STATISTICAL ANALYSIS PLAN

Grunenthal Group

Protocol KF8001-01

NCT03714672 Date: 19Apr2018

A Randomized, Double-Blind, Multi-site, Comparator-Controlled, Phase III Trial to Evaluate the Efficacy and Safety of a Fixed-Dose Combination of Tramadol Hydrochloride and Diclofenac Sodium in Acute Moderate to Severe Pain After Third Molar Extraction

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Approval

Upon review of this document, including table, listing, and figure shells, the undersigned approves the Statistical Analysis Plan. The analysis methods and data presentation are acceptable.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
FAS	Full Analysis Set
FDC	Fixed-dose Combination
HCl	Hydrochloride
HR	Hazard Ratio
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IXR	Interactive X Response
LOCF	Last Observation Carried Forward
LoE	Lack of Efficacy
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
PE	Physical Examination
PID	Pain Intensity Difference
Post-hoc	Unplanned analyses conducted that are not specified in the protocol
PPS	Per Protocol Set
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
SAE	Serious Adverse Event
SD	Standard Deviation
SI	Inernation System of Units
SOC	System Organ Class
SPID	Summed Pain Intensity Difference
TEAE	Treatment Emergent Adverse Event
TOTPAR	Total Pain Relief
VRS	Verbal Rating Scale
WHO-DD	World Health Organization-Drug Dictionary
WOCF	Worst Observation Carried Forward

DEFINITIONS

Allocated subjects	Enrolled subjects who are allocated to IMPs.
Applicable regulatory requirement(s)	Any law(s) and regulation(s) addressing the conduct of clinical trials of IMPs of the jurisdiction where the trial is conducted.
Discontinuation	The act of concluding the participation of an enrolled subject in a trial prior to completion of all activities required by the protocol.
End of the trial	The trial-related end of the trial is defined as the date of last subject out. The subject-related end of trial is defined as date of last contact with the subject according to the protocol.
Enrolled subjects	Subjects who signed an informed consent form.
Screened subjects	Screened subjects are subjects undergoing screening. Screening is any activity concerning subjects who could potentially be enrolled into the trial before the informed consent form is signed.
Enrollment failures	Enrolled subjects who were not allocated to IMP.
First subject allocated	First subject that was randomized and allocated to IMP.
First subject in	Date of first enrolled subject.
Investigational medicinal product	A generic term describing the preparations under investigation in this trial, i.e., the FDC product under development or comparator.
Last subject out	Date of last contact with the last subject according to the protocol.
Subject	Individual who participates in a clinical trial, either as recipient of an IMP or as control.
Treated subjects	Subjects with at least 1 administration of IMP.
Treatment completers	Treatment completers are treated subjects who completed IMP administration according to the protocol.

Enrolled Set	The Enrolled Set will comprise all subjects who signed the informed consent form.
Safety Set	The Safety Set will comprise all subjects allocated and treated with IMPs. Analyses on the Safety Set will be conducted according to actual treatment received.
Full Analysis Set (FAS)	The FAS will comprise all subjects allocated and treated, and with at least 1 non-missing pain relief assessment during the first 4 hours post-baseline. Analyses on the FAS will be conducted according to allocated treatment.
Per Protocol Set (PPS)	The PPS will be defined as a subset of the subjects in the FAS without any major protocol deviations affecting the primary endpoint. Only subjects with no rescue medication use in the first 120 minutes after first dose, who complete at least a follow-up of 4 hours and who comply with the protocol procedures will be included in the PPS. Analyses on the PPS will be conducted according to actual treatment received.
Treatment Emergent Adverse Event (TEAE)	All adverse events occurring beginning with start of study treatment, or those existing adverse events that got worsened after start of study treatment

1. INTRODUCTION

This document outlines in greater details the intended statistical methods described in the protocol to be implemented during the analyses of data collected within the scope of Grunenthal Group Study [Protocol KF8001-01: A randomized, double-blind, multi-site, comparator-controlled, Phase III trial to evaluate the efficacy and safety of a fixed-dose combination of tramadol hydrochloride and diclofenac sodium in acute moderate to severe pain after third molar extraction]. The purpose of this plan is to provide specific guidelines from which the analysis will proceed. Changes made to the SAP after it has been signed but prior to database lock will be documented in an amendment. Any deviations from these guidelines will be documented in the clinical study report (CSR).

2. STUDY OBJECTIVES

The primary objective is:

1. To demonstrate the analgesic efficacy of the tramadol HCl/diclofenac sodium fixed dose combination (FDC) at 2 dose levels (50 mg/50 mg, 25 mg/25 mg) in comparison to the monotherapy of diclofenac sodium 50 mg and tramadol HCl 50 mg. The primary endpoint is pain relief expressed as Total Pain Relief over the 4 hours post-dose period (TOTPAR4).

The specific primary objective breaks down to demonstrating the following:

1. Either tramadol HCl/diclofenac sodium 50 mg/50 mg FDC has superior analgesic efficacy than monotherapy with diclofenac sodium 50 mg,
2. Or tramadol HCl/diclofenac sodium 50 mg/50 mg FDC has superior analgesic efficacy than monotherapy with tramadol HCl 50 mg,
3. Or tramadol HCl/diclofenac sodium 25 mg/25 mg FDC is not inferior to monotherapy with tramadol HCl 50 mg,
4. Or tramadol HCl/diclofenac sodium 25 mg/25 mg FDC is not inferior to monotherapy with diclofenac sodium 50 mg.

The secondary objectives are:

1. To further explore the efficacy of the tramadol HCl/diclofenac sodium FDC at 2 dose levels (50 mg/50 mg, 25 mg/25 mg) in comparison to the monotherapy of diclofenac sodium 50 mg and tramadol HCl 50 mg. The endpoints include:
    a) Total Pain Relief at 6 hours (TOTPAR6), 8 hours post-dose (TOTPAR8)

    b) Summed Pain Intensity Difference (SPID) at 4, 6, 8, and 24 hours post-dose

    c) Time to achieve a 50% reduction of baseline pain (based on the question: *"My starting pain is at least half gone" Yes/No*)

d) Time to onset of first perceptible pain relief (based on the stopwatch question: *"I would like you to stop the 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 difference in the pain that you have had."*)

e) Time to onset of meaningful pain relief (based on the stopwatch question: *"I would like you to stop the stopwatch when you have meaningful pain relief. That is, when the relief is meaningful to you."*)

f) Time to intake of first rescue medication dose

g) Time to request the first dose of rescue medication

2. To compare the overall impression of the subject on the treatment they received. The endpoint is subject's global evaluation of the treatment (5-point Likert Scale) 8 hours or before first intake of rescue medication (whichever was first) and 24 hours after the first dose of Investigational Medicinal Products (IMP).
3. To evaluate the safety profile of the FDC product in comparison to the safety profiles of the monotherapies. The endpoint is incidence and type of adverse events.

