

9.5.8 Subgroup Analyses

Selected analyses may be performed in subgroups. Details will be provided in the SAP.

9.6 Interim Analyses

No interim analyses are planned for this study.

9.7 Measures to Minimize Bias

At Baseline (Week 0), eligible subjects who meet inclusion and do not meet exclusion criteria will be randomized in a 1:1:1 ratio to receive ACP-044 800 mg BID, ACP-044 400 mg QID, or placebo, according to a randomization schedule. Treatment assignments will be blinded to all study subjects, Investigators, site personnel (with the exception of the unblinded pharmacist and verifier), and Sponsor personnel.

In order to maintain the double-blind design of the study, all subjects will receive the same numbers of tablets at the same intervals, regardless of the treatment group to which they are randomized. Placebo tablets will be size- and color-matched to the ACP-044 tablets.

9.7.1 Masking Procedures

This unmasked protocol version provides details of certain study design elements, procedures, and statistical methods that are not available in the masked version of the protocol.

This document is intended for use only by the unmasked Sponsor and restricted clinical service providers and their designated agents for purposes of regulatory document

preparation in conjunction with review by IRBs, IECs, and regulatory authorities. Access to this document by other entities may be considered on a case-by-case basis by the Sponsor.

The information contained herein is UNMASKED and CONFIDENTIAL. Therefore, it must NOT be shared with or communicated to any individual at an investigational site or from site facing members of the clinical operations team of the contract research organization except with explicit and fully documented authorization from the Sponsor.

The key elements revealed herein but that are masked in the masked protocol are the ACP-044 dosing regimens and inclusion criteria specific to the Baseline Pain Assessment Period.

Investigators will receive the masked version of the clinical study protocol.

9.8 Breaking the Study Blind/Subject Code

For the final analysis, the treatment codes for all subjects will be released to the Sponsor after all subjects have completed the study and the clinical database is locked.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind.

If pregnancy occurs during the study, the pregnant subject should be withdrawn and unblinded so that counseling may be offered based on whether the fetus was exposed to the active drug or placebo.

10 STUDY MANAGEMENT AND DATA COLLECTION

10.1 Data Collection and Management Responsibilities

All documents required for the conduct of the study as specified in the ICH GCP guidelines will be maintained by the Investigator in an orderly manner and made available for monitoring and/or auditing by the Sponsor and regulatory authorities.

The Investigator and institution must permit authorized representatives of the Sponsor or designees (including monitors and auditors), regulatory authorities (including inspectors), and the IRB/EC direct (or remote) access to source documents (such as original medical records) as allowed by local regulations. Direct (or remote) access includes permission to examine, analyze, verify, and reproduce any records and reports that are needed for the

evaluation of the study, either in person or through a remote video/electronic medium, if applicable. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

10.2 Source Documents

All study specific information obtained at each study visit must be recorded in the subject's record (source documentation), and then entered into a validated electronic data capture (EDC) database by trained site personnel. The source documentation may consist of source notes captured by site personnel as well as laboratory reports, ECG reports, and electronic source data.

10.3 Case Report Forms

Subject data required by this protocol are to be recorded in an EDC system on eCRFs. The Investigator and his or her site personnel will be responsible for completing the eCRFs. The Investigator is responsible for the accuracy and reliability of all the information recorded on the eCRFs. All information requested on the eCRFs needs to be supplied, including subject identification data, visit date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documentation (unless eCRF is considered the source) at the site.

10.4 Confidentiality

The Investigator must ensure that each subject's anonymity is maintained as described below. On the eCRFs, medical records, or other documents submitted to the Sponsor or designees, subjects must be identified by a subject identification number only. Subject identifiers uniquely identify subjects within the study and do not identify any person specifically. Documents that are not for submission to the Sponsor or designees (e.g., signed ICFs) should be kept in strict confidence by the Investigator in compliance with Federal regulations or other applicable laws or ICH guidance on GCP. Data collection and handling should comply with the European Union General Data Protection Regulation (EU GDPR), where applicable. Acadia has assigned a Data Protection Officer (DPO) as per the EU GDPR.

