AMENDED PROTOCOL

PRODUCT NAME/NUMBER:	CO-CRYSTAL E-58425 (tramadol-celecoxib)
PROTOCOL NUMBER:	ESTEVE-SUSA-301
IND NUMBER:	128177
DEVELOPMENT PHASE:	3
PROTOCOL TITLE:	A Randomized, Double-blind, Active- (Tramadol and Celecoxib) and Placebo-controlled, Parallel Groups, Phase 3 Clinical Trial to Establish the Efficacy of Co-crystal E-58425 for the Management of Moderate to Severe Post-surgical Pain after Bunionectomy
PROTOCOL DATE:	Final Version 1.0; 06 Jul 2016 Final Version 1.1; 26 Aug 2016 (including FDA requested changes) Final Version 2.0; 09 Nov 2016 Final Version 3.0; 15 Feb 2017 Final Version 4.0; 20 Jul 2017
AMENDMENT 1 DATE:	Final Version 1.0; 09 Nov 2016
AMENDMENT 2 DATE	Final Version 1.0; 15 Feb 2017
AMENDMENT 3 DATE	Final Version 1.0; 20 Jul 2017
SPONSORED BY:	Laboratorios del Dr. ESTEVE, S. A. U. Avda. Mare de Déu de Montserrat, 221 08041 Barcelona (Spain) Tel: [redacted]
CONTRACT RESEARCH ORGANIZATION:	Premier Research One Park Drive, STE 150 Durham, NC 27709 Tel: [redacted]

This study will be performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature, and may not be used, divulged, published or otherwise disclosed to others except to the extent necessary to obtain approval of the Institutional Review Board, or as required by law. Persons to whom this information is disclosed should be informed that this information is confidential and may not be further disclosed without the express permission of Laboratorios del Dr. ESTEVE, S. A. U.

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: ESTEVE-SUSA-301

PROTOCOL TITLE: A Randomized, Double-blind, Active- (Tramadol and Celecoxib) and Placebo-controlled, Parallel Groups, Phase 3 Clinical Trial to Establish the Efficacy of Co-crystal E-58425 for the Management of Moderate to Severe Post-surgical Pain after Bunionectomy

PROTOCOL DATE: Final Version 4.0, 20 Jul 2017

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

[redacted] [redacted]

[redacted] Date

[redacted]

Laboratorios del Dr. ESTEVE, S.A.U.

[redacted] [redacted]

[redacted] Date

[redacted]

Premier Research

[redacted] [redacted]

[redacted] Date

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Premier Research

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[redacted] Date

[redacted]

Premier Research

2. SYNOPSIS

PRODUCT NAME/NUMBER	CO-CRYSTAL E-58425 (racemic tramadol hydrochloride and celecoxib)
PROTOCOL NUMBER	ESTEVE-SUSA-301
IND NUMBER	128177
DEVELOPMENT PHASE	3
PROTOCOL TITLE	A Randomized, Double-blind, Active- (Tramadol and Celecoxib) and Placebo-controlled, Parallel-groups, Phase III Clinical Trial to Establish the Efficacy of Co-Crystal E 58425 for the Management of Moderate to Severe Post-surgical Pain after Bunionectomy
INDICATION	Moderate to severe post-surgical pain after bunionectomy
OBJECTIVES	Primary: • To establish the analgesic efficacy of co-crystal E-58425 compared to tramadol and to celecoxib for the management of moderate to severe post-operative pain for 48 hours after bunionectomy by using assessments of pain intensity Secondary: • To assess the analgesic efficacy of co-crystal E-58425 compared to tramadol and to celecoxib for the management of moderate to severe post-operative pain at various time points after bunionectomy by using assessments of pain intensity • To assess the analgesic efficacy of co-crystal E-58425 by means of responder rates, use of rescue medication, time to onset of analgesia, time to perceptible and meaningful pain relief, time to onset of pain intensity decrease, peak pain relief and time to peak pain relief, and the subjects' overall assessment of the study medication • To assess the absolute analgesic efficacy of co-crystal E-58425 compared to placebo for the treatment of moderate to severe post-operative pain for 48 hours at various time points after bunionectomy by using assessments of pain intensity • To assess the safety and tolerability of the co-crystal E-58425
STUDY DESIGN	This is a Phase 3, randomized, double-blind, active- and placebo-controlled, parallel-group, multicenter clinical trial with co-crystal E-58425 compared to tramadol, to celecoxib, and to placebo. Eligible subjects will complete all screening procedures within 28 days before the surgery. At Screening, subjects will provide written informed consent to participate in the study before any protocol specified procedures or assessments are conducted. Subjects will be admitted to the study center on the morning of the scheduled surgery (Day -1), will remain at the study center until post-operative Day 3 (a total of 3 nights at the study center), and will return for the Follow-up Visit, which will occur 5 to 9 days after surgery. On Day -1, regional anesthesia will be established using a popliteal sciatic nerve block (PSB) after which subjects will undergo primary, unilateral, first metatarsal osteotomy with internal fixation with no additional collateral procedure. The regional anesthesia will be continued postoperatively via a continuous anesthetic infusion. Subjects may receive supplemental analgesia with ketorolac 30 mg intravenously during the continuous infusion period and up until 1:00 A.M to help control breakthrough pain if the regional anesthetic infusion appears to be ineffective in the investigator's opinion up until 1:00 A.M. If the regional anesthetic infusion and supplemental analgesia do not effectively control the subject's postoperative pain prior to the 3:00 A.M. anesthetic infusion discontinuation time, the subject will not be eligible to be considered for the study. On Day 1, after regional anesthetic infusion is discontinued between 3:00 and 4:00 A.M, study staff will contact interactive response technology (IRT) system to obtain the moderate and severe pain box numbers for the subject and will retrieve the study medication boxes from stock, 1 for moderate pain and 1 for severe pain. The subject will be instructed to notify a member of the study staff and request treatment when he or she experiences a level of pain that requires medication. When the subject

requests pain medication, they will be asked to rate their pain intensity (PI) using the Numerical Pain Rating Scale (NPRS) assessment, a scale marked from zero to 10 on which subjects circle a single number to indicate their current pain level, with zero representing "No Pain" and 10 representing "Worst Possible Pain."

Subjects with a score ≥5 and ≤9 on the 0-10 NPRS will be randomized into the study and stratified by Baseline pain score (moderate [NPRS 5-6], severe [7-9]) using IRT and the appropriate pain level box will be used. Subjects will be randomly assigned in a ratio of 2:2:2:1 to 1 of 4 treatment groups, respectively:

			TOTAL DAILY DOSE	
		Posology	**Tramadol**	**Celecoxib**
ARM-1	Co-crystal E-58425	200 mg bid	**176 mg**	**224 mg**
ARM-2	Tramadol	50 mg qid	**200 mg**	0
ARM-3	Celecoxib	100 mg bid	0	**200 mg**
ARM-4	Placebo	0 mg qid	0	0

bid = twice daily (every 12 hours); qid = four times daily (every 6 hours)

Subjects with a NPRS score <5 will be asked if they can wait for treatment. If they cannot, they will be dropped from the study and treated according to the standard of care. If they agree to wait, they will be requested to notify a member of the study staff when their pain intensity has increased; NPRS will be readministered at that time. If the subject's pain intensity ratings do not meet the minimum entry criteria within 8 hours of discontinuation of the regional anesthesia, or if they have a PI >9, subjects will not be eligible for randomization and will receive routine postoperative care at the investigator's discretion.

The NPRS pain intensity assessments made just before randomization will serve as the Baseline PI to which all subsequent PI assessments will be compared. Time 0 will be defined as the time of the first dose of study medication. Pain intensity (NPRS) and pain relief (5-point categorical scale) assessments will be recorded in the subject diary at scheduled times during the 48-hour period after Time 0 (15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 42, 46, and 48 hours) and immediately before each use of rescue medication. During the night, subject will be wakened to administer the study medication. Pain assessments will be performed during the night only if the subject is awake. Time to perceptible and meaningful pain relief will be evaluated using the 2 stopwatch method. Pain intensity and pain relief assessments will also be recorded before premature study termination. Subjects will complete a patient's global evaluation of the study medication at the end of the Double-blind Treatment Period (Day 3) before discharge from the study center.

Intravenous (IV) acetaminophen 1 g will be supplied to the subject by the study staff every 4 to 6 hours as needed as rescue medication after treatment with the study medication has been initiated (ie, the double-blind phase) up to a total of 4 g per 24 hours. If subjects are unable to tolerate IV acetaminophen or if there is insufficient pain relief, then oxycodone hydrochloride 5 mg Immediate Release (IR) tablets will be allowed every 4 to 6 hours if needed, up to a total of 30 mg/24 hours.

After randomization, subjects will be encouraged to wait for at least 1 hour after the first dose of study medication before receiving rescue medication to allow time for the study medication to exert its pharmacologic effect.

After randomization, subjects whose pain cannot be adequately managed by a combination of study medication and rescue medication, or who develop unacceptable side effects during the study will be discontinued from study medication or from further study participation. Their pain will be managed conventionally at the investigator's discretion. All end-of-study assessments should be performed for subjects who discontinue from the study, if possible. Pain measurements affected by use of rescue medication will be replaced with pre-rescue pain measurements.

<table>
<tr><td></td><td>Before discharge from the study center on Day 3, study personnel will dispense a prescription for pain medication (if not already dispensed) and an outpatient subject diary in which subjects will record concomitant medications taken and adverse events (AEs) experienced after discharge. Subjects will also be instructed to return the outpatient subject diary to study personnel at the Follow-up Visit.</td></tr>
<tr><td>PLANNED NUMBER OF SUBJECTS</td><td>The planned total number of subjects to be randomized into the study is 630, divided into the treatment groups as follows:<table><tr><th>Treatment group</th><th>Number of subjects</th></tr><tr><td>Co-crystal E-58425</td><td>180</td></tr><tr><td>Tramadol</td><td>180</td></tr><tr><td>Celecoxib</td><td>180</td></tr><tr><td>Placebo</td><td>90</td></tr></table>It is anticipated that this will provide a sample size of at least 142 subjects per group (71 for the placebo group) in the Per Protocol Analysis Set.</td></tr>
<tr><td>STUDY ENTRY CRITERIA</td><td>Inclusion criteria:
Subject must have signed consent before study entry.
Subject must be at least 18 years old, scheduled to undergo primary unilateral first metatarsal osteotomy with internal fixation with no additional collateral procedure.
Male and female subjects are eligible. If female, subject must be either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing 1 of the following effective methods of birth control:
Hormonal methods such as oral, implantable, injectable, vaginal ring, or transdermal contraceptives.
Total abstinence from sexual intercourse since the last menses before study medication administration.
Intrauterine device
Double-barrier method (condoms, sponge, or diaphragm with spermicidal jellies or cream).
Women must use effective methods of birth control from Screening until 4 weeks after the last administration.
If female and of childbearing potential, subject must be non-lactating and non-pregnant (has negative serum pregnancy test results at Screening and negative urine test on the day of surgery prior to surgery).
Subject must have a body weight of 45 kg or more and a body mass index (BMI) of 40 kg/m^2 or less.
Subject must have a qualifying pain score of $\geq$5 and $\leq$9 on the 0-10 NPRS at rest as a result of turning off the popliteal sciatic block for bunionectomy to be eligible for randomization.
Subject must be in good physical health in the investigator’s judgment.
Subject must be sufficiently alert to understand and communicate intelligibly with the study observer.
Exclusion criteria:
Subject’s Baseline pain is <5 or >9 on a 0-10 NPRS.
Subject received any analgesic medication other than short-acting pre-operative or intra-operative anesthetic agents before the end of bunionectomy surgical procedure. Subjects who received any analgesic medication immediately after the bunionectomy surgical procedure was completed and before study medication is administered will also be excluded, with the</td></tr>
</table>