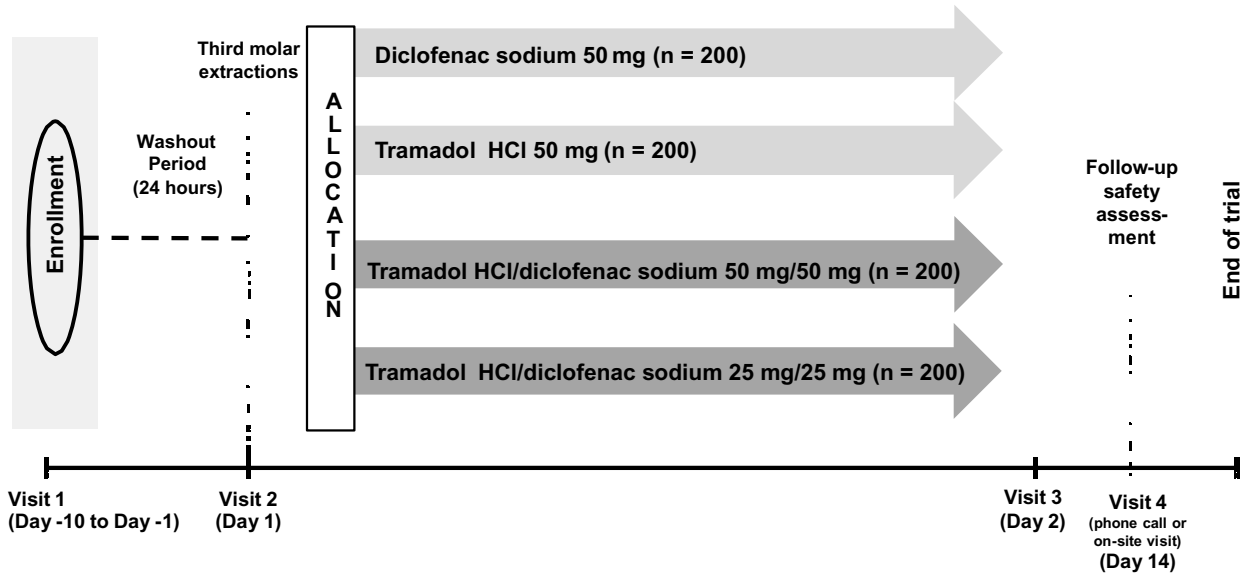
3. STUDY DESIGN

This is a prospective, Phase 3, randomized, double-blind, comparator controlled study of the efficacy and safety of the FDC of Tramadol HCl/diclofenac sodium (25 mg/25 mg and 50 mg/50 mg) in patients with moderate to severe pain after third molar extraction. All subjects will receive a 24-hour treatment course.

The trial is divided into 3 periods. The Enrollment Period comprises the Enrollment Visit [Visit 1] on Day -10 to Day -1 and an at least 24-hour washout of previously used analgesic medication. The Treatment Period includes dental surgery and treatment allocation on Day 1 (Allocation Visit, Visit 2), administration of 2 investigational medicinal product (IMP) doses at the site and of a third dose in an out-patient setting, and an End-of-treatment Visit (Visit 3) at the site. A Follow-up Period concludes with a phone call or an on-site visit (Final Visit) on Day 14 to assess subject's safety. Each subject is expected to be in the trial for approximately 14 days to 24 days.

The summary of the trial can be depicted in the following diagram. A more detailed schedule of events can be found in the protocol Section 1.8.

At the Allocation Visit (Visit 2), the subjects will be monitored for and recorded any adverse event that occurred during or after the surgery.


Enrollment
Washout Period (24 hours)
Third molar extractions
ALLOCATION
Diclofenac sodium 50 mg (n = 200)
Tramadol HCl 50 mg (n = 200)
Tramadol HCl/diclofenac sodium 50 mg/50 mg (n = 200)
Tramadol HCl/diclofenac sodium 25 mg/25 mg (n = 200)
Follow-up safety assess-ment
End of trial
Visit 1 (Day -10 to Day -1)
Visit 2 (Day 1)
Visit 3 (Day 2)
Visit 4 (phone call or on-site visit) (Day 14)

4. DETERMINATION OF SAMPLE SIZE

A total number of 720 subjects or 180 subjects per treatment group are required to achieve an overall power of at least 85% to reject the null hypothesis of at least 1 of the 4 formal statistical tests in the primary analysis of the trial (1-sided t-test, type I error of $\alpha/4$ with α 2.5%) assuming a common standard deviation of change from baseline values of 4 points (TOTPAR4) and an expected treatment difference of at least 2 points (TOTPAR4) on the primary efficacy endpoint in the comparisons between tramadol HCl/diclofenac sodium 50 mg/50 mg and the monotherapies of diclofenac sodium 50 mg and tramadol HCl 50 mg, and using a non-inferiority margin of Δ 1.5 points (TOTPAR4) on the primary efficacy endpoint in the comparisons between tramadol HCl/diclofenac sodium 25 mg/25 mg and the monotherapies of diclofenac sodium 50 mg and tramadol HCl 50 mg. To achieve 180 evaluable subjects per arm and accounting that up to 10% of subjects will not be evaluable for the analysis set for the primary analysis, 200 subjects per arm or 800 subjects in total will be allocated to IMP.

Assuming an enrollment failure rate of about 25% which is usually observed in clinical trials in Mexico, about 1065 subjects are planned to be enrolled (i.e., sign the informed consent) in order to allocate 800 subjects to IMP, i.e., about 130 subjects per trial site in approximately 8 sites.

In summary, the study will be conducted at approximately 8 investigational sites in Mexico, and approximately 1065 patients will be enrolled.

5. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, figures, and data listings. Summary statistics and graphical methods will be used to describe endpoints of interest. For the exact alpha levels for statistical testing for the primary endpoints refer to the Sections 8.6 and 9.1.

The following descriptive statistics will be produced on the basis of the nature of the relevant statistical variable:

- For continuous variables: number of non-missing observations, arithmetic mean, standard deviations, minimum, first quartile (Q1), median (Q2), third quartile (Q3) and maximum.
- For categorical variables: frequencies and percentages.
- For time to event variables: number of non-missing observations, minimum, first quartile (Q1), median (Q2), third quartile (Q3), and maximum.

All the statistical analyses will be performed in the relevant analysis population of interest (see Section 6.0). All the statistical analyses will be performed at least by treatment group.

All summary tables will be presented by treatment group. Baseline summaries will also include a total summary column pooling across the four treatment groups. Summary tables presenting results by study visit will include all scheduled study visits using informative visit labels (i.e., Visit 1, Visit 2, Visit 3, and Visit 4).

Individual subject data obtained from the case report forms (CRFs), local clinical laboratories, radiology, and selected IXR system will be presented by subject in data listings. Listings will include relative study day, where negative values will indicate pre-treatment visits. All data captured on the CRF, including specific descriptions of "other" and comment fields, will be included on the listings. Listings will be sorted by subject number.

The analyses described in this plan are considered *a priori*, in that they have been defined prior to database lock and prior to breaking the blind. Any analyses performed subsequent to breaking the blind will be considered *post-hoc*. *Post-hoc* analyses will be labeled as such on the output and identified in the CSR.

All analyses and tabulations will be performed using SAS® Version 9.4. Tables, listings, and figures will be presented in RTF format. Upon completion, all SAS® programs will be validated by an independent programmer. In addition, all program output will undergo a senior level statistical review. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

5.1 Conventions

The precision of original measurements will be maintained in summaries, when possible. Means, Q1, medians, Q3 and standard deviations will be presented with an increased level of precision; means and Q1, medians, Q3 will be presented to one more decimal place than the raw data, and the standard deviations will be presented to two more decimal places than the raw data.

Summaries of continuous variables that have some values recorded using approximate values (e.g., < or >) will use imputed values. The approximate values will be imputed using the closest exact value for that measurement. For tables where rounding is required, rounding will be done to the nearest round-off unit. For example, if the round-off unit is the ones place (i.e., integers), values ≥ XX.5 will be rounded up to XX+1 while values < XX.5 will be rounded down to XX.

For percentages, unless they are calculated to be exactly 0% or 100%, values of very small or very large percentages will be reported as <0.1% and >99.9%. For by-visit tables, percentages will be based on available data and denominators will generally exclude missing values. For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up" this reason will be included in the table with a count of 0.

