SDR-PRO-TEMPLATE-02

NCT03714672 Date:19Oct2017

Trial code:	KF8001-01
Title of trial:	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
Brief title:	Tramadol/diclofenac fixed-dose combination Phase III trial in acute pain after third molar extraction
Indication:	Moderate to severe acute pain after third molar extraction
Coordinating investigator [a]:	[redacted] DMD, PhD [redacted] [redacted] USA Phone [redacted]
Trial sites:	Multi-site trial (up to 10 sites in Mexico) Documentation of the involved trial sites will be maintained.
Trial sponsor [a]:	Grünenthal S.A. Edificio Torres de las Américas C-3100 Panama City Panama
Sponsor's signatory [a]:	[redacted] MD Head of Clinical Product Development Latin America [redacted]grunenthal.com
Public contact point [a]:	[redacted] Clinical Operations Project Manager [redacted]grunenthal.com

a) Contact detail changes during the course of the trial will be documented and do not require a protocol amendment.

Version	Date	DMS version number	Valid for
Original	08 Apr 2016	1.0	Mexico
Amendment 01	07 Sep 2016	2.0	Mexico
Amendment 02	19 Oct 2017	3.0	Mexico

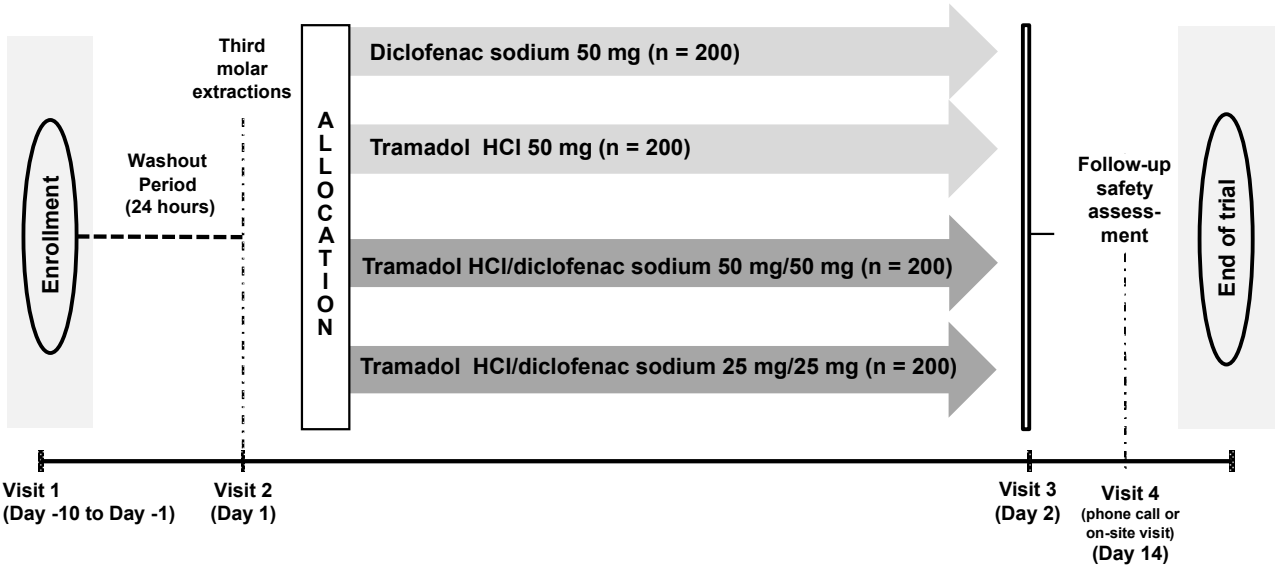
Universal Trial Number: U1111-1179-2333

1 PROTOCOL SYNOPSIS

1.1 Trial design

This is a prospective, randomized, double-blind, diclofenac- and tramadol-controlled, parallel-group, multi-site, interventional Phase III trial to evaluate the analgesic efficacy and safety of administration of fixed-dose combinations (FDCs) of tramadol hydrochloride (HCl)/diclofenac sodium (25 mg/25 mg and 50 mg/50 mg) in subjects with acute moderate to severe pain after third molar extraction. All subjects will receive a 24-hour treatment course.

1.1.1 Flow diagram summary of the trial



The investigational medicinal products (IMPs) will be administered as soon as the subject's baseline pain intensity has been evaluated and meets the criteria of moderate to severe pain (i.e., ≥5 on an 11-point numerical rating scale [NRS]) within 4 hours after the end of the surgery. The IMP administration will be repeated after 8 hours (±10 minutes) at the clinic and after 16 hours (±1 hour) at home.
HCl = Hydrochloride, n = number of subjects treated.

1.1.2 Brief description of the sequence and duration of all trial periods

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.

See Section 1.1.1 for a summary of the trial as a flow diagram and Section 1.8 for a tabular schedule of events.

Each subject is expected to be in the trial for approximately 14 days to 24 days.

1.2 Trial objectives and endpoints/outcomes

Objective	Endpoint/outcome
Primary The primary objective is to demonstrate the analgesic 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 specific primary objective is to demonstrate that: • **Either** tramadol HCl/diclofenac sodium 50 mg/50 mg has superior analgesic efficacy than monotherapy with diclofenac sodium 50 mg, • **Or** tramadol HCl/diclofenac sodium 50 mg/50 mg has superior analgesic efficacy than monotherapy with tramadol HCl 50 mg, • **Or** tramadol HCl/diclofenac sodium 25 mg/25 mg is not inferior to monotherapy with tramadol HCl 50 mg, • **Or** tramadol HCl/diclofenac sodium 25 mg/25 mg is not inferior to monotherapy with diclofenac sodium 50 mg.	*Primary* • Pain relief expressed as Total Pain Relief over the 4 hours post-dose period (TOTPAR4).
Secondary 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.	*Secondary* • Total Pain Relief at 6 hours (TOTPAR6), 8 hours post-dose (TOTPAR8). • Summed Pain Intensity Difference (SPID) at 4, 6, 8, and 24 hours post-dose. • Time to achieve a 50% reduction in baseline pain (pain at least half gone). • Time to onset of first perceptible pain relief. • Time to onset of meaningful pain relief. • Time to intake of first rescue medication dose.

Objective	Endpoint/outcome
To compare the overall impression of the subject on the treatment they received.	• Subject's global evaluation of the treatment (5-point Likert Scale) 8 hours or before first intake of rescue medication (whatever the first) and 24 hours after the first dose of IMPs.
To evaluate the safety profile of the FDC product in comparison to the safety profiles of the monotherapies.	• Incidence and type of adverse events.

Data collected not directly supporting an objective

Data collected	Rationale for collecting data not directly supporting an objective
• Date of signature on the informed consent form, sex, age, smoking status, race, ethnicity, height and weight, body mass index (calculated). • Prior/concomitant medication. • Clinically relevant medical history (prior/concomitant diseases and surgical interventions). • Physical examination outcome. • Radiological examination result. • Details on local anesthesia and surgery. • Surgical outcomes (number of teeth, degree of impaction of each tooth, duration of surgery, amount and timing of all anesthetic drugs). • Vital signs results. • Pregnancy test results. • Clinical laboratory parameters (clinical chemistry, hematology, and coagulation) and urinalysis results.	Demographic data and other subject characteristics; data required to judge on inclusion or exclusion of subjects; data required for safety evaluation.

1.3 Trial subjects - the population to be studied

Subjects are eligible for the trial if they are in good general health (except for the third molars requiring extraction) as it will be determined by medical history evaluation and a physical examination. They must comply with the inclusion/exclusion criteria given.

1.3.1 Inclusion criteria

1. The subject has read the informed consent form, has understood the relevant aspects of the clinical trial, and grants his/her authorization to participate by signing the informed consent form prior to the inclusion in the clinical trial and the performance of any procedure.
2. Male and female subjects >18 years to 60 years.
3. Female subjects of childbearing potential must be practicing an acceptable method of birth control and must have a negative urine pregnancy test at enrollment with confirmation at Visit 2.
4. Subjects are in good health, i.e., the medical record, vital signs, physical examination, and laboratory parameter assessments do not show any abnormal deviations impeding the participation in the clinical trial.
5. Subjects requiring extraction of 3 or more third molars with 2 mandibular impacted third molars.
6. Clinical and radiological diagnosis of impacted lower third molars.
7. Class I and Class II molars according to Pell and Gregory's classification (Gay Escoda et al. 2004).
8. Subjects must be able to swallow the IMPs.

1.3.2 Exclusion criteria

1.3.2.1 Exclusion criteria at Visit 1

1. Findings in the medical record, vital signs, and/or physical examination demonstrating abnormal conditions of subject's general state of health preventing his/her participation in the clinical trial according to the investigator's opinion.
2. Subject unable to speak, read, or write in Spanish language.
3. Clinical laboratory parameters exceed the pre-defined alert ranges (i.e., 1 standard deviation above or below the upper/lower limit of the normal ranges).
4. Known hypersensitivity to the IMPs, the anesthetic to be used during surgery, or to the rescue medication (ibuprofen, ketorolac).
5. Known alcohol or drug abuse in the last 6 months or any history of seizures. Alcohol abuse is defined as the consumption of more than 3 ounces (about 90 mL) of liquor or spirits or 18 ounces (about 530 mL) of beer per day, for 5 consecutive days during the 6-month period. Drug abuse is defined as the use of any recreational drug for 5 consecutive days during the 6-month period.
6. Subjects who take analgesic medication for chronic pain, monoamine oxidase inhibitors, tricyclic antidepressants, neuroleptics, or other drugs that reduce the seizure threshold within 4 weeks of enrollment.
7. Pregnant or lactating women.
8. Subjects who received systemic corticosteroids or opioid analgesics less than 2 weeks before surgery.
9. Subjects with molars linked to the mandibular canal.
10. Subjects requiring immediate dental procedures other than third and fourth molars extraction.

1.3.2.2 Exclusion criteria at Visit 2

11. Subject received a long-acting non-steroidal anti-inflammatory drug (NSAID) within 24 hours or 5 times the elimination half-life of that drug prior to surgery, whatever the longer.
12. Subject received any analgesic medication other than short-acting pre-operative or intra-operative anesthetic agents within 24 hours before taking IMPs.
13. Subject received more than 300 mg of lidocaine in total.
14. Subject received any analgesic medication other than the IMPs immediately after the oral surgical procedure was completed.
15. Baseline pain intensity of the subject after oral surgical procedure remains below 5 points on the 11-point numerical rating scale (NRS).

1.4 Trial treatments

1.4.1 Investigational medicinal products

Subjects will be randomly allocated to 1 of 4 groups of treatments in a 1:1:1:1 ratio.

Group A: Diclofenac sodium 50 mg, enteric-coated tablets, oral.

Group B: Tramadol HCl 50 mg, immediate-release capsules, oral.

Group C: Tramadol HCl/diclofenac sodium 50 mg/50 mg FDC, immediate-release tablets, oral.

Group D: Tramadol HCl/diclofenac sodium 25 mg/25 mg FDC, immediate-release tablets, oral.

In all treatment groups, each dose comprises 1 active treatment and 3 placebo tablets or capsules matching the other active treatment groups. All subjects will receive IMPs on Day 1 covering 24 hours of treatment (1 dose each at 0 hours, 8 hours, and 16 hours).

1.4.2 Rescue medication

Subjects will be encouraged to wait for at least 120 minutes after each dose of IMP before taking any rescue medication to allow for sufficient time for the IMP to take effect.

Rescue medication (ibuprofen 400 mg, oral, as often as every 6 hours) will be allowed in case of pain due to the dental extraction and will be available to the subject throughout the trial. Ketorolac tromethamine (30 mg, intramuscular, as often as every 4 hours to 6 hours) may be applied as second-line rescue medication at the site if ibuprofen 400 mg fails to relieve pain within 2 hours.

The number of units used, frequency of use, and the observation of any possible adverse event must be reported in the case report form (CRF) and in the source document(s).

1.4.3 Anesthetics for standardized surgery

Commercially available cartridges containing 36 mg of lidocaine hydrochloride plus 0.018 mg of epinephrine in a total volume of 1.8 mL will be provided by the sponsor.

1.5 Prior/concomitant medications

The use of antibiotics and other concomitant medications except for analgesics and systemic corticosteroids is allowed at the discretion of the investigator. They have to be in line with common practice of the investigator and with the information provided in the reference safety information

(investigator's brochure). All concomitant medications must be reported in the CRF and the source document(s).

1.6 Statistical analyses

The primary endpoint 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 and time since previous pain relief assessment for all subsequent assessments. TOTPAR scores can be interpreted as estimates of the area under the longitudinal pain relief curve (AUC).

1.6.1 Sample size rationale

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 $\alpha = 2.5\%$) 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 $\Delta = 1.5$ points (TOTPAR4). 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 to 12 sites.

1.6.2 Subject populations

The Safety Set will comprise all subjects allocated and treated with IMPs. 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. The Per Protocol Set (PPS) will comprise a subset of the subjects in the FAS without any major protocol deviations affecting the primary endpoint analysis.

1.6.3 Statistical methods and analysis

Treatment allocation will be stratified to ensure an equal distribution of subjects with severe baseline pain among the 4 treatment groups.

The primary analysis will be performed on the FAS. The primary analysis model will be an analysis of covariance (ANCOVA) with treatment, baseline pain, and site as covariates.

Each of the 4 treatment comparisons of the specific primary objective of the trial will be conducted based on results of the primary analysis and will be investigated by a formal statistical test. The trial will be positive if the null hypothesis of at least 1 of the 4 formal statistical tests gets rejected. A Bonferroni-Holm procedure will be used to control the trial family-wise error rate (FWER) in the strong sense at the pre-defined significance level of $\alpha = 2.5\%$ (1-sided).

For the non-inferiority comparisons, a non-inferiority margin of $\Delta = 1.5$ points (TOTPAR4) will be used.

Missing pain relief assessments in the first 4 hours after first dose as well as pain relief assessments after start of intake of rescue medication use will be imputed as follows:

- by Last Observation Carried Forward (LOCF) for intermittent missing data,
- by substitution by δ of missing data after premature discontinuation from the trial or disregarded pain relief assessments after start of rescue medication intake.

The parameter δ depends on the reason for discontinuation and treatment group. The primary analysis will be repeated as sensitivity analysis on the PPS. Additional sensitivity analyses will use classical single imputation techniques (LOCF, substitution by Zero) to investigate the impact of missing data approach on the constancy assumption.

