Statistical Analysis Plan

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 Number:	ESTEVE SUSA-301 (Amendment 3, 30 June 2017)
Compound:	Co-crystal E 58425
Phase:	3
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3.0	13 December 2017	[redacted]	Updated to clarify some minor ambiguities and inconsistencies with the protocol and incorporate some decisions made at the blinded data review meeting

SIGNATURE PAGE AND APPROVALS

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Laboratorios del Dr Esteve

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ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BOCF	Baseline Observation Carried Forward
CAS	Completers Analysis Set
CRF	Case Report Form
CPMP	Committee for Proprietary Medicinal Products
CSR	Clinical Study Report
ECG	Electrocardiogram
EMA	European Medicines Agency
FAS	Full Analysis Set
FCS	Full Conditional Specification
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
LOCF	Last Observation Carried Forward
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
NPRS	Numeric Pain Rating Scale
PPAS	Per Protocol Analysis Set
QT_C	QT-interval for ECG corrected for heart rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SPID	Sum of Pain Intensity Differences
TEAE	Treatment-emergent Adverse Event
TOTPAR	Total Pain Relief
TTOA	Time To Onset of Analgesia
TTPPR	Time To Peak Pain Relief
WHO	World Health Organization
WOCF	Worst Observation Carried Forward

1. OVERVIEW

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Laboratorios del Dr Esteve protocol ESTEVE-SUSA-301 (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), Amendment 1, dated 9 November 2016, Protocol Version 4.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned, exploratory analysis will be clearly identified as such in the final CSR.

In addition to the study protocol, the following documents were reviewed in preparation of this SAP:

- ICH Guidance on Statistical Principles for Clinical Trials (E9)

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 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.

2.1.2 Secondary Objectives

The secondary objectives are as follows:

- 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 in the first 48 hours and at various time points after bunionectomy by using assessments of pain intensity
- To assess the safety and tolerability of co-crystal E-58425

2.2 Efficacy and Safety Endpoints (Target Variables)

2.2.1 Efficacy Variables

The primary efficacy variable is the sum of pain intensity differences (SPID) up to 48 hours (SPID-48), calculated as described in Section 6.3.

The secondary efficacy variables are as follows:

- SPID up to 4, 6, 12, and 24 hours (SPID-4, SPID-6, SPID-12, and SPID-24)
- Pain intensity at each time point
- Pain intensity difference from baseline 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), calculated as described in Section 6.3
- 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 the numeric pain rating scale (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 analysed as time-to-event data, using the first time at which each response criterion was reached by each subject

2.2.2 Safety Variables

The safety variables are as follows:

- Incidence of treatment emergent adverse events (TEAEs)
- Electrocardiogram (ECG) variables
- Vital signs measurements
- Laboratory safety variables
- Concomitant medication
- Medication exposure

3. OVERALL STUDY DESIGN AND PLAN

This is a randomized, double-blind, placebo and active controlled phase 3 study of co-crystal E-58425. Subjects are eligible for the study if they have pain in the range 5–9 inclusive on an 11-point numeric pain rating scale (NPRS) after bunionectomy.

Subjects will be randomized in a 2:2:2:1 ratio to co-crystal E-58425, tramadol, celecoxib, or placebo. Randomization will be stratified according to whether subjects have a baseline NPRS pain score in the moderate (5–6) or severe (7–9) range. The randomization process proceeds in 2 steps: in the first step, subjects are assigned to 2 possible treatments depending on the stratum for which they qualify based on their baseline pain score, and in the second step, they are assigned to a specific stratum and therefore to a unique treatment arm, once their baseline pain score is known.

Subjects will complete the NPRS at various timepoints up to 48 hours after dosing (15, 30, and 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). Subjects whose pain is not sufficiently managed by the study medication will be able to take rescue medication (either IV acetaminophen or oral oxycodone).

Subjects will be discharged from the study centre on day 3 of the study, after the 48-hour efficacy assessments and the end-of-treatment period safety assessments have been done. Subjects will return to the study on day 7 for follow-up safety assessments, which represents the end of study for each subject.

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.

For full details of the study design, please see the protocol.

4. ANALYSIS AND REPORTING

4.1 Interim Analysis

A blinded interim analysis will be done after approximately half the subjects have been recruited, for the purpose of sample size re-estimation.

To that end, the variance of the primary outcome measure will be calculated from blinded data. Variance estimates of unblinded data can be inflated in the presence of treatment effects, although Friede and Kieser have shown that ignoring the treatment effects and using a naïve pooled estimate of the variance is often the preferred strategy[4]. Nonetheless, simulations have been done to determine the effect of different strategies for estimating the variance from the unblinded data, and those simulations have shown that using the naïve pooled estimate is indeed the preferred strategy for this study.

Details of the simulations results and the detailed rationale for using the naïve pooled estimate for calculating the variance are described in a separate interim analysis plan.

Once the variance has been estimated, that will be used to recalculate the sample size for the study, using the same inputs as the original calculation apart from the new variance. If the new calculation shows that a greater sample size is required, then the sample size will be increased to either the new sample size required or to 900, whichever is the smaller.

If the new calculation shows that a smaller sample size is required than originally estimated, then the study will continue to its original sample size. The sample size will not be reduced.

Full details are specified in the separate interim analysis plan dated 20 January 2017.

4.2 Final Analysis

All final, planned analyses identified in the protocol and in this SAP will be done after the last subject has completed the follow-up assessments on day 7, and all relevant study data have been processed and integrated into the analysis data base, data have been reviewed at a blinded data review meeting, and the database has been locked. Any post-hoc, exploratory analysis that were not identified in this SAP to support planned study analyses will be documented and reported in appendices to the CSR. Any results from unplanned analyses (post-hoc) will also be clearly identified in the text of the CSR.

5. ANALYSIS SETS

The following analysis sets are planned for this study:

- **Safety Set:** The safety set includes all subjects who receive at least 1 dose of study medication
- **All Enrolled Patients Set (ALL):** The ALL set includes all subjects who are entered into the interactive randomisation system and receive the initial assignment to two possible treatment arms, depending on the stratification according to the pain score at baseline will be, irrespective of whether they are subsequently assigned to a specific randomisation stratum and to a unique treatment arm (and to a unique box of study medication)
- **Full Analysis Set (FAS):** The FAS includes all subjects who undergo both steps of the randomization process and so are assigned to a specific randomisation stratum and to a unique treatment arm, irrespective of whether they actually receive any dose of study medication
- **Per Protocol Analysis Set (PPAS):** The PPAS set includes all subjects in the FAS with no major protocol deviations
- **Completers Analysis Set (CAS):** A subset of the PPAS that includes all subjects who have pain assessments up to 48 hours after first dose of study medication (Note: if few patients in the PPAS are excluded from the CAS, no CAS will be defined. This decision will be taken in the blinded data review meeting.)

Inclusion in the analysis sets will be determined at a blinded data review meeting before database lock and before unblinding the treatment assignments.

The following protocol deviations may be considered as major and will lead to an exclusion of subjects form the PPAS:

- Not receiving any dose of study medication
- Lack of any pain intensity assessment following study medication intake and before intake of rescue medication during the first 4 hours after the first study medication intake
- Receiving rescue medication during the first hour after the first study medication intake
- Age < 18 years
- Baseline pain intensity <5 or > 9
- Deviation from the standard surgical or anaesthesia procedures which could interfere with post-surgical pain
- Use of prohibited concomitant medication or non-pharmacological therapies
- Insufficient treatment compliance (less that 6 out of the 8 scheduled doses)
- Insufficient pain intensity assessment compliance which does not allow to fully characterize pain response evolution
- Time between qualifying pain score and first study medication intake > 30 minutes

Additional protocol deviations may be considered major at the blinded data review meeting and will be documented appropriately.