5.2 Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- **Baseline** - A baseline value, unless specified otherwise, is the last non-missing value recorded prior to the first dose of study drug. If an assessment has both a

date and time that exactly match the date and time of first dose of study drug, the assessment will be counted as baseline.

- **Study day** For a given date (*date*), study day is calculated as days since the date of first dose of study drug (*firstdose*):

  Study day date firstdose + 1, where date ≥ firstdose
  Study day date firstdose, where date < firstdose

  Study day 1 is defined as the day of study drug administration.
- **Hours** Durations, expressed in hours, between one hour (*hour1*) and another later hour (*hour2*) are calculated using the following formula: duration in hours (hour2-hour1+1).
- **Days** Durations, expressed in days, between one date (*date1*) and another later date (*date2*) are calculated using the following formula: duration in days (date2-date1+1).
- **Weeks** Durations, expressed in weeks, between one date (*date1*) and another later date (*date2*) are calculated using the following formula: duration in weeks (date2-date1+1)/7.
- **Months** Durations, expressed in months, between one date (*date1*) and another later date (*date2*) are calculated using the following formula: duration in months (date2-date1+1)/30.4375.
- **Years** Durations, expressed in years, between one date (*date1*) and another later date (*date2*) are calculated using the following formula: duration in years (date2-date1+1)/365.25.
- **Body Mass Index (BMI)** - BMI (kg/m^2) weight (kg) / [[height (cm)/100]^2]

Note that age on consent date is collected on the CRF and will not be calculated.

5.3 Handling Partial Dates for Adverse Events and Medications

If only a partial date is available and is required for a calculation, the following standards will be applied:

- Start dates
  a. For missing start day only - Day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month and year as the date being used in the calculation (e.g., first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.
  b. For missing start day and month - Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as the date being used in the calculation (e.g., first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.

- Stop dates
  a. For missing stop day only - Day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31)
  b. For missing stop day and month - Day and month will be imputed as the last day of the year (i.e., 31 December)

A completely missing start date will be imputed as first dose date of study medication and a completely missing end date will be imputed as study completion date.

The date of last dose of study drug will be taken from the Study Exit Status CRF page whenever available. If this is missing, then the last visit date, excluding the follow-up visit, will be used, unless a blinded data review indicates it was earlier.

Any partial dates will be displayed in data listings without imputation of missing days and/or months (e.g., MAR2016 for missing day, and 2015 for day and month both missing).

5.4 Handling of Partial or Missing Times within Study Day

For imputation of the missing primary and secondary endpoints TOTPAR4, 6 and 8, please refer to Section 8.3 as below. Any assessments with partial or missing times will be considered unreliable and removed from the analyses. For assessments with partial times (hours present and minutes missing, or vice versa), the following process will be followed:

- For time points less than 1 hour from start of drug administration for the 24-hour clock : intended format in the CRF,
    - If hour is missing, the minutes will be used to calculate the time from the start of drug administration.
    - If both hour and minutes are missing, the value will remain missing.
- For time points greater than 1 hour from start of the study medication,
    - If the minutes are missing, the missing minutes will be imputed to the same minutes as in the prior sampling time.
    - If the minutes from all prior time points are missing, the missing minutes will be imputed to the minutes of the subsequent time points.
    - If all time points have minutes missing, then they will all be set to 0 minutes.
    - If hour is missing, the value will remain missing.

5.5 Visit Windows

The frequency of the assessments was based on the literature available for previous trials with other kinds of drugs using the dental pain model (third molar extraction). The trial course will comprise 4 visits: 3 visits for which subjects have to be at the trial site, and 1 visit which can be a phone call or an on-site visit. At any time during the trial, the investigator may ask the subject to come for an unscheduled additional visit outside the trial schedule if deemed necessary according to his/her normal practice. Screening period is expected to happen before the informed consent form is signed.

5.6 Review of Blinded Data

A number of analyses may require review of blinded data prior to database lock. The following reviews may occur while the study is ongoing or prior to database lock. Subject ID will be masked in all of these reviews to avoid introducing any bias.

- Concomitant medications are reviewed independent of Subject ID to identify prohibited medications
- Review of adverse event summaries and listings to identify MedDRA preferred terms chosen are consistent with drug's mechanism of action.
- Review of protocol and consent deviations to identify major deviations that would exclude subjects from the per-protocol population.
- Review of subjects with a missing or partial last dose date on the Study Exit Status CRF in order to determine an appropriate imputed date or other missing or partial dates for a parameter of interest; if deemed necessary.
- Reasons for withdrawal which are potentially treatment related

6. ANALYSIS POPULATIONS

The following subject populations will be used for various safety and efficacy analyses:

- The Enrolled Set will comprise all subjects who signed the informed consent form.
- The Safety Set will comprise all subjects allocated and treated with IMPs. Analyses on the Safety Set will be conducted according to actual treatment received.
- The Full Analysis Set (FAS) will comprise all subjects allocated and treated, and with at least 1 non-missing pain relief assessment during the first 4 hours post-baseline. Analyses on the FAS will be conducted according to allocated treatment.
- The Per Protocol Set (PPS) will comprise a subset of the subjects in the FAS without any major protocol deviations (see Section 7.2) affecting the primary endpoint analysis. Only subjects with no rescue medication use in the first 120 minutes after first dose, who complete at least a follow-up of 4 hours and who comply with the protocol procedures will be included in the PPS. Analyses on the PPS will be conducted according to actual treatment received.

7. STUDY POPULATION

7.1 Subject Disposition

Subject disposition information will be summarized for all subjects by treatment group, overall and by site. Summaries will include: the number of randomized subjects, the number of subjects in each analysis population, the number of subjects completing the study (and subsets completing the study on and off treatment), the primary reason for discontinuation of study drug, and the primary reason for discontinuation of study. The visit schedules and their timing are given in Section 1.8 of the protocol.

A listing of all early discontinuations from study drug, as well as discontinuation from the study will be provided.

7.2 Protocol Deviations

In accordance with International Conference on Harmonisation (ICH) E3, Sponsor-defined eligibility violations and post-randomization protocol deviations will be identified and listed

separately by study site and subject. Sources for these deviations may include IXRS, Trial Management or the clinical database. Deviations will be reviewed and classified as follows before database lock:

Deviation type/code as provided by Sponsor may include but is not limited to the following:

- Informed consent
- Randomization error
- Safety
- Efficacy
- IMP / Treatment deviation
- Other protocol deviations

Deviations are then categorized into:

- Major (Any deviation that impacts the safety or efficacy outcome of the study)
- Minor (Any non-major deviation)

A listing and tabulation of protocol deviations will be provided.

7.3 Demographic and Baseline Characteristics

Demographic variables to be summarized include the following: date of signing the informed consent, age at informed consent (in years), gender, ethnicity, race, smoking status, height (in cm), weight (in kg), and body mass index (BMI). The BMI will be calculated.

Baseline characteristics, which includes information from the dental surgical procedure, will be summarized for the following: number of molars extracted, impacted molars classification, impacted molar position, planned surgical procedure, duration of surgery (minutes), amount of Lidocaine used during of surgery (mg), time from end of surgery to first dose of study medications (hours), and baseline pain intensity (both on the numeric 11-point rating scale and as categorized as none/mild/moderate/severe).

Demographic and baseline characteristics will be summarized for all the analysis populations (FAS, PPS and Safety Set).

The frequencies and percentages of subjects in the following categories of smoking status will be summarized: current smokers (every day or on some days per week), recent former smokers (smoked within the last 12 months), long-term former smokers (smoked 1 to more than 15 years ago), and never smoked regularly. The number of cigarettes/cigars/pipes smoked per week will be displayed in the listing for current smokers.

7.4 Medical History

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA) (version 19.0).