1.7 References (synopsis)

Gay Escoda C, Piñera Penalva M, Velasco Vivancos V, Berini Aytés L. Cordales incluidos. Patología, clínica y tratamiento del tercer molar incluído. In: Gay Escoda C, Berini Aytés L. (eds.). Tratado de Cirugía Bucal. Tomo I. Madrid: Ergón; 2004. p. 355-85.

1.8 Schedule of events

Procedure	**Visit 1 (Enrollment Visit)**	**Visit 2 (Allocation Visit)**	**Visit 3 (End-of-treatment Visit)**	**Visit 4 (Final Visit** [phone call or on-site visit]**)**
Day	**-10 to -1**	**1**	**2**	**14**
Obtain informed consent	X			
Distribute subject trial card	X			
Evaluate inclusion/exclusion criteria	X	X		
Obtain radiological confirmation of impacted third molars (if not available from previous visit)	X	(X)		
Record demographic data (date of informed consent, sex, age, race, ethnicity, weight, height) and smoking status	X			
Record medical and dental history	X			
Perform physical examination [a]	X			
Take blood samples for clinical laboratory parameter assessments and urine for urinalysis [a, b]	X			
Record vital signs (pulse rate, systolic and diastolic blood pressure, respiratory rate)	X	X		
Perform urine pregnancy test (female subjects with childbearing potential only)	X	X		
Record prior medication	X			
Record concomitant medication	X	X	X	
Schedule appointment for dental surgery	X			
Record details of local anesthesia and dental surgery (3rd molar extractions)		X		
Allocate subject to treatment group		X		
Dispense IMPs		X		
Handout 2 stopwatches and a pain assessment booklet to each subject		X		
Record administration of IMPs		X		
Record pain intensity (NRS) [c]		X	X	
Record pain relief (5-point VRS) [d]		X		
Record pain at least half gone (YES/NO) [e]		X	X	
Transfer stopwatch times [f] to CRF		X		
Document IMP intake and rescue medication use (request/intake)		X	X	
Dispense IMPs to be taken at home and rescue medication		X		

Procedure	**Visit 1 (Enrollment Visit)**	**Visit 2 (Allocation Visit)**	**Visit 3 (End-of-treatment Visit)**	**Visit 4 (Final Visit** [phone call or on-site visit]**)**
Day	**-10 to -1**	**1**	**2**	**14**
Collect IMPs and rescue medication and perform drug accountability			X	
Record subject's global evaluation of the treatment (5-point Likert scale) [g]		X	X	
Record all adverse events		X	X	X

a) Physical examination results and clinical laboratory parameter and urinalysis data must be available at the latest at Visit 2.

b) Clinical laboratory parameter assessments will be performed by contracted local certified clinical laboratories.

c) 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.

d) 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.

e) Pain at least half gone (YES/NO) will be answered 15, 30, 45, 60, and 90 minutes (±2 minutes), and 2, 3, 4, 5, 6, 7, 8, and 24 hours (±6 minutes) after the first dose of IMPs.

f) Time to onset of first perceptible pain relief (Stopwatch 1) and time to onset of meaningful pain relief (Stopwatch 2).

g) Subject's global evaluation of the treatment will be assessed 8 hours after the first dose of IMPs or before first intake of rescue medication (whatever the first), and 24 hours after the first dose of IMPs.

CRF = case report form; IMP = investigational medicinal product; NRS = numerical rating scale; VRS = verbal rating scale.

2 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3 ABBREVIATIONS AND DEFINITIONS OF TERMS

3.1 Abbreviations

Abbreviation	Explanation
ANCOVA	Analysis of covariance
AUC	Area under the longitudinal pain relief curve
COXIB	Selective cyclooxygenase-2 inhibitor
CRF	Case report form
CRO	Contract research organization
FAS	Full Analysis Set
FDC	Fixed-dose combination
FWER	Family-wise error rate
GCP	Good clinical practice
HCl	Hydrochloride
ICF	Informed consent form
IEC	Independent ethics committee
IMP	Investigational medicinal product
IRT	Interactive Response Technology
IVRS	Interactive voice response system
IWRS	Interactive web response system
LOCF	Last Observation Carried Forward
LoE	Lack of efficacy
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drug
PID	Pain Intensity Difference
PPS	Per Protocol Set
SAE	Serious adverse event
SMO	Site Management Organization
SOP	Standard operating procedure (used as synonym for all procedural documents)
SPID	Summed Pain Intensity Difference
TOTPAR	Total Pain Relief
VRS	Verbal rating scale
WHO-DD	World Health Organization-Drug Dictionary

Système International d'Unités units and standard hematological and biochemical abbreviations are not listed.

3.2 Definition of terms

Term	Definition
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.
Enrollment failures	Enrolled subjects who were not allocated to IMP.
First subject allocated	First subject that was 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.
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.
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.

Use of the terms “must” and “should”

When “must” is used, the action/item is always mandatory. Non-compliance with this instruction constitutes a protocol deviation.

When “should” is used, the action/item is recommended but not mandatory. Non-compliance with this instruction does not constitute a protocol deviation.

4 ETHICS

This trial will be conducted according to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, good clinical practice (GCP), and applicable regulatory requirements.

This trial will be registered in public registries according to the local laws and requirements.

4.1 Independent ethics committees

The relevant independent ethics committees (IECs) for this trial will be provided with all documents required to fulfill their responsibilities. Any updates thereof will be provided according to GCP and applicable regulatory requirements. All correspondence between the IECs and the investigators at the trial sites will be retained in the investigator's site file and copies provided to the CRO/sponsor for the trial master file.

Trial activities will only start when approval from the relevant IECs is available.

Documentation of all involved IECs will be maintained according to GCP and applicable regulatory requirements.

4.2 Subject information and informed consent

Before any trial-related procedure will be performed, freely given informed consent must be obtained.

The informed consent discussion, the information sheet (if used) and the informed consent form provided to subjects must adhere to GCP and applicable regulatory requirements. The informed consent discussion with the subject must be performed by the principal investigator or an appropriately trained delegate. The information sheet and informed consent form agreed with the sponsor must be used. Prior to use, these documents must be approved by the relevant IECs. Each subject must be provided with a duplicate of the signed informed consent form for their records.

Subjects must be informed as soon as possible if new information becomes available that may be relevant to their willingness to continue participation in the trial. The communication of this information must be documented.

4.3 Informing the subject's healthcare provider

Only if the subject agrees in writing in the informed consent form and is being treated by a healthcare provider, e.g., general practitioner, the subject's healthcare provider should be informed about the subject's participation in the trial at trial enrollment. The healthcare provider should be informed about the trial code, the principal investigator's name, and a contact (phone) number at the trial site.

Any communication with the healthcare provider must be documented in the subject's medical records or the investigator's site file.

5 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

5.1 Investigators and trial site personnel

5.1.1 Investigators

The trial may be conducted solely at a dental clinic, or management of a subject may be shared between a dental clinic and a local research facility of a Site Management Organization (SMO). The latter combination is considered a single trial site.

There must be an investigator at each trial site.

If the trial is conducted by a team of individuals at the trial site, the investigator leading and responsible for the team is called the principal investigator. For each of the local research facilities, a principal investigator will be designated and will have primary responsibility for compliance with the protocol and GCP at that site (see Section 5.1.2).

All persons assigned responsibility as principal investigator must sign a declaration of their responsibilities and their agreement to this protocol before any trial-related procedure is performed.

Curriculum vitae and/or other relevant documents confirming the current qualification of the investigators must be provided to the sponsor. This should include any previous training in the principles of GCP, experience obtained from work with clinical trials, and experience with subject care.

Documentation of all involved investigators must be maintained according to GCP and applicable regulatory requirements.

In different countries, there may be country-specific terminology used for the investigator role.

A coordinating investigator will be defined who is responsible for the coordination of principal investigators at multiple trial sites in 1 country.

Documentation of all responsibilities assigned to the coordinating investigator must be maintained according to GCP and applicable regulatory requirements.

5.1.2 Trial site personnel assigned trial-related duties

The principal investigator may define appropriately qualified personnel at a trial site to perform significant trial-related procedures and/or to make trial-related decisions under his/her supervision. In this case, the principal investigator must maintain a signed list of the persons to whom they delegate significant trial-related duties/responsibilities; the delegated trial-related duties/responsibilities must be specified in the list.

When personnel or responsibility changes are made, the principal investigator must ensure that the relevant documentation is updated before any trial-related activities are performed.

Documentation of all involved trial site personnel performing significant trial-related procedures and/or making trial-related decisions must be maintained according to GCP and applicable regulatory requirements.

5.2 Contract research organizations

Contract research organizations (CRO; commercial, academic or other, e.g., local laboratory facilities, trial supply management provider, electronic CRF provider) may be contracted by the sponsor to perform trial-related duties and functions. The extent of the delegation must be documented. All involved CROs will be required to have implemented quality control and quality assurance processes, and to support the sponsor's quality control and quality assurance measures.

Documentation of all involved CROs must be maintained according to GCP and applicable regulatory requirements. Documentation of any delegation of responsibilities to CROs must be maintained in the trial master file.

5.3 The sponsor and sponsor's personnel

The trial sponsor listed on the title page accepts the responsibilities of the sponsor according to GCP and applicable regulatory requirements.

The sponsor must designate appropriately qualified personnel to advise on trial-related topics. The trial site will be provided with contact details for these personnel before any trial-related procedure is performed.

A list of key sponsor personnel involved in the preparation of this protocol and the conduct of the trial, including their full names, titles, roles, and responsibilities, must be maintained.

If non-sponsor monitors are involved in the monitoring of this trial, a list of all non-sponsor monitors including their full names, addresses, and responsibilities, must be maintained.

6 INTRODUCTION AND TRIAL BACKGROUND

6.1 Introduction

The American Society of Anesthesiologists Task Force on Acute Pain Management (2004) states in its update report of the practice guidelines for acute pain management in the perioperative setting that literature supports the administration of 2 analgesics that act by different mechanisms via a single route to provide superior analgesic efficacy with equivalent or reduced adverse effects. The Task Force believes that NSAID, selective cyclooxygenase-2 inhibitor (COXIB), or acetaminophen administration has a dose-sparing effect for systemically administered opioids. Whenever possible, doctors should use the strategy of multimodal or balanced analgesia aiming to individualize therapy of acute pain. This consensus group has suggested that the development of new drug combinations or routes of administration are opportunities to improve pain management meeting the individual needs of every patient.

6.2 Relevant non-clinical and clinical data

Grünenthal is Marketing Authorization Holder for tramadol/diclofenac FDC tablets (25 mg/25 mg or 50 mg/50 mg of tramadol HCl/diclofenac sodium), which are indicated for the relief of acute inflammatory pain of moderate to severe intensity. In adults and young people over 16 years old, the total daily dose of diclofenac sodium must not exceed 200 mg, resulting in a maximum tramadol

HCl daily dose of 200 mg for the FDC as well. The maximum single dose is 1 tablet every 6 hours as needed for pain relief and up to a maximum of 4 tablets per day.

The 25 mg/25 mg tablets are marketed under the tradename Adorlan Comprimidos® or Adorlan Tabletas® in 7 countries in Latin America: Colombia, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, and Panama. Based on the sales of more than 34 million single-dose units since the International Birth Date (05 Oct 2009) of the product, the estimated total cumulative post authorization patient exposure to diclofenac/tramadol was between 8.6 million (with 4 tablets per day) and 11.5 million patient treatment days (with 3 tablets per day) for the time period from Jan 2011 (first launch) to Oct 2015 (data lock point 04 Oct 2015 for most recent Periodic Safety Update Report).

For details about the clinical particulars, contraindications, and special warnings and precautions for use, interactions with other medicinal products and other forms of interaction, and adverse drug reactions, please see the investigator's brochure.

Previous clinical trials in various indications have demonstrated a benefit of the combined treatment with tramadol and diclofenac (see Appendix 18.3).

6.3 Trial rationale

The combination of analgesics is a common therapeutic practice (e.g., in ZALDIAR which combines tramadol HCl and acetaminophen/paracetamol). Combining tramadol with diclofenac is expected to provide the beneficial analgesic effects of the 2 products. The components are anticipated to be complementary. Pre-clinical studies and clinical trials in inflammatory pain models showed that the combination of tramadol and diclofenac has a synergistic and additive effect that allows its administration at tramadol HCl 25 mg and diclofenac sodium 25 mg doses, with analgesic efficacy and safety in inflammatory pain conditions (Rodríguez-Silverio et al. 2011, Auad Saab et al. 2009, Auad et al. 2009).

This trial is conducted in order to complete the dossier on the tramadol HCl/diclofenac sodium FDC to obtain the registration in the Latin American countries. It is expected to demonstrate the safety and efficacy of the FDC product in comparison to the respective monotherapies.

7 TRIAL OBJECTIVES AND ENDPOINTS

The overall objective of the trial is to evaluate the analgesic efficacy and safety 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 specific primary and secondary trial objectives as well as primary and secondary endpoints are listed in Section 1.2.

The primary endpoint is defined in detail in Section 7.1.

7.1 Definition of primary endpoint

Pain relief will be assessed at 15, 30, 45, 60, and 90 minutes, and at 2, 3, 4, 5, 6, 7, 8, and 16 hours after first dose using a 5-point verbal rating scale (VRS) with categories 0 (none), 1 (a little), 2 (some), 3 (a lot), or 4 (complete) (see Section 12.2.1.2).

The primary endpoint of the trial will be 4-hour Total Pain Relief (TOTPAR4). TOTPAR4 is a time-weighted measure of 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.

TOTPAR4 scores will be calculated as $\Sigma PR_{t=4}$ x [time (hours) elapsed since previous observation] where $PR_{t=4}$ is the Pain Relief at time point t = 4 in comparison to the assessment before administration of IMPs (Max and Laska 1991). 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 (Section 10.5) will be set to missing and will be imputed as described in the statistical section (see Section 14.5.5).

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 TRIAL DESIGN

This is a prospective, randomized, double-blind, diclofenac- and tramadol-controlled, parallel-group, multi-site, interventional Phase III trial to evaluate the analgesic efficacy and safety of administrations of tramadol HCl/diclofenac sodium FDCs (25 mg/25 mg and 50 mg/50 mg) in subjects with acute moderate to severe pain after third molar extraction.