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

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. The ALL set will be used for analyses of patient disposition, but will not be used for efficacy or safety analyses.

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

6. GENERAL ISSUES FOR STATISTICAL ANALYSIS

6.1 General Statistical Methodology

Descriptive summaries will be provided where appropriate for each of the primary and secondary variables. In general, tables will summarize data by treatment group.

Continuous, quantitative, variable summaries will include the number of subjects (N) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise specified.

Categorical, qualitative, variable summaries will include the frequency and percentage of subjects in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the analysis set for the treatment groups, unless otherwise specified.

Statistical analysis models will be used to estimate treatment differences or ratios for the co-crystal E-58425 compared to tramadol and to celecoxib for the different study endpoints, as the study confirmatory analysis. Additionally, the absolute analgesic efficacy of co-crystal E-58425 will be estimated by comparison to placebo. Comparisons of tramadol and celecoxib to placebo will serve to assess the trial assay sensitivity.

All statistical tests will be based on a 2-sided test at the significance level of 0.05 and 95% confidence intervals, unless otherwise specified.

Graphical presentations will be employed to illustrate results from the statistical analyses.

All analysis will use SAS® software version 9.3 or later.

6.1.1 Handling of Missing Data

If subjects have missing pain data (ie, pain intensity or pain relief scores) within the 48 h period for the collection of pain rating data, but nonetheless complete the 48-hour period, then any missing timepoints will be replaced by a time-weighted average of the previous and the next available values (ie a linear interpolation for missing values) in the SPID or TOTPAR calculation.

If subjects do not complete the pain intensity assessments for the full 48 hours, then in the primary analysis, the SPID will be calculated up to the last available timepoint, with no imputation for later timepoints. This is equivalent to imputing a value of zero for the change from baseline, ie a baseline-observation-carried-forward (BOCF) analysis. As pain is expected to decrease after baseline, even without treatment, this is a conservative analysis. A similar approach will be used in calculating TOTPAR, which is also conservative, as it assumes zero pain relief where values are missing.

The only exception to the above imputation rule will be for patients who do not complete the full 48 h of assessments because the assessment at the 48-h timepoint was recorded early. In those cases, a further value at exactly 48 h will be imputed using the same value as recorded at the nominal 48-h timepoint, and the SPID will be calculated using both the recorded measurement at the nominal 48-h timepoint and the imputed measurement at exactly 48 h post-dose.

If subjects have no post-baseline pain assessments at all, then a value of zero will be imputed for the SPID; this is also equivalent to a BOCF analysis.

In a sensitivity analysis, subjects who drop out of the study early because of a related AE or lack of efficacy will have later missing timepoints imputed using a worst-observation-carried-

forward (WOCF) method, in which their worst observation at baseline or any time thereafter is imputed. For subjects dropping out early for any other reason, a last-observation-carried-forward (LOCF) imputation will be used.

In a further sensitivity analysis, all subjects who do not have the whole 48 hours of pain data will have later missing timepoints imputed using the WOCF method, in which their worst observation at baseline or any time thereafter is imputed. This is an even more conservative analysis than the BOCF method.

Additionally, an analysis of the most important efficacy endpoints based on the Completers Analysis Set will be performed to further assess the impact of the imputation of missing values on the study results.

As a further sensitivity analysis, a multiple imputation approach will be taken in which missing data are imputed. Details of the multiple imputation methods are specified in section 8.1.1.

No imputation will be done for missing data on stopwatch assessments of perceptible and meaningful pain relief. Instead, if data are missing for those assessments, data will be censored as described in section 8.2.

If the patient's global evaluation of the study medication is missing, a value of 0 (poor) will be imputed.

6.1.2 Adjustment of Pain Scores for Rescue Medication Use

If subjects take rescue medication during the 48-hour period of pain assessments, a pain assessment will be made immediately before the dose of rescue medication. In the primary analysis, that score will be used to impute all scores taken in the 4 hours after the dose of rescue medication, even if the next dose of study medication is taken in that 4 hour period. Provided that another dose of rescue medication has not been taken in that 4-hour period, after the end of the 4-hour period actual pain scores will again be used until either the end of the 48-hour period or the next dose of rescue medication, whichever occurs earlier. If subsequent rescue medication is given, the score measured at the time of the administration of the subsequent rescue medication will continue to be imputed up to 4 hours after that rescue medication intake.

A sensitivity analysis will be done in which that imputation will not be done and all scores will be analysed as recorded.

If patients take other analgesic medication during the study other than allowed rescue medication, then all subsequent pain assessments will be treated as missing and handled as described in section 6.1.1 above.

6.1.3 Pooling of Centres

No pooling of centres is planned. In the unlikely event that any centre recruits too few subjects to be analysed as a centre in its own right, a decision will be made about pooling of centres at the blinded data review meeting.

6.1.4 Visit Windows

As the subjects are confined to the study site for the duration of the efficacy assessment period, the question of visit windows is not relevant.

6.2 Details of Original Efficacy Variables

The following efficacy variables will be collected directly, and will be reported in their own right and used to calculate the derived variables as described in section 6.3.

6.2.1 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, and 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.

If patients assessed their pain intensity at times deviating from the nominal time by more than acceptable windows, then their pain intensity scores will still be included in listings, but will be excluded from summary statistics of pain scores, calculation of SPID, and MMRM analysis of pain by timepoint.

Acceptable windows will be defined during the blinded data review meeting.

6.2.2 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, and 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.

If times of assessments differ from nominal times, then values will be excluded from analyses as described above for pain intensity.

6.2.3 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.

6.2.4 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 centre.

6.3 Derived and Computed Variables

The following derived and computed variables have been initially identified as important for the analysis of efficacy. It is expected that additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the define.xml document that accompanies the analysis datasets. If the SAP is not amended, further derivations related to primary and secondary target variables will be described in the CSR.

Table 1: Derived and Computed Variables

Variable Name	**Description**	**Computation Methods**
Baseline	Baseline value (There will be different variable names for different assessments)	Baseline is defined as the last measurement taken before the first study medication administration
PID-x	The pain intensity difference over 0 hour to the x- hour period after Time 0	PID-x = PI at x timepoint – PI at baseline Note: Negative values of PID correspond to an amelioration of pain in the corresponding assessment time compared to the initial intensity, while positive values correspond to an increase in pain.

Variable Name	Description	Computation Methods
SPID-x	The summed pain intensity difference over 0 hour to the x- hour period after Time 0	SPID-x = PID_t1*(t1 ─ 0) + PID_t2*(t2 ─ t1) + … + PID_n*(t[n] ─ t[n ─ 1]), where PID_t[m] is (PI at baseline – PI at m^{th} time-point), and x is the n^{th} time-point; x=4, 6, 12 24, 48. Note: Negative values of SPID correspond to an average amelioration of pain up to the corresponding assessment time compared to the initial intensity, while positive values correspond to an increase in pain. Actual assessment times will be used for this calculation. If the nominal 48-h timepoint is measured early, then the remaining time to 48 h will be imputed as described in section 6.1.1. If the 48 h timepoint is measured late, then the SPID-48 will be measured up to an imputed value at 48 h based on linear interpolation between the 48 h timepoint and the previous measurement. For SPID up to earlier timepoints, if the final timepoint is not taken at exactly the nominal time, then a value will be imputed by linear interpolation at the final timepoint between the previous and following measurements, and the SPID calculated up to that timepoint. In all SPID calculations, individual values will be excluded from analyses if they differ from nominal timepoints by more than acceptable windows, as described in section 6.2.1.
TOTPAR-x	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_x*(t[n] ─ t[n ─ 1]), where PR_t[m] is pain relief score at m time-point, and x is the n^{th} time-point; x= 6, 12, 24, 48 Note: TOTPAR can only take positive values, corresponding the higher values to higher pain relief and a value of 0 to no pain relief compared to the initial intensity. Actual assessment times will be used for this calculation. If the final measurement is not taken exactly at the nominal timepoint, then imputations will be used as described above for calculation of SPID. In all TOTPAR calculations, individual values will be excluded from analyses if they differ from nominal timepoints by more than acceptable windows, as described in section 6.2.1.

