Official Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ACP-044 for Acute Postoperative Pain Following Orthopedic Surgery (Bunionectomy)

NCT Number: NCT04855240

Document Date: 01 February 2022

CLINICAL STUDY PROTOCOL

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ACP-044 for Acute Postoperative Pain Following Orthopedic Surgery (Bunionectomy)

Protocol Number: ACP-044-004

Amendment 5

Original Protocol Date: 14 January 2021

Protocol Amendment 1 Date: 15 March 2021

Protocol Amendment 2 Date: 06 May 2021

Protocol Amendment 3 Date: 13 August 2021

Protocol Amendment 4 Date: 2 September 2021

Protocol Amendment 5 Date: 01 February 2022

SPONSOR SIGNATURE PAGE

Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ACP-044 for Acute Postoperative Pain Following Orthopedic Surgery (Bunionectomy)

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Signature Page for ACP-044-004 Protocol Amendment 5

Approve	[redacted]-2022 00:24:48 GMT+0000

Approve	[redacted]-2022 16:47:07 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-044-004
EudraCT number	Not applicable
Protocol title	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ACP-044 for Acute Postoperative Pain Following Orthopedic Surgery (Bunionectomy)
Name of investigational product	ACP-044
Indication	Management of acute postoperative pain
Phase of development	2
Sponsor	Acadia Pharmaceuticals Inc. [redacted]
Study hypothesis	ACP-044 is more effective at managing acute postoperative pain following orthopedic surgery than placebo and is safe and well tolerated

Primary Objective To evaluate the efficacy of ACP-044 compared with placebo in the treatment of acute postoperative pain	**Primary Endpoint** • Mean area under the curve (AUC) of the Numeric Rating Scale (NRS) of pain intensity scores from time 0 (when first dose on Day 1 is administered) through 24 hours (AUC_{0-24}) for ACP-044
Secondary Objectives To evaluate the efficacy of ACP-044 compared with placebo in the treatment of acute postoperative pain To evaluate opioid use among ACP-044-treated subjects compared with placebo in the treatment of acute postoperative pain	**Key Secondary Endpoints** • Time to first rescue medication use after time 0 (when first dose on Day 1 is administered) • Proportion of subjects who were opioid free through 24, 48, and 72 hours **Secondary Endpoints** • Mean AUC of the NRS of pain intensity scores from time 0 through 48 and 72 hours (AUC_{0-48}; AUC_{0-72}) for ACP-044 • Mean AUC of the NRS of pain intensity scores from time 0 through 4, 6, and 12 hours (AUC_{0-4}; AUC_{0-6}; AUC_{0-12}), 24-48 hours

	(AUC_{24-48}), and 48-72 hours (AUC_{48-72}) for ACP-044 • Amount of rescue medication taken during 0-24, 24-48, and 48-72 hours (individually), 0-48 hours, and 0-72 hours • Proportion of subjects who did not use rescue medication through 24, 48, and 72 hours • Proportion of subjects who are pain free (NRS ≤2) at 24, 48, and 72 hours • Number of hours subjects are pain free (NRS ≤2) • Proportion of subjects who were opioid free during 24-48 hours and 48-72 hours • Global evaluation of study drug just before time of first rescue medication and at the end of 24, 48, and 72 hours relative to time 0 (when first dose on Day 1 is administered)
Exploratory Objective To evaluate the proportion of subjects with severe pain and to compare the impact of ACP-044 on activities of daily living compared with placebo in the treatment of acute postoperative pain	**Exploratory Endpoints** • Proportion of subjects with severe pain (defined as an NRS pain intensity score ≥7 at any timepoint through 72 hours) • Foot and Ankle Ability Measure (FAAM)
Safety Objective To evaluate the safety and tolerability of ACP-044 compared with placebo in the treatment of acute postoperative pain	**Safety Endpoints** Safety will be evaluated by analyses of the following: • Treatment-emergent adverse events (TEAEs) • Opioid-related adverse events (ORAEs) • Vital signs • Electrocardiograms (ECGs) • Physical examination results • Clinical laboratory tests • Columbia-Suicide Severity Rating Scale (C-SSRS)
Pharmacokinetic Objective	**Pharmacokinetic Endpoints**

To characterize the pharmacokinetic (PK) profile of ACP-044 in subjects treated for acute postoperative pain	• Plasma concentrations of ACP-044 for a total of six (6) samples: Day -1 (predose), Day 1 (one sample taken between 2-3 hours and one sample taken between 4-6 hours, after the first dose of the day), Day 2 (prior to the first dose of the day), and Day 3 (one sample taken between 2-6 hours and one sample taken between 8-12 hours, after the first dose of the day) • 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** • ACP-044 exposure-response relationship: o for efficacy using the primary endpoint, key secondary and selected secondary endpoints o for safety using selected TEAEs
Number of study sites	Approximately 3 sites in the United States (US) will participate in this study.
Number of subjects planned	Approximately 375 subjects will be screened and approximately 240 subjects are planned for enrollment (80 subjects per treatment group), assuming a screen failure rate of approximately 35%.
Test product, dose, and administration	The test products are ACP-044, 400 mg tablets or matching placebo (size- and color-matched) tablets. Study drug doses are to be administered orally prior to surgery through approximately 90 hours after the first dose of study drug on Day -1. Doses to be studied are: • ACP-044, 1600 mg total dose delivered once daily in the morning (provided as 4×400 mg ACP-044 tablets once daily) • ACP-044, 400 mg total dose delivered every 6 hours (provided as 1×400 mg ACP-044 tablet 4 times per day for a total daily dose of 1600 mg) • Placebo size- and color-matched to ACP-044 An unblinded pharmacist and a verifier will prepare the study drug, while keeping all subjects, investigators, and other site

	staff blinded during the study. Neither the pharmacist nor the verifier will have any involvement with subjects or pain assessments. In order to maintain the double-blind design of the study, on each treatment day (Days -1 to Day 3) all subjects will receive four tablets (either active study drug and/or placebo) for the first dose of the day and one tablet (either active study drug or placebo) for the second, third, and fourth doses of the day.
Study design	This study will be conducted as a Phase 2, randomized, double-blind, placebo-controlled, multicenter, inpatient study in subjects with acute postoperative pain (following bunionectomy surgery). The study will compare each of the two active treatment groups receiving a total daily dose of 1600 mg ACP-044, administered either once daily or 400 mg every 6 hours, with a placebo group. The Sponsor, subjects, and Investigators will be blinded to treatment assignment. The study periods are: • Screening: up to 4 weeks (prior to surgery) • Double-blind treatment: Day -1 (post first dose of study drug/day of surgery) to Day 4 • Safety follow-up: approximately 7 days after end of treatment (EOT)/early termination (ET) and approximately 30 days (post last dose of study drug) **Screening Period** During the Screening period, subjects will be assessed for study eligibility. Only those subjects who meet all inclusion and no exclusion criteria will be eligible for the study. All prohibited medications should be discontinued during the Screening period and prior to surgery. Investigators must not withdraw a subject's prohibited medication 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. With approval of the Medical Monitor, rescreening of a subject will be allowed one time if there is an extenuating circumstance that was not under the subject's control or if is due to an identifiable cause, and it is medically appropriate to address that cause, and there is no medical reason that would prevent the subject to be rescreened and enrolled in the study. **Treatment Period**