	exception of ketorolac 30 mg intravenously as supplemental analgesia during the continuous infusion period and up until 1:00 A.M. 3. Subject has a history of seizures or alcohol abuse (eg, drinks >4 units of alcohol per day, a unit being equal to 8 oz. beer, 3 oz. wine, 1 oz. spirits) within the past 5 years, has a history of prescription/illicit drug abuse within 6 months before dosing with study medication, or has positive results on the urine drug screen or alcohol breath test indicative of illicit drug or alcohol abuse. 4. Subject has a history of or positive test results for human immunodeficiency virus or hepatitis B or C. 5. Subject has an active malignancy of any type, or has been diagnosed with cancer within 5 years before Screening (excluding successfully treated squamous or basal cell carcinoma of the skin). 6. Subject is currently receiving anticoagulants (eg, heparin or warfarin) or antiplatelets (except aspirin ≤325 mg/day). 7. Subject has received a course of systemic (either oral or parenteral) or intra-articular corticosteroids within 3 months before Screening (inhaled nasal steroids and topical corticosteroids are allowed). 8. Subject has any ongoing condition, other than one associated with the current primary, unilateral, first metatarsal bunionectomy, that, in the investigator's opinion, could generate levels of pain sufficient to confound assessments of post-operative pain (eg, severe osteoarthritis of the target joint or extremity, fibromyalgia, rheumatoid arthritis, moderate to severe headache, diabetic foot pain or neuropathy). 9. Subject has been receiving or has received chronic (defined as daily use for >2 weeks) opioid (oral codeine, dextromoramide, dihydrocodeine, oxycodone, or morphine-like anti-tussive) therapy defined as >15 morphine equivalents units per day for more than 3 out of 7 days per week over a 1-month period within 12 months of surgery, or has been treated chronically with opioid analgesic (buprenorphine, nalbuphine, or pentazocine) or NSAIDs within 30 days before Screening. 10. Subject received a long-acting Non-Steroidal Anti-Inflammatory Drug (NSAID) within 4 days before initiation of study medication (except aspirin ≤325 mg/day), or a short-acting NSAID within 1 day, with the exception of ketorolac 30 mg intravenously as supplemental analgesia during the continuous infusion period. 11. Subject is under long-term treatment with opioid agonist-antagonists. 12. Subject has used drugs with enzyme-inducing properties, such as rifampicin and St. John's Wort, or any drug known to be a strong inhibitor or inducer of CYP3A4, CYP2C9, or CYP2D6 within 3 weeks before surgery. 13. Subject is pregnant or lactating. 14. Subject had any complication during primary bunionectomy surgery. 15. Subject has received monoamine oxidase inhibitors, tricyclic antidepressants, neuroleptics, or other drugs that reduce the seizure threshold within 4 weeks of study entry. 16. Subject has a history or evidence of a clinically significant (in the investigator's opinion) gastrointestinal (GI) event within 6 months before Screening or has any history of peptic or gastric ulcers or GI bleeding. 17. Subject has clinically significant renal or hepatic disease, as indicated by clinical laboratory assessment (results ≥3 times the upper limit of normal for any liver function test, including aspartate aminotransferase, alanine aminotransferase, bilirubin, and lactate dehydrogenase, or creatinine ≥1.5 times the upper limit of normal). Laboratory tests may be repeated once at Screening to rule out laboratory error. 18. Subject has any clinically significant laboratory or 12-lead electrocardiogram (ECG) finding at Screening that, in the opinion of the investigator, contraindicates study participation (eg, QTc >450 msec [male] or >470 msec [female]). 19. Subject has a known history of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, opioids, or any NSAIDs; history of NSAID-induced bronchospasm (subjects with the triad of asthma, nasal polyps, and chronic rhinitis are at greater risk for

	bronchospasm and should be considered carefully) or to the ingredients of the study medication, or any other drugs used in the study, including anesthetics and antibiotics that may be required on the day of surgery. 20. Subject has received anti-depressive medication with serotonin–norepinephrine reuptake inhibitors (SNRIs; milnaciprin, duloxetine, venlafaxine), diet pills (including fenfluramine and phentermine) or methylphenidate (Ritalin®), or other similar medications for ADHD within 4 weeks of study entry. Subjects receiving selective serotonin reuptake inhibitors (SSRIs) may be included provided they have been on a stable dose for 60 days prior to study participation and plan to remain on that dose throughout the study. 21. Subject is, in the investigator's judgment, at risk in terms of precautions, warnings, and contraindications in the package insert for Ultram® (tramadol hydrochloride) or Celebrex® (celecoxib). Specifically, in situations where participation is contraindicated per the package insert the subject should be excluded. However, in situations where medications or medical conditions listed in the precautions and warnings are present the physician should evaluate the subject's history, physical examination results, laboratory analysis, and ECG carefully and use his/her discretion as to whether the subject is suitable for participation. 22. Subject has a known coagulation disorder. 23. Subject has history of or current medical, surgical, post-surgical, or psychiatric condition that would confound interpretation of safety, tolerability, or efficacy, (eg, uncontrolled diabetes mellitus, uncontrolled hypertension, hemodynamic instability, or respiratory insufficiency, cancer or palliative care). 24. Subject received an experimental drug or used an experimental medical device within 30 days prior to Screening or has previously participated in this trial. 25. Subject is unable to comply with the requirements of the study or, in the investigator's opinion, should not participate in the study. 26. Subject is undergoing concomitant surgical procedure(s) in addition to primary bunionectomy.
INVESTIGATIONAL PRODUCT	Name: Co-crystal E-58425 (tramadol 88 mg/celecoxib 112 mg) Dose, route, frequency: over encapsulated 200-mg immediate-release oral tablet; every 12 hours
REFERENCE PRODUCT(S)	Name: Ultram® (tramadol) Dose, route, frequency: 50-mg immediate-release oral tablet (manufactured by Janssen Ortho; LLC, Gurabo, Puerto Rico 00778) every 6 hours, over encapsulated by ESTEVE Name: Celebrex® (celecoxib) Dose, route, frequency: 100-mg immediate-release oral capsules (Marketing Authorization Holder GD Searle) every 12 hours, over encapsulated by ESTEVE Name: Placebo Dose, route, frequency: matching over encapsulated capsules
RESCUE MEDICATION:	Acetaminophen 1 g IV every 4 to 6 hours, up to 4 g/24 hours, or oxycodone hydrochloride 5 mg Immediate Release (IR) tablet every 4 to 6 hours if needed, up to a total of 30 mg/24 hours.
TREATMENT REGIMENS	After the entry criteria are met, subjects will be randomly assigned in a ratio of 2:2:2:1 to 1 of the 4 treatment groups (Co-crystal E-58425, tramadol, celecoxib, or placebo). After Randomization, subjects will be encouraged to wait for at least 1 hour after the first dose of study medication before receiving rescue medication to allow time for the study medication to exert its pharmacologic effect. Subjects will take study medication 4 times daily, in a blinded manner according to their random treatment arm assignment. All study medications will be over encapsulated to maintain the blind. Study medication will be administered in a predefined manner to ensure adequate blinding and appropriate dosing regimens for active medication and placebo. Study medication will be administered for up to 48 hours after the first dose of study medication.
PLANNED STUDY CENTERS	Approximately 5 to 6 study centers in the United States.

CRITERIA FOR EVALUATION	Efficacy endpoints: Primary efficacy endpoint: The primary efficacy variable will be the Pain Intensity (PI) measured by Numerical Pain Rating Scale (NPRS). The primary analysis endpoint will be the Sum of Pain Intensity Differences (SPID) from 0-48 hours defined as follows. PIDt = Pain Intensity Differences = PIt - PI0 where PI0 = Pain Intensity (PI) at time t = 0h on NPRS PIt = Pain Intensity on NPRS at specific time points The NPRS summed pain intensity difference (SPID) is calculated as a time-weighted sum of the pain intensity difference values at each follow-up time point (difference between the starting pain intensity and the pain intensity at the given assessment time) multiplied by the amount of time (in hours) since the prior assessment. Negative values of PID will correspond to an amelioration of pain, while positive values will correspond to a recrudescence of pain. Secondary efficacy endpoints Secondary efficacy parameters will be the following: • SPID (0-4 hours), SPID (0-6 hours), SPID (0-12 hours), and SPID (0-24 hours) as defined in previous section • PIDt at each time point • Pain intensity at each time point • Pain Relief (PARt) = pain relief at each time point • Total Pain Relief (TOTPAR) for time intervals (t=15 minutes – t=4 hours), (t=15 minutes – t=6 hours), (t=15 minutes – t=12 hours), (t=15 minutes – t=24 hours), and (t=15 minutes – t=48 hours) o TOTPAR is the time-weighted sum of the Pain Relief (PAR) at each time point • Peak pain relief and time to peak pain relief • Stop watches: Time to onset of analgesia, time to perceptible pain relief and time to meaningful pain relief • Time to onset of pain intensity decrease • Overall assessment of study medication • Rescue medication: o Proportion of subjects who take of at least 1 dose of rescue medication up to 4, up to 6, up to 12, up to 24, and up to 48 hours after study medication administration; total amount of rescue medication for the same time intervals o Time to first use of rescue medication. o To avoid interference in efficacy measures (pain intensity assessments, PARt, PIDt, and SPID calculations) at scheduled time points because of use of rescue medication, additional pain assessments will be made just before each administration of rescue medication, asking subjects to report their pain intensity at the current time. These data will be carried over for the duration of effect of the rescue medication taken.

	• Proportions of Responders, defined as follows:
	  ○ Subject who reaches a 50% reduction in pain intensity from baseline sustained until the end of the 48-hour observation period;
	  ○ Subject who reaches a 30% reduction in pain intensity from baseline sustained until the end of the 48-hour observation period;
	  ○ Subject who reaches a pain intensity below 4 on NPRS sustained until the end of the 48-hour observation period;
	  ○ Subject who reaches a 50% reduction in pain intensity as compared to baseline and a pain intensity below 4 on NPRS sustained until the end of the 48-hour observation period;
	  ○ Subject who reaches a 30% reduction in pain intensity as compared to baseline and a pain intensity below 4 on NPRS sustained until the end of the 48-hour observation period.
	• Time-to-response will also be analyzed as time-to-event data, using the first time at which each response criterion was reached by each subject.
	Cumulative proportion of responders analysis plot.

	<u>Safety endpoints:</u> • Clinical laboratory test results will be marked whether the result is below, within, or above the respective reference range and whether it is clinically significant. The number of such values will be counted and tabulated. • For electrocardiogram (ECG) and vital signs parameters, the values that are below, within, or above a defined normal range and the values that are clinically significant may be counted and tabulated by the number and percentage of subjects with such values. • Adverse events will be tabulated by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). • An overview of AEs will be prepared showing the number of AEs and the number of subjects with any AEs, treatment-emergent AEs, treatment-related AEs, serious AEs (SAEs), treatment-related SAEs, severity of AEs, AEs leading to withdrawal, and AEs of special interest. • Various summary tables showing the number of subjects with at least 1 AE and event count by SOC (System Organ Class) and PT (Preferred Term) will be prepared. Additional safety data will be tabulated for each treatment group.
STATISTICAL METHODS	<u>Analysis Sets</u> The primary statistical analysis will be based on the Full Analysis Set (FAS), defined as all randomized subjects. The Per-Protocol Analysis Set (PPAS), defined as all subjects with no major protocol deviations, will be used for sensitivity analyses. Safety analyses will use the Safety Analysis Set (SAS), defined as all subjects who receive at least 1 dose of study medication. The Completers Analysis Set (CAS) will be a subset of the PPAS that includes all subjects who have pain assessments up to 48 hours after first dose of study medication. <u>Subject Characteristics and Disposition</u> Subject characteristics and disposition data will be presented using descriptive statistics only. <u>Efficacy Analyses</u> The primary efficacy analysis will compare treatment groups for the SPID from Time 0 to 48 hours. This will be tested using an analysis of covariance model adjusting for center and baseline pain intensity. To account for the use of rescue medication, any pain measurements taken during a period of time in which rescue medication is active will be replaced by the last pain measurement before rescue medication was taken. Additional sensitivity analyses assessing the impact of rescue use and missing data due to study discontinuation will be performed. Efficacy analyses will be also performed by subgroups defined by moderate or severe baseline pain. Other subgroup analyses may also be done and will be specified in the statistical analysis plan (SAP).

	Primary efficacy analyses will be based on the FAS. The PPAS and the CAS will be used for sensitivity analysis for some efficacy endpoints. Safety analyses will be based on the safety set. All subjects who signed informed consent will be considered study participants. Secondary efficacy outcome measures will be analyzed using similar methods. All statistical methods will be described in full in the SAP that will be prepared before the study is unblinded. <u>Safety Analyses</u> Data listings will be provided for protocol-specified safety data. The number and percentage of subjects with AEs will be displayed for each treatment group by SOC and PT. Summaries of AEs by severity and relationship to study medication will also be provided. Serious adverse events, AEs resulting in discontinuation of study medication and AEs of special interest will be summarized separately in a similar manner. Comparisons between treatment groups for incidence of AEs, AEs of special interest, and significant AEs may be performed. For clinical laboratory, ECG, and/or vital sign variables, the values that are below, within, or above a defined normal range and the values that are clinically significant will be counted and tabulated by the number and percentage of subjects with such values may be performed if required. Any comparisons of safety analyses will be described in detail in the SAP.
SAMPLE SIZE DETERMINATION	The primary outcome measure is SPID (NPRS) up to 48 hours post-dose (SPID-48h). The study is powered to detect differences between the co-crystal E-58425 and each of the 2 active control groups if they exist. Since co-crystal E-58425 must show superiority over both tramadol and celecoxib, the power is set at 90%, which will maintain an overall study power at 81%. To detect a difference of 48 with a Standard Deviation (SD) of 124 at an alpha level of 0.05 and a power of 90% requires 142 subjects per group (71 for the placebo group since a 2:2:2:1 randomization scheme is being used). It is assumed that the comparison versus placebo will be adequately powered since the difference versus placebo will be larger than that for the active comparators. Allowing for approximately a 20% rate of non-evaluable subjects (ie, those not included in the PPAS), a sample size of 180 subjects per group (90 for the placebo group) will be required to achieve 81% overall power and therefore a total of 630 subjects will be randomized. A blinded sample size calculation will be repeated during a blinded interim analysis conducted when approximately 50% of subjects have completed the study using the actual SD of the SPID-48 hours calculated on pooled data. The sample size will not be reduced as a result of this re-estimation. Details will be presented in the SAP.
STUDY AND TREATMENT DURATION	The overall study duration is expected to be 10 months (6 months of active enrollment and 4 months of data management, statistical analyses and reporting). The estimated duration of the study for each subject is approximately 6 weeks, which includes up to a 4-week Screening Period, a 3-day treatment period (72 hours of confinement with 48 hours of treatment), and a post-treatment follow-up visit approximately 1 week after surgery. The maximum study duration for each subject is approximately 40 days. The maximum treatment duration for each subject is 2 days.