Variable Name	Description	Computation Methods
Response-50	Response (50% pain reduction)	Equals 1 if subjects have a 50% reduction in pain intensity from baseline, sustained until the end of the 48 h period, otherwise equals 0. If subjects drop out before the 48 h assessments, they will be considered non-responders.
Response-30	Response (30% pain reduction)	Equals 1 if subjects have a 30% reduction in pain intensity from baseline, sustained until the end of the 48-h period, otherwise equals 0. If subjects drop out before the 48-h assessments, they will be considered non-responders.
Response-4	Response (below 4)	Equals 1 if subjects have a reduction in pain intensity from baseline to below 4 on the NPRS, sustained until the end of the 48-h period, otherwise equals 0. If subjects drop out before the 48-h assessments, they will be considered non-responders.
Response-4-50	Response (below 4 and 50% reduction)	Equals 1 if subjects have a reduction in pain intensity from baseline to below 4 on the NPRS and a 50% reduction from baseline, sustained until the end of the 48-h period, otherwise equals 0. If subjects drop out before the 48-h assessments, they will be considered non-responders.
Response-4-30	Response (below 4 and 30% reduction)	Equals 1 if subjects have a reduction in pain intensity from baseline to below 4 on the NPRS and a 30% reduction from baseline, sustained until the end of the 48-h period, otherwise equals 0. If subjects drop out before the 48-h assessments, they will be considered non-responders.
TTOA	Time to onset of analgesia	Equal to the time to perceptible pain relief, as measured with the first stopwatch, when confirmed by achievement of meaningful pain relief by the subject (as measured with the second stopwatch) within 8 h of dosing. The time will be censored at 8 h if perceptible and meaningful pain relief have not both been recorded by that time point, or at the time of dropout if earlier than 8 h. If rescue medication is taken before meaningful pain relief is recorded (and before 8 h after dosing), then TTOA will be censored at the time of rescue medication.

Variable Name	Description	Computation Methods
TTOPID	Time to onset of pain intensity decrease	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. For any patients who do not have a decrease in pain intensity, this will be censored at 48 h, even for patients who drop out before then.
PPR	Peak pain relief	The minimum (ie most negative) difference from baseline in pain intensity by NPRS, after imputation for any rescue medication (if applicable). Note that if patients have increases from baseline at all post-baseline timepoints, this will be a positive number, and will not actually be a relief.
TTPPR	Time to peak pain relief	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. Subjects who do not experience any pain score lower than baseline will have the time censored at the time of the final pain assessment (48 h after the first dose or early dropout). If a subject records the lowest value of the NPRS at more than one timepoint, the first such timepoint will be used.

For the time to event variables TTOPID and TTPPR, the start time will be taken as the time of the first dose of study medication for all subjects who are dosed. If a patient is randomised in the second step of randomisation but is not then dosed, the start time will be taken as the time of the second step of randomisation.

7. STUDY SUBJECTS AND DEMOGRAPHICS

7.1 Disposition of Subjects and Withdrawals

All subjects who provide informed consent will be accounted for in this study. Descriptive summaries of analysis set data will be presented for all subjects unless otherwise specified and will include the following:

- The frequency and percent of subjects in each analysis set, overall and by treatment group and centre
- The disposition of subjects (including number of study participants, number of subjects undergoing surgery, screening failures, number of subjects randomized in the first randomization step, number of subjects randomized in both randomization steps, number of subjects treated, and number of completers), overall and by treatment group and centre
- Patients who discontinue study medication by reason for discontinuation, overall and by treatment group
- Study withdrawals by reason for withdrawal, overall and by treatment group

In addition, all study withdrawals will be listed.

7.2 Protocol Violations and Deviations

Protocol violations and deviations will be categorized as major or minor at the blinded data review meeting before defining the analysis sets as described in Section 5.

Major protocol violations (ie those leading to exclusion from the PPAS) will be summarized by type of violation, overall and by treatment group. Individual major and minor protocol violations will be listed by subject.

7.3 Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be presented for the safety set. All demographic and baseline characteristics will be presented both overall and by treatment group.

The following demographic and baseline data will be presented:

- Demographics (age, sex, race, and body weight, height, and BMI)
- Medical history: number and percentage of subjects with at least one medical history item in each System Organ Class (SOC) and preferred term
- Prior medications (any medications taken before the baseline visit, irrespective of whether they were recorded in the prior medications log or the concomitant medication log): number and percentage of subjects with at least one drug in each Anatomical Therapeutic Chemical (ATC) level 3 group and preferred term
- Duration of surgery and other surgery characteristics

Demographic and other baseline data will be presented using descriptive statistics only; no hypotheses will be tested.

8. EFFICACY ANALYSIS

This study will examine the efficacy of co-crystal E-58425 in the management of acute pain to support registration with regulatory authorities. The analyses described here are intended as confirmatory analyses.

It may be necessary to complete additional exploratory analyses after the planned analyses are completed. Full details of additional analyses will be presented in the CSR, and any such analyses will be clearly identified as post-hoc.

All statistical tests will be based on a 2-sided test at the significance level of 0.05, unless otherwise specified.

All efficacy variables will be presented with descriptive statistics, broken down by treatment group. In addition, statistical analyses will be presented as described below.

8.1 Primary Efficacy Variable Analysis

In the primary efficacy analysis, the SPID-48h will be compared between the treatment groups. Three separate null hypotheses will be tested:

- The mean SPID-48 in the co-crystal E-58425 group is equal to the mean SPID-48 in the tramadol group
- The mean SPID-48 in the co-crystal E-58425 group is equal to the mean SPID-48 in the celecoxib group
- The mean SPID-48 in the co-crystal E-58425 group is equal to the mean SPID-48 in the placebo group

For the study to be declared successful, all 3 of those null hypotheses must be rejected such that Co-crystal E-58425 shows superiority over each comparator. Because all 3 null hypotheses must be rejected, no adjustment for multiple comparisons is necessary.

The hypotheses will be tested in an analysis of covariance (ANCOVA) model including terms for centre and baseline pain (as a continuous variable). The model will be used to show least squares means of the SPID-48 in each treatment group, and to estimate the difference in least squares means between the co-crystal E-548425 group and each of the 3 control groups, along with 95% confidence intervals and P values associated with those differences.

The primary efficacy analysis will use the FAS.

In the primary analysis, SPID-48 will be imputed as described in Section 6.1.1 if any pain assessments are missing and as described in Section 6.1.2 if subjects take rescue medication.

8.1.1 Sensitivity Analyses of the Primary Efficacy Variable

The primary analysis will be repeated using the PPAS and the CAS as sensitivity analyses.