	On the day of surgery (Day -1), eligible subjects will be randomly assigned in a 1:1:1 ratio to receive 1600 mg ACP-044, administered either once daily or 400 mg every 6 hours, or placebo, according to a randomization schedule. Randomization will be stratified by site. The first dose of study drug will be administered within 60 (±15) minutes prior to the start of surgery. Subjects will then have a popliteal and/or ankle nerve block administered to anesthetize the knee, distal leg, and foot, after which they will enter into surgery. Following surgery, subjects will be administered the remaining three daily doses approximately every 6 hours after the initial dose. The popliteal and/or ankle nerve block will be discontinued approximately 2-4 hours prior to the first dose on Day 1 (i.e., the fifth dose of the study) and nerve block removal; a discontinuation window of approximately 2 hours is permitted. The time at which the first dose on Day 1 is administered will be time 0 for all pain assessments. Study drug administration and study procedures are to be completed on Days -1 through 4 according to the schedule of assessments (Table S-1). Subjects will be encouraged to refrain from taking rescue medication until 1-2 hours following the first dose of study drug on Day 1 (details provided in Section 4.8.1). On Day 4, after the 72 hour pain assessments are performed, the EOT procedures will be completed and subjects will be discharged from the clinical site. **Safety Follow-up Period** Safety will be further assessed during a follow-up visit to occur in the clinic approximately 7 (±3) days after EOT/ET procedures and subjects will receive a follow-up telephone call approximately 30 (+4) days after the last dose of study drug. Subjects should return to standard of care after the follow-up visit that will occur in the clinic 7 (±3) days after the EOT/ET. The study schematic is presented in Figure S–1.
Study duration	The duration of participation for individual study subjects will be approximately 9 weeks, consisting of a screening period of up to 4 weeks, a 4-day treatment period, and a safety follow-up period of approximately 30 (+4) days. The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined

	assessment (note: this includes the safety follow-up visit or contact).
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 ≥18 and ≤65 years of age at the time of Screening 2. Has a body mass index (BMI) <40 kg/m^2 3. Able to understand and provide signed informed consent 4. Able to complete subject-reported outcome measures 5. Is in need of a primary unilateral, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia and sedation 6. Is judged by the Investigator to be American Society of Anesthesiologists Physical Status of I or II (Appendix A) 7. Willing to remain inpatient at the study center for 4 days following surgery 8. Must have a negative COVID-19 diagnostic polymerase chain reaction (PCR) test at Screening and a rapid antigen test on Day -1 predose and is not planning to receive a COVID-19 vaccine within 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 one week before the Screening visit. If subjects have received a COVID-19 booster shot, they will need to have received 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. 9. 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. 10. 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. Note the exception is that a barrier method can be initiated following the Screening visit. 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 immediately prior to surgery. **Exclusion Criteria:** ***Medical Conditions*** 1. Has had a contralateral foot bunionectomy in the past 3 months 2. Has a planned concurrent surgical procedure (e.g. bilateral bunionectomy or collateral procedures like hammertoe correction on the surgical foot) 3. Any subacute or chronic pain condition or use of a medication that would impair/impact the ability to rate the pain associated with the bunionectomy, in the opinion of the Investigator and Medical Monitor ***Concomitant Treatments (Appendix B)*** 4. Has known or suspected regular use of opioids within the previous 6 months

	5. Has taken opioids within 24 hours prior to the scheduled surgery or within five half-lives of the drug, whichever is longer 6. Has a positive drug screen at Screening or Day -1, or a recent (i.e., within the last 5 years) history of drug or alcohol abuse. Subjects using marijuana are not allowed to participate in the study. 7. Has taken any aspirin (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs) within 2 days prior to the scheduled surgery or within five half-lives of the drug, whichever is longer 8. Has initiated treatment with any medications within 1 month prior to study drug administration that could impact pain control or quantitation of their pain response 9. Has been administered systemic steroids within five half-lives or 10 days prior to administration of study drug, whichever is longer ***Medical History, Laboratory Studies, Vital Signs, and Electrocardiogram*** 10. Has current evidence, or medical history of a serious and/or unstable psychiatric, neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, endocrinologic, or other medical disorder, within the previous 12 weeks prior to Screening and on Day -1, that in the judgment of the Investigator and/or Medical Monitor would jeopardize the safe participation of the subject in the study. Also, subject must not have 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. 11. Has an ECG QTcF result at Screening or Day -1 of >480 ms 12. Has a history of myocardial infarction 13. Has a history of uncontrolled diabetes mellitus (DM), Type 1 or 2 DM requiring insulin treatment, or glycosylated hemoglobin (HbA1c) >7% at Screening 14. 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

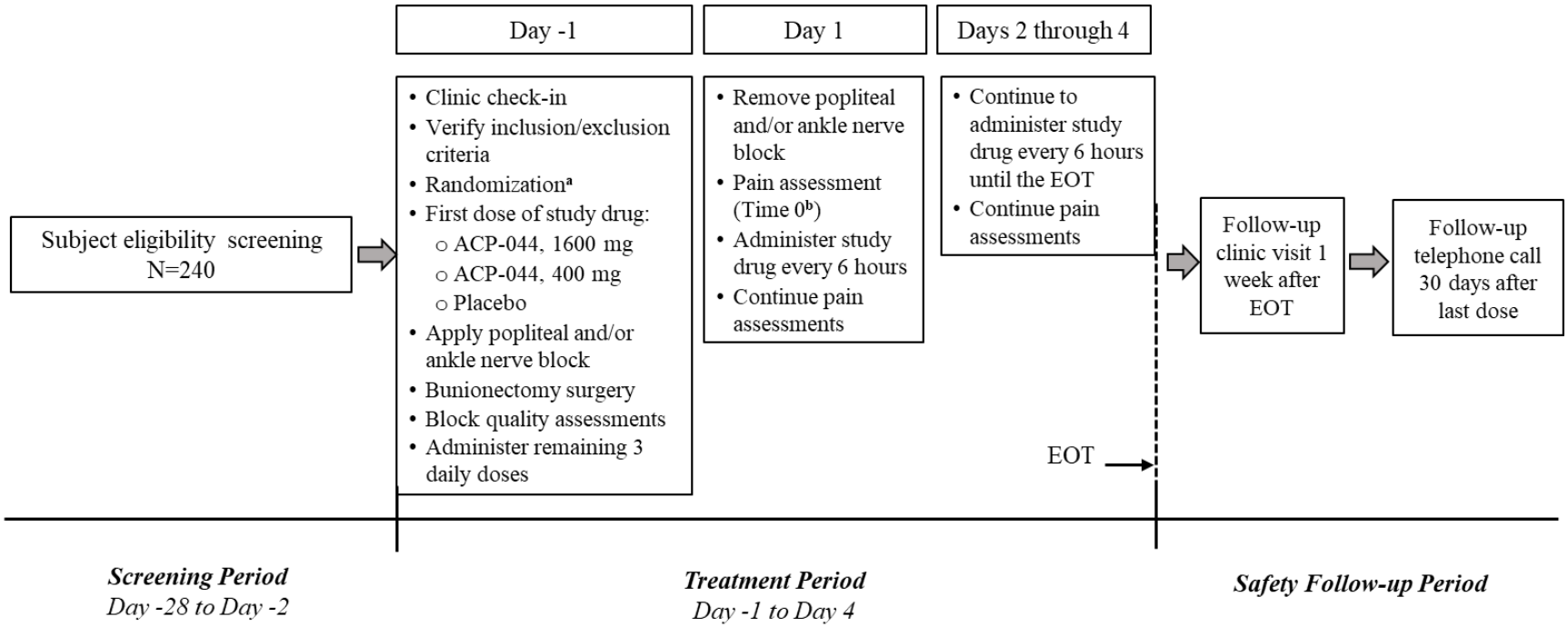
	15. Has clinically significant laboratory abnormalities at Screening that in the judgment of the Investigator or Medical Monitor would jeopardize the safe participation of the subject in the study 16. Known history of infection with hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV). 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. Subjects with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test. ***Other Criteria*** 17. Has received an investigational product or device in a clinical trial within 30 days or within five elimination half-lives, whichever is longer, prior to Screening 18. Is an employee or is a family member of an employee of Acadia Pharmaceuticals Inc. or the clinical research site or the clinical research organization (CRO) administering this study 19. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study
Pharmacokinetic assessments	At each predefined timepoint, a total of six (6) PK samples will be obtained for measurement of concentrations of ACP-044. PK blood samples will be collected Day -1 (predose, within one hour of dosing), Day 1 (one sample taken between 2-3 hours and one sample taken between 4-6 hours, after the first dose of the day), Day 2 (prior to the first dose of the day), and Day 3 (one sample taken between 2-6 hours and one sample taken between 8-12 hours, after the first dose of the day). When possible, an additional PK 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 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	The planned sample size is 240 subjects randomized (80 subjects per treatment group). Randomization will be stratified by site. Assuming a treatment difference in the AUC from 0 to 24 hours is 23 points between the ACP-044 groups and placebo group, and the common standard deviation is 50 points, 76 subjects per treatment arm will provide approximately 80% power to detect the assumed treatment difference between each ACP-044 dose arm and placebo at a 2-sided significance level of 0.05. Assuming no more than 5% of randomized patients will be excluded from primary efficacy analysis, 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 who have undergone bunionectomy with at least one postoperative pain assessment. The Full Analysis Set will be used for the analysis of all efficacy endpoints. The **Per-protocol (PP) Analysis Set** will consist of those subjects in the FAS who did not have any protocol deviations that could potentially have a substantial impact on the primary efficacy outcome. The precise reasons for excluding subjects from the PP Analysis Set will be fully defined and documented prior to the clinical database lock. Subjects will be analyzed based on their randomized treatment assignment. The PP Analysis Set will be used for supportive analyses of selected 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>Subgroup Analysis</u>** Selected analyses will be performed in subgroups and will be defined in the statistical analysis plan (SAP). **<u>Primary Analysis</u>** The primary efficacy variable, $AUC_{0\text{-}24}$, will be analyzed by using analysis of variance (ANOVA) with treatment group