3. TABLE OF CONTENTS

3.1. LIST OF TABLES

4. LIST OF ABBREVIATIONS

AE	adverse event
API	active pharmaceutical ingredient
ASA	American Society of Anesthesiologists
BID	twice daily
BMI	body mass index
BOCF	baseline-observation-carried-forward
CAS	Completers Analysis Set
CFR	Code of Federal Regulations
COX	cyclooxygenase
CRA	Clinical research associate
CS	clinically significant
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ESTEVE	Laboratorios del Dr. ESTEVE, S. A. U.
FAS	full analysis set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS	interactive web response system
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
LOCF	last-observation-carried-forward
MedDRA	Medical Dictionary for Regulatory Activities
MEQ	morphine equivalents units
NCS	not clinically significant
NPRS	Numerical pain rating scale
NPRS PID	NPRS pain intensity difference
NPRS SPID	NPRS summed pain intensity difference
NPRS SPID-4	NPRS SPID over 0 to 4 hours
NPRS SPID-6	NPRS SPID over 0 to 6 hours

NPRS SPID-12	NPRS SPID over 0 to 12 hours
NPRS SPID-24	NPRS SPID over 0 to 24 hours
NPRS SPID-48	NPRS SPID over 0 to 48 hours
NSAID	nonsteroidal anti-inflammatory drug
PARt	pain relief at each time point
PI	pain intensity
PID	paint intensity difference
PK	pharmacokinetic
PP	per-protocol
PPAS	Per-protocol Analysis Set
Premier Research	Premier Research Group Limited
PSB	popliteal sciatic nerve block
PT	preferred term
QID	4 times daily
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SOC	system organ class
SOP	Standard Operating Procedure
SPID	sum of pain intensity differences
TEAE	treatment-emergent AE
TOTPAR	total pain relief
Tramadol HCl	Tramadol hydrochloride
US	United States

5. INTRODUCTION

5.1. Background and Rationale

[redacted]

[redacted]

5.3. Summary of Potential Risks and Benefits

[redacted]

6. OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to establish the analgesic efficacy of co-crystal E-58425 compared to tramadol and to celecoxib for the management of moderate to severe post-operative pain for 48 hours after bunionectomy by using assessments of pain intensity.

6.2. Secondary Objectives

Secondary objectives are as follow:

- To assess the analgesic efficacy of co-crystal E-58425 compared to tramadol and to celecoxib for the management of moderate to severe post-operative pain at various time points after bunionectomy by using assessments of pain intensity
- To assess the analgesic efficacy of co-crystal E-58425 by means of responder rates, use of rescue medication, time to onset of analgesia, time to perceptible and meaningful pain relief, time to onset of pain intensity decrease, peak pain relief and time to peak pain relief, and the subjects' overall assessment of the study medication
- To assess the absolute analgesic efficacy of co-crystal E-58425 compared to placebo for the treatment of moderate to severe post-operative pain for 48 hours at various time points after bunionectomy by using assessments of pain intensity
- To assess the safety and tolerability of the co-crystal E-58425

7. STUDY DESIGN

7.1. Overall Study Design and Plan

This phase 3, randomized, double-blind, active- and placebo-controlled, parallel group, multicenter clinical trial will compare co-crystal E-58425 to tramadol, to celecoxib, and to placebo. Approximately 630 male and female subjects will be randomized. Subjects must be at least 18 years of age and scheduled to undergo primary unilateral first metatarsal osteotomy with internal fixation with no additional collateral procedure. Efforts will be made to enroll subjects ≥65 years old.

Eligible subjects will complete all screening procedures within 28 days before the surgery. At Screening, subjects will provide written informed consent to participate in the study before any protocol specified procedures or assessments are conducted.

Subjects will be admitted to the study center on the morning of the scheduled surgery (Day -1), will remain at the study center until postoperative Day 3 (a total of 3 nights at the study center), and will return for the Follow up Visit, which occurs 5 to 9 days after surgery.

On Day -1, regional anesthesia will be established using a popliteal sciatic nerve block (PSB) after which subjects will undergo primary, unilateral, first metatarsal osteotomy with internal fixation with no additional collateral procedure. The regional anesthesia will be continued postoperatively via a continuous anesthetic infusion. Subjects may receive supplemental analgesia with ketorolac 30 mg intravenously during the continuous infusion period and up until 1:00 A.M. to help control breakthrough pain if the regional anesthetic infusion appears to be ineffective in the investigator's opinion up until 1:00 A.M. If the regional anesthetic infusion and supplemental analgesia do not effectively control the subject's postoperative pain prior to the 3:00 A.M. anesthetic infusion discontinuation time, the subject will not be eligible to be considered for the study.

On Day 1, after regional anesthetic infusion is discontinued between 3:00 and 4:00 A.M., study staff will contact interactive response technology (IRT) system to obtain the moderate and severe pain box numbers for the subject and will retrieve the study medication boxes from stock, 1 for moderate pain and 1 for severe pain. The subject will be instructed to notify a member of the study staff and request treatment when he or she experiences a level of pain that requires medication. When the subject requests pain medication, they will be asked to rate their pain intensity (PI) using the Numerical Pain Rating Scale (NPRS) assessment, a scale marked from zero to 10 on which subjects circle a single number to indicate their current pain level, with zero representing "No Pain" and 10 representing "Worst Possible Pain."

Subjects with a score ≥5 and ≤9 on the 0-10 NPRS will be randomized into the study and stratified by Baseline pain score (moderate [NPRS 5-6], severe [7-9] using interactive response technology (IRT) and the appropriate pain level box will be used. Subjects will be randomly assigned in a ratio of 2:2:2:1 to 1 of the 4 treatment groups, respectively: Co-crystal R-58425 200 mg twice daily (bid; every 12 hours), tramadol 50 mg 4 times daily (qid; every 6 hours), celecoxib 100 mg bid, or placebo qid, respectively (see Table 1).

Subjects with a NPRS score <5 will be asked if they can wait for treatment. If they cannot, they will be dropped from the study and treated according to the standard of care. If they agree to wait, they will be requested to notify a member of the study staff when their pain intensity has increased; NPRS will be readministered at that time. If the subject's pain intensity ratings do not meet the minimum entry criteria within 8 hours of discontinuation of the regional anesthesia, or if they have a PI >9, subjects will not be eligible for randomization and will receive routine postoperative care at the investigator's discretion.

The NPRS pain intensity assessments made just before randomization will serve as the Baseline PI to which all subsequent PI assessments will be compared. Time 0 will be defined as the time of the first dose of study medication. Pain intensity (NPRS) and pain relief (5-point categorical scale) assessments will be recorded in the subject diary at scheduled times during the 48 hour period after Time 0 (15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 42, 46, and 48 hours) and immediately before each use of rescue medication. During the night, subject will be wakened to administer the study medication. Pain assessments will be performed during the night only if the subject is awake. Time to perceptible and meaningful pain relief will be evaluated using the 2 stopwatch method starting at Time 0. Pain intensity and pain relief assessments will also be recorded before premature study termination. Subjects will complete a patient's global evaluation of the study medication at the end of the Double-blind Treatment Period (Day 3) before discharge from the study center.

After randomization, subjects will be encouraged to wait for at least 1 hour after the first dose of study medication before receiving first rescue medication to allow time for the study medication to exert its pharmacologic effect. Subjects may be given acetaminophen 1 g IV every 4 to 6 hours, up to 4 g/24 hours, for pain as rescue medication after the anesthetic infusion is discontinued and treatment with study medication has been initiated. If subjects are unable to tolerate IV acetaminophen or have insufficient pain relief with acetaminophen 1 g IV every 4 to 6 hours, then oxycodone hydrochloride 5 mg Immediate Release (IR) tablets can be administered every 4 to 6 hours as needed for pain, up to a total of 30 mg/24 hours.

Subjects whose pain cannot be adequately managed by a combination of study medication and rescue medication, or who develop unacceptable side effects during the study, will be discontinued from study medication or from further study participation. Their pain will be managed conventionally at the investigator's discretion. All end-of-study assessments should be performed for subjects who discontinue from the study, if possible. Side effects will be managed with pharmacologic and non-pharmacologic methods at the investigator's discretion.

Before discharge from the study center on Day 3, study personnel will dispense a prescription for pain medication (if not already dispensed) and an outpatient subject diary. Subjects will be instructed to record concomitant

medications taken and adverse events (AEs) experienced after discharge in their outpatient subject diary. Subjects will also be instructed to return the outpatient subject diary to study personnel at the Follow-up Visit.

7.2. Discussion of Study Design

The postsurgical bunionectomy pain model was selected for this study as the acute pain model based on its record of assay sensitivity and reproducibility in evaluating putative analgesic agents.[2,3] Studies have demonstrated that subjects given nonsteroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenases (COX)-2 inhibitors for the treatment of pain have had clinically significant reductions in their pain scores and statistically significant differences from placebo.[4,5] This study includes a placebo control group to evaluate whether active treatment is superior to placebo for the efficacy assessments. The pain intensity NPRS to be used in this study is a widely accepted tool to measure a subject's perception of pain.

7.3. Study Center(s)

The study will take place at approximately 5 to 6 centers in the United States. Each center is anticipated to screen a sufficient number of subjects to be able to randomize approximately 630 subjects in total. A study center with a high recruitment rate may be allowed to recruit more subjects if other centers have slow enrollment.

8. SUBJECT POPULATION

8.1. Selection of Study Population

A screening log of potential study candidates and an enrollment log of randomized subjects must be maintained at each study center.

8.2. Study Entry Criteria

8.2.1 Inclusion Criteria

A subject will be eligible for study participation if the subject meets all of the following criteria:

1. Subject must have signed consent before study entry.
2. Subject must be at least 18 years old, scheduled to undergo primary unilateral first metatarsal osteotomy with internal fixation with no additional collateral procedure.
3. Male and female subjects are eligible. If female, subject must be either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing 1 of the following effective methods of birth control :
    - Hormonal methods such as oral, implantable, injectable, vaginal ring, or transdermal contraceptives
    - Total abstinence from sexual intercourse since the last menses before study medication administration
    - Intrauterine device
    - Double-barrier method (condoms, sponge, or diaphragm with spermicidal jellies or cream)

    Women must use effective methods of birth control from Screening until 4 weeks after the last administration.
4. If female and of childbearing potential, subject must be non-lactating and non-pregnant (has negative serum pregnancy test results at Screening and negative urine test on the day of surgery prior to surgery).
5. Subject must have a body weight of 45 kg or more and a body mass index (BMI) of 40 kg/m^2 or less.

6. Subject must have a qualifying pain score of ≥5 and ≤9 on the 0-10 NPRS at rest as a result of turning off the popliteal sciatic block for bunionectomy to be eligible for randomization.
7. Subject must be in good physical health in the investigator's judgment.
8. Subject must be sufficiently alert to understand and communicate intelligibly with the study observer.

8.2.2 Exclusion Criteria

A subject will be excluded from the study if the subject meets any of the following criteria:

1. Subject's Baseline pain is <5 or >9 on a 0-10 NPRS.
2. Subject received any analgesic medication other than short-acting pre-operative or intra-operative anesthetic agents before the end of bunionectomy surgical procedure. Subjects who received any analgesic medication immediately after the bunionectomy surgical procedure was completed and before study medication is administered will also be excluded, with the exception of ketorolac 30 mg intravenously as supplemental analgesia during the continuous infusion period and up until 1:00 A.M.
3. Subject has a history of seizures or alcohol abuse (eg, drinks >4 units of alcohol per day, a unit being equal to 8 oz. beer, 3 oz. wine, 1 oz. spirits) within the past 5 years, has a history of prescription/illicit drug abuse within 6 months before dosing with study medication, or has positive results on the urine drug screen or alcohol breath test indicative of illicit drug or alcohol abuse.
4. Subject has a history of or positive test results for human immunodeficiency virus or hepatitis B or C.
5. Subject has an active malignancy of any type, or has been diagnosed with cancer within 5 years before Screening (excluding successfully treated squamous or basal cell carcinoma of the skin).
6. Subject is currently receiving anticoagulants (eg, heparin or warfarin) or antiplatelets (except aspirin ≤325 mg/day).
7. Subject has received a course of systemic (either oral or parenteral) or intra-articular corticosteroids within 3 months before Screening (inhaled nasal steroids and topical corticosteroids are allowed).
8. Subject has any ongoing condition, other than one associated with the current primary, unilateral, first metatarsal bunionectomy, that, in the investigator's opinion, could generate levels of pain sufficient to confound assessments of post-operative pain (eg, severe osteoarthritis of the target joint or extremity, fibromyalgia, rheumatoid arthritis, moderate to severe headache, diabetic foot pain or neuropathy).
9. Subject has been receiving or has received chronic (defined as daily use for >2 weeks) opioid (oral codeine, dextromoramide, dihydrocodeine, oxycodone, or morphine-like anti-tussive) therapy defined as >15 morphine equivalents units per day for more than 3 out of 7 days per week over a 1-month period within 12 months of surgery, or has been treated chronically with opioid analgesic (buprenorphine, nalbuphine, or pentazocine) or Non-Steroidal Anti-Inflammatory Drug (NSAID)within 30 days before Screening.
10. Subject received a long-acting NSAID within 4 days before initiation of study medication (except aspirin ≤325 mg/day), or a short-acting NSAID within 1 day, with the exception of ketorolac 30 mg intravenously as supplemental analgesia during the continuous infusion period.
11. Subject is under long-term treatment with opioid agonist-antagonists.
12. Subject has used drugs with enzyme-inducing properties, such as rifampicin and St. John's Wort, or any drug known to be a strong inhibitor or inducer of CYP3A4, CYP2C9, or CYP2D6 within 3 weeks before surgery.
13. Subject is pregnant or lactating.
14. Subject had any complication during primary bunionectomy surgery.
15. Subject has received monoamine oxidase inhibitors, tricyclic antidepressants, neuroleptics, or other drugs that reduce the seizure threshold within 4 weeks of study entry.