Subjects' medical and surgical history, including any relevant diseases and surgical interventions, will be recorded at Visit 1. The number and percentage of subjects with a given medical and/or surgical history will be summarized for each system organ class. Summaries will be provided for the FAS, PPS and Safety Set. The verbatim and coded medical histories will be included in a listing.

7.5 Dental History

Subject's dental history will be presented in by-subject listings. The listings will include tooth extractions (within the last 6 months), any other dental surgeries (e.g., root canal), dental or periodontal disease, use of dentures, and other significant dental history.

7.6 Physical Examinations

A directed physical examination will be carried out at Visit 1 (Enrollment Visit). A complete Physical Examination (PE) should include assessments of the general condition, ears, nose and throat, mouth (including teeth and gums), head, neck, heart, and lung. Physical examination results must be available at the latest at Visit 2.

Prior to allocation to treatment, any clinically relevant findings from the physical examination will be documented as part of the medical history.

Physical examination results will be presented in by-subject listings. Summaries will be presented for the Safety Set and will include the number and percentage of subjects within each category by visit and by body system/parameter evaluated. For the physical examination, each body system is assessed as Clinically Significant or Not Clinically Significant.

7.7 Beta-human Chorionic Gonadotropin Pregnancy Test

Urine samples will be collected from women with a childbearing potential at Visit 1 and Visit 2. A urine ß-human chorionic gonadotropin pregnancy dipstick test will be performed at the site. The results of the dipstick test will be listed.

7.8 Radiological Examinations

Radiological examinations of the affected third molars will be conducted at Visit 1 (Enrollment Visit), if this information is not available from a previous X-ray taken up to 1 month before the Enrollment Visit. These data will be presented in a by-subject listing.

7.9 Adverse Events

Adverse events will be documented from the time of enrollment (i.e., Visit 1, the time the informed consent form is signed) up to the time of the last protocol scheduled contact, i.e., date of last visit/contact (can be a phone call, e.g., in case of withdrawal). All adverse events reported spontaneously by subjects at any time point will also be documented. Adverse events occurring in the Enrollment Period but before first administration of an IMP and worsening on or after IMP administration will be documented as new adverse events.

The following information regarding all adverse events will be documented: description (adverse event reported term), start date/time, end date/time or continuation, whether adverse event was serious, intensity, outcome, action taken with IMPs, countermeasures, causal relationship to IMPs. The clinical intensity of an adverse event will be classified as: mild, moderate and severe. For adverse events where the intensity changes over time, the maximum intensity observed during the whole duration of the adverse event will be documented.

7.10 Laboratory Values

Clinical laboratory parameters (hematology, chemistry, coagulation and urinalysis) at Visit 1, Urine pregnancy at Visit 1 and Visit 2, will be collected, listed by subject and visit, and tabulated by visit for each parameter. Clinical laboratory parameter and urinalysis data must be available at the latest at Visit 2.

7.11 Vital Signs

Systolic and diastolic blood pressure, pulse rate, and respiratory rate will be measured at Visit 1 (Enrollment Visit) and Visit 2 (Allocation Visit). All vital signs will be measured in a sitting position after resting for 10 minutes. While resting, the subject should not receive anything to drink or eat.

7.12 Prior and Concomitant Medications

Verbatim terms on case report forms will be mapped to Anatomical Therapeutic Chemical (ATC) class and Generic Drug Names using the World Health Organization (WHO) dictionary (version March 2016).

For the purposes of data reporting by the site, all medications used 14 days prior to enrollment and up to the time of surgery are considered prior medications. Concomitant medications are all medications not stopped before start of surgery or newly added thereafter. Prior medications and concomitant medications will be summarized separately for each treatment by WHO ATC level 1 term, ATC level 3 term and generic drug name, with frequency and percentage of subjects in each dosing arm using each prior medication and each concomitant medication. At each level of subject summarization, a subject is counted once if he/she reported one or more medications at that level. Each summary will be ordered alphabetically by each level of ATC class and by generic drug name within each level of ATC class. Prior and concomitant medications will also be listed separately with these elements as well as the verbatim drug name.

The overall summary and subsets of prior and concomitant medications will be provided for the Safety Set, FAS and PPS.

8. EFFICACY ANALYSES

8.1 Efficacy Variables

8.1.1 Primary Efficacy Variable

The primary endpoint of the trial is 4-hour Total Pain Relief (TOTPAR4). TOTPAR4 is a time-weighted measure of Area under the Longitudinal Pain Relief Curve (AUC) up to 4 hours and is a summary measure that integrates serial assessments of a subject's pain over the duration of 4 hours after first dose (in Appendix A).

In general, the Total Pain Relief (TOTPAR) from the first administration of IMP to a fixed time-point, j, will be defined as:

$TOTPAR_j \quad \sum W_i * PR_i, \text{ with } i \leq j$

where the $\sum$ sums over all observations collected from 0.25 hours after first IMP administration to Hour j and W_i is the time elapsed from the previous observation of pain relief PR_{i-1} to the current observation PR_i. For example, The TOTPAR4 will be calculated as a weighted sum of the observed pain relief scores for the first 4 hours after first dose with weights proportional to the duration of time since the last pain relief assessment.

For the first pain relief assessment, time (hours) elapsed since previous observation is time since first dose of IMP. Pain relief assessments after start of rescue medication intake will be set to missing and will be imputed as described in Section 8.3.

Minimum and maximum potential value for TOTPAR4 are 0 and 16 points, corresponding to a value of 0 (none) or 4 (complete) at all pain relief assessments in the first 4 hours after first dose, respectively.

8.1.2 Secondary Efficacy Variables

The following secondary clinical endpoints will be evaluated:

- Total Pain Relief at 6 hours (TOTPAR6), 8 hours (TOTPAR8) post-dose (in Appendix A)
- Summed Pain Intensity Difference (SPID) at 4, 6, 8, and 24 hours after first dose (in Appendix A)
- Time to achieve a 50% reduction of baseline pain (pain at least half gone) (in Appendix A)
- Time to onset of first perceptible pain relief (stopwatch 1) (in Appendix A)
- Time to onset of meaningful pain relief (stopwatch 2) (in Appendix A)
- Time to intake of first rescue medication dose (in Appendix A)
- Subject's global evaluation of the treatment (5-point Likert Scale; 0 poor to 4 excellent) at 8 hours after the first dose of IMPs or before first intake of rescue

medication (whichever was first) and at 24 hours after the first dose of IMPs (in Appendix A)

Total Pain Relief (TOTPAR) is defined as ΣPR_t x [time (hours) elapsed since previous observation] where PR_t is the Pain Relief at time point t (based on VRS) in comparison to the assessment before administration of IMPs. The subject's pain relief is assessed using a 5-point Verbal Rating Scale (VRS) by completion of the following statement, *"My relief from starting pain is"* with the scale: 0 None; 1 A little; 2 Some; 3 A lot; 4 Complete.

Summed Pain Intensity Difference (SPID) is defined as ΣPID_t x [time (hours) elapsed since previous observation] where PID_t (Pain Intensity Difference) is defined as the difference between baseline pain intensity and pain intensity at time point t (e.g., baseline score time point t score), where pain intensity is evaluated using an 11-point numerical rating scale (NRS) (in Appendix A).

8.1.3 Additional Efficacy Outcomes

The following parameters will also be summarized:

- Pain relief score after first dose over time (in Appendix A)
- Pain intensity score after the first dose over time (based on NRS) (in Appendix A)
- Pain Intensity Difference (PID, NRS) after first dose over time (in Appendix A)
- Peak pain relief score
- Peak pain intensity difference score
- Time to request the first dose of rescue medication (in Appendix A)
- Time to peak pain relief score
- Time to peak pain intensity difference score

Pain relief, pain intensity, and PIDs are defined as described above in Section 8.1.2.