	and site as factors in the model. Each active dose group will be compared to placebo using this model. Details of the analysis procedure will be described in the SAP. **Key Secondary Analyses** Time to first rescue medication use will be analyzed using log rank test stratified by site. Proportion of patients who are opioid free through 24, 48, and 72 hours will be analyzed using stratified Cochran-Mantel-Haenszel (CMH) test controlling for study site. **Secondary Analyses** Continuous secondary variables will be analyzed similarly as the primary efficacy variable. Proportion of patients who are pain free at each specific timepoint will be analyzed using stratified Cochran-Mantel-Haenszel (CMH) test controlling for study site. **General Statistical Approach** Continuous measurement results will be reported using the number of subjects with data values, mean, standard error of the mean, standard deviation, minimum, maximum, and median. For each categorical outcome, the number and percentage of subjects in each category will be reported. All statistical hypothesis tests will be 2-sided at the significance level of 0.05. **Multiple Comparisons / Multiplicity** A fixed sequence method at alpha=0.05 for the primary and key secondary efficacy endpoints will be used to control for multiplicity. The sequence of endpoints for testing is listed in Section 9.2.1. **Safety Analyses** Safety results 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 leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, fatal TEAEs, and SAEs reported after study drug start will all be summarized. Other TEAEs of special interest (e.g., ORAEs) may also be summarized.

	Descriptive statistics for ECG, vital signs and weight, and clinical laboratory parameters, including changes from Day -1 (prior to first dose), will be tabulated by timepoint. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with International Council for Harmonisation (ICH) guidelines. **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. **Pharmacokinetic/Pharmacodynamic (PD) Analyses** A population PK/PD model to describe the exposure response relationship between ACP-044 plasma concentrations and the relevant efficacy and safety endpoints will be developed using appropriate PK/PD methods. Results will be presented in a separate report.
Date	01 February 2022

Figure S–1 Schematic of Study Design for ACP-044-004



Abbreviations: EOT=end of treatment

[a] Subjects to be randomized in a 1:1:1 ratio to receive either a once-daily oral dose of 1600 mg ACP-044, four oral doses of 400 mg ACP-044, or placebo. Randomization will occur just prior to surgery when the first dose of study drug is given.

[b] The time at which the first dose on Day 1 (i.e., the fifth dose of study drug) is administered will be considered time 0 for pain assessments.

Table S–1 Schedule of Events and Assessments for ACP-044-004

	Screening Period	Double-blind Treatment Period							Safety Follow-up Period	
									Clinic visit	Telephone call
Visit Day	**-28 to -2**	**Day -1 Predose**	**Day -1 (Dosing and Postdose)**	**Day 1 (Time 0)**	**Day 2**	**Day 3**	**Day 4 (EOT/ET)**	**Unscheduled Visit[m]**	**7 days after EOT**	**30 days after last dose**
Visit window (# days)		**0**	**0**	**0**	**0**	**0**	**0**		**±3**	**+4**
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Medical and surgical history and demographics	X									
Physical examination	X	X					X[k]		X[k]	
Vital signs[a]	X	X		X	X	X	X	X		
Height, weight[b]	X	X								
12-lead ECG[c]	X	X		X	X	X	X			
Clinical laboratory tests	X	X					X			
Pregnancy test[d]	X	X								
Urine toxicology screen	X	X								
COVID-19 test[e]	X	X								
Clinic check in/out		X					X			
Randomization		X								
Study drug administration			X	X	X	X				
Pain assessment training[f]	X	X								
Bunionectomy			X							
Block Quality Assessment[g]			X							
11-point Numeric Rating Scale (NRS) of pain intensity[h]				X	X	X	X			
Foot and Ankle Ability Measure		X							X	
Rescue medication[i]				X	X	X	X			

Table S–1 Schedule of Events and Assessments for ACP-044-004 (Continued)

	Screening Period	Double-blind Treatment Period							Safety Follow-up Period	
									Clinic visit	Telephone call
Visit Day	-28 to -2	Day -1 Predose	Day -1 (Dosing and Postdose)	Day 1 (Time 0)	Day 2	Day 3	Day 4 (EOT/ET)	Unscheduled Visit[m]	7 days after EOT	30 days after last dose
Visit window (# days)		0	0	0	0	0	0		±3	+4
Global evaluation of study drug				X	X	X	X			
C-SSRS	X	X					X			
PK blood sample collection[j]		X		X	X	X				
Issue diary							X[l]			
Collect diary									X	
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X
Assessment of adverse events	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; COVID-19=Coronavirus disease 2019; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; SAE=serious adverse event

[a] Vital signs will be evaluated starting at Screening; Day -1 predose and on Day 1 every 2 hours for the first 6 hours after the initial dose. Vital signs then to be evaluated every 6 hours thereafter until Day 4/end of treatment. A 15-minute window is permitted for vital sign measurements.

[b] Height and BMI will only be measured and calculated at the Screening visit; weight will be measured at Screening and Day -1 predose.

[c] A single 12-lead ECG will be performed at Screening, on Day -1 predose, on Days 1 through 3 at 1 hour postdose (the first dose of the day), and EOT/ET. A 1-hour window is permitted for the predose ECG and a 20-minute window is permitted for the postdose ECGs.

[d] Applicable to women of childbearing potential. A serum pregnancy test should be performed at Screening and a urine test must be performed at clinic check-in, prior to surgery.

[e] COVID-19 diagnostic polymerase chain reaction (PCR) test at Screening and a rapid antigen test on Day -1 predose.