8.1 Discussion of the trial design

The analgesic control of acute moderate to severe pain after third molar extraction is a well-established model to demonstrate safety and efficacy of analgesic anti-inflammatory drugs (Barden et al. 2004). The randomized design and the use of matching placebos permit a fair and unbiased comparison of the tramadol HCl/diclofenac sodium FDC at 2 levels (25 mg/25 mg and 50 mg/50 mg) with the monotherapies diclofenac sodium 50 mg and tramadol HCl 50 mg.

The TOTPAR was selected as primary variable as it is most sensitive to detect pain differences (Singla et al. 2015). The analysis after 4 hours (TOTPAR4) minimizes the impact an additional intake of rescue medication might have. Furthermore, an analysis after 4 hours allows a comparison of the efficacy of the FDC with the efficacy of the monotherapies (diclofenac or tramadol) before plasma levels drop below published minimum effective concentrations (data on file, Phase I trial for Adorlan).

The tramadol HCl/diclofenac sodium FDC 25 mg/25 mg is currently registered and marketed under the tradename Adorlan Comprimidos® or Adorlan Tabletas® in 7 countries in Latin America for the relief of mild to moderate inflammatory pain: Colombia, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, and Panama.

The selection of the endpoints for the trial matches the requirements laid down in the drafted Guidance for Industry on Analgesic Indications: Developing Drug and Biological Products (Feb 2014).

8.1.1 Rationale for the IMPs and the selected doses

The selected treatments and the doses for the FDC of tramadol and diclofenac were chosen based on the experience gathered in previous clinical trials (Auad Saab et al. 2009 and Auad et al. 2009).

Diclofenac sodium 50 mg and tramadol HCl 50 mg were chosen as comparators since the Mexican and Brazilian Legislation on Fixed-dose Combinations recommends comparing the FDC with the individual components of the combination.

Ibuprofen 400 mg was selected as rescue medication because it has shown efficacy in a randomized double-blind trial in the post-surgical model of extracted third molars (Bakshi et al. 1994). Ketorolac tromethamine 30 mg (intramuscularly) was selected as second-line rescue medication for subjects who do not experience sufficient pain relief with ibuprofen.

8.1.2 Rationale for the number and the frequency of visits/assessments

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).

8.2 Benefit/risk analysis

Subjects participating in this trial will benefit as the medical need of required third molar extraction is covered as well as the proper management of the pain associated with this procedure. The risks are implied in the surgical procedure of dental extraction as pain and bleeding. Adverse events of the drug combination are described in the investigator's brochure. It is expected that their frequencies will be similar to or lower than those with the individual drugs.

The investigators must become familiar with all sections of the investigator's brochure, the ibuprofen product information, and the ketorolac product information prior to initiation of the trial.

9 SUBJECT ENROLLMENT AND TRIAL DISCONTINUATION

9.1 Subject enrollment procedure

Subjects will be screened to identify those who could potentially be enrolled into the trial. Potentially eligible subjects will be asked to enroll into the trial by giving written informed consent.

If required by applicable regulatory requirements, the principal investigator must keep suitable logs of the subject enrollment procedure.

9.1.1 Handling of low enrollment

Trial sites with a low recruitment rate and/or which persistently deviate from the protocol may be required by the sponsor/coordinating investigator/sponsor's authorized delegate to stop further recruitment at once or to cease participation in the trial.

An activated site can be considered to have a low recruitment rate if it has not allocated a subject to treatment within 6 weeks, i.e., less than 6 subjects in 6 weeks, after trial treatment was available at the trial site.

9.2 Inclusion/exclusion criteria

The trial population must comply with the inclusion/exclusion criteria given in Section 1.3.

Subjects will only receive IMP if documentation is available showing that they comply with all of these criteria.

9.3 Subject discontinuation from the trial or IMP

Once a subject enrolls in this trial, whilst protecting subject safety, the trial site should make every effort to retain the subject for the planned duration of the trial.

A subject may withdraw consent at any time.

9.3.1 Subject discontinuation from the trial

If subjects are not eligible to be allocated to the IMPs, they must be classified as enrollment failures and be discontinued from the trial. It is at the discretion of the investigator to discontinue subjects from the trial if they cannot comply with the requirements of the protocol.

A subject must be discontinued from the trial if any of the following criteria are met after enrollment.

- Subject meets exclusion criteria at Visit 2.
- Subject withdraws consent.

9.3.2 Subject discontinuation from the IMPs

The principal investigator may decide to discontinue a subject from the IMPs if she/he considers continued treatment of the subject to pose an undue risk to the subject, e.g., due to particular adverse events. All subjects treated with IMPs must be followed up within the trial until the end of the trial, the subject's death, their withdrawal of consent, or loss to follow-up.

9.3.3 Procedure for the handling of discontinued subjects

9.3.3.1 Handling of subjects who discontinued from the trial

The principal investigator must document any discontinuation of a subject and inform the sponsor. Where applicable, the relevant IECs must be informed with a detailed written explanation.

The following must be done for **all** discontinued subjects, including those who withdrew informed consent:

- Document the main reason for discontinuation from the trial.
- Ensure that all data collected until the day of discontinuation is transferred to the CRF.
- Ensure that any dispensed pain assessment booklet is returned.
- Ensure that any unused IMPs and rescue medication (including all packaging) is returned.
- If possible, perform all tests as defined for the End-of-treatment Visit (Visit 3).
- Complete any other trial-related formalities, e.g., those related to discharge from the trial site.
- For subjects withdrawing consent, document in the source data the date and time of withdrawal.
- Document in writing, if a subject withdraws consent but agrees to attend the End-of-treatment Visit (Visit 3) and the Final Visit (Visit 4).

9.3.3.2 Handling of subjects discontinued from the IMP but not from the trial

If a subject is discontinued from IMP, the overall timeline for subsequent visits will be maintained as close as possible to the originally planned timeline.

Subjects must continue with the subsequent planned Visit 3 and the follow-up phone call/on-site visit (for details, see Section 11.1.2.2 and Section 11.1.3); however, the following does not have to be performed:

- Administer IMPs.
- Check discontinuation criteria.

9.3.3.3 Replacement of subjects

Subjects will not be replaced.

9.3.4 Premature termination or suspension of the trial

The following criteria for premature termination or suspension of the trial apply.

- The trial will be prematurely terminated, if the perception of the benefit/risk ratio becomes unfavorable for the continuation of the trial.
- The trial may be suspended or terminated by the sponsor should the Adorlan® FDC (tramadol HCl/diclofenac sodium 25 mg/25 mg) be withdrawn from the Latin America market for any reasons by the sponsor.
- The sponsor of the trial may suspend it for commercial reasons.

The relevant IECs, the regulatory authorities, or the sponsor or the sponsor's authorized delegate alone or in conjunction have the power to make a binding decision to prematurely terminate or suspend the trial at any or all trial sites. In addition, for an individual trial site, this decision can be made by the principal investigator.

The party prematurely terminating or suspending the trial must promptly inform all other parties (i.e., the principal investigators, the relevant IECs, the relevant regulatory authorities, or the sponsor/the sponsor's authorized delegate, as applicable).

In addition, if the principal investigator decides to terminate or suspend the trial at the trial site, they must promptly inform the subjects, ensure appropriate follow-up for any enrolled subjects, and provide the relevant IECs and the sponsor or the sponsor's authorized delegate, as applicable, with a written explanation of the termination or suspension.

The coordinating investigator must be informed immediately if the trial is prematurely terminated or suspended.

10 TRIAL TREATMENTS

10.1 Investigational medicinal products

10.1.1 Identity and composition – tramadol hydrochloride/diclofenac sodium fixed-dose combination tablets

Name:	**Tramadol HCl/diclofenac sodium immediate-release tablets**
Active components:	Tramadol HCl and diclofenac sodium
Dose (strength):	25 mg/25 mg, 50 mg/50 mg
Supplier:	Tecnandina S.A., Quito, Ecuador

Diclofenac sodium 25 mg is equivalent to 23.279 mg diclofenac base.
Tramadol HCl 25 mg is equivalent to 21.957 mg tramadol base.

For further information about the identity and composition of the IMPs, see the clinical supply specification (available on request).

10.1.2 Identity and composition – diclofenac sodium tablets

Name:	**Voltaren enteric-coated tablets**
Active component:	Diclofenac sodium
Dose (strength):	50 mg
Supplier:	Novartis

For further information about the identity and composition of the IMP, see the prescribing information for Voltaren enteric-coated tablets.

10.1.3 Identity and composition – tramadol capsules

Name:	**Tramadol immediate-release capsules**
Active component:	Tramadol HCl
Dose (strength):	50 mg
Supplier:	Tecnandina S.A., Quito, Ecuador

For further information about the identity and composition of the IMP, see the prescribing information for Tramadol capsules.

10.1.4 Identity and composition – placebo capsules and tablets

Placebos matching tramadol capsules, placebos matching diclofenac tablets, and placebos matching the FDC tablets are supplied by Tecnandina S.A., Quito, Ecuador. For further information about the identity and composition of the IMPs, see the clinical supply specification (available on request).

10.1.5 Packaging and labeling

For detailed information about the packaging and labeling, see the clinical supply specification (available on request).

Primary and secondary package of the trial medication will be identical for all treatment groups. Active treatments and their placebo will be identical in the primary and secondary packaging.

For each subject in every treatment group, there will be 1 treatment box. The treatment box will contain 3 kits, 1 for each dose. Each kit will contain 4 blisters with 1 active treatment and 3 placebos (capsule or tablets). Active treatments and their placebo will be identical in the primary and secondary packaging.

10.1.6 Delivery, storage, and disposal

For detailed information about the distribution of the IMPs, see the clinical distribution specification (available on request).

At the investigator's site, the IMPs will be stored in a secure and temperature-controlled room with restricted access and temperature monitoring. All IMPs must not be stored above 25°C. They must not be frozen or refrigerated in order to maintain the quality of the packaging and labeling. Further special storage conditions are not required.

Subjects should store the IMPs (for the third dose) at home in a place where children have no access to it and return any unused IMP and all packaging material to the site for drug accountability and drug compliance assessments.

Latest at the end of the trial, after the final drug accountability, partially used and unused trial medication will be returned to the appropriate warehouse and destroyed.

Controls will be implemented at the trial sites to ensure documented compliance with these requirements.

10.2 Administration of investigational medicinal products

Please refer to Section 1.4.1 for a description of the IMPs/treatment groups.

Subjects must be healthy except for the impacted lower third molars requiring extraction as it will be determined by medical history, and by physical and radiological examination.

The analgesic therapy will be started as soon as the subject's baseline pain intensity has been evaluated and meets the criteria of moderate to severe pain (i.e., ≥5 on the 11-point NRS) within 4 hours after the end of the surgery. The first dose of IMPs (1 active treatment and 3 placebos) in the post-surgical period will be administered at the site with some purified water (approximately 250 mL). A second dose will be administered 8 hours (±10 minutes) later at the site as well. The times of the IMP intake must be documented in the CRF.

Subjects will stay at the dental clinic or other research facility for at least for 8 hours after the first IMP dose before they can leave the trial site facilities. They should take their last dose of IMPs as an outpatient 16 hours (±1 hour) after the first IMP dose. The time of IMP intake must be documented by the subject in the booklet and be transferred to the CRF at Visit 3 by the investigator. No further IMP intake is planned.

10.3 Method of assigning subjects to treatment groups (allocation)

An electronic data capture system will be used to assign a subject number at the Enrollment Visit (Visit 1). An Interactive Response Technology system (IRT, voice and web based [IVRS or IWRS]) will be used to support the drug supply chain management processes of distribution. Details of the vendor and the system will be filed in the trial master file.

The investigator or person assigned by the investigator must log into the system using their own user identification number and a password. The investigator or person assigned by the investigator will enter the subject's number and other information required by the system to obtain a medication number. The medication number is then used to select the correct package of IMPs and rescue medication to give to the subject.

Treatment allocation (randomization) will be done at the Allocation Visit (Visit 2). Subjects who comply with all inclusion criteria and do not meet any of the exclusion criteria will be randomly allocated to 1 of the 4 treatment groups in a 1:1:1:1 ratio. Treatment assignment will be performed

centrally using an IRT system prior to the first administration of IMP. Allocation will be performed using a stratified block randomization with site and, following the IMMPACT recommendations (Cooper et al. 2016), pain intensity at baseline (categories "moderate" and "severe" as defined in Section 12.2.1.1) as stratification factors.

10.4 Blinding and unblinding

10.4.1 Methods of blinding

This trial will use double-blind and double-dummy methods to guarantee the blinding of all personnel involved in the trial. Active treatments and their placebo will be identical in the primary and secondary packaging. Subjects, sponsor, and investigators will be blinded to the subjects' treatments.

Randomization and blinding will be done in accordance with the sponsor's standard operating procedures (SOPs).

Briefly, each subject will have a treatment box: it will be an identified box with 3 smaller boxes inside. Besides the identification code, each small box will be marked as first, second and third dosage. There will be 4 blisters inside each box. Each blister will contain 1 unit; 3 blisters will have a tablet, and 1 blister a capsule. Only 1 of the units will have an active treatment and the other 3 units will have placebos matching the active treatments.

10.4.2 Methods of unblinding

The investigator, the responsible department at the sponsor, and the responsible Drug Safety department and contract research organization will receive appropriate methods for unblinding of single cases, i.e., IRT (IVRS/IWRS) system access.

Unblinding of the trial will only be carried out after entry of all clinical data and database lock. Unblinding will be initiated by the sponsor's department of Biostatistics according to the sponsor's SOPs for unblinding. Personnel in the sponsor's department of Clinical Trial Supply are unblinded according to the SOP for the blinding assurance within packaging and labeling of clinical trial supplies. The qualified person for pharmacovigilance may be unblinded at any time during the trial.

10.4.3 Identification of IMPs in emergency situations

The code may be broken when it is necessary and in that subject's interest in order to identify the IMPs given, e.g., if knowing the identification of the treatment group would lead to the investigator treating the subject differently. In addition, within the sponsor's Drug Safety department, the code may be broken for regulatory reporting, medico-scientific assessment of adverse events, or on request of the qualified person for pharmacovigilance.