The peak pain relief score is the maximum pain relief assessment for the subject during the 16 observation period (prior to the use of any rescue medication), while time to peak pain relief score is the time from first administration of IMP to the first occurrence of that peak relief score, in hours. The peak pain intensity difference is the maximum pain intensity difference for the subject during the 24 observation period (prior to the use of any rescue medication), while time to peak pain intensity difference is the time from first administration of IMP the first occurrence of that peak intensity difference, in hours.

8.2 Adjustments for Covariates

The primary analysis model will be an analysis of covariance (ANCOVA) with baseline pain intensity as a continuous covariate based on an 11-point scale), and treatment and site as factors. Baseline pain intensity will be included to ensure an equal distribution of subjects with severe baseline pain among the 4 treatment groups.

8.3 Handling of Dropouts or Missing Data

Diligent attempts will be made to limit the amount of missing data in the pain relief assessments used to determine the primary efficacy endpoint. Efforts will be made to encourage but not to enforce subjects to not start rescue medication intake if not needed. Assessments with missing date/time of evaluation will be considered unreliable and removed from all analyses and treated as missing values. Assessments made after the subject's first dose of rescue medication will be considered missing values and excluded from the analyses. Other than the methods outlined below for TOTPAR4, TOTPAR6, and TOTPAR8, no imputations will be performed to replace missing values for any of the other endpoints; those missing values will be left as missing.

8.3.1 Analysis of TOTPARs

For the primary endpoint TOTPAR4, as well as for secondary endpoints TOTPAR6 and TOTPAR8, missing pain relief assessments as well as pain relief assessments after start of intake of rescue medication, will be imputed according to the following methods:

1. LOCF with Delta Substitution
    - Last Observation Carried Forward (LOCF) for intermittent missing data and substitution by δ for missing data after premature discontinuation from the trial or disregarded pain relief assessments after start of rescue medication intake. The value of parameter δ will depend on the reason for discontinuation and treatment arm. The following 3 categories of reason for discontinuation will be distinguished: Discontinuation due to Lack of Efficacy (LoE), adverse events, and other, non-drug related reasons. The parameter will be:
    - δ 0: For missing data after discontinuation due to LoE, discontinuation due to adverse events and for disregarded pain relief assessments after start of rescue medication intake for subjects in the tramadol HCl/diclofenac sodium FDC combination arms
    - δ 0.375: For missing data after discontinuation due to LoE, discontinuation due to adverse events and for disregarded pain relief assessments after start of rescue medication intake for subjects in the monotherapy arms diclofenac sodium 50 mg and tramadol HCl 50 mg
    - δ 0: For missing data after discontinuation due to other, non-drug related reasons

8.3.2 Sensitivity analysis of TOTPARs

For sensitivity analysis, missing and disregarded pain relief assessments will be imputed with the following two imputation methods:

2. LOCF Only
3. LOCF with Zero Substitution
    - LOCF for intermittent missing data;

- And substitution by zero for missing data after premature discontinuation from the trial or disregarded pain relief assessments after start of rescue medication intake.

While the sensitivity analyses below are not mentioned in the protocol, they are added to address the specific concern when rescue medication is given prior to the scheduled assessment time. Clearly, once rescue medication is given the pain levels will drop significantly and measurements post rescue medication are excluded from the analyses. The sensitivity analyses below will enable us to include subjects with rescue medication at the subsequent assessment time point.

4. WOCF with LOCF: Worst Observation Carried Forward (WOCF) is used to replace the scheduled pain relief assessments after the first intake of rescue medication, and LOCF is used to replace all other missing pain assessments. WOCF is defined as carrying forward the worst previous pain assessment, even if it is the baseline assessment.
5. WOCF Only

8.4 Interim Analysis and Data Monitoring

No interim analyses are planned for evaluating efficacy.

8.5 Examination of Subgroups

Subgroup analyses are to be performed for the primary efficacy variable with subjects categorized by levels of baseline pain severity. Furthermore, primary and secondary TOTPAR analyses will be conducted by site.

8.6 Multiple Comparisons/Multiplicity

Testing multiple hypotheses may increase the family-wise type I error rate, the probability to erroneously reject at least 1 true null hypothesis, beyond the pre-specified significance level. In order to control the family-wise type I error rate in the strong sense at the pre-specified 1-sided significance level of α 2.5%, a Bonferroni-Holm procedure (Holm 1979) will be used. The details will be explained later in Section 9.1 of this SAP.

8.7 Multicenter Studies

The study will be conducted at approximately 8 investigational sites in Mexico, about 1065 subjects are planned to be enrolled (i.e., sign the informed consent) in order to allocate 800 subjects to IMP, i.e., about 130 subjects per trial site in approximately 8 sites.

The site will be included as a covariate in the multivariate analysis. If a highly influential site is identified, the differences between treatment groups might be examined with and without the influential site.

9. METHODS OF EFFICACY ANALYSIS

The primary analysis to investigate the primary objective of the trial is based on the primary efficacy endpoint (TOTPAR4) and will be performed on the FAS and repeated as sensitivity analysis on the PPS. Additional sensitivity analyses and the analysis of additional efficacy parameters will be performed on the FAS, unless otherwise specified.

9.1 Primary Efficacy Analyses

The primary endpoint will be TOTPAR4 and the primary analysis performed on the FAS. The TOTPAR4 will be calculated as a weighted sum of the observed pain relief scores during the first 4 hours after first dose with weights proportional to the time since the last pain relief assessment. TOTPAR scores can be interpreted as estimates of the area under the longitudinal pain relief curve. TOTPAR4 will be displayed for each treatment group by study visit using summary statistics, including the number of observations, the mean, Q1, median, Q3, standard deviation (SD), and range (min, max).

The estimate of interest for the primary efficacy analysis is the difference in the primary efficacy endpoint in all subjects in the FAS attributable to the initially allocated trial medication. The FAS analysis will be the primary analysis for all comparisons. The primary objective of the trial is investigated by 4 formal statistical tests (see Table 1). Testing multiple hypotheses, however, may increase the family-wise type I error rate, the probability to erroneously reject at least 1 true null hypothesis, beyond the pre-specified significance level. In order to control the family-wise type I error rate in the strong sense at the pre-specified 1-sided significance level of α 2.5%, a Bonferroni-Holm procedure will be used. The elementary null hypotheses H_{01}, H_{02}, H_{03}, and H_{04} and according statistical tests T_1, T_2, T_3, and T_4 of the primary objective of the trial are listed in Table 1.

Table 1: Statistical tests and null hypotheses (all 1-sided) of the primary objective of the trial

Test	Description	Null Hypothesis	Alternative Hypothesis
T_1	Superiority of tramadol HCl/diclofenac sodium 50 mg/50 mg vs. tramadol HCl 50 mg	$H_{01}: \mu_{T50} \quad \mu_{ADL50/50} \geq 0$	$H_{A1}: \mu_{T50} \quad \mu_{ADL50/50} < 0$
T_2	Superiority of tramadol HCl/diclofenac sodium 50 mg/50 mg vs. diclofenac sodium 50 mg	$H_{02}: \mu_{D50} \quad \mu_{ADL50/50} \geq 0$	$H_{A2}: \mu_{D50} \quad \mu_{ADL50/50} < 0$
T_3	Non-inferiority of tramadol HCl/diclofenac sodium 25 mg/25 mg vs. tramadol HCl 50 mg	$H_{03}: \mu_{T50} \quad \mu_{ADL25/25} \geq \Delta$	$H_{A3}: \mu_{T50} \quad \mu_{ADL25/25} < \Delta$
T_4	Non-inferiority of tramadol HCl/diclofenac sodium 25 mg/25 mg vs. diclofenac sodium 50 mg	$H_{04}: \mu_{D50} \quad \mu_{ADL25/25} \geq \Delta$	$H_{A4}: \mu_{D50} \quad \mu_{ADL25/25} < \Delta$

ADL Adorlan (tramadol HCl/diclofenac sodium); D diclofenac sodium; T tramadol hydrochloride; HCl hydrochloride. Δ 1.5 is the non inferiority margin.