[f] Subjects will be trained on the process for completion of pain assessments.

[g] Block Quality assessments are to be performed and recorded hourly (±15 minutes) on Day -1 until the block is removed, except between 2200 and 0600 hours when the subject is asleep. Between these hours, the subject will not be awaken, except at 0300 hours (±15 minutes) when the assessment is to be completed.

[h] Subjects should not have ice administered to the surgical area within the 30 minutes prior to each pain assessment. Pain (efficacy) assessments are to be recorded hourly (±15 minutes) for a 12 hour interval on Day 1 beginning immediately prior to the fifth dose (time 0) administered in the study. Pain assessments will continue every 3 hours during the subsequent 12 hour interval, and then every 6 hours thereafter until 72 hours, then once daily in the morning until the follow-up clinic visit. Rescue medication use is to be recorded until the safety follow-up clinic visit. Pain intensity should also be obtained immediately prior to rescue medication being taken.

[i] Record name, amount, date, and time of rescue medication ingested and current pain score until the follow-up clinic visit 7 days after EOT.

[j] PK blood samples will be collected Day -1 (predose, within one hour of dosing), Day 1 (one sample taken between 2-3 hours and one sample taken between 4-6 hours, after the first dose of the day), Day 2 (prior to the first dose of the day), and Day 3 (one sample taken between 2-6 hours and one sample taken between 8-12 hours, after the first dose of the day); and in the event of an SAE or an AE leading to discontinuation. A 15-minute window is permitted around each nominal timepoint on Day 1 and beyond.

[k] The physical exam on Day 4 (EOT/ET) must include an exam of the operative site. The physical exam at the follow-up visit 7 (±3) days after the EOT procedures is for examination of the operative site only. Examination of the operative site must include visual inspection.

[l] Diary will be issued to take home which will be returned at the follow-up clinic visit 7 days after EOT.

[m] The designated study procedures are to be completed; however, the Investigator may complete any study procedure deemed necessary.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE(s)	adverse event(s)
AUC	area under the curve
AUC_{0-4}	area under the curve from time 0 to 4 hours
AUC_{0-6}	area under the curve from time 0 to 6 hours
AUC_{0-12}	area under the curve from time 0 to 12 hours
AUC_{0-24}	area under the curve from time 0 to 24 hours
AUC_{0-48}	area under the curve from time 0 to 48 hours
AUC_{0-72}	area under the curve from time 0 to 72 hours
BMI	body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ET	early termination
FAAM	Foot and Ankle Ability Measure
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
NRS	Numeric Rating Scale
PD	pharmacodynamic
PK	pharmacokinetics
PP	per-protocol
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
TEAE(s)	treatment-emergent adverse event(s)
US	United States

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

Acute postoperative pain has limited treatment options, each with their own benefits and shortcomings. The mainstays of acute pain treatment are opioids. While they provide efficacy to the patients that take them, there are significant risks of constipation, tolerance and dependence, respiratory depression, abuse, diversion and potentially addiction. Postoperative pain following surgery is expected to be moderate to severe and often requires opioids for analgesia that thereby improve the quality of the recovery period. Many operative procedures result in pain that follows a predictable course and is typically short in duration. More than thirteen million ambulatory surgeries were performed in hospital-owned facilities in the United States in 2016 (Karaca and McDermott 2019). Following the procedure, patients are typically given opioids to treat their pain and promote recovery. While opioids are often effective in this setting, many physicians have concerns about the potential for subsequent opioid medication misuse, addiction, and diversion. With an ongoing opioid epidemic in the United States that is leading to an average of 128 overdose deaths each day (Wilson et al. 2020), and prescription opioid misuse costing $78.5 billion per year, new nonaddictive pain therapies are critically needed (Florence et al. 2016). There is a growing medical need for non-opioid pain management options. Therefore, Acadia is developing ACP-044, a peripherally-acting molecule with demonstrated efficacy in a wide array of nonclinical models of pain to prevent and treat acute postsurgical pain.

1.2 Investigational Product

ACP-044, is a non-metal based, orally bioavailable, small molecule Reactive Species Decomposition Accelerant (RSDAx) that works by promoting 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) that cause untoward effects via protein nitration and modification of sensory ion channels leading to neuronal sensitization and pain (McConnell et al. 2003; Lee et al. 1998a; Lee et al. 1998b; Chaplan et al. 1994; Hargreaves et al. 1988; Fehrenbacher et al. 2012; Sluka and Willis 1997; Brennan et al. 1996). By removing PN, ACP-044 prevents or disrupts the ensuing pathways causing hypersensitivity thereby preventing the development of hyperalgesia or reversing existing hyperalgesia.

1.3 Nonclinical Data

In vivo, ACP-044 is efficacious in pre-clinical models of acute post-incisional hyperalgesia, both prophylactically and palliatively. This suggests that ACP-044 may be of use in peri-operative settings as a replacement or to reduce the amount of opioid products (i.e., Percocet, Vicodin) often prescribed following minimally invasive surgical procedures.

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 (single oral doses up to 2000 mg) 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 six active and two 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. 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 drug concentration (C_{max}) and 1 hour delay in T_{max}) and had no effect on the extent (area under the 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 and the major metabolite is sulfate conjugate and to a lesser extent is glucuronide 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 P450 (CYP) isozymes tested (1A2, 2C8, 2C19, 2D6, and 3A4) nor 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 volunteer subjects. The present study is a proof of concept study to evaluate the efficacy of ACP-044 as an analgesic for the treatment of acute postoperative pain and to evaluate the safety, tolerability, and pharmacokinetic profile. The postoperative bunionectomy model is a widely used human orthopedic model in the development of analgesic drugs (Desjardins et al. 2002; Daniels et al. 2009; Pollak et al. 2018).

1.5.1 Rationale for Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled inpatient study in subjects with acute postoperative pain following bunionectomy. The study will assess the efficacy of ACP-044 by comparing the same maximum dose of ACP-044, 1600 mg administered either as a single dose or as 400 mg administered every six hours. Guided by nonclinical animal models where ACP-044 provided robust analgesic effects when given prior to incision as a single dose or when administered daily at 24, 48, and 72 h post-incision, dosing in the present study will begin prior to surgery and will continue for 3 days after surgery.

1.5.2 Rationale for Dose Selection

In a nonclinical animal model, a single oral dose of ACP-044 prevented the development of incisional hyperalgesia for at least 3 days, with the highest dose tested (30 mg/kg) producing essentially complete prevention of hyperalgesia. Similarly, daily doses of ACP-044 given postincision provided continuous relief from an ongoing hyperalgesic insult in a dose-dependent manner. It is not clear, 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., once-daily or every 6 hours) 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 as it is the first clinical efficacy study to date. If the study shows treatment with ACP-044 is effective, this could lead to further clinical development of this treatment for pain.

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 volunteers, 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 treatment of postoperative acute pain. 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 acute postoperative pain.

2.1.1 Primary Endpoint

The primary endpoint is AUC of the Numeric Rating Scale (NRS) of pain intensity scores from time 0 (when first dose on Day 1 is administered) through 24 hours (AUC_{0-24}) for ACP-044.