10.5 Study Records Retention

Investigators are required to maintain all essential study documentation as per ICH GCP guidelines. This includes, but is not limited to, copies of signed, dated and completed eCRFs, documentation of eCRF corrections, signed ICFs, audio recordings, subject-related source documentation, and adequate records for the receipt and disposition of all study drug. Investigators should maintain all essential study documentation, for a period of at least 2 years following the last approval of marketing application in an ICH region (US, Europe,

and Japan), or until at least 2 years after the drug investigational program is discontinued, unless a longer period is required by applicable law or regulation. Only the Sponsor can notify an Investigator or vendor when any records may be discarded. Investigators should contact the Sponsor before destroying any files.

10.6 Protocol Exceptions and Deviations

No prospective entry criteria protocol deviations are allowed; all subjects must meet all eligibility criteria in order to participate in the study.

Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If, during the course of a subject's post-enrollment participation in the trial it is discovered that the subject did not meet all eligibility criteria, this will be reported as a major protocol deviation and not a waiver. In this situation, the subject will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the trial will be made by the Sponsor, with medical input from the Investigator, and will be documented. All follow-up safety assessments must be completed and documented as outlined in the protocol (Section 6.8). The Investigator must report any protocol deviation to the Sponsor and, if required, to the IRB/EC in accordance with local regulations, within reasonable time.

10.7 Protocol Amendments

Changes to the protocol may be made only by the Sponsor (with or without consultation with the Investigator). All protocol modifications must be submitted to the site IRB/EC in accordance with local requirements and, if required, to regulatory authorities, as either an amendment or a notification. Approval for amendments must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the changes involve only logistical or administrative aspects of the trial. No approval is required for notifications.

11 QUALITY MANAGEMENT

11.1 Risk Management

The Sponsor utilizes the ICH E6 (GCP) Revision 2 risk management approach that includes methods to assure and control the quality of the trial proportionate to the risks inherent in the trial and the importance of the information collected. The intent is that all aspects of this trial are operationally feasible and that any unnecessary complexity, procedures, and data collection are avoided. The Sponsor's risk management approach includes the following documented activities:

- Critical Process and Data Identification: during protocol development, risks of processes and data that are critical to ensure human subject protection and the reliability of trial results are identified and assessed.
- Risk Identification: risks to critical trial processes, governing systems, investigational product, trial design, data collection, and recording are identified.
- Risk Evaluation: identified risks are evaluated by considering the following factors: (a) likelihood of occurrence, (b) impact on human subject protection and data integrity, and (c) detectability of errors.
- Risk Control: risks that can be avoided, reduced (i.e., mitigated), or accepted are differentiated. Risk mitigation activities are incorporated in protocol design and implementation, study plans, training, processes, and other documents governing the oversight and execution of study activities. Where possible, predefined quality tolerance limits are defined to identify systematic issues that can impact subject safety or data integrity and deviations from the predefined quality tolerance limits will trigger an evaluation and possibly an action. Contingency plans are developed for issues with a high risk factor that cannot be avoided.
- Periodic risk review, communication, and escalation of risk management activities during trial execution and risk outcome reporting in the clinical study report (CSR).

11.2 Quality Control and Quality Assurance

The Sponsor or designees and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Sponsor’s or designee’s monitor is responsible for inspecting the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. The monitor may review documents remotely, as needed, in conjunction with site policies and procedures.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

In accordance with ICH guidance on GCP and the Sponsor’s audit plans, sites participating in this study may be audited. These audits may include a review of site facilities (e.g., pharmacy, drug storage areas, and laboratories) and review of study-related records may

occur in order to evaluate the trial conduct and compliance with the protocol, ICH guidance on GCP, and applicable regulatory requirements.

The Sponsor's or designee's representatives, regulatory authority inspectors and IRB/EC representatives who obtain direct (or remote) access to source documents should also respect subject confidentiality, taking all reasonable precautions in accordance with applicable regulatory requirements to maintain the confidentiality of subjects' identities.

12 ETHICAL CONSIDERATIONS

12.1 Ethical Standard

The study will be conducted in compliance with the protocol, the Declaration of Helsinki, ICH GCP, and other applicable regulatory requirements (e.g., Serious Breach reporting, urgent safety measures, and European Union General Data Protection Regulation [EU GDPR]).