Sensitivity analyses will also be done (using both the FAS and PP set) for alternative imputation methods for SPID-48 if any pain assessments are missing or if subjects take rescue medication. The following imputation schemes will be used:

Table 2: Imputation schemes

Analysis number	Imputation method for missing data	Imputation method if rescue medication is taken	Analysis model
1	WOCF for dropouts for AE, LOCF otherwise	Same as primary analysis	Same as primary analysis
2	WOCF	Same as primary analysis	Same as primary analysis
3	Same as primary analysis	Values analysed as recorded; no imputation	Same as primary analysis
4	Same as primary analysis	Values analysed as recorded; no imputation	Additional adjustment for rescue medication use
5	Multiple imputation	Same as primary analysis	Same as primary analysis

For analysis 4, the ANOVA model will also be adjusted for rescue medication use. This will include terms for the number of rescue medication doses taken of each kind (ie one term for number of acetaminophen doses taken, and one term for the number of oxycodone doses taken), as continuous variables.

For analysis 5, a jump to control multiple imputation analysis on missing pain scores on the ITT population will be done. The analysis has three broad components: i) the multiple imputation process for the placebo data; ii) the multiple imputation process for the treated patient's data; and iii) the analysis model that will be used to draw inference regarding the primary causal estimand along with the method for combining the results across the multiply imputed datasets.

i. The imputation for the placebo group will be carried out in SAS using the full conditional specification method (FCS) with a regression model approach.[5] Since the method assumes the missing data are missing at random (MAR), the result will be that patients will have imputed values that are similar to other patients at that site with similar baseline and post-baseline pain scores. The method then repeats the operation multiple times to iterate to a stable solution. The algorithm will use 20 burn-in iterations before each imputation. The variables included sequentially in the model are sex, centre, baseline pain, and then the post-baseline pain. A minimum of 1000 imputed datasets will be created for the analysis.

ii. The imputation of missing values for treated patients in each individual active treatment group assumes the data after withdrawal are missing not at random (MNAR) while intermittent missing data up to discontinuation from the study are MAR. This imputation process will proceed in a multi-stage fashion. The first stage will be to impute only intermittent missing values for the treated patients assuming the intermittent missing values are MAR. The second stage will impute missing monotone post-withdrawal in a sequential manner using a method proposed by Ratitch and O'Kelly.[6] During the second stage, at each timepoint with missing data on treated patients, PROC MI will be used with a dataset that contains complete data for all placebo patients (observed and imputed under MAR) and the treated patients with missing data at that time point. Therefore, the imputation model will be fit based

solely on placebo patients and the treated patients will have values imputed as if they were placebo patients. The first stage to impute the intermittent missing values will proceed as described for the imputation of missing data in the placebo arm using a FCS method with a regression model. The algorithm will use 20 burn-in iterations before each imputation. The variables included sequentially in the model are sex, centre, baseline pain score and then the post-baseline pain scores. A minimum of 1000 imputed datasets (the number of datasets will match the number of imputed datasets for the placebo arm) will be created for the analysis. The post-withdrawal values in each of the imputed datasets for the imputed arm will then be set to missing, thus leaving a dataset with multiply imputed values and monotone missing data patterns due to early termination. The second stage of the imputation procedure will handle the MNAR imputation for the monotone missing post-withdrawal data in the treated patients. A dataset will then be created with all placebo patients including their observed and imputed data. Treated patients will have all post-withdrawal/post-treatment pain scores set to missing. These groups will then be combined. The second stage imputation will be done sequentially by timepoint for each first stage imputation.

iii. The analysis model will be an analysis of covariance (ANCOVA) with SPID-48 (calculated from the imputed data) as the dependent variable, treatment and centre as categorical variables and baseline pain as a covariate. The causal estimand will be estimated using the difference in the least squares means between the co-crystal E-58425 group and the other treatment groups. The ANCOVA results from the multiply imputed datasets will be combined using the usual Rubin's rules for multiple imputation[7] (Little and Rubin, 1987) and will be done in SAS using PROC MIANALYZE. A significance test of the treatment difference will be tested at the two-sided 0.05 level and corresponding 95% confidence intervals will be calculated.

8.2 Secondary Efficacy Variable Analysis

No formal statistical inferences will be drawn from secondary efficacy analyses. Any P values presented from secondary efficacy analyses will be interpreted in an exploratory sense only.

The following efficacy variables will be analysed in the same manner as the primary analysis, but without any sensitivity analyses:

- SPID-4
- SPID-6
- SPID-12
- SPID-24
- PID at 4, 6, 12, 24 and 48 hours
- TOTPAR-4
- TOTPAR-6
- TOTPAR-12
- TOTPAR-24
- TOTPAR-48

- PAR at 4, 6, 12, 24 and 48 hours

PID at each timepoint and PAR at each timepoint will also be analysed in a mixed model for repeated measures (MMRM) ANCOVA analysis. For each variable (PID and PAR), all post-baseline timepoints will be included in the analysis as dependent variables (except those where the time of measurement deviated from the nominal time by more than acceptable windows: see section 6.2.1). The model will include treatment, timepoint, treatment by timepoint interaction, centre, and baseline as fixed effects, and subject as a random effect. An unstructured covariance matrix will be used to model the within-subject correlations by timepoint. If the model fails to converge, alternative covariance structures, such as compound symmetry, will be tried instead. The model will be used to show estimated treatment effects at each timepoint, together with their 95% confidence intervals and P values, for the comparison of co-crystal E-58425 against each comparator.

Peak pain relief will be compared between the treatment groups using an ANCOVA model, adjusting for centre and baseline pain. The estimated difference in peak pain relief will be presented for co-crystal E-58425 versus each other treatment group, together with its 95% confidence interval and P value.

The following binary variables will be compared between the treatment groups using logistic regression, adjusting for centre and baseline pain. The odds ratio for response (or rescue medication use) will be presented for co-crystal E-58425 versus each other treatment group, together with its 95% confidence interval and P value.

- Responder (50%)
- Responder (30%)
- Responder (score of 4 or less)
- Responder (score of 4 or less and 50%)
- Responder (score of 4 or less and 30%)
- Whether subjects used any rescue medication at any time (yes or no, and by type of rescue medication)
- Whether subjects used any rescue medication in the first 4 hours after dosing (yes or no, and by type of rescue medication)
- Whether subjects used any rescue medication in the first 6 hours after dosing (yes or no, and by type of rescue medication)
- Whether subjects used any rescue medication in the first 12 hours after dosing (yes or no, and by type of rescue medication)
- Whether subjects used any rescue medication in the first 24 hours after dosing (yes or no, and by type of rescue medication)

The number of doses of each kind of rescue medication taken will also be presented with descriptive statistics. In addition, the number of doses of rescue medication taken (ignoring which kind of rescue medication is used) will be compared between the treatment groups using ordinal logistic regression. The model will be used to estimate odds ratios together with their 95% confidence intervals for the comparison of co-crystal E-58425 versus each of the comparators. If some patients take large number of doses, numbers of doses of rescue medication may be combined into categories for the purpose of that analysis; this will be decided at the blinded data review meeting.

As a sensitivity analysis, the analyses of responders will be repeated for a definition which does not include the obligation to have a sustained response up to 48 hours.

Response will be plotted graphically by showing the cumulative proportion of responders over time for each treatment group. Separate graphs will be produced for each of the 5 definitions of response (but without the sensitivity analysis mentioned above).

The patients global assessment of study medication will be presented by tabulating the number and percentage of patients in each category by treatment group. The global assessment will also be compared between treatment groups using ordinal logistic regression. The model will be used to estimate odds ratios together with their 95% confidence intervals for the comparison of co-crystal E-58425 versus each of the comparators.