2.2 Secondary Objectives

The secondary objectives of the study are:

- to evaluate the efficacy of ACP-044 compared with placebo in the treatment of acute postoperative pain
- to evaluate opioid use among ACP-044-treated subjects compared with placebo in the treatment of acute postoperative pain

2.2.1 Key Secondary Endpoints

- Time to first rescue medication use after time 0 (when first dose on Day 1 is administered)
- Proportion of subjects who were opioid free through 24, 48, and 72 hours

2.2.2 Secondary Endpoints

The secondary endpoints are:

- Mean AUC of the NRS of pain intensity scores from time 0 through 48 and 72 hours (AUC_{0-48}; AUC_{0-72}) for ACP-044
- Mean AUC of the NRS of pain intensity scores from time 0 through 4, 6, and 12 hours (AUC_{0-4}; AUC_{0-6}; AUC_{0-12}), 24-48 hours (AUC_{24-48}), and 48-72 hours (AUC_{48-72}) for ACP-044
- Amount of rescue medication taken during 0-24, 24-48, and 48-72 hours (individually), 0-48 hours, and 0-72 hours

- Proportion of subjects who did not use rescue medication through 24, 48, and 72 hours
- Proportion of subjects who are pain free (NRS ≤2) at 24, 48, and 72 hours
- Number of hours subjects are pain free (NRS ≤2)
- Proportion of subjects who were opioid free during 24-48 hours and 48-72 hours
- Global evaluation of study drug just before time of first rescue medication and at the end of 24, 48, and 72 hours relative to time 0 (when first dose on Day 1 is administered)

2.3 Exploratory Objectives

The exploratory objectives are to evaluate the proportion of subjects with severe pain and to compare the impact of ACP-044 on activities of daily living compared with placebo in the treatment of acute postoperative pain.

2.3.1 Exploratory Endpoints

The exploratory endpoints are:

- Proportion of subjects with severe pain (defined as an NRS pain intensity score ≥7 at any timepoint through 72 hours)
- Foot and Ankle Ability Measure (FAAM)

2.4 Safety Objectives

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

2.4.1 Safety Endpoints

Safety will be evaluated by analyses of the following:

- Treatment-emergent adverse events (TEAEs)
- Opioid-related adverse events (ORAEs)
- 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 treated for acute postoperative pain.

2.5.1 Pharmacokinetic Endpoints

The PK endpoints of the study are:

- Plasma concentrations of ACP-044 for a total of six (6) samples: Day -1 (predose), Day 1 (one sample taken between 2-3 hours and one sample taken between 4-6 hours, after the first dose of the day), Day 2 (prior to the first dose of the day), and Day 3 (one sample taken between 2-6 hours and one sample taken between 8-12 hours, after the first dose of the day)
- ACP-044 PK parameters determined using a population PK approach

2.6 Pharmacokinetic/Pharmacodynamic Objective

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

2.6.1 Pharmacokinetic/Pharmacodynamic Endpoints

The PK/PD endpoints include:

- ACP-044 exposure-response relationship:
    - for efficacy using the primary endpoint, key secondary and selected secondary endpoints
    - for safety using selected TEAEs

3 STUDY DESCRIPTION

3.1 Overview of Study Design

This study will be conducted as a Phase 2, randomized, double-blind, placebo-controlled, multicenter, inpatient study in subjects with acute postoperative pain (following bunionectomy surgery). The study will compare each of the two active treatment groups receiving a total daily dose of 1600 mg ACP-044, administered either once daily or 400 mg every 6 hours, with a placebo group. The Sponsor, subjects, and Investigators will be blinded to treatment assignment.

Approximately three sites in the United States (US) will screen approximately 375 subjects and approximately 240 subjects are planned for enrollment (80 subjects per treatment group).

The duration of participation for individual study subjects will be approximately 9 weeks, consisting of a screening period of up to 4 weeks, a 4-day treatment period, and a safety follow-up period of approximately 30 (+4) days.

The study periods are:

- Screening: up to 4 weeks (prior to surgery)
- Double-blind treatment: Day -1 (post first dose of study drug/day of surgery) to Day 4
- Safety follow-up: approximately 7 days after end of treatment (EOT)/early termination (ET) and approximately 30 days (post last dose of study drug)

The study start date is defined as the date the first subject signs the informed consent form.

The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note: this includes the safety follow-up visit or contact). 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. Only those subjects who meet all inclusion and no exclusion criteria will be eligible for the study.

All prohibited medications should be discontinued during the Screening period and prior to surgery. Investigators must not withdraw a subject's prohibited medication 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.

With approval of the Medical Monitor, rescreening of a subject will be allowed one time if there is an extenuating circumstance that was not under the subject's control or if it is due to an identifiable cause, and it is medically appropriate to address that cause, and there is no medical reason that would prevent the subject to be rescreened and enrolled in the study.

3.1.2 Treatment Period (Day -1 to Day 4)

On the day of surgery (Day -1), eligible subjects will be randomly assigned in a 1:1:1 ratio to receive 1600 mg ACP-044, administered either once daily or 400 mg every 6 hours, or placebo, according to a randomization schedule. Randomization will be stratified by site.

The first dose of study drug will be administered within 60 (±15) minutes prior to the start of surgery. Subjects will then have a popliteal and/or ankle nerve block administered to anesthetize the knee, distal leg, and foot, after which they will enter into surgery. Following

surgery, subjects will be administered the remaining three daily doses approximately every 6 hours after the initial dose.

The popliteal and/or ankle nerve block will be discontinued approximately 2-4 hours prior to the first dose on Day 1 (i.e., the fifth dose of the study) and nerve block removal; a discontinuation window of approximately 2 hours is permitted. The time at which the first dose on Day 1 is administered will be time 0 for all pain assessments. Study drug administration and study procedures are to be completed on Days -1 through 4 according to the schedule of assessments (Table S–1). Subjects will be encouraged to refrain from taking rescue medication until 1-2 hours following the first dose of study drug on Day 1 (details provided in Section 4.8.1).

On Day 4, after the 72 hour pain assessments are performed, the EOT procedures will be completed and subjects will be discharged from the clinical site.

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

3.1.3 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 and subjects will receive a follow-up telephone call approximately 30 (+4) days after the last dose of study drug. Subjects should return to standard of care after the follow-up visit that will occur in the clinic 7 (±3) days after the EOT/ET.

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 ≥18 and ≤65 years of age at the time of Screening
2. Has a body mass index (BMI) <40 kg/m^2
3. Able to understand and provide signed informed consent
4. Able to complete subject-reported outcome measures
5. Is in need of a primary unilateral, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia and sedation

6. Is judged by the Investigator to be American Society of Anesthesiologists Physical Status of I or II (Appendix A)
7. Willing to remain inpatient at the study center for 4 days following surgery
8. Must have a negative COVID-19 diagnostic polymerase chain reaction (PCR) test at Screening and a rapid antigen test on Day -1 predose and is not planning to receive a COVID-19 vaccine within 30 days of the last dose study drug. If the subject has received a COVID-19 vaccine, they must be fully vaccinated at least one week before the Screening visit. If subjects have received a COVID-19 booster shot, they will need to have received 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.
9. 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
10. 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. Note the exception is that a barrier method can be initiated following the Screening visit.

    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 immediately prior to surgery.