16. Subject has a history or evidence of a clinically significant (in the investigator's opinion) gastrointestinal (GI) event within 6 months before Screening or has any history of peptic or gastric ulcers or GI bleeding.
17. Subject has clinically significant renal or hepatic disease, as indicated by clinical laboratory assessment (results ≥3 times the upper limit of normal for any liver function test, including aspartate aminotransferase, alanine aminotransferase, bilirubin, and lactate dehydrogenase, or creatinine ≥1.5 times the upper limit of normal). Laboratory tests may be repeated once at Screening to rule out laboratory error.
18. Subject has any clinically significant laboratory or 12-lead electrocardiogram (ECG) finding at Screening that, in the opinion of the investigator, contraindicates study participation (eg, QTc >450 msec [male] or >470 msec [female]).
19. Subject has a known history of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, opioids, or any NSAIDs; history of NSAID induced bronchospasm (subjects with the triad of asthma, nasal polyps, and chronic rhinitis are at greater risk for bronchospasm and should be considered carefully) or to the ingredients of the study medication, or any other drugs used in the study, including anesthetics and antibiotics that may be required on the day of surgery.
20. Subject has received anti-depressive medication with serotonin–norepinephrine reuptake inhibitors (SNRIs; milnaciprin, duloxetine, venlafaxine), diet pills (including fenfluramine and phentermine) or methylphenidate (Ritalin®), or other similar medications for ADHD within 4 weeks of study entry. Subjects receiving selective serotonin reuptake inhibitors (SSRIs) may be included provided they have been on a stable dose for 60 days prior to study participation and plan to remain on that dose throughout the study.
21. Subject is, in the investigator's judgment, at risk in terms of precautions, warnings, and contraindications in the package insert for Ultram® (tramadol hydrochloride) or Celebrex® (celecoxib). Specifically, in situations where participation is contraindicated per the package insert the subject should be excluded. However, in situations where medications or medical conditions listed in the precautions and warnings are present the physician should evaluate the subject's history, physical examination results, laboratory analysis, and ECG carefully and use his/her discretion as to whether the subject is suitable for participation.
22. Subject has a known coagulation disorder.
23. Subject has history of or current medical, surgical, post-surgical, or psychiatric condition that would confound interpretation of safety, tolerability, or efficacy, (eg, uncontrolled diabetes mellitus, uncontrolled hypertension, hemodynamic instability, or respiratory insufficiency, cancer or palliative care).
24. Subject received an experimental drug or used an experimental medical device within 30 days prior to Screening or has previously participated in this trial.
25. Subject is unable to comply with the requirements of the study or, in the investigator's opinion, should not participate in the study.
26. Subject is undergoing concomitant surgical procedure(s) in addition to primary bunionectomy.

8.3. Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the investigator to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation, unless the subject withdraws consent. Whenever possible and reasonable, when study medication is discontinued efforts will be made to collect all study assessments as scheduled up to the completion of the study, unless the subject withdraws consent.

Subject Replacement Criteria

Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, the sponsor will evaluate the need for developing replacement criteria.

Enrolled subjects withdrawn from the study may not reenter. The subject number for a withdrawn subject will not be reassigned to another subject.

9. TREATMENTS

9.1. Identification of Investigational Product(s)

Co-crystal E-58425 will be provided in the form of over encapsulated 100-mg oral tablets.

Co-crystal E-58425 tablets will be supplied as by ESTEVE (manufactured by Esteve, Martorelles, Barcelona, Spain).

Ultram (tramadol) will be supplied as 50-mg, immediate-release, oral tablets (manufactured by [redacted]), over encapsulated by ESTEVE.

Celebrex (celecoxib) 100-mg, immediate-release, oral capsules (Marketing Authorization Holder [redacted]), over encapsulated by ESTEVE.

Placebo will be provided in the form of over encapsulated 100-mg oral tablets. Placebo tablets will be supplied by ESTEVE (manufactured by Esteve, Martorelles, BARCELONA [SPAIN]). All study medications will be over encapsulated to match.

9.2. Labeling and Packaging

Labeling and packaging of Co-crystal E-58425 will be performed by [redacted]).

9.2.1 Labeling

Each container of study medication will be labeled with study specific information meeting all the applicable regulatory requirements.

Carton label text:

- Protocol Code
- Treatment number
- "For oral administration only"
- Quantity of bottles
- Directions for use

- Caution: "New Drug – Limited by Federal Law to Investigational Use" and "Keep out of the sight and reach of children"
- Storage instructions

Bottle label text:

- Protocol code
- Treatment number
- Bottle number
- "For oral administration only"
- Directions for use
- Package contents (quantity)
- Storage instructions
- Caution: "New Drug – Limited by Federal Law to Investigational Use" and "Keep out of the sight and reach of children"

9.2.2 Packaging

Study treatments will shipped in boxes to the centers, each holding 8 bottles, containing 1 capsule per bottle for Bottles 2, 4, 6 and 8 and 2 capsules per bottle per Bottles 1, 3, 5 and 7. Each bottle will be labeled, "Bottle 1-0h", "Bottle 2-6h", etc. All pills will be over-encapsulated, and will all look the same (all capsules will have the same organoleptic characteristics), to maintain blinding.

The boxes will have consecutive numbers and will be distributed per the randomization by IRT, stratified by Baseline pain score (moderate [NPRS 5-6] or severe [NPRS 7-9]).

9.3. Treatments Administered

Subjects will be randomly assigned in a ratio of 2:2:2:1 to 1 of 4 treatment groups as in Table 1. Study medication and/or placebo will be administered 4 times daily for a maximum of 2 days. Study medication will be administered with 8 ounces of water.

Table 1: Study Treatment Arms

			TOTAL DAILY DOSE	
		Posology	**Tramadol**	**Celecoxib**
ARM-1	Co-crystal E-58425	200 mg bid	176 mg	224 mg
ARM-2	Tramadol	50 mg qid	200 mg	0
ARM-3	Celecoxib	100 mg bid	0	200 mg
ARM-4	Placebo	0 mg qid	0	0

Abbreviations: bid = twice daily (every 12 hours); qid = four times daily (every 6 hours)

All subjects will be dosed every 6 hours, (ie, 4 times daily) as displayed in Table 2:

- Co-crystal: the total daily dose will be 400 mg (200 mg every 12 hours):
  400 mg of co-crystal corresponds to 176 mg of tramadol and 224 mg of celecoxib.
- Tramadol: the total daily dose will be 200 mg (50 mg every 6 hours)
- Celecoxib: the total daily dose will be 200 mg (100 mg every 12 hours)

9.4. Dispensing and Storage

The study medication supplied by ESTEVE is to be used exclusively in the clinical study according to the instructions of this protocol. The investigator is responsible for dispensing the study medication according to the dosage scheme and for ensuring proper storage of the study medication.

Until the study medication is dispensed to the subjects, it must be stored at 68°F-77°F (20°C-25°C). Store in accordance with controlled drug regulations, in a securely locked area that is not generally accessible. The key to the storage area is to be kept by the investigator or designee responsible for the IP. The store will be accessible only to those persons authorized by the investigator to dispense the study medication.

9.5. Method of Assigning Subjects to Treatment Groups

In this parallel-group randomized study, subjects who meet study entry criteria will be randomly assigned in a 2:2:2:1 ratio to co-crystal E-58425, tramadol, celecoxib, or placebo. The randomization schedule will be computer generated and will randomly allocate study medication to randomization numbers.

The randomization numbers will be assigned sequentially through central IRT as subjects are entered into the study. The randomization schedule will be stratified by center and baseline pain score (moderate [NPRS 5-6] or severe [NPRS 7-9]).[1]

The randomization schedule will be prepared by Premier Research before the start of the study. No one involved in the study performance will have access to the randomization schedule before official unblinding of treatment assignment. No subject will be randomized into this study more than once.

9.6. Blinding and Unblinding Treatment Assignment

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment.

Study personnel will endeavor to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

Unblinding should be discussed in advance with the medical monitor if possible. For emergency unblinding, study personnel will use the IRT. If the investigator is not able to discuss treatment unblinding in advance, then he or she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment.

The investigator or designee must record the date and reason for study discontinuation on the appropriate case report form (CRF) for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

9.7. Selection of Doses in the Study

The analgesic activity of the co-crystal E-58425 is expected to be superior to the activity predicted by the sum of the individual components.[1] This synergistic pharmacological activity of the co-crystal E-58425 would result from the recruitment of 4 relevant molecular mechanisms of action: μ-opioid receptor agonism, inhibition of the neuronal reuptake of norepinephrine and serotonin, and COX-2 inhibition. In the same way, the dissociation of the co-crystal E-58425 favors a concomitant action of tramadol and celecoxib, with potential implications for the onset, magnitude, duration and consistency of efficacy. On this basis, low doses of the co-crystal E-58425 could achieve a similar efficacy to that of the therapeutic doses of tramadol (eg, 200 mg).

The efficacy of the co-crystal E-58425 due to tramadol and celecoxib will be achieved with lower plasma levels of the current use of each.

9.8. Selection of Timing of Dose for Each Subject

Subjects will receive assigned treatment of study medication after reaching a minimum designated level of postoperative pain intensity. Study medication will be administered in a qid regimen for 48 hours after the first dose, with a maximum of 4 doses (active and/or placebo) in a 24-hour period. The timing of study medication dosing is based on the current dosage and administration recommendations for tramadol and for celecoxib. Table 2 describes treatment administration.

Table 2: Dosing Scheme

	DAY 2					DAY 3		
Treatment Group	**Dose 1 (0 h)**	**Dose 2 (6 h)**	**Dose 3 (12 h)**	**Dose 4 (18 h)**	**Dose 5 (24 h)**	**Dose 6 (30 h)**	**Dose 7 (36 h)**	**Dose 8 (42 h)**
Co-crystal E-58425	200 mg	P	200 mg	P	200 mg	P	200 mg	P
Tramadol	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Celecoxib	100 mg	P	100 mg	P	100 mg	P	100 mg	P
Placebo	P	P	P	P	P	P	P	P

Abbreviations: h = hour; P = placebo

9.9. Dose Adjustment Criteria

Dose adjustment is not allowed in this study.

The regional anesthesia will be continued postoperatively via a continuous anesthetic infusion. Subjects may receive supplemental analgesia with ketorolac 30 mg IV during the continuous infusion period until 1:00 A.M to help control breakthrough pain if the regional anesthetic infusion appears, in the investigator's opinion, to be ineffective. If the regional anesthetic infusion and supplemental analgesia do not effectively control the subject's postoperative pain prior to the 3:00 A.M. anesthetic infusion discontinuation time, the subject will not be eligible to be considered for the study.

9.10. Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the study medication including the date, quantity, batch or code number, and identification of subjects (subject number) who received the study medication. The investigator will not supply the study medication to any person

except those named as subinvestigators on the FDA 1572, designated staff, and subjects in this study. The investigator will not dispense the study medication from any centers other than those listed on the FDA 1572. Study medications may not be relabeled or reassigned for use by other subjects.

Upon completion of the study, unused supplies of the study medication will be returned to sponsor or destroyed as directed.

9.11. Treatment Compliance

All subjects will receive the study medication at the study center under the surveillance of appropriate study personnel. Study medication administration details will be recorded in the subject's CRF.