For every subject whose blind was broken, the following information must be documented according to the sponsor's SOPs:

- The reason for, the date, and time of unblinding.
- The person(s) informed of the treatment allocation must be identified.

In order to maintain the double-blind nature of the trial, the IMP allocation for the subject must not be communicated further unless required for the surveillance of the subject or if necessary for urgent risk to benefit re-evaluation and/or measures for urgent risk minimization.

If required by local regulations, it may be that the IEC or the coordinating investigator needs to be informed.

10.5 Rescue medication

Details on rescue medication are provided in Section 1.4.2.

Subjects can request and take rescue medication at any time after the first administration of the IMPs if their trial medication does not provide sufficient pain relief. However, they will be encouraged (but not required) to refrain from rescue medication intake until at least 120 minutes after the intake of the first dose of IMPs (i.e., until diclofenac and tramadol have reached their maximum plasma concentration) to be able to reliably assess the efficacy of the IMPs first.

The time will be registered when subjects first request rescue medication and the time they take their first dose. Subjects taking rescue medication will be asked to complete the trial procedures as planned.

10.6 Lidocaine/epinephrine for anesthesia

Details on the local anesthetic are provided in Section 1.4.3. The administration details are provided in Section 11.1.2.1.

10.7 Allowed and forbidden concomitant medications

Subjects will be instructed to only use allowed concomitant medications during the trial.

Use of antibiotics and other concomitant medications except for analgesics and systemic corticosteroids is allowed by the protocol, according to the common practice of the investigator and the investigator's brochure. All concomitant medication must be registered in the CRF and the source document(s) (see also Section 1.5).

The allowed and forbidden concomitant medications will be explained to the subject by the investigator.

In emergency situations, subjects should be treated according to standard medical practice (see Section 11.2.1).

For information about potential drug-drug interactions, see the investigator's brochure.

10.8 Documentation of drug accountability

The principal investigator must ensure that documentation is maintained for the receipt, inventory, use, and destruction or return of unused, used, or partially used packages of IMPs and rescue medication. The documentation must include trial treatment name, dates, quantities, subject numbers, batch/serial numbers or other identification numbers, expiration dates, and the means to identify the subject to whom it was given.

Documentation must be maintained for the checking of drug accountability.

Before the unused IMPs and rescue medication supplied to the trial site are returned or destroyed, the principal investigator must allow sponsor representatives to perform drug reconciliation. The entries in the documentation will be compared with the returned and residual IMPs and rescue

medication, and the administration/intake as documented in the CRF, with clarification of any discrepancies or inconsistencies.

11 COURSE OF THE TRIAL AND CONDITIONS

See Section 1.1.1 for a flow diagram summary of the trial and Section 1.8 for a tabular schedule of events.

11.1 Course of the trial

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.

11.1.1 Enrollment Period (Visit 1)

A planned number of 1065 male and female subjects will be enrolled in this trial. During the first visit, the investigator and sub-investigators will explain the objectives of the trial to the potential participant as well as possible benefits and risks. If the subject decides to participate, the informed consent will be obtained and the subject will be assigned a subject number.

Thereafter, the following procedures will be performed and data will be documented in the CRF:

- Evaluate the subject's suitability for the trial and verify selection criteria including inclusion and exclusion criteria defined in Section 1.3.1 and Section 1.3.2.
- Record subject's demographic data (date of signing the informed consent, sex, age, race, ethnic group, body weight and height), and smoking status (see Section 12.1.1 and Section 12.1.5.2). The body mass index will be calculated in the CRF.
- Collect a urine sample and perform a pregnancy test in female subjects with childbearing potential (see Section 12.1.5.3).
- Take blood samples for clinical laboratory parameter assessments and urine for urinalysis. Clinical laboratory parameter assessments will be performed by contracted local certified clinical laboratories. If results of laboratory parameters deviate from normal range values, assessments may be repeated at the discretion of the investigator at an unscheduled visit during the Enrollment Period (see Section 12.3.3).
- Record relevant prior/concomitant diseases and surgical interventions (to be done by a certified physician) (see Section 12.1.3).
- Record dental history (see Section 12.1.4).
- Perform a physical examination (to be done by a certified surgeon) (for details see Section 12.1.5.1).
- Record prior (administered within 14 days before enrollment and up to the time of surgery) and concomitant medications (see Section 12.1.2).
- Perform a radiological examination of the affected third molars and document the impacted ones if this information is not available from a previous X-ray taken up to 1 month before the Enrollment Visit (see Section 12.1.5.4).

- Measure and record the subject's vital signs (pulse rate, systolic and diastolic blood pressure, and respiratory rate) (see Section 12.3.2).
- Schedule an appointment for the dental surgery.
- Inform the subject that tramadol-containing products, like other centrally acting analgesics, may impair the mental and/or physical abilities required for the performance of potential hazardous tasks such as driving a car or operating machinery. Subjects should be aware that they are not supposed to drive a car when they can leave the clinic on the day of surgery.

11.1.2 Treatment Period (Visit 2 and Visit 3)

11.1.2.1 Allocation Visit (Visit 2)

For restrictions concerning meals and fluid intake before and after surgery, please see Section 11.2.3.

Standardized local anesthesia

Extraoral antisepsis will be performed with e.g., 2.0% chlorhexidine. Intraoral antisepsis will be performed with e.g., a 0.12% chlorhexidine rinse. To numb the mouth, blocking of the inferior alveolar, lingual, and buccal nerves will be carried out by using 1-3 cartridges of lidocaine plus epinephrine per third molar not exceeding a maximum total amount of 300 mg of lidocaine per subject (8.3 cartridges). The anesthetics will be provided as cartridges of 1.8 mL with 36 mg of lidocaine hydrochloride plus 0.018 mg of epinephrine. No other kind of anesthetic is allowed. The exact amount of lidocaine administered and times of administration must be documented in the CRF and the source document(s). Maxillary anesthesia will be obtained using local infiltration, posterior superior nerve blocks, and palatal blocks.

When the anesthetic takes effect, the tissue will be opened and the upper and lower molars will be extracted.

Standardized surgery

The dental surgery will be the extraction of 3 or more third molars. Incision from the anterior border of the mandibular ramus continued as a marginal incision to the mesiobuccal part of the mandibular third molar will be made. Thereafter, the buccal mucoperiostal flap is elevated; bone is removed and irrigated with sterile physiologic saline solution. If necessary, splitting of the tooth will be performed. The ipsilateral maxillary third molar will be surgically removed, if indicated. The wounds will be cleaned, irrigated with sterile saline, and closed with sutures, if indicated.

Basic data of the surgical procedure performed, i.e., the number and position of the molars concerned (i.e., 01, 16, 17, or 32), duration (start/end time) of surgery, the degree of impaction of each tooth, and the extent of tissue damage must be recorded in the CRF and the source document(s).

Any deviations from surgical protocol must be thoroughly documented in the CRF. Deviations that may significantly influence postoperative pain assessments or safety and tolerability of the IMP will disqualify the subject for treatment allocation.

Subjects requiring fourth molar extraction are allowed in the trial. Subjects with molars linked to the mandibular canal and those requiring immediate dental procedures other than third and fourth molar extraction must not be included in the trial.

Postoperative baseline examination and treatment allocation

After surgery, subjects will assess their pain on an 11-point NRS. Subjects who report at least moderate baseline pain intensity (≥5 on the NRS) within 4 hours after surgery will be allocated to treatment. If 4 hours elapse without the development of moderate to severe dental pain following the completion of surgery, subjects must not be allocated and must be discontinued from the trial.

The first dose of the IMPs (1 capsule or tablet with active treatment plus 3 placebos) will be administered as soon as subjects report a pain intensity ≥5 on the NRS. The time of dosing will be recorded. The use of cold compresses or ice bags on the cheeks of subjects is allowed 4 hours after the administration of IMP; their use must be avoided in the 30-minute period before each pain assessment.

Subjects who undergo surgery and receive IMPs will stay in the dental clinic or other research facility for at least 8 hours after the initial dose and will receive the second dose of IMPs at 8 hours (±10 minutes). If pain assessments will take place in other research facilities, subjects must be transported to the facility between 15 minutes after the end of surgery and the first IMP administration; the commuting time may be up to 30 minutes. During transfer, subjects must be accompanied by a member of the SMO staff. Both must have written directions in the case of emergency.

Thereafter, they can leave the site and take their third dose of IMPs at home 16 hours (±1 hour) after the first dose of IMPs. They will be asked to document the intake time and to return for Visit 3 the next day at a time which allows a pain assessment 24 hours after the initial IMP dose was given.

At the site, subjects will be provided with 2 stopwatches and a pain assessment booklet. They will be asked to record their pain assessments during the following 8 hours as follows.

- The baseline pain intensity score (11-point NRS) before the first dose of IMPs (Section 12.2.1.1).
- Pain intensity scores at 15, 30, 45, 60, and 90 minutes (±2 minutes), and at 2, 3, 4, 5, 6, 7, 8 hours (±6 minutes) after the first dose of IMPs (Section 12.2.1.1).
- Pain relief on a 5-point VRS at 15, 30, 45, 60, 90 minutes (±2 minutes), and at 2, 3, 4, 5, 6, 7, and 8 hours (±6 minutes) after administration of the first dose of IMPs (Section 12.2.1.2).
- Stopwatch 1: subject documents the moment she/he feels the onset of first perceptible pain relief (Section 12.2.1.5).
- Stopwatch 2: subject documents the moment she/he feels the time to onset of a meaningful pain relief (Section 12.2.1.5).
- Response to the question if pain is at least half gone (see Section 12.2.2).

A summary of scheduled procedures for the Allocation Visit (Visit 2) is as follows:

- Check if any of the exclusion criteria for Visit 2 apply (see Section 1.3.2.2).
- Check availability of results of clinical laboratory parameters (to assess Inclusion Criterion 4 if not done before).
- Perform a radiological examination of the affected third molars and document the impacted ones if not done previously (see Section 12.1.5.4).

- Collect a urine sample and perform a pregnancy test in female subjects with childbearing potential (see Section 12.1.5.3).
- Measure and record the subject's vital signs (pulse rate, systolic and diastolic blood pressure, and respiratory rate) (see Section 12.3.2).
- Record the subject's prior medication stopped before surgery and any concomitant medication (see Section 12.1.2).
- Monitor the subject for and record any adverse event that occurred during or after the surgery (see Section 12.3.1).
- Instruct the subject on how to complete the pain assessments following surgery.
- Hand out stopwatches and a pain assessment booklet (NRS).
- Reinforce instructions regarding procedures for completion of the pain assessments.
- Administer IMPs immediately after the baseline pain assessment and record time.
- Commence time monitoring using the stopwatches provided for first perceptible and meaningful pain relief immediately upon IMP administration.
- Collect the pain assessment booklet and stopwatches before the subject leaves the clinic and transcribe the subject-reported data to the CRF.
- Ask the subject to perform a global evaluation of the treatment they received (5-point Likert scale) before the subject leaves the clinic, i.e., 8 hours after first IMP intake or before the first intake of rescue medication (whatever the first).
- Handout IMPs to be taken 16 hours (±1 hour) after first IMP dose to cover 24 hours of treatment.
- Hand out sufficient rescue medication (ibuprofen 400 mg) to cover 24 hours of treatment of dental pain if insufficiently resolved by the intake of IMPs.
- Hand out an information sheet to the subject with the protocol directions and contact details.
- Hand out a booklet and ask the subject to document at home:
  - Pain intensity and pain relief at 16 hours.
  - The intake of the third dose of IMPs.
  - Any use of rescue medication.
  - Any use of other medication.
  - Adverse events they might experience.
- Check that the subjects are in a condition to leave the site.
- Before subjects leave the site they should be reminded that tramadol-containing products, may impair the mental and/or physical abilities required for the performance of potential hazardous tasks such as driving a car or operating machinery.
- Ask the subject to come to the site on the next day at a pre-set time (24 hours after first IMP intake) for Visit 3.

Dental clinics must have an emergency kit according to local regulations (Norma Oficial Mexicana NOM-005-SSA3-2010). An emergency crash cart will be mandatory at each research facility any time an IMP is being administered.

11.1.2.2 End-of treatment Visit (Visit 3)

At the End-of treatment Visit (Visit 3), i.e., 24 hours after the first intake of the IMP, the following procedures will be performed:

- Collect all unused IMP and rescue medication and all packaging material.
- Perform drug accountability for the IMPs and for any rescue medication taken at home.
- Transfer all information collected in the subject's booklet at home to the CRF.
- Ask the subject to assess the 24-hour pain intensity (NRS), to state if their pain is at least half gone, and to evaluate the treatment they received (5-point Likert scale) in a booklet. Document the data in the CRF.
- Document any newly prescribed concomitant medication or changes in dose or route if applicable.
- Record all adverse events reported since Visit 2.

11.1.3 Final Visit (follow-up phone call or on-site visit on Day 14)

Thirteen days after the surgery day, the subjects will be contacted by phone or will be asked to visit the site to learn about their health status and the possible occurrence of adverse events.

All adverse events that occurred between Visit 3 and Visit 4 will be documented in the CRF and the medical records.

11.2 Conditions during the trial

11.2.1 Medical care

For any adverse events, a causal or symptomatic treatment according to standard medical practice should be provided if deemed necessary by the investigator. The medical care given to, and medical decisions made on behalf of the subjects must be the responsibility of a qualified physician.

See the guidance in the investigator's brochure for precautions and the handling of emergencies.

11.2.2 General restrictions

During hospitalization at the trial site, subjects are not allowed to smoke.

Strenuous or unusual physical activities will not be allowed from the Enrollment Visit until the Final Examination.

If subjects absent themselves from the trial site, they will be warned not to drive cars or operate dangerous machinery for 8 hours after last IMP intake.

11.2.3 Meals and fluid intake restrictions

Subjects may have a low-fat dinner the night before the surgery. They may have soft beverages like Ensure® up to 1 hour before surgery. Drinking water or juices (apple juice, orange juice) and low-fat milk are allowed after surgery. From 3 hours after IMP administration, subjects can have soft food (Jell-O™, mashed potatoes, milk shake, Ensure®). Water and soft food must be provided at room temperature. High-fat meals, ice creams, and sorbets must be avoided.

11.2.4 Counseling of women of reproductive age

All women, including those with tubal ligation, will be considered to be of childbearing potential unless they have been postmenopausal for at least 2 years or have undergone a hysterectomy.