4.2 Exclusion Criteria

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

Medical Conditions

1. Has had a contralateral foot bunionectomy in the past 3 months
2. Has a planned concurrent surgical procedure (e.g. bilateral bunionectomy or collateral procedures like hammertoe correction on the surgical foot)
3. Any subacute or chronic pain condition or use of a medication that would impair/impact the ability to rate the pain associated with the bunionectomy, in the opinion of the Investigator and Medical Monitor

Concomitant Treatments (Appendix B)

4. Has known or suspected regular use of opioids within the previous 6 months
5. Has taken opioids within 24 hours prior to the scheduled surgery or within five half-lives of the drug, whichever is longer
6. Has a positive drug screen at Screening or Day -1, or a recent (i.e., within the last 5 years) history of drug or alcohol abuse. Subjects using marijuana are not allowed to participate in the study.
7. Has taken any aspirin (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs) within 2 days prior to the scheduled surgery or within five half-lives of the drug, whichever is longer
8. Has initiated treatment with any medications within 1 month prior to study drug administration that could impact pain control or quantitation of their pain response
9. Has been administered systemic steroids within five half-lives or 10 days prior to administration of study drug, whichever is longer

Medical History, Laboratory Studies, Vital Signs, and Electrocardiogram

10. Has current evidence, or medical history of a serious and/or unstable psychiatric, neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, endocrinologic, or other medical disorder, within the previous 12 weeks prior to Screening and on Day -1, that in the judgment of the Investigator and/or Medical Monitor would jeopardize the safe participation of the subject in the study. Also, subject must not have 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.
11. Has an ECG QTcF result at Screening or Day -1 of >480 ms
12. Has a history of myocardial infarction

13. Has a history of uncontrolled diabetes mellitus (DM), Type 1 or 2 DM requiring insulin treatment, or glycosylated hemoglobin (HbA1c) >7% at Screening
14. 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
15. Has 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
16. Known history of infection with hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV). 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. Subjects with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test.

Other Criteria

17. Has received an investigational product or device in a clinical trial within 30 days or within five elimination half-lives, whichever is longer, prior to Screening
18. Is an employee or is a family member of an employee of Acadia Pharmaceuticals Inc. or the clinical research site or the clinical research organization (CRO) administering this study
19. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study

4.3 Screen Failures

Rescreening of a subject will be allowed one time, with the approval of the Medical Monitor, if there is an extenuating circumstance that was not under the subject's control, or if it is due to an identifiable cause, and it is medically appropriate to address that cause, and there is no medical reason that would prevent the subject to be rescreened and enrolled in the study. Subjects may be rescreened following a COVID-19 infection as long as they have no sequelae from COVID-19 infection, per Exclusion Criterion 10.

The minimum information that will be captured 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 a subject decides to withdraw consent from all components of 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 and/or safety follow-up visit (whichever visit 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).

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
- 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.

4.5.1.1 Cardiovascular-Related Stopping Criteria

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

- Clinically significant hypotension defined as systolic blood pressure (SBP) <85 mmHg and changes in blood pressure with decrease in SBP ≥20 mmHg or diastolic BP (DBP) ≥10 mmHg
- 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 >480 ms or QTcF increases ≥60 ms from Baseline

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 Day 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 (including the safety follow-up clinic visit [7 days after EOT]) 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 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 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:

- opioids, NSAIDs and, importantly, drugs that are used to treat chronic pain (e.g., gabapentin, pregabalin, carbamazepine, and tricyclic antidepressants, and duloxetine)
- systemic corticosteroids
- immune suppressant drugs

4.8 Permitted, Restricted, and Prohibited Medications

Prohibitions and restrictions for concomitant medications should be followed between the initial screening visit and the safety follow-up clinic visit that occurs 7 days after EOT/ET as specified in Appendix B.

Permitted concomitant medications should remain at a stable dose throughout the study. Ondansetron may be used at the discretion of the Investigator to treat moderate or severe nausea and vomiting.

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 will be encouraged to refrain from taking rescue medication until 1-2 hours after removal of the nerve block. The allowed rescue medication in the present study is 400 mg of ibuprofen every 4 to 6 hours as needed for pain. The total daily dose of ibuprofen should not exceed 3200 mg (8 tablets). If ibuprofen does not provide the necessary pain relief, subjects may take hydrocodone/acetaminophen 5 mg/325 mg every 4 to 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 3250 mg (10 tablets).

4.9 Lifestyle Considerations

4.9.1 Activity

Walking should be limited until after the 72-hour pain assessment.

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Description

The investigational product will be ACP-044, 400 mg 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, tablet(s) will be administered orally four times per day.

ACP-044 doses to be studied are:

- ACP-044, 1600 mg total dose delivered once daily in the morning (provided as 4×400 mg ACP-044 tablets once daily)
- ACP-044, 400 mg total dose delivered every 6 hours (provided as 1×400 mg ACP-044 tablet 4 times per day for a total daily dose of 1600 mg)
- Placebo size- and color-matched to ACP-044

5.1.1 Formulation, Appearance, Packaging, and Labeling

The Sponsor will supply ACP-044, 400 mg tablets and matching placebo tablets packaged in HDPE bottles, each containing 30 tablets.

ACP-044 is a white to off-white powder. ACP-044, 400 mg tablets include the active compound (ACP-044) and the following excipients: microcrystalline cellulose, polyvinylpyrrolidone, croscarmellose sodium, silicon dioxide magnesium stearate, [redacted] coating. 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 [See USP controlled conditions] in a secure area with restricted access and according to local and national regulations.

5.1.3 Dosing and Administration

An unblinded pharmacist and unblinded verifier will prepare the study drug to be dispensed by site staff, while keeping all subjects, investigators, and other site staff blinded during the study. The unblinded verifier will cross check the preparation of the study drug to ensure accuracy of the study drug to be dispensed. Neither the pharmacist nor the verifier will have any involvement with subjects or pain assessments.

On Day -1, subjects will be randomized 1:1:1 to receive 1600 mg ACP-044, administered either once daily or 400 mg every 6 hours, or placebo (Table 5-1). 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. The first daily dose of study drug (either active and/or placebo) will be administered as four tablets on Day -1 prior to the application of the popliteal and/or ankle nerve block (see Section 3.1.2) and one tablet (either active study drug or placebo) will be administered for the second, third, and fourth doses of the day. Subjects will receive study drug (either active or placebo) according to this schedule on Day 1 through Day 3.

Study drug doses are to be administered orally prior to surgery through approximately 90 hours after the first dose of study drug on Day -1.

Table 5-1 Blinded Daily Dosing Regimen

	First Daily Dose	Second Daily Dose	Third Daily Dose	Fourth Daily Dose
Placebo	PPPP	P	P	P
ACP-044 400 mg (every 6 hours)	XPPP	X	X	X
ACP-044 1600 mg (once-daily)	XXXX	P	P	P

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

5.1.4 Method of Assigning Subjects to Treatment Groups

On Day -1 eligible subjects who meet inclusion and do not meet exclusion criteria will be randomized in a 1:1:1 ratio to receive 1600 mg ACP-044, administered either once daily or 400 mg every 6 hours, or placebo, according to a randomization schedule.

5.1.5 Blinding

Treatment assignments will be blinded to all study subjects, Investigators, site personnel, and Sponsor personnel. An unblinded pharmacist and unblinded verifier will prepare the study drug to be dispensed by site staff (see Section 5.1.3). 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.

5.1.6 Study Drug Compliance

Study drug dosing will be observed by the clinical site staff. If a subject misses a dose, they should not take an extra dose. Missed doses will be documented as protocol deviations.

5.1.7 Overdose

An overdose is a deliberate or inadvertent administration of a treatment 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

An unblinded pharmacist will keep current and accurate records of the study drug product 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 supplied is for use in this study only and should not be used for any other purpose. An unblinded 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 study drug 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 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 the follow-up safety assessment at the clinic may not be possible. In those cases, the follow-up 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 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 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 informed consent form (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 Day -1 will be captured as concomitant medication.

6.3 Block Quality Assessment

Postoperatively, assessments of the popliteal block depth (Block Quality Assessment) will be performed and recorded hourly (±15 minutes) at the top of each hour until 2200 hours. Between the hours of 2200 and 0600 hours, Block Quality Assessments will continue to be performed hourly (±15 minutes) if subject is awake, but, even if asleep, the subject will be awakened to perform a Block Quality Assessment at 0300 hours (±15 minutes). Block Quality Assessments will continue until the block is removed.