9.12. Concomitant Therapies

Treatment with the following medications and therapies before study entry (see Section 8.2) or during the study is not allowed:

- All medications (except hormonal contraceptives and vitamins) will be prohibited within 5 half-lives of the prohibited medication (or, if half-life is unknown, within 48 hours) before dosing with study medication until discharge from the study center on Day 3. Exceptions include study-designated rescue medications, anesthetics, antibiotics, and concomitant medication for chronic stable illness, which will be permitted according to the judgment of the investigator.
- Analgesic medication other than short-acting pre-operative or intra-operative anesthetic agents before the popliteal sciatic block for bunionectomy is removed, ie, before taking study medication, is prohibited. All analgesic medication taken immediately after the bunionectomy is completed and before study medication is administered is excluded, with the exception of ketorolac 30 mg intravenously supplemental analgesia during the continuous infusion period and up until 1:00 A.M.
- Chronic (defined as daily use for >2 weeks) opioid (oral codeine, dextromoramide, dihydrocodeine, oxycodone, or morphine-like anti-tussive) therapy, defined as >15 morphine equivalent units per day for more than 3 out of 7 days per week over a 1-month period within 12 months of surgery.
- Long-acting NSAID within 4 days before initiation of study medication (except aspirin ≤325 mg/day for cardiovascular prophylaxis) or short-acting NSAID within 1 day.
- Regular use of opioid analgesic (buprenorphine, nalbuphine, or pentazocine) within 30 days before Screening.
- Long-term use of opioid agonist-antagonists.
- Liver-inducing enzyme cytochrome P450: antiinfectives (eg, rifampicin, rifabutin, nevirapine, griseofulvin) or anti-epileptics (phenobarbital, phenytoin).
- Monoamine oxidase inhibitors, tricyclic antidepressants, neuroleptics, or other drugs that reduce the seizure threshold within 4 weeks of study entry.
- Serotonin–norepinephrine reuptake inhibitors (milnaciprin, duloxitene, venlafaxine), diet pills (including fenfluramine and phentermine), or methylphenidate (Ritalin®), or similar ADHD medications within 4 weeks of study entry.
- Any investigational drug or device or investigational therapy will be prohibited within 30 days before Screening.

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate CRF.

9.13. Other Restrictions

Other restrictions include the following:

- Alcohol use is prohibited from 24 hours before surgery until discharge from the study center on Day 3.
- No smoking upon admission to the study center until discharge from the study center on Day 3.
- Nothing by mouth from midnight before surgery until 1 hour after surgery.

9.14. Rescue Medication

After randomization, subjects will be encouraged to wait for at least 1 hour after the first dose of study medication before receiving first rescue medication to allow time for the study medication to exert its pharmacologic effect. Subjects may be given acetaminophen 1 g IV every 4 to 6 hours, up to 4 g/24 hours, for pain as rescue medication after the anesthetic infusion is discontinued and treatment with study medication has been initiated. If subjects are unable to tolerate IV acetaminophen or have insufficient pain relief with acetaminophen 1 g IV every 4 to 6 hours, oxycodone hydrochloride 5 mg Immediate Release (IR) tablets can be administered every 4 to 6 hours as needed for pain, up to a total of 30 mg/24 hours

Acetaminophen has been selected because its mechanism of action differs from tramadol and celecoxib, while oxycodone has been chosen as a secondary rescue medication because, although it is contraindicated with other NSAIDs, it is expected that secondary rescue medication will be required by few subjects and primarily for subjects randomized to the placebo group.

Subjects whose pain cannot be adequately managed by a combination of study medication and rescue medication, or who develop unacceptable side effects during the study, will be discontinued from study medication or from further study participation. Their pain will be managed conventionally at the investigator's discretion. All end-of-study assessments should be performed for subjects who discontinue from the study, if possible.

All concomitant medications used will be recorded in the source document and on the case report form.

9.15. Treatment after End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

Subjects will be discharged home with a prescription for pain-relief medication and a subject diary in which to record AEs and concomitant medications.

10. STUDY PROCEDURES

Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (Section 17.1). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Screening

Subjects will sign an ICF before any screening-related procedures are performed. Screening assessments must be performed within 28 days before the bunionectomy surgery (Day -1). The following procedures will be performed at Screening:

1. Assign a screening number.
2. Review inclusion/exclusion criteria.
3. Record demographics and detailed medical history, including medications taken within 30 days before Screening.
4. Perform a complete physical examination (excluding genitourinary examination) with review of body systems and include classification of ASA physical status classification.
5. Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a resting position for 5 minutes.
6. Record any AEs and concomitant medications.
7. Measure height and weight and calculate body mass index (BMI).
8. Record 12-lead electrocardiogram (ECG).
9. Collect blood and urine samples for clinical laboratory tests (hematology, chemistry, and urinalysis; see Section 10.8.4 for a complete list of required laboratory tests).
10. Collect a blood sample for serum pregnancy test from female subjects of childbearing potential.
11. Collect a urine sample for the drug screen.
12. Perform podiatric examination and obtain radiograph (a radiograph taken within the previous 6 months will be acceptable).
13. Remind the subject not to use prohibited concomitant medications (see Section 9.12) and to comply with all study restrictions, including nothing by mouth starting from midnight before surgery.
14. Train the subject on the use of self-assessment measures.

10.2. Day of Surgery (Day -1)

The day of surgery (Day -1) is defined as a time period that includes the time of surgery (primary, unilateral, first metatarsal osteotomy with internal fixation with no additional collateral procedure) and the immediate postoperative period of up to 24 hours. During this period, the following events will occur:

10.2.1 Preoperative

1. Review inclusion and exclusion criteria and verify that the subject continues to meet all study entry criteria.
2. Update medical history (including adverse reactions experienced and concomitant medications taken, if applicable, since Screening).
3. Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a resting position for 5 minutes.
4. Perform a physical examination.
5. Collect a urine sample for the pregnancy test from female subjects of childbearing potential.
6. Collect a urine sample for the drug screen.
7. Perform alcohol breathalyzer test.
8. Train the subject on how to assess their pain level after surgery.

Subjects who are deemed ineligible for study participation before surgery will be considered screen failures.

10.2.2 Surgery and Standardized Regional Anesthesia

Subjects who continue to meet all study entry criteria will undergo standard first metatarsal bunionectomy procedure under a standardized regimen of regional anesthesia. The local anesthetic technique to be used for this surgery comprises a combination of a PSB to establish and maintain surgical field anesthesia and a continuous sciatic infusion to provide an effective method of controlling pain in the immediate postoperative period.

The PSB will be administered using modifications of the Singelyn technique.[6] Subjects will receive midazolam and/or propofol for initial sedation at the anesthesiologist's discretion. After adequate sedation is achieved, the anesthesiologist will inject approximately 5 mL lidocaine 1% (plain) (or suitable short acting local anesthetic without epinephrine) locally to anesthetize the skin, and will determine the location of the sciatic nerve for the PSB. Once the appropriate location is determined, the anesthesiologist will inject 40 mL of ropivacaine 0.5% to establish the PSB. Subsequently a catheter will be placed in the proximity of the popliteal sciatic nerve for delivery of postoperative anesthesia. If the PSB is not sufficient to provide adequate intraoperative anesthesia, a standard Mayo block may be established using lidocaine 2% (plain) not to exceed 25 mL. The time, date, dose, and route of all local anesthetics will be recorded in the CRF. (NOTE: While lidocaine 2% plain is the preferred local anesthetic to establish the Mayo block, an alternative plain short-acting local anesthetic or plain combination of 2 local anesthetics may be substituted if necessary. If mepivacaine is used for the Mayo block, the amount of mepivacaine should be added to the amount of mepivacaine used postoperatively for the popliteal block in order not to exceed maximum allowed daily dose of 1000 mg).

10.2.3 Postoperative Regional Anesthesia

Postoperative pain will be managed using a continuous anesthetic infusion through the catheter previously placed adjacent to the popliteal sciatic nerve in a manner adapted from the method described by Singelyn et al (1997) and Zetlaoui and Bouaziz (1998).[8,9] Mepivacaine 0.5% (plain) will be infused starting at 8 mL per hour and not to exceed 14 mL per hour. Alternatively, ropivacaine 0.2% (ropivacaine 0.5% diluted with saline to a final concentration of 0.2%) may be substituted and infused starting at 1 - 8 mL per hour, not to exceed 8 mL per hour. Maintenance of the block may require additional procedures such as periodic boluses of the anesthetic through the catheter or an increase in the rate of infusion of the anesthetic.

Additionally, subjects may receive supplemental analgesia with ketorolac 30 mg IV during the continuous infusion period up until 1:00 A.M to help control breakthrough pain if the regional anesthetic infusion is ineffective in the investigator's opinion.

All subjects' continuous anesthetic infusion will be discontinued between 3:00 and 4:00 A.M. the morning after surgery.

The time, date, dose, and route of all local anesthetics and systemic medications used in the postoperative period will be recorded in the eCRF.

10.3. Day 1 (Pretreatment/Randomization)

The following study procedures will occur on the day after surgery and before dosing on Day 1:

1. Discontinue regional anesthetic infusion between 3:00 and 4:00 A.M. An IV catheter should have been placed for delivery of postoperative analgesia or other required medication and will be maintained until discharge.
2. Contact IRT to obtain the moderate and severe pain box numbers for the subject. Retrieve the study medication boxes from stock, 1 for moderate pain and 1 for severe pain.

3. Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a resting position for 5 minutes.
4. Review the NPRS assessment training with the subject and instruct the subject to notify a member of the study staff and request treatment when he or she experiences a level of pain that they feel requires medication.
5. Prior to the first dose of study medication, perform clinical laboratory tests.
6. Prior to the first dose of study medication, perform a 12-lead ECG.
7. When the subject requests pain medication, administer the NPRS pain intensity assessment; subjects with a score ≥5 and ≤9 on the 0-10 NPRS will be eligible for randomization into the study.
8. Assign the corresponding study medication box; subjects with a score ≥5 and ≤9 on the 0-10 NPRS will be randomized and stratified by Baseline pain level (moderate [NPRS 5-6] or severe [7-9]) using IRT, and assigned the appropriate pain level treatment box. The qualifying NPR pain assessment will serve as Baseline.
9. Subjects with a NPRS score <5 will be asked if they can wait for treatment. If they cannot, they will be dropped from the study and treated according to the standard of care. If they agree to wait, they will be requested to notify a member of the study staff when their pain intensity has increased. If the subject's pain intensity ratings do not meet the minimum entry criteria within 8 hours of discontinuation of the regional anesthesia, subjects will not be eligible for randomization and will receive routine postoperative care at the investigator's discretion.
10. Subjects with a NPRS score >9 will be dropped from the study and treated according to the standard of care.
11. Record and review concomitant medications.
12. Record AEs.

10.4. Treatment Period (Day 1 through Day 3)

Once the pain intensity entry criteria are met and the subject is randomized, the first dose of study medication will be administered by study personnel with 8 ounces of water. After first dose (defined as Time 0), the subject will remain at the study center for subsequent dosing and completion of efficacy and safety assessments. Study medication will be administered in a qid regimen for 48 hours after the first dose, with a maximum of 4 doses (active and/or placebo) in a 24-hour period.

10.4.1 First Dose (Time 0 through Hour 6)

The following events will be completed between first dose (Time 0) and Hour 6:

1. Administer first dose of study medication – see Table 2 (Time 0).
2. Start 2 stopwatches and instruct the subjects to stop the first stopwatch when they experience perceptible pain relief and the second stopwatch when they experience meaningful pain relief.
3. Continue to record pain intensity (NPRS) assessments first and pain relief (5-point categorical scale) assessments second at 15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, and 6 hours after Time 0, and immediately before each use of rescue analgesia. During the night, subject will be wakened to administer the study medication. Pain assessments will be performed during the night only if the subject is awake.
4. Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature), after the subject has been in a resting position for 5 minutes, immediately before and 1 hour after each dose of study medication.

5. Encourage subjects to wait for at least 1 hour after the first dose of study medication before receiving first rescue medication to allow time for the study medication to exert its pharmacologic effect.
6. Record and review concomitant medications.
7. Record AEs.

10.4.2 Subsequent Doses

The following procedures and assessments will be completed during the Double-blind Treatment Period when subsequent doses of study medication will be administered:

1. Administer study medication in a QID regimen for 48 hours after the first dose, with a maximum of 4 doses (active and/or placebo – see Table 2) in a 24-hour period. Subjects are to be wakened during the night to administer study medication.
2. Administer pain intensity (NPRS) assessments first and pain relief (5-point categorical scale) assessments second at 7, 8 10, 12, 14, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 42, 46, and 48 hours and immediately prior to administration of any rescue medication. During the night, the subject will be wakened to administer the study medication. Pain assessments will be performed during the night only if the subject is awake.
3. Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature after the subject has been in a resting position for 5 minutes) immediately before and 1 hour after each study medication administration each day.
4. Record concomitant medications.
5. Record AEs.
6. Administer the patient's global evaluation of study medication at the end of the treatment period (Day 3) before discharge from the study center.
7. Conduct clinical laboratory tests and a 12-lead ECG before discharge from the study center on Day 3.
8. Dispense prescription for postoperative pain medications and outpatient subject diary before discharge from the study center on Day 3.
9. Discharge subject from study center on Day 3.

10.4.3 Duration of Treatment

The total treatment period is 48 hours.