All women of childbearing potential must be counseled on the need to practice medically acceptable methods of birth control during the trial and on the importance of avoiding pregnancy. Medically acceptable methods of birth control are methods with a failure rate (percentage of women experiencing an unintended pregnancy within 1 year of use of the method) of less than 1%, e.g., hormonal contraceptives or intra-uterine devices used according to the product's instruction for use, or double barrier method (male or female condom; diaphragm). The combination of 2 independent methods will result in multiplied failure rates per year, e.g., 0.63% for the concomitant use of a condom (with a 9% failure rate) and a diaphragm (with a 7% failure rate).

Note: A female condom and a male condom must not be used together as friction between the 2 can result in either product failing.

Women will be counseled to contact the investigator or trial site staff immediately if pregnancy is suspected once an informed consent form is signed and up to the Final Visit.

11.2.5 Counseling of male subjects

Male subjects will be counseled to contact the investigator or trial site staff immediately if a pregnancy of their partner is suspected.

11.3 Subject trial cards

Subjects who are allocated in the trial will receive a subject trial card (the time of card distribution will be given in Section 1.8). The subject trial card will list the following information:

- Name of the subject and a statement that she/he is currently participating in a clinical trial.
- Trial code.
- Name of the principal investigator for that trial site.
- Contact (phone) number at the trial site.

The card will be collected at the last visit if the subject visits the site.

11.4 Provisions of any additional care of subject after trial termination

After trial termination, subjects will be treated by their physicians according to the standard medical practice in the country concerned.

12 TRIAL ASSESSMENTS

12.1 Collection of demographic data and other baseline characteristics

12.1.1 Demographic data, height and weight

Demographic data are: date of signing the informed consent, sex, age (in years), race, ethnic group, body weight, height, and body mass index.

Body weight will be measured in light clothes. The body mass index will be calculated.

12.1.2 Prior and concomitant medication

All medication requiring prescriptions (including oral contraceptives), over-the-counter medication, traditional medicine, phytotherapy, and any other treatment ingested or applied to the skin or mucosal surface within 14 days prior to enrollment and up to the end of the trial must be recorded in the CRF. Toothpastes and mouthwashes need not be documented.

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 surgery or newly added thereafter.

Any addition to or change in dosage, regimen, or route for concomitant medications during the trial must be recorded in the CRF as a new entry.

12.1.3 Relevant prior/concomitant diseases and surgical interventions

Subjects' medical and surgical history, including any relevant diseases and surgical interventions, will be recorded in the CRF at Visit 1 by a certified physician.

All medical conditions controlled by medication must be recorded.

Childhood illnesses do not need to be documented, unless they could potentially give rise to an adverse event based on the pharmacology of the trial treatments or related to trial procedures.

12.1.4 Dental history

Subject's dental history will be recorded at Visit 1 and should 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.

12.1.5 Other baseline characteristics

12.1.5.1 Physical examination

A directed physical examination must be carried out by a certified surgeon and should include assessments of the general condition, ears, nose and throat, mouth (including teeth and gums), head, neck, heart, and lung. The outcome of the physical examination will be documented.

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

12.1.5.2 Smoking status

Subjects will be asked if they are 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), of never smoked regularly. The number of cigarettes/cigars/pipes smoked per week will be recorded for current smokers.

12.1.5.3 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 (see Section 1.8). The results of the dipstick test will be directly entered into the CRF and the medical records.

12.1.5.4 Radiological examination

If not done before Visit 1, an X-ray has to be collected during the Enrollment Period or – at the latest – at the Allocation Visit (see Section 1.8) to obtain a radiological confirmation of impacted third molars. The position of the impacted molars (i.e., 01, 16, 17, or 32) must be recorded on the appropriate CRF page and in the subject's medical records.

12.2 Collection of efficacy data

For the timings of assessments, see the schedule of events (Section 1.8).

12.2.1.1 Pain intensity (numerical rating scale)

Pain intensity will be evaluated using an 11-point NRS.

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".

The pain intensity score assessed before IMP intake will be considered the baseline pain intensity and will be used for stratification.

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.

12.2.1.2 Pain relief

The subject's pain relief will be assessed using a 5-point 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)

12.2.1.3 Total Pain Relief

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 (Max and Laska 1991).

The TOTPAR will be calculated at 4, 6, and 8 hours.

12.2.1.4 (Summed) Pain Intensity Difference

Pain Intensity Difference (PID_t) will be defined as the difference between baseline pain intensity and pain intensity at time point t, and Summed Pain Intensity Difference (SPID) defined as ΣPID_t x [time (hours) elapsed since previous observation] (Max and Laska 1991).

The PID (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.

The Summed Pain Intensity Difference (SPID) at 4, 6, 8, and 24 hours post-dose will be calculated.

12.2.1.5 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.*"

12.2.2 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.

12.2.3 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 8 hours after the first dose of IMPs or before first intake of rescue medication (whatever the first) and 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)

12.2.4 Rescue medication request and intake

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) must be documented in the CRF and the source document(s).

The time from baseline to the first dose of rescue medication will be calculated.

The amount of rescue medication used within 24 hours after surgery will be calculated based on drug accountability information available.

12.3 Collection of safety data

The following safety data will be collected: Adverse events, clinical laboratory parameters, and vital signs.

For the timings of assessments, see the schedule of events (Section 1.8).

Clinically relevant abnormal values (investigator's judgment) must be recorded as adverse events.

12.3.1 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).

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.

Lack of efficacy (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 Section 18.1 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.

Special procedures for serious adverse events

If SAEs occur that are not tolerable, the investigator will decide for that subject whether to stop the trial and/or treatment of the subject. For further details, see Section 9.3.

Expectedness of adverse events

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.

Furthermore, reports that add significant information about the specificity or severity of a known, already documented adverse reaction constitute unexpected adverse events. For example, an adverse event more specific or more severe than expected would be considered "unexpected".

Definition of adverse drug reactions

An adverse drug reaction is any untoward and unintended response to an IMP or a medicinal product related to any dose administered.

A list of adverse drug reactions seen for the IMPs is given in the reference safety information, i.e., in the investigator's brochure.

Documentation of adverse events

The subjects will be questioned about possible adverse events with non-leading questions before administration of the IMP and at regular intervals thereafter as defined in Section 1.8.

All adverse events reported spontaneously by subjects at any time point will also be documented.

All adverse events will be documented in the CRF with the following information where appropriate:

- 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.

Definition of intensity

The clinical intensity of an adverse event will be classified as:

Mild:	Signs and symptoms that can be easily tolerated. Symptoms can be ignored and disappear when the subject is distracted.
Moderate:	Symptoms cause discomfort but are tolerable; they cannot be ignored and affect concentration.
Severe:	Symptoms which affect usual daily activity.

For adverse events where the intensity changes over time, the maximum intensity observed during the whole duration of the adverse event will 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.

Definition of outcome at the time of last observation

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

- Recovered/Resolved
- Recovering/Resolving
- Not recovered/Not resolved
- Recovered/Resolved with sequelae.
- Fatal
- Unknown (unknown should only be used, if at the time of the last visit for a subject in a trial, the outcome of the adverse event is unknown to the investigator, e.g., because the subject is lost to follow-up).

In the event of irreversible congenital anomalies, the choice “not resolved” should be used. “Fatal” should only be used when death is possibly related to the adverse event (note: the causal relationship of the IMP to the adverse event is not to be considered for this decision). If there is more than 1 adverse event, only the adverse event leading to death (possibly related) will be attributed with the outcome “fatal”.

Definition of countermeasures

“Countermeasures” will be defined as:

None:	No countermeasure given.
Newly started medication:	A newly started medication or change in dose or route of application of a medication due to the adverse event (to be listed on the prior/concomitant medication page) that is used as a countermeasure.

Trial discontinuation:	It was necessary to discontinue the subject from the trial due to the adverse event.
Other:	All other countermeasures, e.g., physical therapy, surgery.

Except for none, multiple countermeasures for 1 adverse event can be recorded.

Classification of action taken with IMPs when an adverse event occurs:

- Dose reduced.
- Drug interrupted.
- Drug withdrawn.
- Dose not changed.
- Not applicable.
- Unknown.

Classification of causation

The causal relationship of an adverse event to IMPs will be classified using the following terminology. The given criteria for each term are for consideration and are neither exhaustive nor required to be fulfilled in total for the selection of the respective term:

Terms for classification of causation	Criteria for the selection of causality classification terms
Conditional/ Unclassified:	Additional data for a proper assessment are under examination.
Unassessable/ Unclassifiable:	The available data cannot be judged because information is insufficient or contradictory, and cannot be supplemented or verified.
Not related:	Data with sufficient evidence to accept that there is no causal relationship to IMP administration (i.e., there is no temporal relationship to IMP administration or proved other cause).
Unlikely:	Data without sufficient evidence to accept that there is no causal relationship to IMP administration, but also with no evidence or argument to suggest a causal relationship (e.g., the temporal relationship to IMP administration makes a causal relationship improbable, and other drugs, chemicals, or underlying disease[s] provide plausible explanations).
Possible:	Data with limited evidence or argument to suggest a causal relationship (e.g., there is a reasonable time sequence to administration of the drug, but the adverse event could also be explained by concurrent disease[s] or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear).
Probable/likely:	Data with sufficient evidence or argument to suggest a causal relationship (e.g., there is a reasonable time sequence to administration of the drug, the adverse event is unlikely to be attributed to concurrent disease[s] or other drugs or chemicals, and a clinically reasonable response on withdrawal [dechallenge]).
Certain:	Data with clear evidence for a causal relationship (i.e., a clinical event, including laboratory test abnormality, occurs in a plausible time relationship to drug administration, and it cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug [dechallenge] should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, using a satisfactory

rechallenge procedure if necessary).

Follow-up of subjects with an adverse event

Any adverse event or clinically relevant abnormal laboratory or vital sign result will be followed until it reaches a satisfactory resolution, or becomes stable, or clinical judgment indicates that further evaluation is not warranted.

Notification of serious adverse events

All SAEs (including death, irrespective of cause) during the trial, regardless of their relationship to IMPs, must be reported as soon as possible but no later than 24 hours after learning of the event. Before any trial-related procedure is performed, the trial site must be provided with contact details at the CRO/sponsor's Drug Safety department (drugsafety.mx@grunenthal.com) for this reporting.

The investigator must submit a report, called a Safety Reporting Form, which includes a description of the event, the therapy instituted, and trial procedures. The following information should be communicated with the first notification of an SAE:

- Trial identifier
- Subject's identifier.
- Subject's date/year of birth (if available, see local data protection requirements) or age (at adverse event onset).
- Subject's sex.
- First administration of IMPs (date and time, if available).
- Last administration of IMPs (date and time, if available).
- Adverse event verbatim term (specific diagnosis, if possible).
- Adverse event onset (date and time, if available).
- A brief description of the event, the course, and the countermeasures taken.
- Intensity
- Seriousness criterion.
- Outcome
- Concomitant medication at onset of the event and whether one of the concomitant medications is also suspected to have caused the event.
- Relevant history/pre-existing medical conditions.
- Investigator's assessment of the relationship to IMPs.
- Whether and when blinding was broken (see Section 10.4.3).

All additional information concerning the adverse event until trial termination or definite outcome must be communicated per follow-up report without delay.

The immediate and follow-up reports must only identify the subjects using the unique subject identifier.

The investigator must comply with applicable regulatory requirement(s) related to the reporting of SAEs to the regulatory authorities and the relevant IECs. Based on the investigator SAE reports, the sponsor's Drug Safety Department will generate Drug Safety Update Reports. They will monitor

the Suspected Unexpected Serious Adverse Reaction reports to detect any possible safety signals and generate early safety alerts if necessary.

12.3.2 Vital signs

Vital signs will be measured at time points specified in Section 1.8 and comprise pulse rate, systolic and diastolic blood pressure, and respiratory rate.

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.

12.3.3 Safety laboratory

Sampling for clinical laboratory parameter assessment and for urinalysis will be done at the Enrollment Visit (see schedule of events in Section 1.8). The blood samples will be taken by direct venipuncture or by means of an indwelling venous cannula.

Clinical laboratory parameter assessment will be performed by contracted local certified clinical laboratories. Details on the clinical laboratories will be held in the trial master file and the investigator's site file.

A table of the reference ranges for each of the clinical laboratory parameters measured with a description of the methods will be provided by the clinical laboratory before the trial start and will be filed in the investigator's site file and the trial master file. Changes in the reference ranges or in the methodology during the course of the trial must be communicated by the local clinical laboratory to the investigators and to the sponsor.

Throughout the clinical part of the trial, the investigator must provide feedback regarding the clinical relevance of any laboratory value outside the reference range.

Additional determination of several parameters from blood may be added at the discretion of the investigator.

If clinical laboratory parameters exceed the pre-defined alert ranges (i.e., 1 standard deviation above or below the upper/lower limit of the normal range) the subject must not be allocated to treatment.

The original printouts of the clinical laboratory parameter and (if applicable) urinalysis values will be considered source documents and will be stored in the subject files. Data will be transferred from the printouts to the CRF by the investigator.

For each subject, up to 3 blood samples (total volume 12 mL) will be drawn for clinical laboratory parameter assessments.

The following clinical laboratory parameters will be assessed:

Clinical chemistry panel (sample volume approximately 6 mL)	
Sodium	Total bilirubin
Potassium	Alkaline phosphatase
Chloride	Creatine kinase
Bicarbonate	Lactate dehydrogenase
Urea	Uric acid
Creatinine (serum)	Calcium

Clinical chemistry panel (sample volume approximately 6 mL)	
Glucose	Phosphorus
Aspartate transaminase	Albumin
Alanine transaminase	Total protein
Gamma-glutamyl transferase	Lipase
Cholesterol	Triglycerides
Hematology panel (sample volume approximately 3 mL)	
Hemoglobin	Platelet count
Hematocrit	White blood cell count; manual differential white blood cell count if automatic differential white blood cell count is abnormal
Red blood cell count	Mean cell volume
Mean cell hemoglobin	Mean cell hemoglobin concentration
Coagulation panel (sample volume approximately 3 mL)	
Activated partial thromboplastin time	International normalized ratio (derived from the prothrombin time)
Prothrombin time	

Urinalysis panel	
pH	Protein
Glucose	Ketones
Urobilinogen	Bilirubin
Hemoglobin	Nitrite
Leukocytes	

If urinalysis results are positive for leukocyte esterase, nitrite, protein, or blood, a microscopic examination of urine must be performed. Results will be reported only for the parameters that are present.