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 at the time of popliteal and/or ankle nerve block removal, for the subsequent 72 hours, and for the 7 days after EOT. Subjects will be asked:

> "Please describe your foot pain at the present time from 0 to 10 where "0" means "no pain at all" and "10" means "the worst pain imaginable".

Trained study coordinators will present the NRS scale and all other questionnaires at the designated times.

Pain (efficacy) assessments are to be recorded hourly (±15 minutes) for a 12-hour interval on Day 1 beginning immediately prior to the fifth dose (time 0) administered in the study. Pain assessments will continue every 3 hours during the subsequent 12 hour interval, and then every 6 hours thereafter until 72 hours, then once daily in the morning until the follow-up clinical visit. Pain assessments should also be obtained immediately prior to the administration of rescue medication.

Subjects should not have ice administered to the surgical area within the 30 minutes prior to each pain assessment. Pain assessments should be performed before blood sample collection, ECG, and other procedures.

Subjects will be provided a diary upon discharge to document their pain from EOT to the follow-up clinic visit that occurs 7 days after EOT.

6.4.2 Global Evaluation of Study Drug

For the global evaluation of study drug subjects will be asked to provide a graded response (4=excellent, 3=very good, 2=good, 1=fair, or 0=poor) to the statement "How would you rate the study drug you received to delay or reduce your foot pain?" The time at which the statement is completed will be recorded.

Evaluation of study drug will be completed just before receiving the first dose of rescue medication, and at the end of 24 hours, 48 hours, and 72 hours relative to time 0 (when the first dose on Day 1 is administered). The evaluation of study drug should be performed before blood sample collection, ECG, and other procedures.

6.4.3 Foot and Ankle Ability Measure

The FAAM is a validated, self-reported evaluative instrument specific to those with leg, ankle, and foot musculoskeletal disorders (Martin et al. 2005). The questionnaire consists of 21 movements the subject rates as "no difficulty at all", "slight difficulty", "moderate

difficulty", "extreme difficulty", "unable to do", and "N/A", and an overall grade for the level of function during usual activities of daily living, graded on a scale of 0 to 100 with 100 being at the level of function prior to the foot and ankle problem and 0 being the inability to perform any of their usual daily activities.

The FAAM will be completed prior to the subject receiving their first dose on Day -1 and at the follow-up visit conducted 7 days after the EOT procedures.

6.5 Safety Assessments

6.5.1 Physical Examination

A complete, general physical examination will be conducted at Screening and a brief physical exam, including mental status exam, will be conducted on Day -1 and Day 4/EOT/ET. Height will only be measured and reported at Screening and weight will be measured and recorded at Screening and Day -1 predose. An exam of the operative site will also be performed on Day 4 (EOT/ET) prior to discharge and at the follow-up visit 7 (±3) days after the EOT procedures are completed. Both exams must include visual inspection of the operative site.

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, sitting systolic and diastolic blood pressure, and pulse rate. The sitting blood pressure should be measured after the subject has been sitting for ≥3 minutes.

Vital signs will be evaluated at Screening, Day -1 predose, and on Day 1 every 2 hours for the first 6 hours after the initial dose. Vital signs will then be evaluated every 6 hours thereafter until Day 4/EOT/ET. 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, Day -1 predose, on Days 1 through 3 at 1 hour postdose (the first dose of the day), and Day 4/EOT/ET. A 1-hour window is permitted for the predose ECG; a 20-minute window is permitted for the postdose ECG. ECGs should be performed prior to blood sampling and vital signs but after pain assessments are completed.

Electrocardiograms should be performed before blood sampling or at least 30 minutes after blood sampling. 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. ECG tracings and results (ventricular rate, PR, QRS, QT, QTcF, and QTcB intervals) will be included in the subject's study records.

At Screening, if the ECGs has 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.

On Day -1, 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).

6.5.5 Laboratory Evaluations

Clinical laboratory sample collection (including HbA1c 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,
  - Mg should only be performed at Visit 1 (Screening)
- 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)
- 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)
  - Vitamin B12 should only be performed at Visit 1 (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 before surgery on Day -1 (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
    - COVID-19 rapid antigen test on Day-1 predose
- Urinalysis (UA)
    - Blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH, nitrates
- Urine toxicology screen with repeat testing
    - Urine toxicology screen will test for controlled substances. The following controlled substances may be tested with a urine toxicology screen according to the schedule presented in Table 6–1: amphetamine, barbiturates, benzodiazepines, cocaine, methadone, morphine/opiates, methamphetamine, marijuana (THC), phencyclidine (PCP), ecstasy (MDMA). Negative drug screens are required for study eligibility.
        - If there is a positive urine drug screen (UDS) for a medication that is known to give a false positive on UDS panel, the subject has a valid prescription for such medication and that medication is not prohibited in this study, and the subject denies use of the positive prohibited medication, 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 toxicology screen
Day -1 predose	CHEM, CBC, UA, COVID-19[a] ,urine pregnancy, and urine toxicology screen
Day 4 (EOT/ET)	CHEM, CBC, UA

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 and a rapid antigen test on Day -1 predose.

6.6 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.

PK blood samples will be collected Day -1 (predose, within one hour of dosing), Day 1 (one sample taken between 2-3 hours and one sample taken between 4-6 hours, after the first dose of the day), Day 2 (prior to the first dose of the day), and Day 3 (one sample taken between 2-6 hours and one sample taken between 8-12 hours, after the first dose of the day). A 15-minute window is permitted around each nominal timepoint on Day 1 and beyond.

Pharmacokinetic samples will also be collected, if possible, at any ET visit or the visit immediately following any SAE or following any AE leading to discontinuation, even if it is an unscheduled visit.

6.6.1 Blood Sampling

Six (6) 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.

6.6.2 Specimen Preparation, Handling, Storage, and Shipment

PK 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 time point, 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.

6.7 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.

The first evaluation is a follow-up visit that will be conducted at the clinic approximately 7 (±3) days after EOT visit. The assessments to be conducted at this visit include:

- Examination of the operative site, which must include visual inspection (at the follow-up visit 7 days after EOT)
- FAAM (at the follow-up visit 7 days after EOT)
- Collect diary (at the follow-up visit 7 days after EOT)
- Concomitant medications
- AEs

The second evaluation is a follow-up telephone call to occur approximately 30 (+4) days after the last dose of study drug. The subject will be asked about the following during the telephone call:

- Concomitant medications
- AEs

6.8 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, and measurement of vital signs. 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 the time of informed consent, or scheduled surgery/procedure.
- Overdose of concomitant medication without any signs or symptoms. 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

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
- **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 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 5.1.7).

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

The primary endpoint is AUC_{0-24} based on the pain intensity scores from 0 to 24 hours assessed using NRS.

Let Δ_{auc_1} and Δ_{auc_2} be the difference between each of the two ACP-044 dose groups and placebo group in the mean $AUC_{0-24,}$ respectively.