10.5. Follow-Up (Day 7 ± 2 days) Visit

The subject will be instructed to return to the study center for the Follow-up Visit 5 to 9 days after surgery (Day 7 ± 2 days). At the Follow-up Visit, the following procedures will be performed:

1. Perform a targeted physical examination, and record any changes from previous visit.
2. Perform X-ray and examination of the foot.
3. Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a resting position for 5 minutes.
4. Record concomitant medications taken since discharge from the study center.
5. Record AEs occurring since discharge from the study center.
6. Collect and review subject diary.
7. Perform serum pregnancy test for female subjects of childbearing potential.

8. Collect blood and urine samples for routine laboratory tests.
9. Perform 12-lead ECG.

10.6. Study Duration

The overall study duration is expected to be 10 months (6 months of active enrollment and 4 months of data management, statistical analyses and reporting).

The estimated duration of the study for each subject is approximately 6 weeks, which includes up to a 4-week Screening Period, a 3-day treatment period (72 hours of confinement with 48 hours of treatment), and a post-treatment follow-up visit approximately 1 week after surgery.

The maximum study duration for each subject is approximately 40 days.

10.7. Efficacy Assessments

At assessment time points throughout the study, the pain intensity assessment will be completed first and the pain relief assessment will be completed second. Subjects will not be permitted to compare their responses with their previous responses. Efforts should be made to perform the assessments at the scheduled times. The actual assessments time must always be recorded.

10.7.1 Pain Intensity

Subjects will assess their current pain intensity using a 0-10 NPRS. The NPRS is a scale numbered zero to 10 with “No Pain” as the left anchor (0) and “Worst Possible Pain” as the right anchor (10). Each subject will be instructed to circle a single number on the line to indicate his or her current pain intensity. Pain intensity will be assessed before Time 0, at 15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 42, 46, and 48 hours after Time 0, and immediately before each use of rescue analgesia. During the night, subject will be wakened to administer the study medication. Pain assessments will be performed during the night only if the subject is awake.

10.7.2 Pain Relief

Subjects will assess their pain relief relative to Time 0 using a 5-point categorical scale. Subjects will be asked “How much relief have you had since your starting pain?” with response choices of none = 0, a little = 1, some = 2, a lot = 3, and complete = 4. Pain relief will be assessed at 15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 42, 46, and 48 hours after Time 0, and immediately before each use of rescue analgesia. During the night, subject will be wakened to administer the study medication. Pain assessments will be performed during the night only if the subject is awake.

10.7.3 Stopwatch Assessment

Two stopwatches will be started immediately after the subject has swallowed the last tablet of the first dose of study medication with 8 ounces of water. Each subject will be instructed, "Stop the first stopwatch when you first feel any pain relief whatsoever. This does not mean you feel completely better, although you might, but when you first feel any relief in the pain you have now" (perceptible pain relief). The subject will also be instructed, "Stop the second stopwatch when you feel the pain relief is meaningful to you" (meaningful pain relief). If the subject does not press the stopwatches within 8 hours after Time 0, the subject will discontinue use of the stopwatches.

10.7.4 Patient's Global Evaluation of Study Medication

For the patient's global evaluation of study medication, the subject will be asked "How effective do you think the study medication is as a treatment for pain?" with response choices of 0 = poor, 1 = fair, 2 = good, 3 = very good, or 4 = excellent. The subject will complete the patient's global evaluation of study medication at the end of the treatment period (Day 3) before discharge from the study center.

10.8. Safety Evaluations

Safety will be evaluated by the incidence of treatment-emergent AEs (TEAEs), physical examination findings, clinical laboratory test results, and changes in vital sign and ECG measurements.

10.8.1 Physical Examination

A complete physical examination (excluding the genitourinary exam) will be performed at Screening and before surgery on Day -1. A targeted physical examination, including an examination of the subject's surgical center, will be performed before discharge from the study center and at the Follow-up Visit.

10.8.2 Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, will be measured after the subject has been in a resting position for 5 minutes. Vital signs will be measured at Screening and before surgery on Day -1. From Day 1 through discharge from the study center, vital signs will be measured immediately before and 1 hour after each dose of study medication each day. Vital signs will also be measured at the Follow-up Visit.

10.8.3 Electrocardiograms

A 12-lead ECG will be performed at Screening, on Day 1 before the first dose of study medication, before discharge from the study center, and at the Follow-up Visit.

10.8.4 Clinical Laboratory Tests

The following clinical laboratory tests will be performed at Screening, before the first dose of study medication on Day 1, before discharge from the study center, and at Follow-up.

Hematology:	hemoglobin, hematocrit, platelet count (or estimate), red blood cell count, white blood cell count (including differential)
Serum Chemistry:	glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, sodium, potassium, calcium, chloride, bicarbonate, lactate dehydrogenase, albumin
Urinalysis (dipstick):	pH, specific gravity, blood, glucose, protein, ketones, nitrate, leukocytes

The following laboratory tests will also be performed:

- Alcohol breathalyzer test will be performed before surgery on Day -1.
- Urine drug screen samples will be collected at Screening and before surgery on Day -1 to test for amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamines, opiates, phencyclidine, and tetrahydrocannabinol.
- For female subjects of childbearing potential, a blood sample for the serum pregnancy test will be collected at Screening and at Follow-up; a urine pregnancy test sample will be collected before surgery on Day -1.

Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures and will be sent to a central laboratory for analyses.

Dipstick determination of pH, specific gravity, blood, glucose, protein, ketones, and nitrate will be tested locally at each center. If a dipstick test result is abnormal, a biochemistry urinalysis and a microbiology analysis will be performed, if needed.

11. ADVERSE EVENTS

Adverse events will be collected from the time of signing of the ICF through to the completion of the clinical study (including the Follow-up Visit) or premature subject discontinuation from the clinical study.

11.1. Definitions

11.1.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition.

An AE is defined as treatment emergent if the first onset or worsening is after the first administration of study medication and not more than 7 days after the last administration of study medication.

11.1.2 Definition of Serious Adverse Events

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event

Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent another of the outcomes listed in the definition above.

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 elective hospital admission to treat a condition present before exposure to the study medication, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE.

A newly diagnosed pregnancy in a subject that has received a study medication is not considered as an SAE unless it is suspected that the study medication(s) interacted with a contraceptive method and led to the pregnancy. A congenital anomaly in an infant born to a mother who was exposed to the study medication during pregnancy is an SAE.

11.1.3 Significant Adverse Events

All laboratory results will be reviewed by the investigator and any that are deemed clinically significant will be recorded as AEs. Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of study medication or significant additional concomitant therapy.

11.1.4 Definition of Severity

The clinical "severity" of an AE will be classified as:

Mild:	Causes no limitation of usual activities
Moderate:	Causes some limitation of usual activities
Severe:	Prevents or severely limits usual activities

11.1.5 Definition of Start Date, Stop Date, and Duration

Start Date and Time:	The date at which the AE is first noted
Stop Date and Time:	The date at which the AE is known to be resolved. If it is not known to have stopped, then indicate "ongoing."
Duration:	A time in days, hours, or minutes.

11.1.6 Action(s) Taken

Action(s) taken with study medication as a result of an AE may consist of the following:

- Dose not changed
- Drug withdrawn

11.1.7 Definition of Expectedness

An AE is expected when its nature or severity is consistent with the known AE profile of the product. For a study medication, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An AE is unexpected when its specificity or severity is not consistent with the current IB. For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis and (b) hepatitis with a first occurrence of fulminate hepatitis.

11.1.8 Definition of Relationship to Study Medication(s)

The categories for classifying the investigator's opinion regarding the relationship of an AE to study medication(s) are listed below.

Related	A reasonable possibility exists of a relationship between the AE and the study medication.
Not related	No reasonable possibility exists of a relationship between the AE and study medication.

In situations where causality is unassessable, the AE will be considered related.

11.1.9 Definition of Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as follows:

- Resolved
- Resolved with sequelae
- Ongoing
- Death
- Unknown

Death should only be selected as an outcome when the AE resulted in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "death" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2. Management of Adverse Events

11.2.1 Documentation of Adverse Events

The investigator is responsible for the detection and documentation of any clinically relevant observations meeting the criteria and definition of an AE or SAE. The subject will be allowed to spontaneously report any issues since the evaluation; then the investigator will then monitor and/or ask about or evaluate AEs using non-leading questions, such as "How are you feeling?"

All AEs will be documented in the CRF with the following information, where appropriate:

- AE name or term
- When the AE first occurred (start date)
- When the AE stopped (stop date), or an indication of "ongoing"
- How long the AE persisted (optional)
- Severity of the AE
- Seriousness
- Actions taken
- Outcome
- Investigator opinion regarding the relationship of AE to the study medication(s)

11.2.2 Follow-up of Subjects with an Adverse Event

Any AE will be followed to a satisfactory resolution until it becomes stable or until it can be explained by another known cause(s) (ie, concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record.

11.2.3 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If pharmacologic treatment is given, it must be documented in the CRF. The decision about whether the subject may continue in the study will be made by the investigator after consultation with the sponsor and/or medical monitor.

If AEs occur in a subject that are not tolerable despite conventional treatment, the investigator must decide whether to stop the subject's involvement in the study.

For double- or triple-blinded studies, it is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.4 Reporting of Serious Adverse Events

The investigator or designee must report all SAEs promptly to Premier Research Pharmacovigilance within 24 hours of first becoming aware of the event. The investigator or designee must complete and date the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and CRF, and sending the SAE form to the Premier Research via one of the following methods:

Email: [redacted]

Fax number: [redacted]

For questions regarding the reporting of SAEs, investigators should contact the Medical Monitor, [redacted].

The written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee must provide the following information, if available:

- Reporter (study center and investigator)
- Subject's study number
- Subject's year of birth
- Subject's gender
- Date of first dose of study medication(s) (if available)
- Date of last dose of study medication(s), if applicable and available
- Adverse event term
- Investigator's opinion of the relationship to study medication(s). ("Is there a reasonable possibility that the study medication caused the SAE? Yes or No?")
- Date of occurrence of the event (if available)
- A brief description of the event, outcome to date, and any actions taken (if available)
- The seriousness criteria(on) that were met (if available)
- Concomitant medication at onset of the event (if available)
- Relevant medical history information (if available)
- Relevant laboratory test findings (if available)
- Whether and when the investigator was unblinded as to the subject's treatment assignment (if available)

Any missing or additional relevant information concerning the SAE should be provided to the recipient(s) of the initial information as soon as possible on a follow-up SAE Report Form, together with the following information (adverse event, date of occurrence, subject ID, study ID, study medication, and center number); this will allow the follow-up information to be linked to the initial SAE report.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his/her health authorities, IRB, principal and coordinating investigators, study investigators, and institutions.

Originals SAE Forms are to be kept by the investigator in the Investigator's File.

The investigator shall be nullify by forwarding a follow up report an event reported to Premier that does not meet the SAE criteria or should not have been reported because it is a protocol exemption.

Serious AEs will be collected and reported up to 2 weeks after the subject's last study visit if the investigator considers the SAE is related to the study medication or the clinical study procedures.

11.2.5 Adverse Events of Special Interest

Adverse events of special interest comprise the most common AEs observed with tramadol use (ie, cumulative incidence of adverse reactions observed in ≥10% of subjects who used Ultram for up to 7 days in chronic trials of nonmalignant pain (N=427): dizziness/vertigo (26%); nausea (24%); constipation (24%); headache (18%); and somnolence (16%).[11] The following will be also considered as adverse events of special interest, since they are typically related to opioids administration: fatigue, inability to concentrate, itching, difficulty with urination, confusion, dry mouth and vomiting/retching.[12] All episodes of post-operative vomiting and any anti-emetic drug

use will be properly documented and analyzed. The details of the analysis will be included in the statistical analysis plan (SAP).

11.2.6 Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of study medication on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

The investigator must report any pregnancy within 24 hours of first becoming aware of the event by completing a pregnancy report form and faxing it to Premier Research Pharmacovigilance [redacted] or email to [redacted]

12. DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) will not be used in this study.

13. STATISTICS

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock; the SAP will include any specifications of subgroup analyses for selected efficacy and safety variables.

Each efficacy and safety endpoint will be summarized descriptively by treatment group. Summary statistics will be provided for all demographic, efficacy, and safety parameters listed below. Unless otherwise indicated, all statistical tests will be 2 sided and differences will be considered statistically significant if $P \leq 0.05$.

To avoid interference in efficacy measures (pain intensity assessments, pain relief at each time point [PARt], pain intensity differences [PIDt], and Sum of Pain Intensity Differences [SPID] calculations) at scheduled time points because of use of rescue medication, additional assessments will be made just before each administration of rescue medication, asking subjects to report their pain intensity/pain relief at the current time. These data will be carried over for the duration of effect of the rescue medication taken (4 hours for acetaminophen and 4 hours for oxycodone hydrochloride).

13.1. Primary Endpoint

The primary efficacy variable will be the pain intensity (PI) measured by NPRS.

The primary analysis endpoint will be the SPID from 0-48 hours defined as follows.

- PIDt = Pain Intensity Differences = PIt - PI0 where
- PI0 = PI at time t = 0h on NPRS
- PIt = Pain Intensity on NPRS at specific time points

The SPID is calculated as a time-weighted sum of the pain intensity difference values at each follow-up time point (difference between the starting pain intensity and the pain intensity at the given assessment time) multiplied by the amount of time (in hours) since the last, non-missing assessment.