The following time-to-event variables will be compared between the treatment groups using Cox proportional hazards regression, adjusting for centre and baseline pain. The hazard ratio for response (or rescue medication use) will be presented for co-crystal E-58425 versus each other treatment group, together with its 95% confidence interval and P value. The median and first and third quartiles of the time to event will also be estimated, together with their 95% confidence intervals, and the times to event will be shown graphically with Kaplan-Meier graphs.

- TTOA
- Time to perceptible pain relief
- Time to meaningful pain relief
- Time to onset of pain intensity decrease
- TTPPR
- Time to response (50%)
- Time to response (30%)
- Time to response (score of 4 or less)
- Time to response (score of 4 or less and 50%)
- Time to response (score of 4 or less and 30%)
- Time to first use of rescue medication

Calculation of TTOA and TTPPR are described in Section 6.3. Time to perceptible and meaningful pain relief are recorded directly in the CRF, and will be censored at 8 h (even in the case of early dropout) if a time is not recorded, and will be censored at the time of the first rescue medication dose if rescue medication is taken before pain relief is recorded or before 8 h, whichever is the earlier. Time to response is the time at which the definition of response is first met, or if it is not met, it is censored at 48 hours (even in the case of early dropout). Time to first use of rescue medication is also censored at 48 hours or at the time of early dropout (or the time of the second randomisation for subjects who are never dosed with study medication) for subjects who do not take rescue medication. The start time for those time to event variables will be the time of the first dose of study medication, or the time of the second randomisation in the case of any patients who undergo both randomisation steps but are not dosed with study medication.

The raw NPRS scores, the change from baseline in NPRS, and the raw pain relief scores at each timepoint will be presented with descriptive statistics and graphs.

8.3 Subgroup Analysis of Efficacy Variables

For assessing consistency of efficacy results, the primary and key secondary efficacy analyses will be repeated separately for subgroups of subjects defined by:

- moderate (NPRS = 5 or 6) or severe (NPRS = 7, 8 or 9) baseline pain
- age => 65 years vs. < 65 years old
- gender
- race (if some categories have only few patients, they may be combined into an "other" group for this analysis: this will be determined at the blinded data review meeting)
- centre

For all of these subgroups, primary and key secondary endpoint analysis models will be repeated, including subgroup and subgroup*treatment interaction as fixed effects. These statistical models will be used to calculate least squares mean estimates for the treatment differences or odds ratios, as appropriate, the corresponding two-sided 95% confidence intervals and p-values from 2-sided test on no difference between co-crystal E-58425 and each of the comparators in each level of the defined subgroup. P-value from the interaction test will also be presented. Results will further be illustrated using Forest Plots.

9. SAFETY AND TOLERABILITY ANALYSIS

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each subject:

- Adverse events
  - Adverse events (AEs), treatment-emergent AEs (TEAEs), and serious adverse events (SAEs)
  - AEs leading to withdrawal
  - Any deaths
- Clinical laboratory test results (chemistry, haematology, urinalysis)
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature)
- Electrocardiogram variables (ECG)
- Concomitant medications
- Study medication exposure

All safety analyses will use the safety analysis set.

9.1 Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA dictionary (the most recent version before starting the trial will be used).

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.

If the start date and time of an AE are partially or completely missing, the AE will be assumed to be treatment-emergent if it cannot be definitely shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach). Missing dates and times will not be replaced.

The following are used for guidance for programmers.

- If the start time of an AE is missing, but the start date is complete, an AE will only be excluded from TEAEs if the start day is before the day of first dose of study medication or the start day is after the last day of the treatment-emergent period.
- If the start time and day are missing but the start month is complete, an AE will only be excluded from TEAEs if the start month is before the month of the first dose of study medication, or the start month is after last month of the treatment-emergent period, or if the stop date/time is before the first dose of study medication.
- If the start day and months are missing but the start year is complete, an AE will only be excluded from TEAEs if the start year is before the year of the first dose of study medication, or if the start year is after the last year of the treatment-emergent period, or if the stop date/time is before the first dose of study medication.

If the start date is completely missing, an AE will not be excluded from TEAEs unless the stop date/time is before the first dose of study medication.

All AEs will be summarized in a table whose rows give the number and percentage of subjects reporting at least one AE and the number of reported AEs for each of the following:

- Any AE
- Any TEAE
- Any serious TEAE
- Any drug-related serious TEAE
- Any serious TEAE leading to death
- Any drug-related TEAE
- Any severe TEAE
- Any TEAE requiring additional therapy
- Any TEAEs leading to discontinuation of study medication
- Any TEAEs of special interest

Summaries of incidence rates (frequencies and percentages of subjects reporting at least one AE) and the number of reported AEs of individual TEAEs by MedDRA SOC and preferred term will be prepared. Such summaries will be displayed for all TEAEs, TEAEs by maximum intensity, and TEAEs by strongest relationship to study medication.

Each subject will be counted only once within each preferred term. If a subject experiences more than 1 TEAE within a preferred term, only the TEAE with the strongest relationship or the maximum intensity, as appropriate, will be included in the summaries of relationship and intensity.

The most frequent TEAEs, defined as PTs reported in more than 5% of subjects in any treatment group will also be summarised.

The proportion of patients reporting at least one TEAE will be compared pairwise between co-crystal E-58425 and each of the comparators using logistic regression, adjusting for centre. The adjusted odds ratio for the treatment effect will be presented together with its 95% confidence interval, as well as the corresponding P value. The same statistical test will be used for the comparison between pairwise treatment groups of the proportion of patients reporting at least one TEAEs leading to withdrawal of study medication, at least one SAEs, and at least one TEAE of special interest, described in the following sections.

In the AE data listings, all AEs will be displayed. Adverse events that are not treatment-emergent will be flagged.

9.1.1 Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages of subjects) and number of episodes of TEAEs leading to withdrawal of study medication, by treatment group, SOC, and preferred term, will be prepared.

A data listing of AEs leading to withdrawal of study medication will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2 Serious Adverse Events

A summary of incidence rates (frequencies and percentages of subjects) and number of episodes of SAEs by treatment group, SOC, and preferred term will be prepared.

A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF.

9.1.3 TEAEs of special interest

As specified in the protocol, TEAEs of special interest include the following:

- Common AEs observed with tramadol: dizziness, vertigo, nausea, constipation, headache, and somnolence
- Common AEs observed with opioids: fatigue, inability to concentrate, itching, difficulty with urination, confusion, dry mouth, and vomiting

A summary of incidence rates (frequencies and percentages of subjects) and number of episodes of TEAEs of special interest, by treatment group, SOC, and preferred term, will be prepared.

Additional summaries will be provided on TEAEs from each of the following classes:

- Nausea and vomiting
- Central nervous system depression such as somnolence, sedation, disorientation/confusion and dizziness.

These lists of preferred terms considered to be of special interest will be checked at the blinded data review meeting, which will be held before database lock.

9.2 Clinical Laboratory Test Results

Descriptive summaries of absolute values and changes from baseline values will be presented for clinical chemistry and haematology tests by treatment and timepoint.

The number of subjects with clinical laboratory values (chemistry, haematology, and urinalysis) categorised as below, within, or above normal ranges (or as either normal or abnormal for urinalysis variables that do not have quantitative ranges) and whether they are clinically significant or not will be tabulated for each clinical laboratory analyte by treatment group and time.

The number of subjects with clinical laboratory values (chemistry, haematology, and urinalysis) categorized as below, within, or above normal ranges (or as either normal or abnormal for urinalysis variables that do not have quantitative ranges), will be tabulated showing change from baseline (shift tables) for each clinical laboratory analyte by treatment group and by time.