The null hypotheses are: $\Delta_{auc\_i} = 0$ and the alternative hypothesis is: $\Delta_{auc\_i} \neq 0$, i=1,2

9.2.1 Multiple Comparisons/Multiplicity

A fixed-sequence method at alpha=0.05 for the primary and key secondary efficacy endpoints will be used to control for multiplicity. The following will be the sequence for testing:

1. 400 mg Q6H compared to placebo on mean AUC_{0-24} of NRS of pain intensity scores
2. 1600 mg QD compared to placebo on mean AUC_{0-24} of NRS of pain intensity scores
3. 400 mg Q6H compared to placebo on time to first rescue medication use after time 0
4. 400 mg Q6H compared to placebo on proportion of subjects who were opioid free through 24 hours
5. 1600 mg QD compared to placebo on time to first rescue medication use after time 0

6. 1600 mg QD compared to placebo on proportion of subjects who were opioid free through 24 hours
7. 400 mg Q6H compared to placebo on proportion of subjects who were opioid free through 48 hours
8. 1600 mg QD compared to placebo on proportion of subjects who were opioid free through 48 hours
9. 400 mg Q6H compared to placebo on proportion of subjects who were opioid free through 72 hours
10. 1600 mg QD compared to placebo on proportion of subjects who were opioid free through 72 hours

The testing procedure will stop once a p-value in the sequence is greater than 0.05. P-values that are less than or equal to 0.05 prior to stopping, will be declared statistically significant; p-values after stopping will be nominal.

9.3 Sample Size Determination

The planned sample size is 240 subjects randomized (80 subjects per treatment group). Randomization will be stratified by site.

Assuming a treatment difference in the AUC from 0 to 24 hours is 23 points between the ACP-044 groups and placebo group, and the common standard deviation is 50 points, 76 subjects per treatment arm will provide approximately 80% power to detect the assumed treatment difference between each ACP-044 dose arm and placebo at a 2-sided significance level of 0.05. Assuming no more than 5% of randomized patients will be excluded from primary efficacy analysis, 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** includes all randomized subjects who received at least one dose of study drug and who have undergone bunionectomy with at least one postoperative pain assessment. The Full Analysis Set will be used for the analysis of all efficacy endpoints.

The **Per-protocol (PP) Analysis Set** will consist of those subjects in the FAS who did not have any protocol deviations that could potentially have a substantial impact on the primary efficacy outcome. The precise reasons for excluding subjects from the PP Analysis Set will be fully defined and documented prior to the clinical database lock. Subjects will be analyzed

based on their randomized treatment assignment. The PP Analysis Set will be used for supportive analyses of selected 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

Continuous measurement results will be reported using the number of subjects with data values, mean, standard error of the mean, standard deviation, minimum, maximum, and median. For each categorical outcome, the number and percentage of subjects in each category will be reported. All statistical hypothesis tests will be 2-sided at the significance level of 0.05.

9.5.2 Primary Analyses

The primary efficacy variable, AUC_{0-24}, will be analyzed by using analysis of variance (ANOVA) with treatment group and site as factors in the model. Each active dose group will be compared to placebo using this model. P-value and associated 95% confidence interval for treatment difference between each active dose and placebo will be presented. Missing pain assessment at scheduled time point will be imputed. The details of missing data imputation and multiplicity adjustment will be described in the SAP.

9.5.3 Key Secondary Analyses

Time to first rescue medication use will be analyzed using log rank test stratified by site.

Proportion of patients who are opioid free through 24, 48, and 72 hours will be analyzed using stratified Cochran-Mantel-Haenszel (CMH) test controlling for study site.

9.5.4 Secondary Analyses

Continuous secondary variables will be analyzed similarly as the primary efficacy variable. Proportion of patients who are pain free at each specific timepoint will be analyzed using stratified Cochran-Mantel-Haenszel (CMH) test controlling for study site.

9.5.5 Exploratory Analyses

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

9.5.6 Safety Analyses

Safety results 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, and SAEs reported after study drug start will all be summarized. Other TEAEs of special interest (e.g., ORAEs) may also be summarized.

Descriptive statistics for ECG, vital signs and weight, and clinical laboratory parameters, including changes from Day -1 (prior to first dose), will be tabulated by timepoint. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines.

9.5.7 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.

9.5.8 Pharmacokinetic/Pharmacodynamic Analyses

A population PK/PD model to describe the exposure response relationship between ACP-044 plasma concentrations and the relevant efficacy and safety endpoints will be developed using appropriate PK/PD methods. Results will be presented in a separate report.

9.5.9 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

On Day -1 eligible subjects who meet inclusion and do not meet exclusion criteria will be randomized in a 1:1:1 ratio to receive 1600 mg ACP-044, administered either once daily or 400 mg every 6 hours, 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. An unblinded pharmacist and a verifier will prepare the study drug and shall have no role in pain assessment or patient care.

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.

9.8 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 6.7). 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 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 American Society of Anesthesiologists Physical Status Classification System

Examples below include (but are not limited to) those provided.

ASA I: A normal healthy patient. Example: Healthy, non-smoking, no or minimal alcohol use.

ASA II: A patient with a mild systemic disease. Example: Mild diseases only without substantive functional limitations. Current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled diabetes mellitus/hypertension (DM/HTN), mild lung disease.

ASA III: A patient with severe systemic disease. Example: substantive functional limitations; one or more moderate to severe diseases. Poorly controlled DM or HTN, chronic obstructive pulmonary disease (COPD), morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, end stage renal disease (ESRD) undergoing regularly scheduled dialysis, history (>3 months) of myocardial infarction (MI), cerebrovascular accident (CVA), transient ischemic attack (TIA), or coronary artery stent (CAD)/stents.

ASA IV: A patient with a severe systemic disease that is a constant threat to life. Example: recent (<3 months) MI, CVA, TIA or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, disseminated intravascular coagulation (DIC), acute respiratory distress (ARD) or ESRD not undergoing regularly scheduled dialysis.

Source: American Society of Anesthesiologists 2020

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	• Allowed as rescue medication when used with hydrocodone (hydrocodone/acetaminophen 5 mg/325 mg) every 4 to 6 hours • Total daily dose should not exceed 3250 mg (10 tablets)
Anticoagulant	**PROHIBITED** • heparin • warfarin • rivaroxaban • dabigatran • apixaban • edoxaban • enoxaparin • fondaparinux	• Prohibited throughout the study
Anticonvulsants	**PROHIBITED** • gabapentin • pregabalin • carbamazepine	• Prohibited throughout the study

Medication Class	Medication[a]	Prohibition/restrictions
Antidepressants	**PROHIBITED** • tricyclic antidepressants • duloxetine	• Prohibited throughout the study
Anxiolytics	**PROHIBITED** • benzodiazepines	• Benzodiazepines are prohibited, except for IV midazolam for sedation preceding placement of the popliteal catheter
	RESTRICTED • midazolam	• IV midazolam may be used for sedation preceding placement of the popliteal catheter
Nonsteroidal anti-inflammatory drug (NSAID)	**PROHIBITED** • aspirin	• Prohibited use within 2 days prior to scheduled surgery or within five half-lives of the drug, whichever is longer • Prohibited throughout the study
	RESTRICTED • ibuprofen	• Allowed rescue medication is 400 mg of ibuprofen every 4 to 6 hours as needed for pain • Total daily should not exceed 3200 mg (8 tablets)
Opioids	**PROHIBITED** • methadone • oxycodone • codeine	• Prohibited use within the previous 6 months of Screening • Prohibited use within 24 hours prior to scheduled surgery or within five half-lives of the drug, whichever is longer • Subjects who have a history of drug abuse are not eligible for this study • Hydrocodone/acetaminophen 5 mg/325 mg is allowed as a rescue medication every 4 to 6 hours as needed for pain. o Subjects will be encouraged to refrain from taking rescue medication until 1-2 hours after stopping the nerve block o Ibuprofen (400 mg) alone should be used prior to using hydrocodone/acetaminophen 5 mg/325 mg • Morphine allowed during Day -1 as indicated in the Anesthetic and Surgical Guidelines
	RESTRICTED • hydrocodone • morphine	

Medication Class	Medication[a]	Prohibition/restrictions
Steroids and immunosuppressant drugs	**PROHIBITED** • hydrocortisone • prednisone • prednisolone	• Prohibited throughout the study

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