The trial will be positive if at least 1 of the according 4 statistical tests rejects the according null hypothesis.

According the Bonferroni-Holm procedure, the p-values of the 4 tests T_1, T_2, T_3, and T_4 will be sorted in ascending order $p_{(1)} < p_{(2)} < p_{(3)} < p_{(4)}$ and the following algorithm will be applied to the corresponding null hypotheses $H_{(01)}$, $H_{(02)}$, $H_{(03)}$, $H_{(04)}$:

- Step 1. If $p_{(1)} < \alpha/4$ 0.625%, reject $H_{(01)}$ and move to the next step. Otherwise retain all null hypotheses and stop.
- Step 2. If $p_{(2)} < \alpha/3$ 0.833%, reject $H_{(02)}$ and move to the next step. Otherwise retain $H_{(02)}$, $H_{(03)}$ and $H_{(04)}$ and stop.
- Step 3. If $p_{(3)} < \alpha/2$ 1.25%, reject $H_{(03)}$ and move to the next step.

  Otherwise retain $H_{(03)}$ and $H_{(04)}$ and stop.
- Step 4. If $p_{(4)} < \alpha$ 2.5%, reject $H_{(04)}$ and move to formally testing null hypotheses related to secondary endpoints. Otherwise retain $H_{(04)}$.

The primary analysis will use an ANCOVA model with treatment, site, and baseline pain (measured on an 11-point NRS) as covariates. The pain intensity score assessed before IMP intake will be considered the baseline pain intensity and site will be used as a covariate.

9.2 Sensitivity Analyses

9.2.1 Analysis for TOTPAR in Presence of Missing Data

For the TOTPAR analysis, missing pain relief assessments after first dose as well as pain relief assessments after start of intake of rescue medication, will be imputed by LOCF for intermittent missing data, and substitution by δ for missing data after premature discontinuation from the trial or disregarded pain relief assessments after start of rescue medication intake (Section 8.3 in SAP). Furthermore, to investigate whether results of the trial are sufficiently similar to results of past historical trials with respect to all design features that can influence the estimation of treatment effect (constancy assumption), single imputation methods used in historical trials of the active comparators diclofenac and tramadol will be applied as well, namely LOCF only, and LOCF for intermittent missing data and substitution by zero (no relief from baseline pain) for missing data after premature discontinuation from the trial or disregarded pain relief assessments after start of rescue medication intake (Section 8.3 in SAP). Finally additional WOCF+LOCF and WOCF only sensitivity analyses (Section 8.3 in SAP), are added to address the specific concern when rescue medication is given prior to the scheduled assessment time. Clearly, once rescue medication is given the pain levels will drop significantly and measurements post rescue medication are excluded from the analyses as well. These sensitivity analyses will enable the use of time points for subjects after their use of rescue medication by using their imputed values.

At the conclusion of imputation of the missing data based on each of the imputation methods, the same identical analysis as described for the primary endpoint (Section 9.1) will be once again conducted to examine the robustness of the outcome. This analysis will be conducted in the FAS population.

9.2.2 Alternate Analysis Population

The primary efficacy analysis will be repeated for the TOTPARs as a sensitivity analysis on the PPS. Additional sensitivity analyses and the analysis of additional efficacy parameters will be performed on the FAS only, unless otherwise specified.

9.2.3 Subgroup Analyses

Pain intensity will be evaluated based on the following scale: None (score 0), Mild (1< score<5), Moderate (5< score< 6), and Severe (score> 7). However subject inclusion criteria at baseline require pain intensity level of Moderate or Severe after the surgical procedure. Subgroup analyses will be performed on TOTPAR4 for subjects with a moderate pain intensity (score 5 or 6) at baseline and for subjects with a severe pain intensity (score 7, 8, 9, 10) at baseline. Furthermore, subgroup analyses will be performed per site for TOTPAR4, TOTPAR6, and TOTPAR8. These analyses will follow the same ANCOVA model as stated before. The by-site analyses will additionally include a site-by-treatment interaction factor in the model, and besides the FAS, will also be performed on the PPS. In all of these cases, the TOTPARs used will be those based upon imputations using the LOCF and delta substitution method.

9.3 Secondary Efficacy Analyses

The analysis of the following list of the secondary endpoints is given below:

1. Total Pain Relief at 6 hours (TOTPAR6), 8 hours (TOTPAR8) post-dose
2. Summed Pain Intensity Difference (SPID) at 4, 6, 8, and 24 hours after first dose
3. Time to achieve a 50% reduction of baseline pain (pain at least half gone)
4. Time to onset of first perceptible pain relief (stopwatch 1)
5. Time to onset of meaningful pain relief (stopwatch 2)
6. Time to intake of first rescue medication dose
7. Subject's global evaluation of the treatment (5-point Likert Scale; 0 poor to 4 excellent) at 8 hours after the first dose of IMPs or before first intake of rescue medication (whichever was first) and at 24 hours after the first dose of IMPs

TOTPARs and SPIDs at each of their summary time points will be analyzed using the same ANCOVA model described for the primary endpoint. Note that alpha levels for secondary analyses are not adjusted for multiple comparisons.

The time to onset of event endpoints will be presented using Kaplan-Meier plots. Medians will be compared across the groups using Wilcoxon Log-rank test, and Hazard Ratios (HR) will be compared across the groups using Cox Hazard Ratio model. Time to onset will be defined as date/time from the first administration of IMPs to the date/time when the subject first reports the event (50% reduction of baseline pain, perceptible pain relief, meaningful pain relief, and intake of rescue medication each separately). The summaries will include quartiles and HR and their corresponding 95% confidence intervals. Please see Appendix B for details on the determination of event and censoring time points.

Note that alpha levels for secondary analyses are not adjusted for multiple comparisons.

Subject's global assessment of the treatment will also be summarized with descriptive statistics (patient counts and percentages for each assessment category) at 8 and 24 hours.

9.4 Exploratory Efficacy Analyses

The following exploratory analyses will be performed on these additional efficacy outcomes:

1. Pain Relief Score after first dose over time
2. Pain Intensity Score after the first dose over time (based on NRS)
3. Pain Intensity Difference (PID, NRS) after first dose over time
4. Peak pain relief score
5. Peak pain intensity difference
6. Time to request the first dose of rescue medication
7. Time to peak pain relief score
8. Time to peak pain intensity difference

Pain relief scores, pain intensity scores, and pain intensity difference scores over time will be analyzed at each time point using the same ANCOVA model described for the primary endpoint, TOTPAR4. Peak pain relief score and peak pain intensity difference will also be analyzed using the same ANCOVA model described for the primary endpoint.

Time to peak pain relief score and time to peak pain intensity difference be presented using Kaplan-Meier plots. Medians will be compared across the groups using Wilcoxon Log-rank test, and Hazard Ratios (HR) will be compared across the groups using Cox Hazard Ratio model. The summaries will include quartiles and HR and their corresponding 95% confidence intervals along with the p-values. Please see Appendix B for details on the determination of event and censoring time points. Note that alpha levels for exploratory analyses are not adjusted for multiple comparisons.