Laboratory values will be displayed in the data listings and those that are outside the normal range will be flagged, along with corresponding normal ranges

9.3 Vital Signs

Descriptive summaries of absolute values and changes from baseline will be calculated for systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), temperature, and respiratory rate (RR). These summaries will be presented by treatment and timepoint.

Summaries of whether vital signs are below, within, or above the normal ranges, and whether results are clinically significant, will also be presented by treatment and timepoint.

Shift tables will be presented for vital signs by treatment and timepoint, showing the number of vital sign measurements below, within, or above the normal ranges, and whether any

abnormalities are clinically significant. Normal ranges for vital signs are defined in the table below (Table 3).

Table 3: Normal ranges for vital signs

Vital signs:	Normal Ranges
Temperature	35–37.5ºC
Respiratory Rate	12–20 bpm
Pulse Rate	40–100 bpm
Systolic Blood Pressure (Supine)	80–140 mmHg
Diastolic Blood Pressure (Supine)	40–90 mmHg

9.4 ECGs

Descriptive summaries of absolute values will be presented for ECG measures of PR interval, QRS interval, QT interval, QT_C interval (as reported by the ECG machine), and HR. These summaries will be presented by treatment and timepoint. Summaries of the investigator's overall interpretation will also be presented by treatment and timepoint.

Summaries of whether ECG are below, within, or above the normal ranges, and whether results are clinically significant, will also be presented by treatment and timepoint.

Shift tables will be presented for ECG variables by treatment and timepoint, showing the number of ECG measurements below, within, or above the normal ranges, and whether any abnormalities are clinically significant. Normal ranges for ECG variables are shown in the table below.

Table 4: Normal ranges for ECG

Electrocardiogram (ECG):	Normal Ranges
Ventricular Rate (Supine)	40–100 bpm
PR interval	120–200 ms
QRS duration	70–120 ms
QT	350–450 ms
QT_C	350–450 ms

9.5 Concomitant Medication

Concomitant medications will be analysed in the same way as prior medications.

A concomitant medication is defined as any medication that was administered during the treatment period, with the exception of the protocol-specified treatment and rescue medication. This includes medications that started before the Treatment Period and continued

while on treatment (which may have been recorded in the prior medications log) and medications that started during the Treatment Period. The frequency and percentage of patients taking each concomitant medications will be summarized by ATC class 3 and preferred term for all subjects in the safety set, by treatment group. Moreover a table summarizing the patients who take antiemetic concomitant medication will be produced.

If the start/stop dates of a medication are partially or completely missing, then the medication will be assumed to be concomitant if it cannot be definitely shown that it was not administered during the treatment period. Missing dates will not be replaced.

Thus, the following approach will be taken for exclusion from concomitant medications because of discontinuation before start of treatment:

- If the stop day is missing but the month is complete, then the medication will be excluded from concomitant medications only if the stop month is before the month of the first dose of study medication.
- If the stop day and month are missing but the year is complete, then the medication will be excluded from concomitant medications only if the stop year is before the year of the first dose of study medication.
- If the stop date is completely missing, then the medication will not be excluded.

For concomitant medication exclusion (because of the late start after the end of the Treatment Period):

- If the start day is missing but the month is complete, then the medication will be excluded from concomitant medications only if the start month is after the last month of the treatment period.
- If the start day and month are missing but the year is complete, then the medication will be excluded from concomitant medications only if the start year is after the year of the treatment period.
- If the start date is completely missing, then the medication will not be excluded.

9.6 Exposure and Compliance

Investigational product administration will be summarized in terms of the number of doses received, and in terms of duration of exposure, from first dose to last dose of the study treatment. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided by treatment group.

Compliance will be calculated as the number of doses the subject actually received as a percentage of the number of doses the subject would have received if the study were completed.

10. CHANGES FROM PLANNED ANALYSIS

No changes from the analyses specified in the protocol are planned.

11. OTHER PLANNED ANALYSIS

No other analyses are planned for this study.

12. REFERENCES

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
2. ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999. http://www.amstat.org/about/ethicalguidelines.cfm
3. RSS. (1993) The Royal Statistical Society: Code of Conduct, April 1993. http://www.rss.org.uk/main.asp?page=1875.
4. Friede T, Kieser M, 2013. Blinded sample size re-estimation in superiority and noninferiority trials: bias versus variance in variance estimation. Pharmaceutical statistics, 12(3), pp.141-146.
5. Carpenter, J. R., and Kenward, M. G. (2013), Multiple Imputation and its Application (Statistics in Practice), Wiley.
6. Ratitich, B. and O'Kelly, M. (2011), "Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures," PharmaSUG. Available at http://www.pharmasug.org/proceedings/2011/SP/PharmaSUG-2011-SP04.pdf
7. Little, R. and Rubin, D. (1987), Statistical Analysis with Missing Data, New York: Wiley.

13. TABLES, LISTINGS, AND FIGURES

The description of the planned tables, listings and figures will be provided in this section in the next version of this SAP

13.1 Planned Table Descriptions

The following are planned summary tables for the study. The numbering is intended to be compatible with the format of clinical study reports as per ICH E3 (ICH, 1995), so tables are included in section 14 of the report.

Tables will be split according to population adding an additional table extension digit, e.g. Table 14.1.2.1 will split into 14.1.2.1.1 (FAS), 14.1.2.1.2 (PPAS), 14.1.2.1.3 (CAS), and 14.1.2.4 (SAS).

Table Number	Population(s)	Table Title / Summary	Supporting listing
14.1 Demographic and baseline tables			
14.1.1	ALL	Analysis populations	16.2.1.1
14.1.2	ALL	Analysis populations by centre	16.2.1.1
14.1.3	ALL	Disposition of patients	16.2.1.2
14.1.4	ALL	Disposition of patients by centre	16.2.1.2
14.1.5	All patients not fully randomised	Summary of reasons for screening failure	16.2.2.2
14.1.6	FAS	Summary of reasons for discontinuation of study medication	16.2.1.3
14.1.7	FAS	Summary of reasons for withdrawal	16.2.1.3
14.1.8	FAS	Summary of major protocol violations	16.2.2.1
14.1.9	FAS	Summary of demographic data: age, body weight, height, and BMI	16.2.4.1
14.1.10	FAS	Summary of demographic data: sex, ethnicity, and race	16.2.4.1
14.1.11	FAS	Medical history by SOC and preferred term	16.2.4.2
14.1.12	FAS	Prior medication by ATC level 3 and preferred term	16.2.4.3
14.1.13	FAS	ASA classification	16.2.4.4
14.1.14	FAS	X-ray and podiatric examination	16.2.4.5
14.1.15	FAS	Duration of bunionectomy procedure	16.2.4.6
14.2 Efficacy tables			
14.2.1	FAS, PPAS, CAS	SPID-48: summary statistics	16.2.6.2
14.2.2	FAS, PPAS, CAS	SPID-48: primary ANCOVA analysis	16.2.6.2
14.2.3.1	FAS, PPAS	SPID-48: sensitivity analysis 1 (WOCF for dropouts due to AEs or lack of efficacy)	16.2.6.2
14.2.3.2	FAS, PPAS	SPID-48: sensitivity analysis 2 (WOCF imputation for all missing data)	16.2.6.2
14.2.3.3	FAS, PPAS	SPID-48: sensitivity analysis 3 (no imputation for rescue medication use)	16.2.6.2