12.4 Appropriateness of measurements

The selection of the outcome measures pain intensity and pain relief and the derived parameters SPID and TOTPAR to support the secondary endpoints are commonly used in single-dose acute pain trials (Cooper et al. 2016). The visual analog scale is amongst the most popular scales to measure acute pain. The assessment of the onset of the analgesic effect using the double-stopwatch method is standardized and reliable (Desjardins et al. 2002).

The TOTPAR was selected because this summary measure is widely used and acknowledged for the scientific evaluation of single-dose trials (Sriwatanakul et al. 1983) and is an accepted endpoint for acute pain trials (Singla et al. 2015). The TOTPAR scores can be interpreted as estimates of the area under the longitudinal pain relief curve. The time-frame of 4 hours has been chosen as it coincides with the time point the comparator concentrations drop below published minimum effective concentrations, and as it minimizes the impact of potential rescue medication intake.

12.5 Compliance

Compliance is the adherence to all requirements of the trial protocol.

Trial site compliance will be assured by the implementation of a quality system and the performance of a combination of trial site visits, training, and monitoring visits. Non-compliance should lead to prompt action by the sponsor to secure compliance.

Subject compliance will be confirmed by a comparison of IMPs dispensed and returned and by IMP administration by the investigator in a controlled environment.

13 DOCUMENTATION OF TRIAL DATA

The trial documentation must be adequate for the reconstruction of the trial.

13.1 Case report forms

The investigator must verify and confirm by signing that the CRFs have been checked and are complete, accurate, and compatible with the source documents. All CRF entries, corrections, and alterations must be made by the investigator or other authorized personnel under their supervision.

Case report forms for each subject will be provided to the investigator by the sponsor in electronic format to document the trial data.

The investigator and personnel delegated the task will use CRFs to record information required by the protocol. All personnel entering data will receive instruction on how to complete the CRF.

The investigator will be required to verify that the CRF entries are complete, accurate, and compatible with source documents.

All CRF entries, corrections, and alterations will be made by the investigator or other authorized personnel under their supervision. Entries will be checked against appropriate source documents by authorized sponsor representatives as deemed appropriate in the monitoring guidelines.

The data will be processed using a validated electronic CRF system. Access to the system will be protected with a personal user name and password. Dedicated users (e.g., the investigator, designated persons at the trial site, authorized sponsor representatives, and from other parties involved, e.g., data management) will be identified and receive access rights according to their role in the trial. They will be trained on the use of the system for their intended role before access rights are granted and will be able to review data during the trial via a secure internet connection.

All entries and modifications to the CRF will be stored with the personal identification of the person who made the entry/changes, a date/time stamp, and the reason for change, if applicable.

The CRF must be signed electronically by the investigator. Any changes made to the CRF pages after the investigator has signed will require re-signing by the investigator.

13.2 Subject reported outcomes

Subject’s pain assessments (NRS), pain relief scores, responses to the question if pain is at least half gone, and IMP/rescue medication intake at home will be captured by paper.

All subject reported outcomes reported on paper will stay as source data at the trial site. The investigator is responsible for the accurate transfer of these data into the CRFs (see Section 13.1).

13.3 Data management

Data management will be performed by sponsor personnel or by authorized sponsor representatives. Documentation of the responsibilities and delegation thereof will be maintained in the trial master file.

Queries and corrections

During data entry in the CRF, automatic queries will be raised to clarify missing data, inconsistencies, and incorrect values. Additional queries will be issued via the CRF system to the investigator to clarify inconsistencies (e.g., resulting from additional electronic validation checks or medical and manual reviews). Resolutions of queries will be made by the investigator or the trial site's designated persons. The query is to be answered directly in the electronic CRF system and the original value will be changed, if necessary.

Corrections to the data without raising a query to the investigator will only be made by the data management CRO when the errors and their solutions are self-evident and if they do not change the actual meaning of the data as recorded by the investigator.

A list of all self-evident corrections will be defined in the data management plan and will be sent to the investigator for approval at the beginning of the trial. If the investigator does not approve the list of self-evident corrections, data clarification forms will be created.

External trial data

External trial data (e.g., clinical laboratory parameters) being provided on separate printouts will be entered manually directly from the printouts.

The transferred data will be reconciled against other CRF data (details of reconciliation will be specified separately in the data validation plan or data management plan but may include trial code, trial site number, subject number, age, dates of visits). Procedures will be implemented to resolve discrepancies.

At the end of the trial, the providers/vendors providing these data will provide the data management CRO with a complete and clean data transfer.

Coding

Medication names will be coded using the World Health Organization-Drug Dictionary (WHO-DD). Medical history terms and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Coding will be reviewed by the sponsor's personnel according to standard procedures.

Database lock

When all data have been received and entered into the clinical trial database, all data checks and quality control checks have been performed, all queries are resolved, and the final statistical review has been held without resulting in new queries, the clinical trial database will be considered clean and the data will be locked.

13.4 Source data

Source data is defined by GCP as "all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)".

Source data comprise clinical documentation, data, and records (e.g., clinic/hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, and data and records arising from departments such as the pharmacy, laboratory, and medico-technical departments) that describe or record the methods, conduct, or results of the trial, the factors affecting the trial, and the actions taken.

All source data arising from the trial will be kept by the investigator, who must provide direct access for trial-related monitoring, audits, ethics committee review, and regulatory inspection.

In certain circumstances, data may only be recorded in the trial-specific CRF and not in other documents. When this occurs, the CRF is considered to be the source document. Data expected to be only recorded in the CRF are: race/ethnicity and sex.

The nature and location of all source data/clinical documentation will be identified and documented by the investigator to ensure that all sources of original data required to complete the CRF are known to the sponsor and/or trial site personnel and are accessible for verification during trial-related monitoring, audits, relevant IEC review, and inspection(s).

During trial conduct, the vendor is responsible for data security related to data captured in the electronic CRF or IRT.

All data captured from all subjects will be sent to the sponsor in human readable form on a read-only compact disc/DVD for filing/archiving according to sponsor SOPs.

The investigator will receive all data captured for his or her subjects, in a human readable form, on a read-only compact disc/DVD for his or her files.

13.5 Investigator's site file and the trial master file

The principal investigator is responsible for the filing of all essential documents in an investigator's site file. The sponsor is responsible for the timely filing of all essential documents in the trial master file. As applicable, these files must be available at monitoring visits and during audits or regulatory inspections.

After trial completion, the principal investigator must ensure that all source data/documentation related to the trial is recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. The principal investigator must take measures to prevent accidental or premature destruction of these documents.

The principal investigator must keep the investigator's site file, the source data/documentation arising from the trial according to the prescribed record retention period in the country and/or according to the hospital policy, but at least until informed by the sponsor that the trial-related records are no longer required.

14 QUANTITATIVE ANALYSES

14.1 Statistical methods and sample size determination

14.1.1 Sample size rationale

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 $\alpha = 2.5\%$) assuming a common standard deviation of change from baseline values of 4 points (TOTPAR4) (Bakshi et al. 1994, Hersh et al. 2004) and an expected treatment difference of at least 2 points (TOTPAR4) (Auad et al. 2009, Singla et al. 2014) 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 $\Delta = 1.5$ points (TOTPAR4) (see Section 18.2) 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 to 12 sites.

14.2 General description of statistical analyses

The statistical analysis of this trial will be performed as described and summarized in the protocol. Full details of the planned statistical analyses will be described in the trial statistical analysis plan.

The statistical analysis of this trial will be planned, performed, and reported by sponsor personnel or by authorized sponsor delegates, in accordance with sponsor SOPs/SOPs of the sponsor's delegate.

Data collected and derived in the trial will be listed.

Summary statistics and graphical methods will be used to describe endpoints of interest.

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, 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, third quartile (Q3), and maximum.

All the statistical analyses will be performed in the relevant analysis population of interest (see Section 14.3). All the statistical analyses will be performed at least by treatment group.

14.3 Analysis populations (analysis sets)

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

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

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. Further details of the definition of the PPS will be specified in the statistical analysis plan.

14.4 Analysis of demographic data and other baseline characteristics

Subject disposition as well as demographic and baseline data and other subject characteristics (e.g., medical history and prior and concomitant medications) will be descriptively summarized for the Safety Set, FAS, and PPS.

14.5 Analysis of efficacy data

The primary analysis to investigate the primary objective of the trial (see Section 1.2) 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 only.

14.5.1 Analysis population for primary efficacy analysis

The primary analysis to investigate the primary objective of the trial (see Section 1.2) is based on the primary efficacy endpoint (TOTPAR4) and will be performed on the FAS.

The rationale to choose the FAS as analysis set for the non-inferiority comparisons of the primary analysis (for superiority comparisons the FAS population is used as a standard) is the preservation of the value of randomization and estimation of real world effectiveness, properties desirable for non-inferiority trials as well (Wiens and Zhao 2007). It is important to carefully choose conservative imputation methods (see Section 14.5.5) in order to avoid that subjects who discontinue the trial before full treatment effects are shown, diminish the difference between treatments making them appear more similar than they are and therefore inflate the risk of falsely accepting therapeutic non-inferiority when it is not justified. The primary analysis will be repeated as sensitivity analysis on the PPS. Additional sensitivity analyses and the analysis of additional efficacy parameters will be performed on the FAS only.

14.5.2 Overall testing strategy

The primary objective of the trial (see Section 1.2) 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 $\alpha = 2.5\%$, a Bonferroni-Holm procedure (Holm 1979) 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}: $\mu_{T50} - \mu_{ADL50/50} \geq 0$	H_{A1}: $\mu_{T50} - \mu_{ADL50/50} < 0$
T_2	Superiority of tramadol HCl/diclofenac sodium 50 mg/50 mg vs. diclofenac sodium 50 mg	H_{02}: $\mu_{D50} - \mu_{ADL50/50} \geq 0$	H_{A2}: $\mu_{D50} - \mu_{ADL50/50} < 0$
T_3	Non-inferiority of tramadol HCl/diclofenac sodium 25 mg/25 mg vs. tramadol HCl 50 mg	H_{03}: $\mu_{T50} - \mu_{ADL25/25} \geq \Delta$	H_{A3}: $\mu_{T50} - \mu_{ADL25/25} < \Delta$
T_4	Non-inferiority of tramadol HCl/diclofenac sodium 25 mg/25 mg vs. diclofenac sodium 50 mg	H_{04}: $\mu_{D50} - \mu_{ADL25/25} \geq \Delta$	H_{A4}: $\mu_{D50} - \mu_{ADL25/25} < \Delta$

ADL = Adorlan (tramadol HCl/diclofenac sodium); D = diclofenac sodium; T = tramadol hydrochloride; HCl = hydrochloride.

$\Delta = 1.5$ 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 $H_{(04)}$.

14.5.3 Analysis of primary endpoint

14.5.3.1 Primary analysis

The primary endpoint will be TOTPAR4 (see Section 7.1). 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.

The estimand 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 (Mallinckrodt et al. 2012). The FAS analysis will be the primary analysis for all comparisons.

Null hypotheses $H_{01} - H_{04}$ and alternative hypotheses $H_{A1} - H_{A4}$ of the formal statistical tests of the primary efficacy analysis are provided in Table 1. The primary analysis will use an ANCOVA model with treatment, site, and baseline pain (measured on an 11-point NRS) as covariates.

A detailed description of missing data imputation methods is provided in Section 14.5.5.

14.5.3.2 Sensitivity analysis

The following sensitivity analyses will be performed to assess the robustness of the primary analysis results to the choice of analysis population and missingness assumptions:

Sensitivity analysis 1: Full Analysis Set

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 here as well, namely LOCF 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.

Sensitivity analysis 2: Per Protocol Set

The primary analysis will be repeated on the PPS.

14.5.4 Analysis of additional efficacy outcomes

The pain intensity scores (NRS) at all the time points (see Section 1.8) after the first dose of IMPs will be analyzed by an ANCOVA model with treatment, site, and baseline pain as covariates.

Pain relief expressed as Total Pain Relief after 6 hours and after 8 hours (TOTPAR6, TOTPAR8) will be analyzed with the same ANCOVA model and missing data handling as the primary analysis.

The specification of the statistical analysis of the following additional efficacy outcomes including statistical analysis models, formal statistical tests, and further specifications in detail will be provided in the statistical analysis plan:

- Pain intensity score reductions (Pain Intensity Difference [PID], NRS) for each time point after the first dose of IMPs.
- Summed Pain Intensity Difference (SPID) at 4, 6, 8, and 24 hours after the first dose of IMPs.
- Pain relief scores for each time point after the first dose of IMPs.

- Time to onset of first perceptible pain relief (Stopwatch 1).
- Time to onset of meaningful pain relief (Stopwatch 2).
- Time to achieve a 50% reduction in baseline pain (pain at least half gone).
- Time to request the first dose of rescue medication.
- Time to first intake of rescue medication.
- Subject's global evaluation of the treatment (5-point Likert scale) 8 hours or before first intake of rescue medication (whatever the first) and 24 hours after the first dose of IMPs.

14.5.5 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.

Primary analysis

For the primary analysis, missing pain relief assessments in the first 4 hours 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.

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 LoE, adverse events, and other, non-drug related reasons. The parameter will be

- $\delta = 0$: 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.
- $\delta = 0.375$: 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.
- $\delta = 0$: For missing data after discontinuations due to other, non-drug related, reasons.

The size of parameter δ is chosen to result in a TOTPAR4 penalty of $\Delta/2$ in case the trial discontinuation/start of rescue medication intake occurs 2 hours after first dose, with non-inferiority margin $\Delta = 1.5$ points (TOTPAR4) as determined in Section 18.2.

Sensitivity analysis 1: Full Analysis Set, single imputation methods

To investigate the constancy assumption, missing and disregarded pain relief assessments will be imputed with the following single imputation methods used in historical trials of the active comparators as well:

- Last Observation Carried Forward.
- Last Observation Carried Forward for intermittent missing data, and substitution by Zero (no relief from starting pain) for missing data after premature discontinuation from the trial or disregarded pain relief assessments after start of rescue medication intake.