10. SAFETY ANALYSES

The following safety data will be collected: Adverse events, clinical laboratory parameters, and vital signs. All safety analyses will be based on the Safety population. Clinically relevant abnormal values (per investigator's judgment) must be recorded as adverse events.

Safety and tolerability will be assessed throughout the study by monitoring and evaluating treatment emergent adverse events (TEAEs), including any complications resulting from the study drug administration, and changes in vital signs and in clinical safety laboratory test and PE findings. All safety and tolerability endpoints will be summarized by treatment. Baseline for all safety endpoints will be defined as the last recorded observation before the administration of the study drug. Safety measures, including AEs, clinical safety laboratory tests, vital signs, PEs, and concomitant medication usage, will be summarized descriptively. For quantitative variables, descriptive statistics, including number of observations, means, Q1, medians, Q3, SDs, and

ranges, will be provided for the values themselves as well as for the changes from Baseline by treatment group at each study visit. Qualitative variables will be summarized using counts and percentages in each treatment group at each study visit.

10.1 Adverse Events

Definition of adverse events

An adverse event is any untoward medical occurrence in a subject enrolled in a clinical trial. An adverse event can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Pre-existing diseases or conditions occurring before enrollment are not considered to be adverse events unless there is an untoward change in intensity, frequency, or quality after enrollment.

LoE, as such, is not considered to be an adverse event while its consequences (e.g., deterioration of the treated disease) are considered to be an adverse event.

A newly diagnosed pregnancy of an enrolled female subject will not be considered an adverse event itself unless it is suspected that the trial treatment interacted with a contraceptive method. In this case, the pregnancy will be considered an adverse event. A congenital anomaly as an outcome of this pregnancy will be considered a serious adverse event (SAE).

All newly diagnosed pregnancies of enrolled female subjects must be reported to the CRO/sponsor's Drug Safety department within 24 hours after first knowledge. These pregnancies will be documented using a Pregnancy Reporting Form with all available information provided and followed up to determine the outcome post parturition.

For newly diagnosed pregnancies of partners of enrolled subjects, a reasonable attempt (i.e., due diligence) must be made to report the pregnancy to the CRO/sponsor's Drug Safety department within 24 hours after first knowledge.

Definition of serious adverse events

An 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/birth defect.
- Is considered a clinically important medical event. The medical concepts included in Appendix A should be taken into account when applying this seriousness criterion.

An elective hospital admission, e.g., for pre-planned surgery, will not be considered an SAE if documented at enrollment. Short-lasting (<24 hours) hospital admissions, e.g., for clinical check-ups, not meeting any of the other above mentioned criteria will also not be considered SAEs.

Analysis of adverse events

Adverse events will be coded to System Organ Class (SOC) and preferred term using MedDRA (version 19.0). The tabular summaries will be provided for AEs, with the number and percentage of subjects reporting each type of event presented by each treatment group and placebo. If a subject reports the same preferred term more than once, it is counted only once within that category. Further, for a given tabulation, the preferred term will only be counted once at its worst severity and strongest relationship to treatment.

Any adverse event which occurs after first administration of the IMPs or pre-existing adverse event which worsens (adverse change in intensity, frequency, or quality) after first administration of the IMPs compared to the complaint present before first intake of the IMPs is considered as a TEAE.

TEAEs will be summarized for each treatment group by SOC and Preferred Term. Additional summaries by time to onset, duration, intensity, relationship to IMP (Related/Not Related), outcome, expectedness, and countermeasures will also be produced. Events reported as ”Conditional/Unclassified”, “Assessable/Unclassifiable”, “Possible”, “Probable/Likely”, or “Certain” will be included in the Related category. Events reported as “Unlikely Related” or “Not Related” will be included in the Not Related category. Expectedness will be assessed by the sponsor. An unexpected adverse event is one where the nature or intensity is not consistent with the information in the investigator’s brochure. Definition of intensity (mild, moderate, or severe) and countermeasures (none, newly started medication, trial discontinuation, or other) is described in the protocol Section 12.3.1.

Subjects with SAEs will be summarized and additionally listed. Special attention will be given to those subjects who discontinue treatment due to an adverse event or who experience a severe adverse event or SAE.

The incidence of all adverse events and TEAEs leading to premature discontinuation from treatment will be presented descriptively.

Selected subset of adverse events

Selected adverse events of interest will be summarized in a separate table:

- Nausea
- Vomit
- Abdominal Pain
- Gastrointestinal Bleeding
- Dizziness
- Hypotension

10.2 Clinical Laboratory Evaluation

Clinical laboratory parameter data (clinical chemistry, hematology, and coagulation) and urinalysis results will be descriptively summarized by type of laboratory test and time point.

Both conventional and SI units are provided and will be summarized in separate tables and listings.

Descriptive statistics for the chemistry and hematology values will be presented. Continuous laboratory parameters will be summarized by n (%), Mean, Q1, Median, Q3, SD and (Min, Max). Categorical laboratory parameters will be summarized by treatment group for each target visit using counts and percent of subjects in each category. Missing n (%) will be indicated in all tables. Listings of laboratory parameter results will be presented.

10.3 Vital Signs

Descriptive statistics will be calculated for each parameter of the vital signs (diastolic blood pressure, systolic blood pressure, pulse rate, and respiratory rate) collected at Visit 1 and Visit 2. For the summary tabulations of vital signs at baseline, baseline will be defined as the last non-missing value prior to the first dose of study drug. Change from baseline in these vital signs will also be calculated and summarized as the value at Visit 2 minus the baseline value.

10.4 Prior and Concomitant Medications

Verbatim terms on case report forms will be mapped to Anatomical Therapeutic Chemical (ATC) class and Generic Drug Names using the World Health Organization (WHO) dictionary (version March 2016).

For the purposes of data reporting by the site, all medication used 14 days prior to enrollment and up to the time of surgery is considered prior medication. Concomitant medication is all medication not stopped before start of surgery or newly added thereafter. Prior medications and concomitant medications will be summarized separately for each treatment by WHO ATC level 1 term, ATC level 3 term and Preferred Term (generic name) with frequency and percentage of subjects in each dosing arm using each prior medication and each concomitant medication. At each level of subject summarization, a subject is counted once if he/she reported one or more medications at that level. Each summary will be ordered alphabetically by each level of ATC class and generic drug name within each level of ATC class. Prior and Concomitant medications will also be listed separately with these elements as well as the verbatim drug name.

The overall summary and subsets of prior and concomitant medications will be provided for the Safety Set, FAS and PPS.

11. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

For subject's dental history, summary of that data as suggested by Section 14.4 of the study protocol will not be provided but instead will be displayed in a by-subject data listing.

Two sensitivity analyses have been added to this SAP beyond what is stated in the protocol to address the specific concern when rescue medication is given prior to the scheduled assessment time. Clearly, once rescue medication is given the pain levels will drop significantly and measurements post rescue medication are excluded from the analyses. The sensitivity analyses stated in Section 8.3 and 9.2.1 of this document will enable us to include subjects with rescue

medication at the subsequent assessment time point while the primary analyses and the primary endpoint remain the same as stated in the protocol.

In addition, 4 exploratory efficacy endpoints have been added to the analyses: peak pain relief score, peak pain intensity difference score, time to peak pain relief score, and time to peak pain intensity difference score, as stated in Section 8.1.3 and further described in Section 9.4. Each of these is considered a routine endpoint in dental study models and each was added for completeness of the analyses.