Table Number	Population(s)	Table Title / Summary	Supporting listing
14.2.3.4	FAS, PPAS	SPID-48: sensitivity analysis 4 (adjusted analysis for rescue medication)	16.2.6.2
14.2.3.5	FAS, PPAS	SPID-48: sensitivity analysis 5 (multiple imputation)	16.2.6.2
14.2.4.1	FAS	SPID-48: subgroup analysis by baseline pain, summary statistics	16.2.6.2
14.2.4.2	FAS	SPID-48: subgroup analysis by baseline pain, ANCOVA analysis	16.2.6.2
14.2.4.3	FAS	SPID-48: subgroup analysis by age, summary statistics	16.2.6.2
14.2.4.4	FAS	SPID-48: subgroup analysis by age, ANCOVA analysis	16.2.6.2
14.2.4.5	FAS	SPID-48: subgroup analysis by sex, summary statistics	16.2.6.2
14.2.4.6	FAS	SPID-48: subgroup analysis by sex, ANCOVA analysis	16.2.6.2
14.2.4.7	FAS	SPID-48: subgroup analysis by race, summary statistics	16.2.6.2
14.2.4.8	FAS	SPID-48: subgroup analysis by race, ANCOVA analysis	16.2.6.2
14.2.4.9	FAS	SPID-48: subgroup analysis by centre, summary statistics	16.2.6.2
14.2.4.10	FAS	SPID-48: subgroup analysis by centre, ANCOVA analysis	16.2.6.2
14.2.5.1	FAS	SPID by timepoint: summary statistics	16.2.6.2
14.2.5.2	FAS	SPID by timepoint: ANCOVA analysis	16.2.6.2
14.2.6.1	FAS	TOTPAR by timepoint: summary statistics	16.2.6.4
14.2.6.2	FAS	TOTPAR by timepoint: ANCOVA analysis	16.2.6.4
14.2.7.1	FAS	TOTPAR-48: subgroup analysis by baseline pain, summary statistics	16.2.6.4
14.2.7.2	FAS	TOTPAR-48: subgroup analysis by baseline pain, ANCOVA analysis	16.2.6.4
14.2.7.3	FAS	TOTPAR-48: subgroup analysis by age, summary statistics	16.2.6.4
14.2.7.4	FAS	TOTPAR-48: subgroup analysis by age, ANCOVA analysis	16.2.6.4
14.2.7.5	FAS	TOTPAR-48: subgroup analysis by sex, summary statistics	16.2.6.4
14.2.7.6	FAS	TOTPAR-48: subgroup analysis by sex, ANCOVA analysis	16.2.6.4
14.2.7.7	FAS	TOTPAR-48: subgroup analysis by race, summary statistics	16.2.6.4
14.2.7.8	FAS	TOTPAR-48: subgroup analysis by race, ANCOVA analysis	16.2.6.4
14.2.7.9	FAS	TOTPAR-48: subgroup analysis by centre, summary statistics	16.2.6.4
14.2.7.10	FAS	TOTPAR-48: subgroup analysis by centre, ANCOVA analysis	16.2.6.4

Table Number	Population(s)	Table Title / Summary	Supporting listing
14.2.8.1	FAS	Pain intensity and pain intensity difference by timepoint: summary statistics	16.2.6.1
14.2.8.2	FAS	Pain intensity difference by timepoint: ANCOVA analysis	16.2.6.1
14.2.8.3	FAS	Pain intensity difference by timepoint: MMRM analysis	16.2.6.1
14.2.9.1	FAS	Pain relief by timepoint: summary statistics	16.2.6.3
14.2.9.2	FAS	Pain relief by timepoint: ANCOVA analysis	16.2.6.3
14.2.9.3	FAS	Pain relief by timepoint: MMRM analysis	16.2.6.3
14.2.10.1	FAS	Peak pain relief: summary statistics	16.2.6.5
14.2.10.2	FAS	Peak pain relief: ANCOVA analysis	16.2.6.5
14.2.11.1	FAS	Peak pain relief: subgroup analysis by baseline pain, summary statistics	16.2.6.5
14.2.11.2	FAS	Peak pain relief: subgroup analysis by baseline pain, ANCOVA analysis	16.2.6.5
14.2.11.3	FAS	Peak pain relief: subgroup analysis by age, summary statistics	16.2.6.5
14.2.11.4	FAS	Peak pain relief: subgroup analysis by age, ANCOVA analysis	16.2.6.5
14.2.11.5	FAS	Peak pain relief: subgroup analysis by sex, summary statistics	16.2.6.5
14.2.11.6	FAS	Peak pain relief: subgroup analysis by sex, ANCOVA analysis	16.2.6.5
14.2.11.7	FAS	Peak pain relief: subgroup analysis by race, summary statistics	16.2.6.5
14.2.11.8	FAS	Peak pain relief: subgroup analysis by race, ANCOVA analysis	16.2.6.5
14.2.11.9	FAS	Peak pain relief: subgroup analysis by centre, summary statistics	16.2.6.5
14.2.11.10	FAS	Peak pain relief: subgroup analysis by centre, ANCOVA analysis	16.2.6.5
14.2.12	FAS	Responder analysis	16.2.6.6
14.2.13	FAS	Rescue medication use	16.2.6.10
14.2.14.1	FAS	Number of doses of rescue mediation: summary statistics	16.2.6.11
14.2.14.2	FAS	Number of doses of rescue medication: ordinal logistic regression analysis	16.2.6.11
14.2.15.1	FAS	Time to onset of analgesia, onset of pain intensity decrease, and peak pain relief: quartiles of distribution	16.2.6.7
14.2.15.2	FAS	Time to onset of analgesia, onset of pain intensity decrease, and peak pain relief: Cox regression analysis	16.2.6.7
14.2.16.1	FAS	Time to response: quartiles of distribution	16.2.6.8
14.2.16.2	FAS	Time to response: Cox regression analysis	16.2.6.8

Table Number	Population(s)	Table Title / Summary	Supporting listing
14.2.17.1	FAS	Time to first use of rescue medication: quartiles of distribution	16.2.6.12
14.2.17.2	FAS	Time to first use of rescue medication: Cox regression analysis	16.2.6.12
14.2.17.3	FAS	Patient global evaluation of study drug: summary statistics	16.2.6.13
14.2.17.4	FAS	Patient global evaluation of study drug: ordinal logistic regression	16.2.6.13
14.3 Safety and tolerability tables			
14.3.1 Displays of adverse events			
14.3.1.1	SAS	Summary of all Aes	16.2.7.1
14.3.1.2	SAS	TEAEs by SOC and preferred term	16.2.7.1
14.3.1.3	SAS	TEAEs by severity	16.2.7.1
14.3.1.4	SAS	TEAEs by relationship to study medication	16.2.7.1
14.3.2 Displays of serious and other significant adverse events			
14.3.2.1	SAS	SAEs by SOC and preferred term	16.2.7.2
14.3.2.2	SAS	Aes leading to withdrawal from the study by SOC and preferred term	16.2.7.3
14.3.2.3	SAS	TEAEs of special interest by SOC and preferred term	16.2.7.4
14.3.2.4	SAS	Summary of TEAEs of nausea and vomiting	16.2.7.4
14.3.2.5	SAS	Summary of TEAEs of central nervous system depression	16.2.7.4
14.3.3 Laboratory data tables			
14.3.3.1	SAS	Clinical chemistry results: absolute values	16.2.8.1
14.3.3.2	SAS	Clinical chemistry results: change from baseline	16.2.8.1
14.3.3.3	SAS	Clinical chemistry results: normal range indicators and clinical significance by time	16.2.8.1
14.3.3.4	SAS	Shift tables of clinical chemistry results	16.2.8.1
14.3.3.5	SAS	Haematology results: absolute values	16.2.8.2
14.3.3.6	SAS	Haematology results: change from baseline	16.2.8.2
14.3.3.7	SAS	Haematology results: normal range indicators and clinical significance by time	16.2.8.2
14.3.3.8	SAS	Shift tables of haematology results	16.2.8.2
14.3.3.9	SAS	Urinalysis results: normal range indicators and clinical significance by time	16.2.8.3
14.3.3.10	SAS	Shift tables of urinalysis results	16.2.8.3
14.3.4 Other safety and tolerability tables			
14.3.4.1	SAS	Vital signs results: absolute values	16.2.9.2