14.5.6 Subgroup analyses

Subgroup analyses will be performed for subjects with a moderate pain intensity at baseline (with scores of 5 or 6 on the 11-point NRS) and for subjects with a severe pain intensity at baseline (with scores of 7 to 10 on the 11-point NRS). Furthermore, subgroup analyses will be performed per site.

14.6 Analysis of safety data

The analysis of safety data will be performed for the Safety Set and will be listed with all corresponding information.

14.6.1 Adverse events

A definition of adverse event is given in Section 12.3.1.

The original terms used by the investigators in the CRFs to identify adverse events will be coded using the most recent version of the MedDRA at the time of database lock.

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 treatment emergent adverse event.

Treatment emergent adverse events will be summarized for each treatment group by System Organ Class and Preferred Term. Additional summaries by time to onset, duration, intensity, relationship to IMP, outcome, expectedness, and countermeasures will also be produced.

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 adverse events and adverse events leading to premature discontinuation from treatment will be presented descriptively.

14.6.2 Clinical laboratory parameters and urinalysis

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

14.6.3 Vital signs

Descriptive statistics will be calculated for each parameter of the vital signs collected at Visit 1 and Visit 2.

15 QUALITY SYSTEM, AUDIT AND INSPECTION

15.1 Quality system

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs.

15.2 Data quality assurance

The accuracy and reliability of the trial data will be assured by careful CRO/investigator selection and oversight by the performance of a combination of trial site visits, training, monitoring visits, remote verification by the sponsor or appropriate use of electronic tools by the trial site, data cleaning, and audits.

Trial site monitoring as defined in GCP will be performed by sponsor personnel or by authorized sponsor delegates at pre-defined intervals depending on the progress of the trial.

Corrections, amendments, or clarifying statements resulting from monitoring visits should be made by the investigator where necessary.

Appropriate checking against source documents must be done by the sponsor.

Audits as defined by GCP should be performed for this trial. The auditors will be independent of the trial and its performance.

15.3 Inspections

The principal investigator, any investigators, the sponsor, or personnel at other establishments, must cooperate with any inspection of the documents, facilities, records, and other resources deemed appropriate by the inspecting authorities to be related to the trial and that may be located at the trial site, at the sponsor, or at other establishments.

The sponsor must be notified as soon as possible about any upcoming regulatory authority inspection.

16 GENERAL CONDITIONS AND AGREEMENTS

16.1 Insurance

If required by applicable regulatory requirements, the sponsor will arrange suitable insurance for the subjects included in this trial and provide the investigator with the relevant terms and conditions of this insurance. The investigator must inform all subjects about this insurance and (if requested) be prepared to explain the relevant terms and conditions of this insurance to the subject.

If changes to the trial are implemented after the initial insurance was arranged, e.g., due to protocol amendments, the sponsor will notify the insurance company of these changes in accordance with the insurance conditions. If changes to insurance arise, the sponsor will inform the investigators who will then inform their subjects about relevant changes.

16.2 Legal regulations

This trial will be carried out in compliance with any applicable regulatory requirements with respect to the use of narcotics.

Before initiating the trial, if required by the applicable regulatory requirements, the sponsor or its authorized legal representative and/or the investigator will submit any required documents to the appropriate authorities for review, acceptance, and/or permission to begin the trial.

16.3 Contracts

Specific contracts between the relevant parties, i.e., between the investigator/other parties at the trial sites and the sponsor or its local offices or CRO or its affiliates authorized by the sponsor, will be used to set out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. This protocol and other documentation may serve as the basis of such contracts. In case of discrepancies with other contracts, the provisions of the protocol prevail.

In addition, responsibility for insurance or indemnity to cover any liability of the investigator that may arise directly or indirectly from the investigator's participation in the trial will be specified in a contract between the investigator and sponsor, if applicable.

16.4 Subject data and data protection

Subject trial data will be stored in a manner maintaining confidentiality in accordance with applicable regulatory requirements.

The investigator should ensure that any documents or data given to the sponsor or authorized sponsor representatives do not contain information that would affect the confidentiality of the subject's identity.

The investigator will obtain permission for direct access to original subject data from the subject as part of the written informed consent procedure (see Section 4.2). This gives permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor personnel or its representatives, and auditors) with direct access must take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the subject's identity and sponsor's proprietary information.

16.5 Public disclosure

The results of this trial will be publically disclosed in accordance with the sponsor's disclosure policy, the European Federation of Pharmaceutical Industries and Associations (EFPIA) Principles for Responsible Clinical Trial Data Sharing and applicable regulatory guidance (e.g., on www.cofepris.gob.mx).

The results (or parts thereof) of this trial may be published as a full publication (e.g., journal publication) or at a congress (e.g., as a poster or presentation). The sponsor reserves the right to review any proposed full publication or poster or presentation of the results of this trial by the coordinating investigator before they are submitted for publication or public disclosure.

Neither the sponsor nor the coordinating investigator has the right to prohibit publication or public disclosure unless it can be shown to affect possible patent rights.

16.6 Trial results reporting

A final report integrating clinical and statistical results will be prepared by the sponsor. The coordinating investigator will approve the final report on behalf of the participating investigators.

The sponsor will provide the competent authority/ies and relevant IECs with a summary of the trial results in accordance with applicable regulatory requirements.

All principal investigators will be provided with a summary of the trial results.

16.7 Approval

16.7.1 Sponsor

This protocol has been approved in accordance with sponsor SOPs.

16.7.2 Coordinating investigator

This protocol has been approved by the coordinating investigator.

17 REFERENCES

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18 APPENDIX

18.1 List of potentially important medical concepts – classified by System Organ Class

Blood and lymphatic system disorders		
Agranulocytosis	Aplastic anaemia	Blast cell proliferation (myeloproliferative and lymphoprolipherative disorders)
Bone marrow depression	Disseminated intravascular coagulation (DIC)	Haemolytic anaemia
Histiocytosis	Loss of anticoagulation control	Pancytopenia
Splenic haemorrhage, infarction or thrombosis	Thrombocytopenia (<30000)	Thrombotic thrombocytopenic purpura
Cardiac disorders		
Angina unstable	Atrial flutter	Atrioventricular block complete
Cardiac arrest	Cardiac failure acute	Cardiac fibrillation
Cardiac tamponade	Cardiogenic shock	Cardiomyopathy acute
Coronary artery spasm	Cor pulmonale decompensated	Myocardial infarction
Torsade de pointes	Ventricular fibrillation	Ventricular tachycardia
Ear and labyrinth disorders		
Deafness	Vestibular ataxia	
Endocrine disorders		
Adrenocortical insufficiency acute		
Eye disorders		
Cataract/lens opacity	Glaucoma	Keratitis/corneal opacification
Macular degeneration	Optic neuropathy, atrophy	Papilloedema
Ptosis	Retinal artery/vein occlusion	Retinitis
Scotoma	Sudden visual loss	Uveitis
Vitreous detachment		
Gastrointestinal disorders		
Colitis haemorrhagic	Gastric ulcer haemorrhage	Gastric ulcer perforation
Haematemesis	Haemoperitoneum	Ileus
Intestinal ischaemia	Intestinal perforation	Melaena
Mesenteric occlusion	Mesenteric vein thrombosis	Pancreatitis
Peritonitis		
General disorders and administration site conditions		
Malignant hyperthermia		
Hepatobiliary disorders		
Hepatic failure	Hepatitis fulminant	Hepatic necrosis
Hepatorenal syndrome	Portal hypertension	Reye's syndrome

Immune system disorders		
Amyloidosis	Anaphylactic reaction	Anaphylactic shock
Graft versus host disease		
Infections and infestations		
Endotoxic shock	Sepsis	Toxic shock syndrome
Transmission of an infectious agent via a medicinal product		
Injury, poisoning and procedural complications		
Transplant failure	Wound dehiscence	
Metabolism and nutrition disorders		
Diabetic coma	Failure to thrive	Hypercalcaemia (CTC IV)
Hyperkalaemia (CTC IV)	Hypocalcaemia (CTC IV)	Hypokalaemia (CTC IV)
Lactic acidosis	Porphyria	Shock hypoglycaemic
Tetany		
Musculoskeletal and connective tissue disorders		
Aseptic necrosis bone	Fracture pathological	Muscle necrosis
Osteomalacia	Rhabdomyolysis	Systemic lupus erythematosus
Systemic sclerosis		
Nervous system disorders		
Amnesia	Anticholinergic syndrome	Aphasia
Cerebral oedema	Chorea	Coma
Convulsions	Demyelination	Encephalitis
Encephalopathy	Epilepsy	Guillain-Barré syndrome
Hydrocephalus	Intracranial haemorrhage	Meningitis
Multiple sclerosis	Myasthenia gravis	Myelitis
Neuroleptic malignant syndrome	Opisthotonus	Paralysis
Paresis	Parkinson’s syndrome	Serotonin syndrome
Stroke	Tunnel vision	
Pregnancy, puerperium and perinatal conditions		
Abortion	Eclampsia	Intra-uterine death
Psychiatric disorders		
Anorexia nervosa	Delirium	Drug abuse
Drug dependence	Homicidal ideation	Intentional misuse
Self-injurious ideation/attempt	Suicidal ideation/attempt	Suicide completed
Renal and urinary disorders		
Anuria	Goodpasture’s syndrome	Haemolytic uraemic syndrome
Nephritis/nephritic syndrome	Nephrotic syndrome	Oliguria
Renal failure acute	Renal tubular necrosis	Urinary obstruction/retention
Reproductive system and breast disorders		
Metrorrhagia/uterine heamorrhage	Priapism	

Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure	Adult respiratory distress syndrome	Alveolitits allergic
Asphyxia	Bronchospasm	Laryngeal oedema
Pulmonary fibrosis	Pulmonary haemorrhage	Pulmonary infarction
Pulmonary vasculitis	Respiratory arrest	Status asthmaticus
Pulmonary oedema		
Skin and subcutaneous tissue disorders		
Angioneurotic oedema	Erythema nodosum	Pemphigus
Stevens-Johnson syndrome	Toxic epidermal necrolysis	Vascular purpura
Vascular disorders		
Acute circulatory failure	Embolism	Malignant hypertension
Necrosis ischaemic	Thrombosis	

Status: Jul 2012

CTC = Common Toxicity Criteria also referred to as the Common Terminology Criteria for Adverse Events (CTCAE).

18.2 Justification of non-inferiority margin

On 30 Mar 2016, an updated literature search in PubMed yielded 7 publications, none of which provided elements that could serve to identify a rationale for a non-inferiority margin.

The search string used was ((((third molar removal) OR third molar extraction) OR third molar surgery)) AND ((non-inferiority) OR clinically relevant difference).

Farrar (2000) has pointed out that the absence of taking a next dose or a dose of rescue medication, under the assumption that these can be taken freely, can be seen as the patient's most unambiguous way to express that his/her perceived pain relief is evaluated by him/her as sufficient. In a series of repeated experiments mainly in cancer breakthrough pain, Farrar has concluded that a mean TOTPAR equal to 33% of the maximum possible TOTPAR has the optimal combination of sensitivity and specificity to predict that a patient does not feel the need to take another dose of analgesic (Farrar et al. 2010). Because the maximum value for TOTPAR4 = 16 and following Farrar's approach, a TOTPAR4 = 5.33 would be a clinically relevant effect, though not necessarily a minimum clinically relevant effect.

Clinical trials in pain are known for their relevant placebo effect which has to be taken into account when proposing a clinically relevant difference to placebo. A mean TOTPAR4 value of 2.37 was found for placebo by pooling across all trials in pain after third molar removal with diclofenac 50 mg, as available in the public domain (Bakshi et al. 1994), or with any dose of tramadol available at Grünenthal in-house (Reports ICSR031-00, ICSR033-00, TRAMAP-ANAG-02, TRAMAP-ANAG-07, TRAMAP-ANAG-10, TRAMAP-ANAG-12, TRAMAP-ANAG-13, CAPSS-128). Thus, a difference to placebo in TOTPAR4 value by 5.33-2.37 = 2.96 ≈ 3 can be assumed to represent a clinically relevant difference, although not necessarily a minimum clinically relevant difference.

We believe that a choice of a non-inferiority margin $\Delta = 0.5*3 = 1.5$ (½ of the clinically meaningful effect of 3 points TOTPAR4) reflects the largest loss of effect that would still be clinically acceptable.

18.3 Previous clinical trials with a combined treatment of tramadol and diclofenac

The benefits of the diclofenac and tramadol combination have been shown in previous clinical trials using various formulations (Table 2).

Table 2: Previous clinical trials with combination of tramadol and diclofenac

Author	Indication	Design	Number of subjects	Treatment groups and dosage	Results
Auad Saab et al. 2009	Postoperative pain (orthopedic surgery)	Prospective, double-blind, randomized, controlled, single-dose Phase IIIb pilot trial	30	- T/D FDC 25 mg/25 mg po, 1 tablet + placebo - T/D FDC 25 mg/25 mg po, 2 tablets - D 50 mg + placebo	T/D 25 mg/25 mg (2 tablets) provided the best pain relief at 3 hours and at 6 hours and the shortest time to achieve a 20% decrease in the pain intensity (0.75 hours).
Auad et al. 2009	Postoperative pain (bunionectomy)	Prospective, randomized, controlled, single-dose, double-blind, multi-site, multinational Phase III trial	110	- T/D FDC 25 mg/25 mg po, 1 tablet + placebo - T/D FDC 25 mg/25 mg po, 2 tablets - D 50 mg + placebo	Both T/D FDC groups had a greater total pain relief at 4 h and 8 h when compared to the D 50 mg control group. At 90 min, there were significant differences in pain intensity in favor of the T/D 50 mg/50 mg group. T/D FDC groups had an earlier onset of effect, an earlier peak of maximum pain relief, and a longer time to administer the first dose of rescue medication compared to D 50 mg.
Mok et al. 1996	Postoperative pain (abdominal surgery)	Randomized, double-blind	80	- T 50 mg IV + D 50 mg IM - T 50 mg IV + placebo IM - Meperidine 50 mg IV + placebo IM - Placebo IV + D 50 mg IM	T+D provided the best pain relief with a 1 h peak, lasting 6 h.