Negative values of PID will correspond to an amelioration of pain, while positive values will correspond to a recrudescence of pain.

13.1.1 Secondary Endpoints

The secondary endpoints are the following:

- SPID (0-4 hours), SPID (0-6 hours), SPID (0-12 hours), and SPID (0-24 hours) as defined in previous section
- PIDt at each time point
- Pain intensity at each time point
- Pain Relief (PARt) = pain relief at each time point
- Total Pain Relief (TOTPAR) for time intervals (t=15 minutes – t=4 hours), (t=15 minutes – t=6 hours), (t=15 minutes – t=12 hours), (t=15 minutes – t=24 hours), and (t=15 minutes – t=48 hours)
    - TOTPAR is the time-weighted sum of the Pain Relief (PAR) at each time point

The summed time-weighted pain relief score over 0 hour to the x-hour period after Time 0	TOTPAR_x = PR_t1*(t1 ─ 0) + PR_t2*(t2 ─ t1) + … + PR_n*(t[n] ─ t[n ─ 1]), where PR_t[m] is pain relief score at m^{th} time point, and x is the n^{th} time point; x = 6, 12, 24, 48

Where PR measured as 5-point categorical scale: 0 = None; 1 = A little; 2 = Some; 3 = A lot; 4 = Complete.

- Peak pain relief and time to peak pain relief
- Stop watches: time to onset of analgesia, time to perceptible pain relief, and time to meaningful pain relief
- Time to onset of pain intensity decrease
- Subject's overall assessment of study medication
- Rescue medication:
    - Proportion of subjects who take of at least 1 dose of rescue medication up to 4, up to 6, up to 12, up to 24, and up to 48 hours after first dose of study medication; number of doses of rescue medication for the same time intervals
    - Time to first use of rescue medication.
- Proportion of Responders, where Responders are:
    - Subject who reaches a 50% reduction in pain intensity from baseline sustained until the end of the 48-hour observation period;
    - Subject who reaches a 30% reduction in pain intensity from baseline sustained until the end of the 48-hour observation period;
    - Subject who reaches a pain intensity below 4 on NPRS sustained until the end of the 48-hour observation period;
    - Subject who reaches a 50% reduction in pain intensity as compared to baseline and a pain intensity below 4 on NPRS sustained until the end of the 48-hour observation period;
    - Subject who reaches a 30% reduction in pain intensity as compared to baseline and a pain intensity below 4 on NPRS sustained until the end of the 48-hour observation period.
- Time-to-first-response will also be analyzed as time-to-event data, using the first time at which each response criterion was reached by each subject.
- Cumulative proportion of responders analysis plot

13.2. Sample Size Determination

The primary outcome measure is SPID (NPRS) up to 48 hours post dose (SPID-48h). The study is powered to detect the superiority of co-crystal E-58425 to each of the 2 active control groups.

A difference in pain intensity of 1 on a 0-10 NPRS is considered to be the minimum detectable change for an individual time point. Since SPID is the time-weighted average of pain intensity over a 48-hour period, the minimum detectable change of 10 mm from a single measurement must be multiplied by 48 hours. Therefore, the minimum detectable change in the primary outcome measure of SPID-48 hours is considered to be 48.

Data from another bunionectomy study that used SPID-48 hours as a primary endpoint to compare two doses of tapentadol with placebo (ClinicalTrials.gov identifier NCT01516008) was used to estimate the expected SD in SPID-48 hours for the present study. In that study, the SD of the SPID-48 hours ranged from 107 to 124. Therefore, conservatively, the SD of SPID-48 hours for the present study is assumed to be 124.

Since co-crystal E-58425 must show superiority over both tramadol and celecoxib, the power of each individual comparison is set at 90%, which will maintain an overall study power at 81%.

To detect a difference of 48 with an SD of 124 at an alpha level of 0.05 with a power of 90% requires 142 subjects per group (71 for the placebo group since a 2:2:2:1 randomization scheme is being used). It is assumed that the comparison versus placebo will be adequately powered since the difference versus placebo is believed to be larger than that of the active comparators.

Allowing for approximately a 20% rate of non-evaluable subjects (ie, those not included in the PPAS), a total of 630 subjects, 180 subjects per active group and 90 subjects for the placebo group will be randomized.

A blinded sample size re-estimation will be conducted when approximately 50% of subjects have completed the study and the actual pooled SD of the SPID-48 will be calculated on blinded/pooled data (see Section 13.4.6). The sample size will not be reduced as a result of this re-estimation. The exact time when this procedure will be made will be decided based on the observed actual accrual rate and it will be specified in the SAP.

13.3. Analysis Sets

The following 3 analysis populations are planned for this study:

- Safety Set: all subjects who receive at least 1 dose of study medication.
- Full Analysis Set (FAS): all randomized subjects
- Per-protocol Analysis Set (PPAS): all subjects in the Full Analysis Set with no major protocol deviations
- Completers Analysis Set (CAS): A subset of the PP set that includes all subjects who have pain assessments up to 48 hours after first dose of study medication

Inclusion in the analysis sets will be determined prior to database lock and prior to unblinding the treatment assignments.

If a subject is randomized incorrectly or is administered the incorrect study medication, analyses of the Full Analysis Set will be based on the assigned treatment whereas all other analyses will be based on the actual treatment.

Primary efficacy analyses will be based on the FAS. The PP Set and the CAS will be used for sensitivity analysis for some efficacy endpoints. Safety analyses will be based on the Safety Set.

All subjects who signed informed consent will be considered study participants.

13.4. Statistical Analyses

This section presents a summary of the planned statistical analyses.

Unless otherwise indicated, all testing of statistical significance will be two-sided, and a difference resulting in a *P* value of ≤0.05 will be considered statistically significant. To declare the study successful, co-crystal E-58425 will need to show a statistically significant advantage over each comparator (tramadol and celecoxib). Moreover, a comparison with placebo will be performed to assess the co-crystal E-58425 absolute efficacy. Because all 3 comparisons must be statistically significant to declare the study successful, no formal adjustment for multiple comparisons is needed.

For analyses involving study center, if the number of subjects per center is small, centers may be pooled for analysis, or omitted from statistical models. The final determination will be made prior to database lock.

For continuous variables, summary statistics will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, summary statistics will typically include the number and percentage of subjects in each category.

13.4.1 Disposition

The numbers of subjects randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported. This analysis will be based on all study participants.

13.4.1.1 Protocol Deviations

Protocol deviations will be collected ongoing through the study. Protocol deviations excluding subjects from the PP analysis set will be agreed and signed off by the sponsor prior to database lock and unblinding.

13.4.2 Subject Characteristics

Demographic variables will include age, gender, race, weight, height, and BMI. Baseline subject characteristics will include surgery duration and other surgery characteristics.

Medical history and study medication administration will be summarized descriptively by treatment group and presented in listings.

Prior and concomitant medications will be summarized by treatment group and by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms.

The remaining subject characteristic variables will be summarized descriptively by treatment group and overall. No formal statistical analyses will be performed.

These analyses will be conducted for the Safety Set.

13.4.3 Efficacy

13.4.3.1 Primary Analysis

The primary efficacy analysis will compare treatment groups for the SPID from time 0 to 48 hours. This will be tested using an analysis of covariance model adjusting for center and baseline pain intensity. In addition, 95% confidence intervals for pairwise differences between treatments will be estimated.

To account for the use of rescue medication, any pain measurements taken during a period of time in which rescue medication is active will be replaced by the last pain measurement before rescue medication was taken.

Additional sensitivity analyses assessing the impact of rescue use and missing data due to study discontinuation will be performed.

The details of the sensitivity analyses and handling of missing data will be described in the SAP written prior to database lock.

13.4.3.2 Secondary Analyses

Each efficacy endpoint will be summarized descriptively by treatment group.

Continuous secondary endpoints will be analyzed similarly to the primary endpoint.

For ordinal secondary endpoints such as pain relief score at each scheduled time point, peak pain relief (ie, the lowest value of the PID), and patient's global evaluation of study medication, descriptive summaries include the number and percentage of subjects within each category for each treatment group. Nominal *P* values from ordinal logistic regression, adjusting for baseline pain intensity and center, as appropriate comparing the placebo group with other treatment groups will be provided, but no formal statistical inferences will be drawn on the basis of these tests.

For each time-to-event endpoint, the Kaplan-Meier method will be used to evaluate the treatment effect. Time to peak pain relief will be taken as the time to the lowest value of the NPRS after baseline, provided that the lowest value after baseline is lower than the baseline value. Time to onset of pain intensity decrease will be measured as the time at which the difference from baseline pain intensity (PID) is decreased ≥1 point in NPRS for the first time after the first study medication intake. Time to perceptible pain relief confirmed by meaningful pain relief will be based on data collected using the 2-stopwatch method following the first dose of study medication. In addition to the raw data from the stopwatches, a derived measure "time to onset of analgesia" will be defined as the time to perceptible pain relief if subsequently confirmed by meaningful pain relief. The 4 time-to-event variables will be right censored at 8 hours for subjects who reach the event during the 8-hour interval after Time 0, or those who require rescue medication before achieving the event. The summary table will provide the number of subjects analyzed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals for the estimated median. *P* values from log-rank tests will also be used to examine treatment effect. Cox proportional hazard models may be used to further explore such potential covariates as gender, baseline pain intensity, and center.

For the proportion of subjects using rescue medication, a logistic regression model that adjusts for baseline pain intensity and center will be used to evaluate the treatment effect.

Efficacy analyses will be also performed by subgroups defined by moderate or severe baseline pain.

13.4.4 Exposure

Investigational product administration will be summarized in terms of each subject's mean, mode, and final dose, and in terms of duration of exposure. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided by treatment group.

13.4.5 Safety Analyses

The safety endpoints are the incidence of TEAEs, physical examination findings, and changes in ECG and vital sign measurements.

Data listings will be provided for protocol-specified safety data. The Medical Dictionary for Regulatory Activities (Version 19.0 or higher) will be used to classify all AEs with respect to system organ class and preferred term. The number and percentage of subjects with AEs will be displayed for each treatment group by

SOC and PT. Summaries of AEs by severity and relationship to study medication will also be provided. Serious adverse events, AEs resulting in discontinuation of study medication and AEs of special interest will be summarized separately in a similar manner. Subject listings of AEs, SAEs and AEs causing discontinuation of study medication will be produced. Comparisons between treatment groups for incidence of AEs, AEs of special interest may be performed. Any comparisons of safety analyses will be described in detail in the SAP.

For vital sign measurements and ECG parameters, descriptive statistics will be provided at each scheduled time point for each treatment group. Changes from Baseline for vital signs and ECG parameters will be calculated for each subject, and descriptive statistics will be provided on changes in vital signs from Baseline for each treatment group at each scheduled time point after Baseline. No formal statistical tests will be performed. For clinical laboratory, ECG, and vital sign variables, the values that are below, within, or above a defined normal range and the values that are clinically significant will be counted and tabulated by the number and percentage of subjects with such values and will be tabulated showing change from baseline (shift tables).

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values for each treatment group at each time point. The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges, [or other specific ranges of interest] will be tabulated showing change from baseline (shift tables) for each clinical laboratory analyte by treatment group and by time. Pre- and post-treatment values will also be presented with an analysis of mean changes from baseline.

Laboratory values, vital sign measurements and ECG measurements that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges, if provided. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing. For laboratory values, vital sign measurements and ECG parameters individual data and mean values by treatment groups will also be shown in graphical displays.

The number and percentage of subjects with normal and abnormal findings in the complete physical examination will be displayed for each treatment group.

The results of the safety analyses described in this section are to be taken as descriptive measures of differences among treatment groups, and not as formal statistical hypothesis tests or indicators of important clinical differences.

Safety analyses will be conducted for the safety analysis population.

13.4.6 Interim Analysis

An interim analysis is planned. A blinded sample size re-estimation following the methodology described in Keiser and Friede[10] will be conducted when approximately 50% of subjects have completed the study and the actual pooled SD of the SPID-48 will be calculated on blinded/pooled data. If that SD is >124, the sample size will be increased accordingly to maintain an overall study power of at least 81%, up to a maximum of 900 subjects. The sample size will not be reduced if the SD is smaller. The exact time when this procedure will be made will be decided based on the observed actual accrual rate and it will be specified in the SAP.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 15). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study center at any time (Section 14.6), and/or to discontinue the study (Section 14.5).

ESTEVE agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 17.2), the investigator indicates that he/she has carefully read the protocol, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including the April 1996 ICH Guidance for Industry E6 GCP, and in agreement with the 2013 version of the Declaration of Helsinki. While delegation of certain aspects of the study to subinvestigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (eg, subinvestigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, study medications, and their specific duties within the context of the study. Investigators are responsible for providing ESTEVE with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited/inspected by an independent person/regulatory body. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.2. Center Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study center. The study center will not be authorized for study initiation until:

1. The study center has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
2. All regulatory documents have been submitted to and approved by the sponsor or its designee.
3. The study center has a Clinical Trial Agreement in place.
4. Study center personnel, including the investigator, have participated in a study initiation meeting.