The study will be performed in accordance with current US Health Insurance Portability and Accountability Act (HIPAA) regulations, US FDA GCP Regulations (US CFR 21 parts 50, 54, 56, and 312), and ICH guidance on GCP (E6) and clinical safety data management (E2A).

In accordance with Directive 75/318/EEC, as amended by Directive 91/507/EEC, the final clinical study report will be signed by an Investigator and/or Coordinating Investigator who will be designated prior to the writing of the clinical study report.

12.2 Institutional Review Board/Ethics Committee

The Investigator or designee will provide the IRB/EC with all requisite material, including a copy of the protocol, informed consent, any subject information or advertising materials, and any other requested information. The study will not be initiated until the IRB/EC provides written approval of the protocol and the informed consent and until approved documents have been obtained by the Investigator and copies received by the Sponsor. All amendments will be sent to the IRB/EC for information (minor amendment) or for submission (major amendment) before implementation. The Investigator will supply the IRB/EC and the Sponsor with appropriate reports on the progress of this study, including any necessary safety updates, in accordance with the applicable government regulations and in agreement with policy established by the Sponsor.

12.3 Informed Consent Process

Properly executed, written informed consent must be obtained from each subject prior to any screening procedures.

The informed consent must, at a minimum, include the elements of consent described in the ICH guidance on GCP and the US CFR 21 part 50.25. A copy of the ICF planned for use will be reviewed by the Sponsor or designee for acceptability and must be submitted by the Investigator or designee together with the protocol, to the appropriate IRB/EC for review and approval prior to the start of the study at that investigational site. Consent forms must be in a language fully comprehensible to the prospective subject. The Investigator must provide the Sponsor or designee with a copy of the IRB/EC letter approving the protocol and the ICF before the study drug supplies will be shipped and the study can be initiated.

The consent form must be revised if new information becomes available during the study that may be relevant to the subject's willingness to continue participation. Any revision must be submitted to the appropriate IRB/EC for review and approval in advance of use.

12.3.1 Consent and Other Informational Documents Provided to Subjects

The subject must be given a copy of the signed informed consent and the original maintained in the designated location at the site.

12.3.2 Consent Procedures and Documentation

It is the Investigator or designee's responsibility to obtain written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The subject must be given ample time to decide about study participation and opportunity to inquire about details of the study. The IRB/EC-approved consent form must be personally signed and dated by the subject and by the person who conducted the informed-consent discussion. The Investigator or appropriate site personnel must document the details of obtaining informed consent in the subject's study documents.

The subject must also indicate his/her understanding of the study. The subject must provide written agreement prior to any screening visit procedures being performed indicating his/her agreement to participate in the study.

Records related to a study subject's participation will be maintained and processed according to local laws, and where applicable, the European Union General Data Protection Regulation (EU GDPR). The consent and study information documentation will include statements describing local and regional requirements concerning data privacy, and who to contact for questions.

13 PUBLICATION PLAN

All publication rights are delineated in the Clinical Study Agreement and/or other separate agreements with the Investigator and/or Institution, as applicable.

14 CONFLICT OF INTEREST POLICY

14.1 Finance, Insurance, and Indemnity

Arrangements for finance, insurance, and indemnity are delineated in the Clinical Study Agreement and/or other separate agreements with the Investigator and/or Institution, as applicable.

15 LITERATURE REFERENCES

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16 APPENDICES

Appendix A New York Heart Association Class Guidelines

The NYHA heart failure functional classifications are provided below.

NYHA Class I (mild): Patients with cardiac disease but without resulting in limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation (rapid or pounding heart beat), dyspnea (shortness of breath), or anginal pain (chest pain).

NYHA Class II (mild): Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

NYHA Class III (moderate): Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

NYHA Class IV (severe): Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Source: New York Heart Association 1994

Appendix B Prohibited and Restricted Medications

Subjects taking prohibited medications at study entry will not be eligible for the study.

Subjects who require current treatment with a prohibited medication will be withdrawn from the study.