Table Number	Population(s)	Table Title / Summary	Supporting listing
14.3.4.2	SAS	Vital signs results: change from baseline	16.2.9.2
14.3.4.3	SAS	Vital signs results: normal range indicators and clinical significance	16.2.6.2
14.3.4.4	SAS	Shift tables of vital signs results	16.2.9.2
14.3.4.5	SAS	ECG results: absolute values	16.2.9.3
14.3.4.6	SAS	ECG results: change from baseline	16.2.9.3
14.3.4.7	SAS	ECG results: normal range indicators and clinical significance	16.2.9.3
14.3.4.8	SAS	ECG results: investigator's overall interpretation	16.2.9.3
14.3.4.9	SAS	Shift tables of ECG results	16.2.9.3
14.3.4.10	SAS	Summary of concomitant medications by ATC level 3 and preferred term	16.2.9.4
14.3.4.11	SAS	Summary of antiemetic medications by preferred term	16.2.9.4
14.3.4.12	SAS	Summary of exposure and compliance	16.2.5.2

13.2 Planned Listing Descriptions

The following are planned data and patient data listings for the study. The numbering is intended to be compatible with the format of CSRs as per ICH E3 (ICH, 1995), so listings are included in section 16.2 of the report.

Data Listing Number	Population	Data Listing Title / Summary
16.2.1 Patient disposition		
16.2.1.1	All patients	Assignment to analysis populations and treatment group
16.2.1.2	All patients	Study completion status
16.2.1.3	FAS	List of reasons for discontinuation of study medication and withdrawal from the study
16.2.1.4	All patients	List of visit dates
16.2.2 Protocol deviations		
16.2.2.1	All patients	List of all protocol violations
16.2.2.2	All patients	List of violations of inclusion or exclusion criteria
16.2.3 Patients excluded from the efficacy analysis		
16.2.3.1	All patients	List of patients excluded from the FAS, PPAS, or CAS analysis sets, with reasons for exclusion
16.2.4 Demographic and other baseline characteristics		
16.2.4.1	FAS	Demographic data
16.2.4.2	FAS	Medical history

Data Listing Number	Population	Data Listing Title / Summary
16.2.4.3	FAS	Prior medications
16.2.4.4	FAS	ASA classification
16.2.4.5	FAS	X-ray and podiatric examination
16.2.4.6	FAS	Bunionectomy procedure details
16.2.5 Drug compliance listings		
16.2.5.1	FAS	Drug administration data – individual doses
16.2.5.2	FAS	Drug administration data – calculated variables on overall treatment period
16.2.6 Individual efficacy listings		
16.2.6.1	FAS	Pain intensity and pain intensity difference at each timepoint
16.2.6.2	FAS	Sum of pain intensity differences
16.2.6.3	FAS	Pain relief at each timepoint
16.2.6.4	FAS	TOTPAR scores
16.2.6.5	FAS	Peak pain relief
16.2.6.6	FAS	Response classification
16.2.6.7	FAS	Time to onset of analgesia, onset of pain intensity decrease, and peak pain relief
16.2.6.8	FAS	Time to response
16.2.6.9	FAS	List of rescue medication
16.2.6.10	FAS	Rescue medication use by time period
16.2.6.11	FAS	Number of doses of rescue medication used
16.2.6.12	FAS	Time to first use of rescue medication
16.2.6.13	FAS	Patient global evaluation of study drug
16.2.7 Adverse event listings		
16.2.7.1	SAS	Listing of all AEs
16.2.7.2	SAS	Listing of SAEs
16.2.7.3	SAS	Listing of AEs leading to withdrawal
16.2.7.4	SAS	Listing of TEAEs of special interest
16.2.8 Laboratory data listings		
16.2.8.1	SAS	Clinical chemistry results
16.2.8.2	SAS	Hematology results
16.2.8.3	SAS	Urinalysis results
16.2.9 Listings of other clinical observations and measurements		
16.2.9.1	SAS	Vital signs results
16.2.9.2	SAS	ECG results
16.2.9.3	SAS	Concomitant medications

13.3 Planned Figure Descriptions

The following are planned summary figures for the study. Figures will numbered according to the ICH E3 guidelines CSRs (ICH, 1993), and so will be included in section 14, after the tables.

Figure Number	Population	Figure Title / Summary	Supporting table or listing
14.4 Efficacy figures			
14.4.1	FAS	Pain intensity by timepoint and treatment	14.2.8.1
14.4.2	FAS	Pain intensity difference by timepoint and treatment	14.2.8.1
14.4.3	FAS	Pain relief by timepoint and treatment	14.2.9.1
14.4.4	FAS	Kaplan–Meier graph of TTOA by treatment	16.2.6.7
14.4.5	FAS	Kaplan–Meier graph of time to perceptible pain relief by treatment	16.2.6.7
14.4.6	FAS	Kaplan–Meier graph of time to meaningful pain relief by treatment	16.2.6.7
14.4.7	FAS	Kaplan–Meier graph of time to onset of pain intensity decrease by treatment	16.2.6.7
14.4.8	FAS	Kaplan–Meier graph of TTPPR by treatment	16.2.6.7
14.4.9	FAS	Kaplan–Meier graph of time to response (50%) by treatment	16.2.6.8
14.4.10	FAS	Kaplan–Meier graph of time to response (30%) by treatment	16.2.6.8
14.4.11	FAS	Kaplan–Meier graph of time to response (score of 4 or less) by treatment	16.2.6.8
14.4.12	FAS	Kaplan–Meier graph of time to response (score of 4 or less and 50%) by treatment	16.2.6.8
14.4.13	FAS	Kaplan–Meier graph of time to response (score of 4 or less and 30%) by treatment	16.2.6.8
14.4.14	FAS	Kaplan–Meier graph of time to first use of rescue medication by treatment	16.2.6.12
14.4.15	FAS	Cumulative proportion of response (50%) by treatment	16.2.6.8
14.4.16	FAS	Cumulative proportion of response (30%) by treatment	16.2.6.8
14.4.17	FAS	Cumulative proportion of response (score of 4 or less) by treatment	16.2.6.8
14.4.18	FAS	Cumulative proportion of response (score of 4 or less and 50%) by treatment	16.2.6.8
14.4.19	FAS	Cumulative proportion of response (score of 4 or less and 30%) by treatment	16.2.6.8
14.4.20	FAS	Forest plot of subgroup analyses of SPID-48	14.2.4.1, 14.2.4.3, 14.2.4.5. 14.2.4.7

Figure Number	Population	Figure Title / Summary	Supporting table or listing
14.4.21	FAS	Forest plot of subgroup analyses of TOTPAR-48	14.2.7.1, 14.2.7.3, 14.2.7.5. 14.2.7.7
14.4.22	FAS	Forest plot of subgroup analyses of peak pain relief	14.2.11.1, 14.2.11.3, 14.2.11.5. 14.2.11.7

14. TABLE SHELLS

Table shells are provided in a separate document.