Author	Indication	Design	Number of subjects	Treatment groups and dosage	Results
Filippi et al. 1999	Postoperative pain after disc surgery	Randomized open label	60	Group 1: no standard pain therapy, subjects received on demand different analgesics Group 2: standardized pain therapy, oral D up to 75 mg per dose + oral T up to 200 mg per dose	Subjects in the T+D group had lower pain levels than the control group at 24, 48, and 72 h.
Wilder-Smith et al. 2003	Post Cesarean pain	Randomized, double-blind, placebo-controlled, single dose	120	- T 100 mg IM + placebo IM - D 75 mg IM + placebo IM - T 100 mg IM + D 75 mg IM - Placebo IM + Placebo IM	The T+D group had the longest median time to the first rescue medication dosage.
Hussain et al. 2008	Post hysterectomy pain	Randomized, double-blind, placebo-controlled	70	- Placebo supp. + T 317 mg PCA - D 100 mg supp. + T 258 mg PCA	The group with the placebo suppository used more T to relieve pain.
Vasallo-Comendeiro and Arjona Fonseca 2011	Gynecological and obstetric surgery	Analytical, observational, prospective, cohort trial	50	- T 1 mg/kg IV + D 75 mg IV - Pethydine 1 mg/kg IV + dipyrone 600 mg IV	Analgesia of T+D combination was superior to the one with pethydine + dipyrone.
De Sousa Santos et al. 2012	Third molar surgery, postoperative pain	Randomized, double-blind, crossover, split mouth	30	- T 50 mg po + dexamethasone 4 mg po 1 h before surgery - T 50 mg po + D 50 mg po 1 h before surgery	Tramadol + dexamethasone group presented lower pain scores.
Mitra et al. 2012	Pain after Cesarean section	Randomized, double–blind, parallel, controlled	204	- D 100 mg 64up. Every 8 h for 24 h plus either - Acetaminophen IV 1 g every 6 h - T 75 mg IV every 6 h	Pain intensity scores as an area under the curve (AUC) was lower in the T+D group. The use of rescue medication was similar in both groups.

Author	Indication	Design	Number of subjects	Treatment groups and dosage	Results
Shareef et al. 2014	Post Cesarean pain	Randomized	90	- T 100 mg IM x2 - D 75 mg IM x2 - (T 50 mg IM + D 50 mg IM) x2	T+D combination achieved earlier analgesia compared with montherapies.
Chandanwale et al. 2014	Moderate to severe pain in: musculoskeletal conditions, osteoarthritis flare, rheumatoid arthritis flare, postoperative pain	Open label	204	- T 50 mg + D 75 mg FDC po, 1 tablet twice a day, 5 days - T 37.5 mg + paracetamol 325 mg FDC po, 2 tablets, 3-4 times a day, 5 days	Subjects on T+D FDC had a significant reduction in pain on Day 3 and Day 5 compared to the tramadol + paracetamol group.

T = tramadol; D = diclofenac; h = hour; IM = intramuscular; IV = intravenous; po = oral; 65up. = suppository; PCA = patient-controlled analgesia; FDC = fixed-dose combination.

18.4 Rescue medication and comparator prescribing information

The rescue medication (ibuprofen, ketorolac) and comparator (Voltaren [diclofenac], tramadol) prescribing information provided with the protocol are examples. Copies of the versions used in the trial will be filed in the trial master file.

19 PROTOCOL AMENDMENTS

19.1 Protocol Amendment 01

Amendment rationale

This amendment has been implemented to change the following:

- The Universal Trial Number was corrected.
- The sponsor's address was updated.
- New exclusion criteria (9 and 10) concerning restrictions for dental surgery were added at Visit 1. Details on the reading of Exclusion Criterion 5 were provided. Two exclusion criteria were shifted to be assessed at Visit 1 instead of at Visit 2.
- In sections referring to allowed and forbidden medication, it was added that systemic corticosteroids are not allowed during the trial.
- Standardized anesthesia for dental surgery was changed from the administration of lidocaine only to lidocaine plus epinephrine. The anesthetic was added as trial treatment (Section 1.4.3 and Section 10.6 were added).
- The use of cold compresses or ice bags is allowed from 4 hours after the first administration of IMP up to 30 minutes before each pain assessment.

- It was specified in Section 11.1.2.1 that that the postsurgical follow-up can be performed in a dental clinic or in an SMO's research facilities. Every research facility must have a responsible clinical investigator. It was added, that emergency equipment has to be available at the site.
- Dietary restrictions before and after surgery were added.
- It was specified in the schedule of events and in Section 11.1.1 that only local safety laboratories will be used in this trial.
- For the detection of safety signals and early safety reporting, a cross-reference to the sponsor's Drug Safety procedures was added.

Detailed description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

In the table below, deleted text is crossed out and new text is highlighted using italics.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section: Front Page	
Grünenthal ~~Group~~ ~~Product Development Latin America~~ ~~255 Alhambra Cir #435,~~ ~~Coral Gables~~ ~~FL 33134, United States~~	Grünenthal *S.A.* *Edificio Torres de las Américas* *C-3100 Panama City* *Panama*
Trial sites: Multi-site trial (~~approximately~~ 8 ~~to 12~~ sites in Mexico)	Trial sites: Multi-site trial (*up to* 8 sites in Mexico)
Universal Trial Number: U1111-1179-2333~~3~~	Universal Trial Number: U1111-1179-2333
Section 1.3.2.1: Exclusion criteria at Visit 1	
… 5. Known alcohol or drug abuse ~~within~~ 6 months or any history of seizures. …	… 5. Known alcohol or drug abuse *in the last* 6 months or any history of seizures. *Alcohol abuse is defined as the consumption of more than 3 ounces (about 90 mL) of liquor or spirits or 18 ounces (about 530 mL) of beer per day, for 5 consecutive days during the 6-month period. Drug abuse is defined as the use of any recreational drug for 5 consecutive days during the 6-month period.* *…* *7. Pregnant or lactating women.* *8. Subjects who received systemic corticosteroids or opioid analgesics less than 2 weeks before surgery.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
	9. Subjects with molars linked to the mandibular canal. *10. Subjects requiring immediate dental procedures other than third and fourth molars extraction.*
Section 1.3.2.2: Exclusion criteria at Visit 2	
~~7. Pregnant or lactating women.~~ ~~12. Subjects who received systemic corticosteroids or opioid analgesics within 2 weeks prior to surgery.~~	Note: Due to the shift of Exclusion Criteria 7 and 12 to Section 1.3.2.1 and the addition of new exclusion criteria (9 and 10) to Section 1.3.2.1, the Exclusion Criteria 8-11 and 13 listed for Visit 2 were renumbered to read Exclusion Criteria 11-15.
Section 1.4.3: Anesthetics for standardized surgery	
New section	*Commercially available cartridges containing 36 mg of lidocaine hydrochloride plus 0.018 mg of epinephrine in a total volume of 1.8 mL will be provided by the sponsor.*
Section 1.5: Prior/concomitant medications	
The use of antibiotics and other concomitant medications except for analgesics is allowed at the discretion of the investigator…	The use of antibiotics and other concomitant medications except for analgesics *and systemic corticosteroids* is allowed at the discretion of the investigator…
Section 1.8: Schedule of events	
… Take blood samples for clinical laboratory parameter assessments and urine for urinalysis [a]	… Take blood samples for clinical laboratory parameter assessments and urine for urinalysis [a, *b*] … *b) Clinical laboratory parameter assessments will be performed by contracted local certified clinical laboratories.* …
Section 3.1: Abbreviations	
New abbreviation	SMO Site Management Organization
Section 5.1.1: Investigators	
	The trial may be conducted solely at a dental clinic, or management of a subject may be

Changes to this protocol include:	
Formerly read:	**Now reads:**
	shared between a dental clinic and a local research facility of a Site Management Organization (SMO). The latter combination is considered a single trial site.
There must be an investigator at each trial site.	There must be an investigator at each trial site.
If the trial is conducted by a team of individuals at the trial site, the investigator leading and responsible for the team is called the principal investigator. …	If the trial is conducted by a team of individuals at the trial site, the investigator leading and responsible for the team is called the principal investigator. *For each of the local research facilities, a principal investigator will be designated and will have primary responsibility for compliance with the protocol and GCP at that site (see Section 5.1.2).* …
Section 10.2: Administration of investigational medicinal product	
… Subjects will stay at the clinic for at least for 8 hours after the first IMP dose before they can leave the trial site facilities. They should take their last dose of IMPs as an outpatient 16 hours (±1 hour) after the first IMP dose. …	… Subjects will stay at the *dental* clinic *or other research facility* for at least for 8 hours after the first IMP dose before they can leave the trial site facilities. They should take their last dose of IMPs as an outpatient 16 hours (±1 hour) after the first IMP dose. …
Section 10.6: Lidocaine/epinephrine for anesthesia	
New section	*Details on the local anesthetic are provided in Section 1.4.3. The administration details are provided in Section 11.1.2.1.*
Section 10.7 (formerly 10.6): Allowed and forbidden concomitant medications	
… Use of antibiotics and other concomitant medications except for analgesics is allowed by the protocol, according to the common practice of the investigator and the investigator's brochure…	… Use of antibiotics and other concomitant medications except for analgesics *and systemic corticosteroids* is allowed by the protocol, according to the common practice of the investigator and the investigator's brochure…
Section 11.1.1: Enrollment Period (Visit 1)	
… Take blood samples for clinical laboratory parameter assessments and urine for urinalysis.	… Take blood samples for clinical laboratory parameter assessments and urine for urinalysis.

Changes to this protocol include:	
Formerly read:	**Now reads:**
If results of laboratory parameters deviate…	*Clinical laboratory parameter assessments will be performed by contracted local certified clinical laboratories.* If results of laboratory parameters deviate…
Section 11.1.2.1: Allocation Visit (Visit 2)	
Standardized local anesthesia …To numb the mouth, blocking of the inferior alveolar, lingual, and buccal nerves will be carried out by using 1-3 ~~shots~~ of lidocaine per third molar not exceeding a maximum total amount of 300 mg per subject. …	*For restrictions concerning meals and fluid intake before and after surgery, please see Section 11.2.3.* **Standardized local anesthesia** …To numb the mouth, blocking of the inferior alveolar, lingual, and buccal nerves will be carried out by using 1-3 *cartridges* of lidocaine *plus epinephrine* per third molar not exceeding a maximum total amount of 300 mg *of lidocaine* per subject *(8.3 cartridges). The anesthetics will be provided as cartridges of 1.8 mL with 36 mg of lidocaine hydrochloride plus 0.018 mg of epinephrine. No other kind of anesthetic is allowed.* …
Standardized surgery …	**Standardized surgery** … *Subjects requiring fourth molar extraction are allowed in the trial. Subjects with molars linked to the mandibular canal and those requiring immediate dental procedures other than third and fourth molar extraction must not be included in the trial.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Postoperative baseline examination and treatment allocation … The first dose of the IMPs (1 capsule or tablet with active treatment plus 3 placebos) will be administered as soon as subjects report a pain intensity ≥5 on the NRS. The time of dosing will be recorded. …	**Postoperative baseline examination and treatment allocation** … The first dose of the IMPs (1 capsule or tablet with active treatment plus 3 placebos) will be administered as soon as subjects report a pain intensity ≥5 on the NRS. The time of dosing will be recorded. *The use of cold compresses or ice bags on the cheeks of subjects is allowed 4 hours after the administration of IMP; their use must be avoided in the 30-minute period before each pain assessment.* …
… Subjects who undergo surgery and receive IMPs will stay in the clinic for at least 8 hours after the initial dose and will receive the second dose of IMPs at 8 hours (±10 minutes). …	… Subjects who undergo surgery and receive IMPs will stay in the *dental* clinic *or other research facility* for at least 8 hours after the initial dose and will receive the second dose of IMPs at 8 hours (±10 minutes). *If pain assessments will take place in other research facilities, subjects must be transported to the facility between 15 minutes after the end of surgery and the first IMP administration; the commuting time may be up to 30 minutes. During transfer, subjects must be accompanied by a member of the SMO staff. Both must have written directions in the case of emergency.* …
---	*…* *Dental clinics must have an emergency kit according to local regulations (Norma Oficial Mexicana NOM-005-SSA3-2010). An emergency crash cart will be mandatory at each research facility any time an IMP is being administered.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 11.2.3: Meals and fluid intake restrictions	
New section	*Subjects may have a low-fat dinner the night before the surgery. They may have soft beverages like Ensure® up to 1 hour before surgery. Drinking water or juices (apple juice, orange juice) and low-fat milk are allowed after surgery. From 3 hours after IMP administration, subjects can have soft food (Jell-O™, mashed potatoes, milk shake, Ensure®). Water and soft food must be provided at room temperature. High-fat meals, ice creams, and sorbets must be avoided.*
Section 12.3.1: Adverse events	
Notification of serious adverse events … The investigator must comply with applicable regulatory requirement(s) related to the reporting of SAEs to the regulatory authorities and the relevant IECs.	**Notification of serious adverse events** … The investigator must comply with applicable regulatory requirement(s) related to the reporting of SAEs to the regulatory authorities and the relevant IECs. *Based on the investigator SAE reports, the sponsor's Drug Safety Department will generate Drug Safety Update Reports. They will monitor the Suspected Unexpected Serious Adverse Reaction reports to detect any possible safety signals and generate early safety alerts if necessary.*

19.2 Protocol Amendment 02

Amendment rationale

This amendment has been implemented to change the following:

- The planned number of trial sites was increased.
- Changes in the sponsor's signatory and the public contact point were made.

Detailed description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

In the table below, deleted text is crossed out and new text is highlighted using italics.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section: Front Page	
Trial sites: Multi-site trial (up to ~~8~~ sites in Mexico) Documentation of the involved trial sites will be maintained.	**Trial sites:** Multi-site trial (up to *10* sites in Mexico) Documentation of the involved trial sites will be maintained.
Coordinating investigator [a]: [redacted] DMD, PhD …	**Coordinating investigator [a]:** [redacted] DMD, PhD *(*[redacted]*)* ...
Sponsor' signatory: [redacted] ~~PhD~~ Head of Clinical Product Development Latin America	**Sponsor's signatory [a]** [redacted] *MD* Head of Clinical Product Development Latin America [redacted]*grunenthal.com*
Public Contact: [redacted] ~~grunenthal.com~~ ~~Phone (+55)~~ [redacted] ~~Ext.~~ [redacted]	**Public Contact [a]:** [redacted] *Clinical Operations Project Manager* [redacted]*grunenthal.com*