Subjects who have previously taken a prohibited medication during the study will be withdrawn from the study unless:

- the prohibited medication has been discontinued AND
- withdrawal from the study presents an unacceptable medical risk to the subject

The justification to allow the subject to continue in the trial will be made by the Sponsor/Medical Monitor with medical input from the Investigator, and will be documented. If allowed to remain in the trial, this will be reported as a major protocol deviation and not a waiver.

The table below lists prohibitions and restrictions by medication class, including representative medications within class. A **prohibited** medication is not allowed. A **restricted** medication is allowed only under certain conditions.

Medication Class	Medication[a]	Prohibition/restrictions
Analgesics	**RESTRICTED** • acetaminophen	• Only acetaminophen (not combinations including acetaminophen) is allowed as rescue medication for OA pain in the knee (at a maximum daily dose of 2500 mg) • Subjects are encouraged to limit the amount of rescue medication (i.e., acetaminophen) taken during the study. Subjects must discontinue taking study-provided rescue medication during the Baseline Pain Assessment Period and for at least 24 hours prior to the start of study visits. Rescue medication use during the Baseline Pain Assessment Period through Visit 3 and within 24 hours of the study visits (Visits 5, 6, and 8) will be documented in the EDC.
Anticonvulsants	**PROHIBITED** • gabapentin • pregabalin • carbamazepine	• Prohibited use within 4 weeks prior to Screening and throughout the study
Antidepressants	**PROHIBITED** • tricyclic antidepressants • duloxetine • monoamine reuptake inhibitors	• Prohibited use within 4 weeks prior to Screening and throughout the study

Medication Class	Medication[a]	Prohibition/restrictions
	• serotonin norepinephrine reuptake inhibitors	
Anxiolytics	**PROHIBITED** • chlordiazepoxide • diazepam • flurazepam • alprazolam • clonazepam • lorazepam • oxazepam • temazepam • midazolam • triazolam	• Prohibited at study entry and throughout the study
HMG-CoA reductase inhibitor (Statin)	**RESTRICTED**	• HMG-CoA reductase inhibitors are restricted and cannot be initiated after screening and throughout the study. Subjects who are on a stable dose of a statin at screening may be eligible for enrollment.
Miscellaneous	**PROHIBITED** • intra-articular injections into the index knee, approved and unapproved (i.e., hyaluronic acid and corticosteroids) • unapproved treatments (e.g., platelet-rich plasma, topical capsaicin, lidocaine, and diclofenac) • cannabidiol (CBD) • COVID-19 vaccine	• Prohibited use within 3 months of Screening and throughout the study • Prohibited throughout the study • Use of CBD is prohibited within 1 month prior to Screening and throughout the study • Subject must not be planning to receive a COVID-19 vaccine during Screening through 30 days of the last dose of study drug. If the subject has received a COVID-19 vaccine, they must be fully vaccinated at least 1 week before the Screening visit and be symptom free
Nonsteroidal anti-inflammatory drugs (NSAIDs)	**PROHIBITED** • ibuprofen	• Prohibited use following Screening • Prohibited use within 7 days or five half-lives of the drug prior to the Baseline Pain Assessment Period, whichever is longer

Medication Class	Medication[a]	Prohibition/restrictions
	RESTRICTED • aspirin	• Aspirin, at a dose of up to 81 mg per day, is allowed for prophylaxis of coronary and cerebrovascular events if stable for 30 days prior to Screening and the dose is expected to remain the same throughout the duration of the study • Aspirin should not be used with an anticoagulant
Opioids	**PROHIBITED** • methadone • oxycodone • codeine • morphine • hydrocodone • fentanyl	• Prohibited use following Screening • Prohibited use within 7 days or five half-lives of the drug prior to the Baseline Pain Assessment Period, whichever is longer • Prohibited use of immediate- or extended-release or controlled-release opioids, transdermal fentanyl, or methadone within 3 months of Screening • Use of opioids, for the treatment of pain other than OA of the knee, with a morphine equivalent dose of ≥30 mg per day for more than 2 days per week within 1 month prior to Screening
Steroids and immunosuppressant drugs	**PROHIBITED** • oral corticosteroids	• Prohibited use within 30 days prior to the screening visit • Prohibited throughout the study

[a] Medications within each class include but are not limited to the examples listed in this table.