APPENDICES

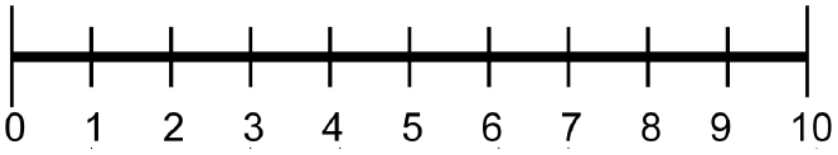
Appendix A: Definitions for Efficacy Endpoints

1. Pain Intensity and Numerical Rating Scale (NRS)

11-point Numerical Rating Scale (NRS) is used to evaluate pain intensity.

Pain Intensity Rating Scale

Please rate your pain by selecting the one number that best describes how much pain you have right now:



No Pain

Pain as bad as you can imagine

Pain intensity: Subjects will be asked to assess their current pain by selecting a number corresponding to their pain, with anchors at 0 for "no pain" and 10 for "pain as bad as you can imagine". The subjects will be asked to answer the following question:
"Please rate your pain by selecting the one number that best describes how much pain you have right now".

Pain intensity will be categorized as:

- None NRS score of 0
- Mild NRS score of ≥1 and <5
- Moderate NRS score of ≥5 and ≤6
- Severe NRS score of ≥7

NRS pain scores will be assessed before the first dose of IMPs, and 15, 30, 45, 60, and 90 minutes (±2 minutes), and 2, 3, 4, 5, 6, 7, 8, 16, and 24 hours (±6 minutes) after the first dose of IMPs.

2. Pain Relief and Verbal Rating Scale (VRS)

The subject's pain relief will be assessed using a 5-point Verbal Rating Scale (VRS) by completion of the following statement.
"My relief from starting pain is"

- None (0)
- A little (1)
- Some (2)
- A lot (3)
- Complete (4)

Pain relief will be assessed 15, 30, 45, 60, and 90 minutes (±2 minutes), and 2, 3, 4, 5, 6, 7, 8, and 16 hours (±6 minutes) after administration of the first dose of IMPs.

3. Total Pain Relief at 4, 6, and 8 hours (TOTPAR4, TOTPAR6, and TOTPAR8)

Total Pain Relief (TOTPAR) will be defined as ΣPR_t x [time (hours) elapsed since previous observation] where PR_t is the Pain Relief at time point t in comparison to the assessment before administration of IMPs. The TOTPAR will be calculated at 4, 6, and 8 hours.

4. Peak Pain Relief

Peak pain relief will be defined as the maximum pain relief score for the subject over the 16 hours after administration of the first dose of IMPs, but prior to the intake of any rescue medications.

5. Pain Intensity Difference (PID)

Pain Intensity Difference (PID_t) will be defined as the difference between baseline pain intensity and pain intensity at time point t (e.g., baseline score time point t score). The PID (11-point NRS) compared to baseline at 15, 30, 45, 60, and 90 minutes, and at 2, 3, 4, 5, 6, 7, 8, and 24 hours will be calculated.

6. Summed Pain Intensity Difference (SPID)

Summed Pain Intensity Difference (SPID) will be defined as ΣPID_t x [time (hours) elapsed since previous observation]. The SPID at 4, 6, 8, and 24 hours post-dose will be calculated.

7. Peak Pain Intensity Difference

Peak pain intensity difference will be defined as the maximum pain intensity difference for the subject over the 24 hours after administration of the first dose of IMPs, but prior to the intake of any rescue medications.

8. Subject's Global Evaluation of the Treatment (Likert Scale)

The subject's overall impression (overall assessment) of the analgesic efficacy of the IMPs will be obtained at 8 hours after the first dose of IMPs or before first intake of rescue medication (whichever happens first) and at 24 hours after the first dose of IMPs. Subjects will be asked the following question and will be requested to also record the time at which it was answered:
"How would you rate the study medication you received for pain?"

- Excellent (4)
- Very good (3)
- Good (2)
- Fair (1)
- Poor (0)

9. Time to Achieve a 50% Reduction of Baseline Pain

The subject's 50% reduction of starting pain will be assessed by answering the following statement with YES or NO:
"My starting pain is at least half gone"
The subject should be reminded that each assessment should be performed independently of previous assessments.

10. Time to Onset of First Perceptible and Meaningful Pain relief

At the time of dosing with the IMPs, the investigator will start 2 stopwatches for each subject. The subject will be instructed to stop the first stopwatch at the time of first perceptible pain relief and the second stopwatch at the time when they first experience meaningful pain relief. The definitions of the perceptible and meaningful pain relief are as follows:

Time to onset of first perceptible pain relief

When the subject begins to feel any pain-relieving effect from the IMPs.
Subject instruction:
"I would like you to stop the 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 difference in the pain that you have had."

Time to onset of meaningful pain relief

When the subject feels their pain relief is meaningful to them.
Subject instruction:
"I would like you to stop the stopwatch when you have meaningful pain relief. That is, when the relief is meaningful to you."

11. Time to Request and Intake of First Rescue Medication

The day/actual time of ibuprofen (and of ketorolac if needed) request and the day/actual time and amount of ibuprofen intake (or ketorolac administration) will be documented in the CRF and the source document(s). The time from administration of IMP to the first dose of rescue medication will be calculated.

12. Time to Peak Pain Relief and Peak Pain Intensity Difference Scores

The first day/time where the subject reaches their maximum pain relief and their maximum pain intensity difference, as described in items 4 and 7 above, respectively, will be considered the event times for these two endpoints.

Appendix B: Rules for Censoring in Time to Event Analyses

Below are the detailed rules for determining the time of the event and the censoring times for the various time-to-event analyses to be performed for this study.

Time-to-Event Variable	Event Time Point	Censor Time Point
Time to achieve a 50% reduction of baseline pain	The first time point where pain half gone is indicated, prior to the use of any rescue medication.	Subjects without events are censored at the earlier of the time of their first use of rescue medication and the time of their last, non-missing pain half gone assessment.
Time to onset of first perceptible pain relief*	The time when perceptible pain relief stopwatch is stopped, prior to the use of any rescue medication.	Subjects without events (as indicated by checking the "no" perceptible pain relief box or taking rescue medication prior to the occurrence of perceptible pain relief) are censored at the earlier of the time of their first use of rescue medication, the minutes/seconds entered for time of perceptible pain relief (which is when the stopwatch was stopped and so no longer assessed), and 8 hours.
Time to onset of meaningful pain relief*	The time when meaningful pain relief stopwatch is stopped, prior to the use of any rescue medication.	Subjects without events (as indicated by checking the "no" meaningful pain relief box or taking rescue medication prior to the occurrence of meaningful pain relief) are censored at the earlier of the time of their first use of rescue medication, the minutes/seconds entered for time of meaningful pain relief (which is when the stopwatch was stopped and so no longer assessed), and 8 hours.
Time to intake of first rescue medication dose	The time of first intake of rescue medication within 24 hours of first dose.	Subjects without events are censored at the time of their 24 hour global assessment (at the time when rescue meds were to be turned in), and if one did not take place, then at 24 hours (i.e., when subjects were to turn in their unused rescue medication as Visit 3).
Time to request the first dose of rescue medication	The time of the first request for rescue medication within 24 hours of first dose.	Subjects without events are censored at the time of their 24 hour global assessment (at the time when rescue meds were to be turned in), and if one did not take place, then at 24 hours (i.e., when subjects were to turn in their unused rescue medication as Visit 3).
Time to peak pain relief score	The first time point where the subject experiences their peak pain relief score among assessments made prior to use of any rescue medication.	All subjects with post-baseline assessments have events – there is no censoring.
Time to peak pain intensity difference score	The first time point where the subject experiences their peak pain intensity difference score, among assessments made prior to use of any rescue medication.	All subjects with post-baseline assessments have events – there is no censoring.

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