14.3. Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study. Subjects may only be rescreened once 30 days or more after the original Screening Visit. If a subject is eligible to enter the study after having previously failed screening, the subject will be assigned a new subject identification number.

14.4. Study Documents

All documentation and material provided by ESTEVE for this study are to be retained in a secure location and treated as confidential material.

14.4.1 Investigator's Regulatory Documents

The regulatory documents are listed in the Study Manual.

The regulatory documents must be received from the investigator and reviewed and approved by ESTEVE or its designee before the study center can initiate the study and before Premier will authorize shipment of study medication to the study center. Copies of the investigator's regulatory documents must be retained at the study center in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the co-crystal E-58425 IB, electronic case report form (eCRF) completion guidelines, copies of regulatory references, copies of IRB correspondence, and study medication accountability records should also be retained as part of the investigator's regulatory documents. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

14.4.2 Case Report Forms

The study data will be recorded by the investigators in an electronic CRF (eCRF) built using [redacted]. By signing the Investigator's Agreement (Section 17.2), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a subinvestigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

Subject assessments during hospitalization will be performed on paper subject diary, and assessments made after discharge will be done on a paper subject diary.

14.4.3 Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be electronically transferred from the central/local laboratory to the sponsor or its designee. An anonymized paper copy of the laboratory results will be provided to the study center and should be retained with each subject's source data.

14.4.4 Data Quality Control

Steps to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel prior to the study, and periodic monitoring visits by Premier Research. Data will be reviewed for accuracy and completeness by Premier Research during and after center monitoring visits, and any discrepancies will be resolved with the investigator or designees as appropriate.

14.4.5 Monitoring Procedures

ESTEVE or its designee will conduct center visits to monitor the study and ensure compliance with the protocol, ICH Guidance for Industry E6 Good Clinical Practice (GCP), and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study center at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized [sponsor] personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on center, the CRA(s) will review:

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures
- AE procedures
- storage and accountability of study medication and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in the study manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 17.2), the investigator agrees to meet with the CRA(s) during study center visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow ESTEVE or designee auditors or inspectors from regulatory agencies to review records, and to assist the inspectors in their duties, if requested.

14.4.6 Data Management

Premier Research will be responsible for activities associated with the data management of this study using [redacted] The standard procedures for handling and processing records will be followed per GCP and Premier Research's standard operating procedures (SOPs). A comprehensive data management plan (DMP) will be developed including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study center personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study manual.

14.4.7 Quality Assurance/Audit

This study will be subject to audit by ESTEVE or its designee. Audits may be undertaken to check compliance with GCP guidelines, and can include the following:

- center audits
- TMF audits
- database audits
- document audits (eg, protocol and/or CSR)

ESTEVE or its designee may conduct additional audits on a selection of study centers, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study center, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The investigator

agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify ESTEVE immediately.

14.5. Study Termination

The study may be terminated at ESTEVE's discretion at any time and for any reason The Independent Ethics Committee(s) (IECs) and Competent Authority(ies) (CAs) should be informed promptly should that occur.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study, or potential study subjects
- A decision on the part of ESTEVE to suspend or discontinue development of the study medication
- If the CA obtains information that raises doubts about the safety or scientific validity of the clinical study, the CA can suspend or prohibit the study (Code of Federal Regulations Title 21, Part 312, Subpart C, Section 312.44).
- Should the study be prematurely terminated or suspended for any reason, the Investigator/institution must promptly inform the study subjects and assure appropriate therapy and follow-up for the subjects

14.6. Study Center Closure

At the end of the study, all study centers will be closed. ESTEVE may terminate participation of a study center at any time. Examples of conditions that may require premature termination of a study center include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.6.1 Record Retention

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until:

- At least 2 years after the last marketing authorization for the study medication has been approved or the sponsor has discontinued its research with the study medication, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the study medication

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of her/his intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

14.7. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of ESTEVE. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

14.8. Use of Information and Publication

After completion of the study, a clinical study report will be prepared according to the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3) by Premier Research in close collaboration with the Investigators and ESTEVE. All publications and presentations must be based upon the clinical study report.

ESTEVE will retain ownership of all data.

ESTEVE is committed to communicate the results of the study, positive or negative, in media of public access, and will particularly enforce the publication of the results in scientific publications, playing an active role in the preparation of the paper, in agreement with the principal investigator and participating in the submission to the corresponding editors. The manuscript should mention the Ethics Committee involved.

If an Investigator wishes to publish results from this clinical study, written permission to publish must be obtained from ESTEVE in advance. As some of the information regarding the study medication and development activities at ESTEVE may be of a strictly confidential nature, ESTEVE keeps the right to review the manuscript before its submission to journals, meetings or conferences.

ESTEVE may choose to publish or present data from this study. If an Investigator is offered first authorship, he/she will be asked to critically review the article for important intellectual content and approve the version to be published. ESTEVE has the right to use the results for registration and internal presentation and for promotion of the ESTEVE's commercial interests.

15. ETHICAL AND LEGAL CONSIDERATIONS

15.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the 2013 version of the Declaration of Helsinki, and the applicable regulations of the country(ies) in which the study is conducted.

15.2. Subject Information and Informed Consent

A properly constituted, valid IRB must review and approve the protocol, the investigator's informed consent document, and related subject information and recruitment materials before the start of the study.

All subjects will receive written and oral information regarding the study at an interview prior to joining the study. The information will emphasize that participation in the study is voluntary and that the subject may withdraw from the study at any time and for any reason. The information must be written in a language that is understandable to the subject. All subjects will be given the opportunity to ask questions about the study and will be given sufficient time to decide whether to participate in the study.

It is the responsibility of the investigator to ensure that written informed consent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care. A copy of the subject information including the signed consent form will be provided to the subject.

15.3. Approval by Institutional Review Board

For Investigational New Drug (IND) studies, the minimum standards of conduct and requirements for informed consent are defined in the FDA regulations.

A valid IRB must review and approve this protocol before study initiation. Written notification of approval is to be provided by the investigator to the sponsor's monitor/project manager before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written

approval must consist of a completed sponsor form, IRB Approval Form or written documentation from the IRB containing the same information.

Until written approval by the IRB has been received by the investigator, no subject may undergo any procedure not part of routine care for the subject's condition.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by ESTEVE before implementation. This written approval will consist of a completed IRB Approval form or written documentation from the IRB containing the same information.

15.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

16. REFERENCES

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17. ATTACHMENTS

17.1. Schedule of Events

	Screening (-28 days to -1 day before surgery)	Surgery Day -1	Day 1 (before dosing)	Treatment Period Day 1 through Day 3		Follow-up Day 7 ± 2 days (5 to 9 days after surgery) or ET
				First dose (Time 0)	Subsequent doses	
Written informed consent	X					
Inclusion/exclusion criteria	X	X (update)				
Demographics	X					
Medical history	X	X (update)				
Physical examination[a]	X	X				X
Vital signs[b]	X	X	X	X	X	X
Height, weight, and BMI	X					
12-lead electrocardiogram	X		X		X[c]	X
Clinical laboratory tests (hematology, chemistry, urinalysis)	X		X		X[d]	X
Pregnancy test for female subjects[e]	X	X				X
Urine drug screen[f]	X	X				
Alcohol breathalyzer test		X				
X-ray and podiatric examination[g]	X[h]					X
First metatarsal bunionectomy procedure[i]		X				
Discontinue anesthetic block between 3:00 and 4:00 AM[j]			X			
Assign randomization number			X[k]			
Subject training on self-assessments measures	X	X	X			
Pain intensity and relief assessments[l]			X	X	X	
Administer study medication[m]				X	X	
Start stopwatches for perceptible and meaningful pain relief[n]				X		
Patient's global evaluation of study medication[o]					X	
Concomitant medication	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Dispense postoperative pain medication and outpatient subject diary[p]					X	
Discharge subject from the study center[q]					X	
Collect and review diary for completion						X

Continued

Abbreviations: BMI = body mass index; ET = early termination; NPRS = numerical pain rating scale.

a A complete physical examination (excluding the genitourinary examination) will be performed at Screening and before surgery on Day -1. A targeted physical examination, including an examination of the subject's surgical site, will be performed at the Follow-up Visit.

b Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, will be measured after the subject has been in a resting position for 5 minutes. Vital signs will be measured at Screening and before surgery on Day -1. From Day 1 through discharge from the study center, vital signs will be measured immediately before and 1 hour after each dose of study medication each day. Vital signs will also be measured before study termination.

c A 12-lead ECG to be administered before discharge on Day 3.

d Clinical laboratory tests to be performed before discharge on Day 3.

e Serum pregnancy test at Screening and at Follow-up and urine pregnancy test before surgery on Day -1. Test results must be negative for the subject to continue in the study.

f Collected at Screening and before surgery on Day -1. Test results must be negative for the subject to continue in the study except in cases where a valid physician's prescription can be verified.

g Radiographs taken within 6 months before Screening will be acceptable. X-ray and podiatric examination will be performed at the Follow-up Visit.

h X-ray and podiatric examination only.

i Primary unilateral first metatarsal osteotomy with internal fixation with no additional collateral procedure.

j Immediately after the block is discontinued, study staff will pull 2 random study medication kits, 1 for moderate pain and 1 for severe pain. Subjects will be instructed to request pain medication when they experience pain.

k When a subject requests pain medication, the Pain intensity (NPRS) assessment will be conducted and the qualifying pain score must be ≥5 and ≤9; subjects will be randomized into the study and stratified by Baseline pain score (moderate [NPRS 5-6], severe [7-9], using interactive response technology and the appropriate pain level kit will be used.

l Pain intensity (NPRS) assessments will be recorded by the subject in the inpatient subject diary; the qualifying pain score serves as the Baseline pain score before the first dose of study medication (Day 1/Time 0). Pain intensity (NPRS) and pain relief (5-point categorical scale) assessments will be recorded at the following time points:

- First dose: to 15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, and 6 7, 8 hours after Time 0, and immediately before the use of rescue analgesia
- Subsequent doses: 7, 8, 10, 12, 14, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 42, 46, and 48 hours after Time 0 and immediately before each use of rescue analgesia.
- Before premature study termination.

m The first dose of study medication will be administered within 8 hours after the anesthetic block has been discontinued when pain intensity is ≥5 and ≤9 on the NPRS. Study medication will be administered from Day 1 through Day 3 for a total of 48 hours.

n Start stopwatches as soon as the first dose of study medication is administered.

o Subjects will complete a patient's global evaluation of study medication at the end of the treatment period (Day 3) before discharge from the study center.

p Before discharge from the study center on Day 3.

q On Day 3

17.2. Investigator's Agreement

PROTOCOL NUMBER:	ESTEVE-SUSA-301
PROTOCOL TITLE:	A Randomized, Double-blind, Active- (Tramadol and Celecoxib) and Placebo-controlled, Parallel-groups, Phase 3 Clinical Trial to Establish the Efficacy of Co-Crystal E-58425 for the Management of Moderate to Severe Post-surgical Pain after Bunionectomy
FINAL PROTOCOL:	Final Version 4.0, 20 Jul 2017
AMENDMENT 1	Final Version 1.0, 09 Nov 2016
AMENDMENT 2	Final Version 1.0, 15 Feb 2017
AMENDMENT 3	Final Version 1.0, 20 Jul 2017

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all subinvestigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with ESTEVE and Premier Research during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical trials on a study medication during and after study completion.

Principal Investigator:

Printed Name: [redacted]

Signature: [redacted]

Date: [redacted]

APPENDICES

A. Address List
B. Study Specific Requirements
C. Regulations and Good Clinical Practice Guidelines

A. Address List

1. Sponsor

Sponsor

Name:	Laboratorios del Dr. ESTEVE, S. A. U.
Address:	Avda. Mare de Déu de Montserrat, 221
	08041 Barcelona (Spain)
Phone:	[redacted]
Project Manager:	[redacted]

2. Clinical Research Organization

Name:	Premier Research
Address:	One Park Drive, Suite 150
	Durham, NC 27709
Phone:	[redacted]
Fax:	[redacted]
Project Manager:	[redacted]
Study Statistician:	[redacted]

3. Drug Safety

Medical Monitor

Name:	[redacted]
Address:	Premier Research
	One Park Drive, Suite 150
	Durham, NC 27709
Phone:	[redacted]
Fax:	[redacted]

Pharmacovigilance

Name:	[redacted]
Address:	1st Floor, Rubra 2 Mulberry Business Park Fishponds Road Wokingham, RG41 2GY United Kingdom
Phone:	[redacted]
Fax:	[redacted]

4. Monitor

Name:	[redacted]
Address:	One Park Drive, Suite 150 Durham, NC 27709
Phone:	[redacted]
Fax:	[redacted]

5. Coordinating/Principal Investigator

Name:	[redacted]
Address:	[redacted]
Phone:	[redacted]

6. Laboratories

Central Laboratory

Name:	[redacted]
Address:	[redacted]
	[redacted]
Phone:	[redacted]
Fax:	[redacted]

B. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf