Protocol

Official Title: A randomized, double-blind, parallel group, single-center, placebo controlled study to evaluate the efficacy and safety of an acetaminophen-pregabalin combination in the prevention and treatment of post-surgical dental pain in healthy patients

NCT Number: NCT03652818

Version: 3.0

Date: 09 June 2018

2. CLINICAL PROTOCOL SYNOPSIS

TITLE:	A randomized, double-blind, parallel group, single-center, placebo-controlled study to evaluate the efficacy and safety of an acetaminophen-pregabalin combination in the prevention and treatment of post-surgical dental pain in healthy patients.
SPONSOR	Nevakar, Inc. [redacted] NJ 08807
STUDY NUMBER:	CP-NVK009-0001
PRINCIPAL INVESTIGATOR:	[redacted] M.D.
SITE:	JBR Clinical Research [redacted] , Utah 84124
STUDY OBJECTIVES:	The primary objective of this study is to assess the efficacy and safety of pregabalin [redacted] when used alone and in combination with acetaminophen [redacted] in a dental pain model. A secondary objective is to test whether a pre-operative dose of [redacted] pregabalin [redacted] increases the time to significant post-operative pain (NRS ≥5) and hence, time to first analgesia consumed post-operatively.
HYPOTHESIS:	Acetaminophen [redacted] + pregabalin [redacted] as a combination, offers significantly more pain relief than either acetaminophen [redacted] alone or pregabalin [redacted] alone in a dental impaction pain model.
STUDY DESIGN:	The study will be a double-blind, parallel group, single-center, placebo-controlled study. The study will have both pre- and post-surgical doses assessed over approximately a 24-hour period. There will be five arms or study medication groups. Treatments will be randomized in a 1:1:1:1:1 ratio and stratified by sex. A randomization code will be generated that will randomly assign patients to treatment groups. Within each of the five arms there will be equal proportions of male and female subjects. The targeted number of patients to be randomized in each treatment group for Stage I will be 20 for a total of 100 patients. If the decision is made by the Sponsor to continue the study after analyzing Stage I, Stage II will be under an amended protocol with new IRB approval. Patients will report to the Clinical Research Unit (CRU) the morning of the scheduled surgery and be monitored on-site for approximately 24 hours

STUDY DESIGN: *(cont.)*

following the surgical extraction of up to four third molars, of which two must be impacted mandibular third molars.

The initial dose of study medication (either pregabalin [redacted] or placebo [redacted] will be administered 60 minutes (±10 minutes) prior to the surgical procedure. Dose 2 will be given post-surgically when patients report at least moderate pain on the categorical scale and a score of ≥5 on 0-10 PI-NRS. Patients who do not have at least moderate pain on the categorical scale and a score of ≥5 on 0-10 PI-NRS by 7 hours post-surgery (7 hours after the last suture placed), will be considered to have Insufficient Pain (ISP) and will not be administered any additional study medications, but can receive rescue medication upon request. Subsequent to Dose 2, patients can request rescue analgesic at any time. Patients have the right to withdraw from the study at any time.

Stage I of this study will include a single cohort of 20 patients in each arm (N=100), randomized in a 1:1:1:1:1 ratio.

The study medication groups for Stage I are:

	Pre-Surgery	Post-Surgical Dose 2		N
	[redacted]	[redacted]	[redacted]	
GRP A	PBO[1]	PBO[1]	PBO[2]	20
GRP B	PBO[1]	PBO[1]	APAP[3]	20
GRP C	PBO[1]	Pregab[4]	PBO[2]	20
GRP D	PBO[1]	Pregab[4]	APAP[3]	20
GRP E	Pregab[4]	PBO[1]	APAP[3]	20

1. PBO[1] = Placebo [redacted]
2. PBO[2] = Placebo [redacted]
3. APAP = Acetaminophen [redacted]
4. Pregab = Pregabalin [redacted]

In all likelihood, the vast majority of patients, if not all patients, will have moderate to severe pain and ≥5 on the 0-10 PI-NRS prior to Hour 7. At the initiation of Dose 2, Pain Intensity (PI) and Pain Relief (PR) will be collected on the 0-10 NRS at 0.5, 0.75, 1, 1.25, 1.75, and 2.25 hours (± 5 minutes) and then collected at Hours 3.25, 4.25, 5.25, 6.25, 8.25, 10.25, 12.25 and 24 (± 10 minutes).

At the initiation of Dose 2, the patients will be given a stopwatch and asked to press the stopwatch if and when they first perceive any relief (FPR). At this time, patients will be given a second stopwatch and asked to press this stopwatch if and when the pain relief becomes meaningful to them (MPR). If a patient requires a rescue analgesic after Dose 2, the time of rescue as well

STUDY DESIGN: ***(cont.)***	as PI and PR will be collected at that time. Patients who do not experience any pain relief after Dose 2 will be encouraged, but not required, to wait at least 1 hour before using rescue therapy. Patient Global Evaluation of the study medication will be collected at 12.25 hours post-surgery or at the time of first rescue medication administration or at the time of patient withdrawal, whichever occurs first, with a 0-4 categorical rating scale: (0) poor, (1) fair, (2) good, (3) very good, and (4) excellent.
EFFICACY MEASUREMENTS:	• Categorical Pain Intensity: (only at Baseline prior to Dose 2) None (0) Mild (1) Moderate (2) Severe (3) • Numerical Rating Scale Pain Intensity: (PI-NRS) (0 = no pain and 10 = worst imaginable pain) • Numerical Rating Scale Pain Relief (PR-NRS) (0 = no relief and 10 = complete relief) • Stop Watches: First Perceptible and Meaningful Relief (FPR= First Perceptible Relief, MPR = Meaningful Pain Relief and FPR-C = FPR that is confirmed by MPR) • Global Evaluation: Poor (0) Fair (1) Good (2) Very Good (3) Excellent (4) **Efficacy Parameters:** • SPID 0-6, 0-8, 0-12 and 0-24 (Time weighted Sum Pain Intensity Difference Scores over 6, 8, 12 and 24 hours based on the 0-10 PI-NRS); • TOTPAR 0-6, 0-8, 0-12 and 0-24 (Time weighted Total Pain Relief over 6, 8, 12 and 24 hours based on the 0-10 PR-NRS); • Time from end of surgery (last suture) to administration of Dose 2; • Pain Intensity Difference Rating (PID): scored on the 0-10 PI-NRS at each observation time after Dose 2 administration; • Pain Intensity Rating (PI): scored on the 0-10 PI-NRS at each observation time after Dose 2 administration; • Pain Relief Rating (PR): scored on the 0-10 PR-NRS at each observation time after Dose 2 administration; • SPI 0-6, 0-8, 0-12 and 0-24 (Time weighted Total Pain Intensity Scores over 6, 8, 12 and 24 hours based on the 0-10 PI-NRS);

EFFICACY MEASUREMENTS: ***(cont.)***	• Duration of pain reduction, as measured by the time to treatment failure (i.e. time to first dose of rescue medication after Dose 2 or withdraw from the study due to lack of efficacy prior to rescue); • Cumulative % of patients with onset of First Perceptible Relief Confirmed and Meaningful Pain Relief after Dose 2; • The cumulative proportion of treatment failures over time after Dose 2 administration (failure defined as requiring rescue analgesic medication or withdraw from the study due to lack of efficacy); • Patient Global Evaluation of study treatment; • Total doses of rescue analgesia at 12.25 and 24 hours.
OTHER MEASUREMENTS:	Following signing of the informed consent/assent forms (ICF) until the completion of the study, patients will be monitored for safety. Vital signs will be collected at Screening, Prior to Dose 1, End of Surgery and every 4 hours following end of surgery or immediately prior to Dose 2, whichever occurs first, and every 4 hours following Dose 2 throughout the 24-hour post-operative monitoring period. For subject's not receiving Dose 2, additional vital signs will be taken at discharge. Patients will continue to be periodically monitored throughout the 24-hour stay at the CRU and all adverse events spontaneously reported by the patients or observed by the research coordinators will be recorded.

PHARMACOKINETIC ASSESSMENTS (PK): ***(Stage I Only)***	In Stage I, prior to surgery, patients will have two indwelling catheters placed in the largest available arm veins, [redacted] catheter for PK draws [redacted]. At pre-set time points, a blood sample of approximately 4 mL (collected in K3EDTA tube) will be collected, spun down and divided into 2 cryotubes (primary and backup), labeled and frozen. The precise time of dosing and PK blood draws should be carefully captured and meticulously recorded. The times for blood sampling are: **Pre-operatively:** An initial PK blood sample will be collected at least 5 minutes but not more than 30 minutes before administering Dose 1 of study medication. **Post-surgically:** The next blood sample will be collected immediately prior to [redacted] (within 5 min) of Dose 2. "Time 0" is the beginning of the [redacted] of Dose 2. **Post Dose 2 @15 minutes:** To be drawn within 3 mins of completing the [redacted] of study medication ([redacted] takes ~15 minutes to complete). Post Dose 2 @ 30 (± 3 min) and 60, 90, 120, 150, 180 (± 5 min) and also @ 240, 360, 480 (± 15 min) minutes: The total amount of blood drawn for PK sampling is approximately 48 mL (12 blood samples of approximately 4 mL). The bioanalytical laboratory will perform the pharmacokinetic (PK) analysis on collected blood samples and provide a report on the plasma levels of acetaminophen and pregabalin. A complete listing of the scheduled and actual time of sample collections will be provided. Actual sample collection time will be used for calculating the pharmacokinetic parameters. The peak concentration (C_{max}) would be the primary end-point; however, other parameters, as appropriate, will also be calculated. The peak concentration will be the observed maximum plasma drug concentration; the time to peak concentration (t_{max}) will be the collection time at which C_{max} is first observed. Areas under the plasma concentration-time curve from time zero to the time of the last measurable concentration (AUC_{0-t}) will be calculated by the linear trapezoidal method. $AUC_{0-\infty}$ will be extrapolated if allowed by the data. The PK Collection Lab Manual Guidelines for the site will be provided by the PK Lab. There will not be additional PK sampling beyond Stage I.
ESTIMATED DURATION OF PATIENT PARTICIPATION IN THE STUDY:	The patients must have the surgical procedure within 30 days of screening. The inpatient part of the study will be approximately 24 hours and there will be a 15-day ± 1-day follow-up period. The maximum number of days totals 46 from screening through completion of the study.

DURATION OF STUDY:	The study will be completed when the last patient completes the last follow up phone call. The expectation is that Stage I of the study will be completed within 4 months of the first patient entry.
NUMBER OF PATIENTS:	For Stage I of the study, approximately 150 male and female patients will be screened to enroll up to 100 patients per American Society of Anesthesiologists (ASA) Category I (healthy) or Category II (mild systemic disease) patients.
SAMPLE SIZE DETERMINATION:	The sample size for the study was determined from past experience with the Dental Impaction Pain Model. With a sample size of 20 per treatment group, a 15-25% incremental efficacy benefit for either SPID12 or TOTPAR12 should be evident when comparing Acetaminophen [redacted] to Placebo or the Acetaminophen [redacted] + Pregabalin [redacted] to Acetaminophen [redacted]
INCLUSION CRITERIA:	1. Patients must be capable of reading, comprehending, and signing the informed consent form. Patients less than 18 years of age must be capable of reading, comprehending and signing a Patient Assent form and their parents/legal guardian must comprehend and sign a Parent/Legal Guardian Consent Form; 2. Male and female patients between 17-55 years of age; 3. Body Mass Index (BMI) $\leq$32.4 kg/m^2; 4. Patients are ASA Category I or II and are in good physical health as judged by a thorough history and physical examination; 5. Patients without infections in the area of the impacted teeth; 6. Patients must agree to refrain from ingesting acetaminophen, gabapentanoids, or systemic analgesics (orally, nasally, parenterally, or topically) for 3 days or 5 half-lives of the drug, whichever is longer, prior to day of surgery and during the study; 7. No alcohol for a minimum of 1 day prior to the surgery; 8. Female patients must be of non-child bearing potential, defined as postmenopausal for more than 1 year or surgically sterile (hysterectomy, tubal ligation/occlusion) or practicing an acceptable method of contraception (hormonal oral, patch, or implant, double barrier method, intrauterine device, vasectomized or same sex partner, or abstinence). Patients using hormonal birth control must have been on a stable dose of treatment for at least 30 days and received at least 1 cycle of treatment prior to randomization. At Screening and at the day of surgery, all females of childbearing potential must have a negative (serum at

INCLUSION CRITERIA: *(cont.)*	screening and urine on day of surgery 1) pregnancy test and not be breastfeeding; 9. Patients must have a negative urine drug screen for drugs of abuse (including cotinine) at Screening and at the day of surgery. a. Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test (e.g., amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder) may be eligible for participation in the study if they have been on a stable dose for >30 days from screening. b. Patients who did not report concomitant medication use, which is later identified during the urine drug screen, cannot be enrolled in the study. c. Subjects taking medical marijuana are not allowed to participate in the study. 10. At the discretion of the PI, a positive drug screen result may be permitted if the patient has been on a stable dose of an allowed medication for >30 days from screening; 11. Patients who are scheduled to undergo the surgical removal of up to 4 third molars of which at least two have to be mandibular molars with a difficulty rating of 4 or 5 and meeting the following criteria: • two full bony impactions • two partial bony impactions • one full bony impaction in combination with one partial bony impaction (see Appendix 1 for Impaction Difficulty Rating Scale); 12. Patients able to comprehend and follow the requirements of the study (including availability on scheduled visit dates) based upon the research site's judgment.
EXCLUSION CRITERIA:	1. Patients with a history of any significant medical condition that, in the opinion of the PI or his designee, would place the patient at increased risk such as: hepatic, renal, endocrine, cardiac, neurological, psychiatric, gastrointestinal, pulmonary, hematologic, or metabolic disorders, including glaucoma, diabetes, emphysema, and chronic bronchitis; 2. Patients should not be experiencing any oral infections or symptoms of a concomitant illness (e.g., respiratory tract infection) at the time of a scheduled surgery;

EXCLUSION CRITERIA: *(cont.)*	3. Patients with a history of any type of malignancy within the past 5 years other than minor skin related cancers; 4. Patients with conditions that affect the absorption, metabolism, or passage of drugs out of the body, (e.g., sprue, celiac disease, Crohn's disease, colitis, or liver, kidney, or thyroid conditions); 5. Patients with any history of alcohol or substance abuse according to DSM V or not satisfying inclusion criteria 9 (including a positive urine drug screen test); 6. Patients who currently have or have had a history of uncontrolled hypertension; 7. Patients with a known allergy or hypersensitivity to any local anesthetic drug, acetaminophen, ibuprofen, other NSAIDS, gabapentin or pregabalin; 8. Patients receiving stable, chronic doses of benzodiazepines; 9. Patients judged by the PI to be unable, unlikely or unwilling to comply with the requirements of the protocol; 10. Patients who have used an investigational drug within 30 days prior to the screening day or have previously participated in any Nevakar trial; 11. Patients who have donated blood within 3 months prior to the screening day; 12. Patients who are employees or relatives of employees of JBR Clinical Research, [redacted] or Nevakar, Inc.
SAFETY EVALUATION:	All potential patients will undergo a urine drug screen (including cotinine) at the screening visit. In addition, females will have a serum pregnancy test. All the study and rescue medications being evaluated in this study are marketed products in the United States and are being used within their currently indicated dosages. The placebo [redacted] prepared at [redacted] under GMP conditions. Adverse events (AEs) will be recorded in the eCRF following signing of the ICF/assent forms and if voluntarily reported by the patient or observed by the study staff regardless of severity or potential association with the study medication or study procedures. In addition, any new AEs will be recorded in the eCRF at the time of follow-up telephone call at Day 15 (± 1) after discharge from the Clinical Research Unit. This follow-up telephone call designates the patient has completed the study. Treatment-emergent AEs (TEAE) will be summarized by incidence and severity. The events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT). The severity, relationship to treatment, action

SAFETY EVALUATION: *(cont.)*	taken, and outcome of the events will be documented in the source and captured in the eCRF. The incidence of all adverse events and drug-related adverse events will be evaluated. In the event of any health-related emergency, the clinical site will have trained medical staff and a fully equipped emergency crash cart on site.
STATISTICAL ANALYSIS:	A detailed methodology for the statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be signed off prior to the database lock. The SAP may modify the plans outlined in the protocol; however, any major modifications to the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. All computations will be performed using SAS® version 9.4 (SAS Institute, Cary, NC). Since this is a proof-of-concept study, statistically significant treatment differences will be declared if the probability of random occurrence among or between treatments, p, is ≤0.10 (one-sided), and no adjustments for multiple comparisons/end points will be performed. For this study, the criteria for proceeding to Stage II (e.g., SPID12 ≤ 15-25% between groups) will be determined upon evaluation of the data: • APAP [redacted] + Pregabalin [redacted] versus APAP [redacted] • APAP [redacted] + Pre-operative Pregabalin [redacted] versus APAP [redacted] Pain Intensity Difference (PID) data will be generated as the difference in response between the Baseline Pain scores and the treatment pain scores at each time point within each patient. If the Sponsor makes the decision to move ahead with Stage II of this study, the [redacted] Data Management Group will generate the sample size for Stage II based on the Stage I interim analysis using an 80% power and a two-sided alpha of p > 0.10. Stage II will not include any additional PK sampling. The Statistical Analysis Plan (SAP) will be finalized and signed prior to unblinding of the study. Safety Data: (Listings and Tables Only) • Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Respiratory Rate (RR) and Heart Rate (HR) at Screening, immediately Prior to Dose 1, End of Surgery and every 4 hrs. following end of surgery or immediately prior to Dose 2, whichever occurs first, and every 4 hours following Dose 2. • Analysis of incidence and severity of all adverse events.

RESCUE ANALGESIC:	Ibuprofen 400 mg will be used as the rescue analgesic. Patients can rescue at any time after receiving Dose 2 of the study medication with the rescue analgesic, but not more often than every 4 hours or more than four doses in 24 hours. At the time the patient takes the first dose of rescue analgesic, PI and PR scores and Global Evaluation (if prior to the 12.25-hour assessment) will be recorded. Subjects receiving rescue medication will continue to be assessed for both efficacy and safety at the regularly scheduled observation time points throughout the entire 24-hour observation period (Time "0" will remain associated with Dose 2). In the event a subject does not have sufficient pain relief from 400mg ibuprofen, the PI may administer additional rescue (oxycodone 5mg; failing that, oral tramadol 50mg).

Statistical Analysis Plan (SAP)

Official Title: A randomized, double-blind, parallel group, single-center, placebo controlled study to evaluate the efficacy and safety of an acetaminophen-pregabalin combination in the prevention and treatment of post-surgical dental pain in healthy patients

NCT Number: NCT03652818

Version: 1.0

Date: 10 September 2018

[redacted]

Statistical Analysis Plan (SAP)

Protocol Title:	A randomized, double-blind, parallel group, single-center, placebo-controlled study to evaluate the efficacy and safety of an acetaminophen-pregabalin combination in the prevention and treatment of post-surgical dental pain in healthy patients
Protocol Number:	CP-NVK009-0001
Protocol Version, Date	V3, 9 JUN 2018
[redacted] **ID:**	4444-0001
Document Version, Date:	FINAL 1.0, 10 Sep 2018

Prepared by:

[redacted] Clinical Research Services

On behalf of:

Nevakar, Inc.

Confidentiality statement:

- The information provided in this document is strictly confidential.
- The recipients of the SAP must not disclose the confidential information contained within this document or any related information to other persons without the permission of the sponsor.
- In addition, the recipients of the SAP must keep this confidential document in a controlled environment which prevents unauthorized access to the document.

SIGNATURE PAGE

[redacted] _____ _____
Date

[redacted] _____ _____
Date

Approved at Nevakar, Inc. by:

[redacted] _____ 9/11/18
Date

REVISION HISTORY

Version/Date	Version name	Section	Changes implemented
Version 1.0/ 10-Sep-2018	FINAL 1.0		N/A

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

The following abbreviations will be used within this SAP.

Abbreviation or special term	Explanation
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
FPR	First Perceptible Relief
ICH	International Conference on Harmonisation
Kg	Kilogram
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MPR	Meaningful Pain Relief
PI	Pain Intensity
PID	Pain Intensity Difference
PI-NRS	Numerical Rating Scale Pain Intensity
PR	Pain Relief
PR-NRS	Numerical Rating Scale Pain Relief
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SPI	Time Weighted Sum Pain Intensity

SPID	Summed Pain Intensity Difference
TEAE	Treatment-emergent Adverse Event
TFLs	Tables, Figures, and Listings
TOTPAR	Total Pain Relief
WOCF	Worst Observation Carried Forward

2. CHANGES IN THE PLANNED ANALYSIS

The following changes have been made in the Statistical Analysis Plan (SAP) from the planned analyses stated in version 3.0 of the protocol dated 19 June 2018:

- Stage I of the study will include a single cohort of 23 subjects in each arm (N=115), randomized in a 1:1:1:1:1 ratio. The rationale for the addition of the 15 subjects is to ensure sufficient data for the intended primary analyses. Subjects with "Insufficient Pain" who did not receive dose 2 and subjects with emesis after dose 2 may not have achieved measurable exposure to the study drug. The number of subjects falling into these categories has been higher than expected to date. It has been determined having a total sample size of 115 subjects will provide enough data to proceed with the statistical analyses proposed in the protocol.

3. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations, and data displays for study protocol CP-NVK009-0001 v3.0, A randomized, double-blind, parallel group, single-center, placebo-controlled study to evaluate the efficacy and safety of an acetaminophen-pregabalin combination in the prevention and treatment of post-surgical dental pain in healthy subjects, dated 09June2018 for final analysis. The table of contents and templates for the tables, figures, and listings (TFLs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonization (ICH) E9, Food & Drug Administration Developing Drug and Biological for Analgesic Indications as well as Committee for Medicinal Products for Human Use Development of Medicinal Products Intended for the Treatment of Pain Drug Guidelines.

All data analyses and generation of TFLs will be performed using SAS 9.4® or higher.

4. STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study is to assess the efficacy and safety of pregabalin [redacted] when used alone and in combination with acetaminophen [redacted]

4.2 Secondary Objective

The secondary objective of the study is to test whether pregabalin [redacted] when compared to placebo (both given pre-operatively), increases time to first analgesic consumed post-operatively.

5. STUDY DESIGN

5.1 General Study Design

The study will be a double-blind, parallel-group, single-center, placebo-controlled study. The subjects will be evaluated after the post-surgical dose of study medication for a full 24-hour period and there will be five treatment groups. Subjects will be randomized to 1 of the 5 treatment groups in a 1:1:1:1:1 ratio and stratified by sex. The targeted number of subjects to be randomized in each treatment group for Stage I will be 23 for a total of 115 subjects.

Subjects will report to the Clinical Research Unit (CRU) the morning of the scheduled surgery and be monitored on-site for 24 hours following the surgical extraction of up to four third molars, of which two must be impacted mandibular third molars.

The initial dose of study medication (either pregabalin [redacted] or placebo [redacted]) will be administered 60 minutes (±10 minutes) prior to the surgical procedure. Dose 2 will be given post-surgically when subjects report at least moderate pain on the categorical scale and a score of ≥5 on 0-10 PI-NRS. Subjects who do not have at least moderate pain on the categorical scale and a score of ≥5 on 0-10 PI-NRS by 7 hours post-surgery (7 hours after the last suture placed), will be considered to have Insufficient Pain (ISP) and will not be administered any additional study medications, but can receive rescue medication upon request. Subsequent to Dose 2, subjects may request rescue analgesia at any time.

In all likelihood, the vast majority of subjects, if not all subjects, will have moderate to severe pain and ≥5 on the 0-10 PI-NRS prior to Hour 7. At the initiation of Dose 2, Pain Intensity (PI) and Pain Relief (PR) will be collected on the 0-10 NRS at 0.5, 0.75, 1, 1.25, 1.75, and 2.25 hours (± 5 minutes) and then collected at Hours 3.25, 4.25, 5.25, 6.25, 8.25, 10.25, 12.25, and 24 (± 10 minutes).

At the initiation of Dose 2, the subjects will be given a stopwatch and asked to press the stopwatch if and when they first perceive any relief (FPR). At this time, subjects will be given a second stopwatch and asked to press this stopwatch if and when the pain relief becomes meaningful to them (MPR). If a subject requires a rescue analgesic after Dose 2, the time of rescue as well as PI and PR will be collected at that time. Subjects who do not experience any pain relief after Dose 2 will be encouraged, but not required, to wait at least 1 hour before using rescue therapy. Subject Global Evaluation of the study medication will be collected at Hour 12.25 (12.25 hours post-surgery) or at the time of first rescue medication if before Hour 12.25 (12.25 hours after Dose 2) or at the time of subject withdrawal, whichever occurs first, with a 04 categorical rating scale: (0) poor, (1) fair, (2) good, (3) very good, and (4) excellent.

Stage I of this study will include a single cohort of 23 subjects in each arm (N=115), randomized in a 1:1:1:1:1 ratio. A randomization code will be generated

that will randomly assign subjects to treatment groups. Within each of the five arms there will be equal proportions of male and female subjects.

The study medication groups for Stage I are:

	Pre-Surgery	Post-Surgical Dose 2		N
	[redacted]	[redacted]	[redacted]	
GRP A	PBO[1]	PBO[1]	PBO[2]	23
GRP B	PBO[1]	PBO[1]	APAP[3]	23
GRP C	PBO[1]	Pregab[4]	PBO[2]	23
GRP D	PBO[1]	Pregab[4]	APAP[3]	23
GRP E	Pregab[4]	PBO[1]	APAP[3]	23

1. PBO[1] = Placebo [redacted]
2. PBO [2]= Placebo [redacted]
3. APAP = Acetaminophen [redacted]
4. Pregab = Pregabalin [redacted]

For Stage I of the study, approximately 150 male and female subjects ages 17-55 will be screened to enroll up to 115subjects per American Society of Anesthesiologists (ASA) Category I (healthy) or Category II (mild systemic disease) subjects.

5.2 Randomization and Blinding

The randomization schedule will randomly assign one of the five treatments to the subjects. The randomization numbers will be assigned in a sequential order. The subjects will be stratified by sex. The randomization number assigned to the subject will be recorded in the Case Report Form (eCRF). The study will remain blinded until it completes.

As described in the protocol extensive measures are in place to ensure blinding including the use of a blinded study administrator and blinded staff to manage randomization, preparation and administration of study medication. In addition, measures are in place to physically shield the eyes of the patient to keep him/her blinded as to both the [redacted] medications.

Upon study completion and data base lock, [redacted] SOP BST001-SOP (v3.0), The Generation and Release of Randomization Codes, will be followed for the treatment unblinding.

5.3 Study Treatments and Assessments

Each subject entered into the study will be given the first dose of the randomly assigned study medication 60 minutes (± 10 minutes) prior to initiating the surgical procedure. For this initial dose, subjects will be administered only the [redacted] of either pregabalin or placebo. If emesis occurs prior to surgery, the subject will be excluded from the study and replaced.

Dose 2 will be given post-surgically when subjects report at least moderate pain on the 4-point categorical scale of none (0), slight (1), moderate (2) or severe (3) and also a score of ≥5 on 0-10 PI-NRS. Subjects who do not have at least moderate pain on the categorical scale and a score of ≥5 on 0-10 PI-NRS by 7 hours post-surgery (7 hours after the last suture placed), will be considered to have ISP and will not be administered any additional study medications, but can receive rescue medication upon request. Subsequent to Dose 2, subjects can request rescue analgesic at any time. Dose 2 will consist of the capsule (either pregabalin [redacted] or placebo) and the [redacted] (either acetaminophen [redacted] or [redacted]. The [redacted] will be over a 15-minute period and the [redacted] will be administered immediately prior to the initiation of the [redacted]. Any scheduled blood draws will be performed according to the PK Blood Draw Table included in study Protocol v3.0. The blood draws will be taken from a separate indwelling catheter [redacted].

Subjects enrolled in the trial, investigators and their staff involved in protocol procedures or who are involved in data collection, data entry, and data analysis will be blinded to the identity of the study medications until the database is locked.

The duration of in-house study medication evaluations for efficacy and safety will last approximately 24 hours after Dose 2. A team of blinded coordinators and/or investigators will conduct all the evaluations.

A detailed description of procedures and assessments to be conducted during this study is summarized in the Scheduled of Study Assessments in Table 1 below.

Table 1: Schedule of Study Assessments

	Screening	Day of Surgery	Post-Op	Follow Up Post-Surgery Call
Procedures	**Day -30 to 0**	**Day 1**	**Day 2**	**Day 15 (±1 day)**
Written informed consent and/or assent	X			
Demography: Age, height, weight, & BMI	X			
Inclusion / Exclusion assessment	X	X		
Significant medical history	X	X		

[redacted]

Oral Exam	X	X		
Vital signs (BP, pulse, respiratory rate)[1]	X	X	X	
Serum pregnancy test for females	X			
Urine pregnancy test (dipstick)		X		
Urine drug testing (dipstick) (cotinine)	X	X		
Dental Surgery & Randomization Criteria		X		
Study medication administration		X		
Surgical removal of impactions		X		
Categorical and NRS PI at Baseline		X		
Pain intensity and Pain Relief		X	X	
Perceptible & Meaningful Stopwatches 1 & 2 after Dose 2		X		
Rescue therapy if needed (ibuprofen 400 mg)		X	X	
Patient Global Evaluation[2]		X		
Prior and Concomitant Therapy[3]	X	X	X	X
Safety monitoring[4]	X	X	X	X
Patient Discharge			X	
Follow-up interview				X

[1] Vital Signs will be obtained at screening, prior to Dose 1, end of surgery and every 4 hrs. Following end of surgery or immediately prior to Dose 2, whichever occurs first, and every 4 hours following Dose 2. For subject's not receiving Dose 2, additional vital signs will be taken at discharge

[2] Baseline = when patients report pain ≥5 on NRS & at least Moderate on categorical scale after surgery

[3] Follow-up pain measurements will be taken at the following times after initiation of Dose 2: 0.5, 0.75, 1, 1.25, 1.75, and 2.25 hours (± 5 minutes) and then collected at Hours 3.25, 4.25, 5.25, 6.25, 8.25, 10.25, 12.25, and 24 (± 10 minutes)

[4] At time of first rescue or 12.25 hours post-surgery or at the time of patient withdrawal, whichever occurs first

[5] Screening, Day of Surgery, Day of discharge and follow-up telephone call

[6] Prior to discharge the subject will be assessed for safety, including for dizziness and somnolence. Subjects will be required to have a ride home at discharge.

6. STUDY ENDPOINTS

6.1 Primary Efficacy Endpoints

- SPID 0-4, 0-6, 0-8, 0-12, and 0-24 (Time-weighted Sum Pain Intensity Difference Scores over 4, 6, 8, 12, and 24 hours based on the 0-10 point PI-NRS);
- TOTPAR 0-4, 0-6, 0-8, 0-12, and 0-24 (Time-weighted Total Pain Relief over 4, 6, 8, 12 and 24 hours based on the 0-10 PR-NRS)

6.2 Secondary Efficacy Endpoints

- Time from end of surgery (last suture) to administration of Dose 2;
- Pain Intensity Difference Rating (PID): scored on the 0-10 PI-NRS at each observation time after Dose 2 administration;
- Pain Intensity Rating (PI): scored on the 0-10 PI-NRS at each observation time after Dose 2 administration;
- Pain Relief Rating (PR): scored on the 0-10 PR-NRS at each observation time after Dose 2 administration;
- SPI 0-4, 0-6, 0-8, 0-12, and 0-24 (Time weighted Total Pain Intensity Scores over 4, 6, 8, 12, and 24 hours based on the 0-10 PI-NRS);
- Duration of pain reduction, as measured by the time to treatment failure (i.e., time to first dose of rescue medication after Dose 2 or withdraw from the study due to lack of efficacy prior to rescue);
- Cumulative % of subjects with onset of First Perceptible Relief, First Perceptible Relief-Confirmed and Meaningful Pain Relief after Dose 2;
- The cumulative proportion of treatment failures over time after Dose 2 administration (failure defined as requiring rescue analgesic medication or withdraw from the study due to lack of efficacy);
- Patient Global Evaluation at first rescue or 12.25 hours post-surgery, whichever is first;
- Total doses of rescue analgesic at 6, 8, 12, and 24 hours.

6.3 Safety Endpoints

- Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Respiratory Rate (RR), and Heart Rate (HR) at Screening, Prior to Dose 1, End of Surgery, and every 4 hours following end of surgery or immediately prior to Dose 2, whichever occurs first, and every 4 hours following Dose 2. For subject's not receiving Dose 2, additional vital signs will be taken at discharge.
- Analysis of the incidence and severity of all adverse events will be performed.

7. SAMPLE SIZE AND POWER

The sample size is thought to be reasonable for the objectives of this trial, based on historical experience with the dental pain model. However, no formal power calculations were performed.

8. ANALYSIS POPULATIONS

8.1 Randomized Population

This includes all randomized subjects.

8.2 Efficacy Analysis Population

This includes all randomized subjects who received study medication post-surgically and did not experience emesis or other major protocol deviations. Subjects meeting the definition of experiencing emesis or who had major protocol deviations will be determined and documented prior to database unblinding. This population will be used for all efficacy summaries.

8.3 Safety Population

The Safety Population will include all randomized subjects who received the study medication. This population will be used for all safety summaries.

9. STATISTICAL METHODS

9.1 General Statistical Conventions

All statistical procedures will be completed using SAS version 9.4® or higher.

Since this is a proof-of-concept study mainly to investigate whether expected treatment benefit can be detected for the treatment groups of interest when compared to the control treatment group of interest, no adjustments for multiple comparisons/end points will be performed.

The key comparisons in the order of interest will be:

- GRP D (APAP [redacted] + Pregabalin [redacted]) versus GRP B (APAP [redacted])
- GRP C (Pregabalin [redacted]) versus GRP B (APAP [redacted])
- GRP C (Pregabalin [redacted]) versus GRP A (Placebo)
- GRP B (APAP [redacted]) versus GRP A (Placebo)
- GRP D (APAP [redacted] + Pregabalin [redacted]) versus GRP A (Placebo)
- GRP D (APAP [redacted] + Pregabalin [redacted]) versus GRP C (Pregabalin [redacted])
- GRP E (APAP [redacted] + Pregabalin [redacted] pre-surgery) versus GRP D (APAP [redacted] + Pregabalin [redacted])

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum. Unless otherwise specified, minimum and maximum will be reported to the precision as the data collected, one more decimal place for the mean and median, and two more decimal places for the standard deviation.

For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place.

For summary purposes, unless otherwise specified, baseline for efficacy analysis will be defined as the last available value prior to Dose 2. Baseline for safety analysis will be defined as the last available value prior to Dose 2 for GRP A-D and Dose 1 for GRP E, respectively. All summaries will be presented by treatment group.

All subject data, including those derived, will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within subject listings only. All listings will be sorted by subject number, date/time, and visit. The treatment group as well as subject's sex and age will be stated on each listing. Unless otherwise stated, data listings will be based on all randomized subjects.

9.2 Handling of Missing Data and Outliers

If a subject discontinues from the study after Dose 2, LOCF (last observation carried forward) for Pain Intensity scores, and "0" for Pain Relief will be used for

the missing observations. If a subject takes a rescue analgesic, the following scheme will be used in the statistical analyses to account for all the subsequent pain intensity (PI) and related pain relief (PR) scores immediately after the first rescue analgesic: a). For PI, the PI score at the time of first rescue medication will be used; b). For PR, a "0" will be used in the statistical analysis.

The above imputation precedes any LOCF or WOCF to be performed for the missing data. Please refer to Appendix B for imputation rule for the respective efficacy endpoint.

9.2.1 Handling of Missing or Incomplete Dates

Because of the short duration of the study, only AE date with day missing is expected. If this happens, imputation rules are defined below:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date;
- Otherwise, impute the AE start day as 1.

9.3 Subject Disposition

Subject disposition information will be summarized by treatment group and overall. The number and percent will be presented for:

- Subjects who are screened
- Subjects who are randomized
- Subjects who took first dose of study drug
- Subjects who took second dose of study drug
- Subjects who are included in the Efficacy Analysis Population, Safety Population,
- Subjects who completed the study
- Subjects who withdraw early from the study will be presented

The primary reason for early withdrawal will also be tabulated.

The number of subjects randomized will be used as the denominator for the all percentage calculations. Subject disposition info will also be listed.

Treatment Misallocations:

If a subject was randomized but took incorrect treatment, then they will be analyzed as randomized for all efficacy analyses, but will be analyzed as treated for all safety analyses.

9.4 Protocol Deviations

All protocol deviations will be documented.

9.5 Derived Variables

The following table provides the derivation rules for all demographic and efficacy parameters applicable for this study.

Table 2. Derivation Rule

Variables	Formula
Demographic and Baseline characteristics	
Age at informed consent (in years)	integer ((date of informed consent – date of birth + 1)/ 365.25)
Body mass index (BMI) (kg/m^2)	weight (kg)/[height (m)] ^{2}
Derivation of Efficacy Parameters	
Time weighted sum pain intensity difference scores (SPID) [Time Frame: 0-4, 0-6, 0-8, 0-12, 0-24 hours]	SPID: The time-weighted sum of PID over 4, 6, 8, 12 and 24 hours, denoted SPID [0-4], SPID[0-6], SPID[0-8], SPID[0-12] and SPID[0-24], respectively, can be calculated using trapezoidal rule by following the below algorithm: **Before trapezoidal rule is applied:** Order the n observed PID after Dose 2 as PID_i, where PID_0 is the baseline PID and PID_n is the n^{th} (last) observed PID. Let ti = number of hours from PID_0 to PID_i, derived as (Actual time of PID_i assessment – Actual time of PID_0 assessment)/60 minutes. For subjects who take rescue med, PI score after rescue med should be replaced by PI score at the time of first rescue medication. **Trapezoidal rule implementation:** For SPID[0-x], if no PID_i exists with $t_i = x$ and $t_n > x$ then interpolate PID at time x as PID_x. Let t_j be the last t <x and t_k be the first t > x. Then, $PID_x = PID_j + (x - t_j) * (PID_k - PID_j)/(t_k - t_j)$ and $wPID_x = (PID_x + PID_j)/2 * (x - t_j)$ Otherwise, if no PID_i exists with $t_i = x$ and $t_n < x$ then let t_j be the last t <x, two approaches of extrapolation will be used:

	1. Primary: LOCF $PID_x = PID_j$ and $wPID_x = (PID_x + PID_j)/2 * (x - t_j)$ 2. Supportive: WOCF if subject is still on the study at time point X. PID_x = worst PID_i where $0<t_i<x$ and $wPID_x = (PID_x + PID_j)/2 * (x - t_j)$ For SPID[0-x], if no PID_i exists with $t_i = x$ then, $SPID[0\text{-}x] = wPID_x + \sum_{i,1\le t_i<x} \frac{(PID_i+PID_{i-1})}{2} * (t_i - t_{i-1})$ Otherwise, for SPID[0-x] if there is a PID_i with $t_i = x$, then $SPID[0\text{-}x] = \sum_{i,1\le t_i\le x} \frac{(PID_i+PID_{i-1})}{2} * (t_i - t_{i-1})$ No other interpolation or imputation of missing values will be performed. PID at time point 0 is equal to 0. PID: pain intensity (PI) score at a given time point minus baseline pain intensity score. Numerical rating scale for PI ranges from 0 to 10.
Time weighted total pain relief (TOTPAR) [Time Frame: 0-4, 0-6, 0-8, 0-12, 0-24 hours]	TOTPAR: The time-weighted sum of PR scores over 4, 6, 8, 12 and 24 hours, denoted TOTPAR[0-4], TOTPAR[0-6], TOTPAR[0-8], TOTPAR[0-12] and TOTPAR[0-24], respectively, can be calculated using trapezoidal rule by following the below algorithm **Before trapezoidal rule is applied:** Order the n observed PR after dose 2 as PR_i, where PR_0 is the baseline PR and PR_n is the n^{th} (last) observed PR. Let ti = number of hours from PR_0 to PR_i, derived as

	(Actual time of PR_i assessment – Actual time of PR_0 assessment)/60 minutes. For subjects who take rescue med, PR score after rescue med should be replaced by 0 **Trapezoidal rule implementation:** For TOTPAR[0-x], if no PR_i exists with $t_i = x$ and $t_n > x$ then interpolate PR at time x as PR_x. Let t_j be the last t <x and t_k be the first t > x. Then, $$PR_x = PR_j + (x - t_j) * (PR_k - PR_j)/(t_k - t_j)$$ and $$wPR_x = (PR_x + PR_j)/2 * (x - t_j)$$ Otherwise, if no PR_i exists with $t_i = x$ and $t_n < x$ then let t_j be the last t <x, two approaches of extrapolation will be used: 1. Primary: LOCF if subject is still on the study at time point x. $$PR_x = PR_j$$ Otherwise, $$PR_x = 0$$ and $$wPR_x = (PR_x + PR_j)/2 * (x - t_j)$$ 2. Supportive: WOCF if subject is still on the study at time point x. PR_x = worst PR_i where $0<t_i<x$ Otherwise, $$PR_x = 0$$ and $$wPR_x = (PR_x + PR_j)/2 * (x - t_j)$$ For TOTPAR[0-x], if no PR_i exists with $t_i = x$, $$TOTPAR[0\text{-}x] = wPR_x + \sum_{i,1 \le t_i < x} \frac{(PR_i + PR_{i-1})}{2} * (t_i - t_{i-1})$$

	Otherwise, for TOTPAR[0-x] if there is a PR_i with $t_i = x$, then $TOTPAR[0\text{-}x] = \sum_{i,1 \le t_i \le x} \frac{(PR_i + PR_{i-1})}{2} * (t_i - t_{i-1})$ No other interpolation or imputation of missing values will be performed. PR at time 0 is considered to be equal to 0. PR was scored at each observation time after Dose 2 administration. Numerical rating scale for PR ranges from 0 to 10.
Time from end of surgery to dose 2 (hours)	Time/date Dose 2 – time/date end of surgery (last suture)
Duration of pain reduction	First rescue medication date/time - Dose 2 time/date. If the subject does not take rescue medication post-Dose 2, their data will be censored at the last pain assessment after Dose 2 administration.
Change from Baseline Derivations	
Change from baseline	Post baseline value – Baseline
Percentage change from baseline	[(Post baseline value – Baseline)/Baseline]*100

9.6 Time Windows

Because some subjects may complete their assessments at times differing from the scheduled times, each such score will be adjusted so as to reflect more accurately the score that would have been observed had it been recorded at the scheduled time. For the visit-wise summary, time windows will be created for each observation time for both Pain Intensity and Pain Relief. At the initiation of Dose 2, Pain Intensity (PI) and Pain Relief (PR) will be collected on the 0-10 NRS at 0.5, 0.75, 1, 1.25, 1.75, and 2.25 hours (± 5 minutes) and then collected at Hours 3.25, 4.25, 5.25, 6.25, 8.25, 10.25, 12.25, and 24 (± 10 minutes).

- If an assessment is performed within a time point window, the corresponding value will be assigned to that scheduled time point.
- If an assessment is outside a time point window, the corresponding value will be assigned to the scheduled time point corresponding to the window containing it.
- Unscheduled assessments will be included in the visit window assignment.

Please refer to Appendix A for windowing detail.

For subjects who took rescue medication or withdraw from study, approaches described in section 9.2 will be applied to impute the missing value. Otherwise, LOCF or WOCF will be applied in which last or worst observation post baseline will be used to impute the missing value for a given visit window. LOCF serves as the primary imputation method, while WOCF is supportive.

If more than one observation occurs within a given window, the observation with the smallest absolute value of difference from the scheduled time point will be used. If both observations have the same absolute value of difference from the scheduled time point, the latest of the observations will be used. If multiple assessments are taken at the exactly same time, the more severe score will be used.

9.7 Demographics and Baseline Characteristics

9.7.1 Demographics

Age, height, weight, BMI, and other continuous demographic variables at baseline will be summarized descriptively by treatment group and overall. Sex, primary race, ethnicity, and other categorical variables will be summarized using the Randomized Population, Efficacy Analysis Population, and Safety Population, respectively.

9.7.2 Medical and Surgical History

A summary of medical history will be presented by treatment group and overall for system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities® (MedDRA) Version 20.1 or higher.

9.7.3 Prior and Concomitant Medications and Procedures

Medications used in this study will be coded by using the latest available version of the World Health Organization Drug Dictionary Enhanced (WHODDE).

Prior medications: are defined as those medications with a start date prior to the first dose of study drug.

Concomitant medications: are defined as those medications with a start date on or after the first dose of study drug. Prior medications that are ongoing during the study are also considered concomitant medications.

Upon request, prior medications and concomitant medications will be summarized descriptively by treatment group and overall using frequency tables and listings.

9.8 Efficacy Analyses

Unless otherwise specified, summary of GRP A, B, C, D, and E will be included in the efficacy summary tables. The planned treatment comparison will be performed for specific endpoints. Please refer to Appendix B for the planned efficacy analysis.

9.8.1 Analysis of Covariance Model

For time weighted SPID and SPI, time intervals are 0-4, 0-6, 0-8, 0-12, and 0-24 based on the 0-10 point PI-NRS. For time weighted TOTPAR, time intervals are 0-4, 0-6, 0-8, 0-12, and 0-24 based on the 0-10 point PR-NRS.

These efficacy endpoints will be analyzed via an analysis of covariance (ANCOVA) model with treatment group and sex as fixed effects and baseline score prior to Dose 2 as covariate if applicable. For the comparison of interest, point estimates, standard errors, and one-sided 90% confidence intervals of the between-treatment group differences will be presented.

A bar chart with standard error bars for SPID and TOTPAR at 0-4, 0-6, 0-8, 0-12, and 0-24hr post Dose 2 will also be provided for each treatment group.

9.8.2 Time to Event Analysis

Time from end of surgery (last suture) to administration of Dose 2 will be summarized by descriptive statistics for each treatment group as well as GRP A to D combined.

The duration of pain reduction, as measured by the time to treatment failure (i.e. time to first dose of rescue medication after Dose 2, subjects will be censored at the last pain assessment), will be modeled using proportional hazards regression models adjusting for treatment group, sex, and baseline pain intensity score as covariates. Results will be reported as point estimates and standard errors for the hazard ratios with one-sided 90% confidence intervals. The Kaplan-Meier method will be used to plot the survival distribution functions for each treatment group. The Kaplan-Meier estimated median time along with one-sided 90% CI for the median will be provided.

Additionally, binomial proportion of the subjects with treatment failure (Yes/No) at 6, 8 12, and 24 hr post Dose 2 will be summarized by treatment group.

9.8.3 Repeated Measures Analysis

A mixed-effect repeated measures model will be used to analyze Pain Intensity (PI), Pain Intensity Difference (PID), and Pain Relief (PR) across different time points post-surgery. The model for this analysis will include the fixed, categorical effects of treatment group, sex, visit, and treatment group-by-visit interaction, as well as the continuous, fixed covariates of baseline pain score and baseline pain score-by-visit interaction. An unstructured covariance structure will be used to model the within-subject errors. The Kenward-Roger (Kenward and Roger 1997) approximation will be used to estimate denominator degrees of freedom. If the model does not converge with both the Hessian and the G matrix being positive definite under the default fitting algorithm used by PROC MIXED, the Fishers scoring algorithm will be implemented by specifying the SCORING option in SAS.

The cumulative distribution of pain intensity percent reduction and pain relief at 6, 8, 12, & 24 hrs post Dose 2, respectively, will be plotted.

Pain intensity and pain relief scores over all time points will also be plotted for each treatment group.

9.8.4 Other Analysis

The use of rescue analgesia will be summarized as follows:

- Time to 1st dose of rescue medication: summary statistics will be provided by treatment group for subjects who took rescue medication during the study.
- Subjects who used any dose of rescue medication: summary statistics will be provided by treatment group at 6, 8, 12, & 24 hours.

Cumulative % of subjects with onset of First Perceptible Relief (FPR), First Perceptible Relief-Confirmed (FPR-C) and Meaningful Pain Relief (MPR) after Dose 2 will be plotted and descriptive summary statistics including 90% confidence interval of the median will be presented for each treatment group in the table.

Patient Global Evaluation will be summarized with descriptive statistics by treatment group.

9.9 Safety Analyses

The Safety Population will consist of all randomized subjects who received the study medication.

No statistical tests will be performed.

9.9.1 Adverse Events

All Adverse events (AEs) will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or higher.

A treatment-emergent adverse event (TEAE) is defined an AE that was not present prior to Dose 2 for GRP A-D and Dose 1 for GRP E, but appeared following treatment or was present at treatment initiation but worsened after treatment or becomes an SAE. Only TEAE will be summarized though all AE will be listed.

Two types of TEAE will be determined as follows:

a. $TEAE_{0\text{-}24hr}$: 24 hrs following Dose 2 for GRP A-D; 24hrs following Dose 1 for GRP E;

b. $TEAE_{24hr\text{-}15D}$: 24 hrs up to Day 15 following Dose 2 for GRP A-D; 24hrs to Day 15 following Dose 1 for GRP E.

An overall adverse event summary table will be presented for each TEAE type and it will include the following:

- All TEAEs

- TEAEs related to study drug
- TEAEs leading to study discontinuation
- Serious TEAEs

TEAEs will be summarized by SOC, PT, and treatment group and overall. The following summaries will be presented at the subject (number [%] of subjects) level for $TEAE_{0\text{-}24hr}$ and $TEAE_{24hr\text{-}15D}$ separately:

- TEAEs by SOC and PT
- TEAEs related to study drug by SOC and PT

If needed, the following summaries will also be provided by treatment group and overall.

- TEAEs by SOC, PT, and maximum severity
- Serious TEAEs by SOC and PT
- Serious TEAEs related to study drug by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT

For the incidence at the subject level by SOC and PT, if a subject experiences more than one event within the same SOC and PT, only one occurrence will be included in the incidence.

For the TEAE incidence at the subject level by SOC, PT, and severity, if a subject experiences more than one event within the same SOC and PT, only the most severe occurrence will be included in the incidence. For an AE with severity missing prior to Dose 2 for GRP A-D and Dose 1 for GRP E, the missing severity will be imputed as mild and for an AE with severity missing post-Dose 2 for GRP A-D and Dose 1 for GRP E the missing severity will be imputed as severe and subsequently be included in the summary table.

A TEAE will be considered as related if the event is Possibly, Probably, or Definitely related. If the relationship to study drug is missing, the TEAE will be treated as related and subsequently be included in the summary table. If a subject experiences more than one event within the same SOC and PT, only the most related occurrence will be included in the incidence.

All observed AE records will be listed with $TEAE_{0\text{-}24hr}$ and $TEAE_{24hr\text{-}15D}$ flagged. Additional listings will be presented for AEs leading to discontinuation and serious AEs.

9.9.2 Clinical Laboratory Evaluations

All clinical laboratory data and abnormalities will be listed.

9.9.3 Vital Signs

Observed value and change from baseline for vital sign measurements (pulse, systolic blood pressure, diastolic blood pressure, and respiration rate) will be summarized by treatment group at each scheduled time point using descriptive statistics. For a given subject, if repeat is performed per parameter and time point, the average will be taken and be included in the summary. Nominal visit will be used in the analysis.

10 INTERIM ANALYSIS

If the Sponsor makes the decision to move ahead with Stage II of this study, the [redacted] biostatistician will generate the sample size for Stage II based on the Stage I interim analysis using an 80% power and a one-sided alpha of $p>0.10$. Stage II will not include any additional PK sampling.

APPENDIX A - VISIT WINDOW

Because some subjects may complete their PI and PR assessments at times differing from the scheduled times, each such score will be adjusted so as to reflect more accurately the score that would have been observed had it been recorded at the scheduled time. Time windows will be created for each observation time for both Pain Intensity and Pain Relief. Subsequent to Dose 2 (time 0), Pain Intensity (PI) and Pain Relief (PR) will be collected on the 0-10 NRS at 0.5, 0.75, 1, 1.25, 1.75, and 2.25 hours (± 5 minutes) and then collected at Hours 3.25, 4.25, 5.25, 6.25, 8.25, 10.25, 12.25, and 24 (± 10 minutes).

- If an assessment is performed within a time point window, the corresponding value will be assigned to that scheduled time point.
- If an assessment is outside a time point window, the corresponding value will be assigned to the next scheduled time point.
- Unscheduled assessment will be included in the visit window assignment.

In the cases that multiple assessments fall in the same window:

- The assessment which is closest to the scheduled time (absolute value in difference from scheduled time) will be used.
- If both assessments have the same absolute value in difference from scheduled time, the latest of the assessments will be used.
- If multiple assessments are taken at the exactly same time, the more severe score will be used.

The relative time (rel_time in minute) from time 0 is defined as the collect time minus Dose 2 time. Unless otherwise specified in the specific analyses, the analysis visit windows will follow the rules in the following table.

No.	Scheduled Time Point (minutes)	Visit Window Based on rel_time (minutes)
1	30	0<rel_time≤35
2	45	35<rel_time≤50
3	60	50<rel_time≤65
4	75	65< rel_time ≤80
5	105	80<rel_time ≤110

6	135	110<rel_time≤140
7	195	140<rel_time≤205
8	255	205<rel_time≤265
9	315	265<rel_time≤325
10	375	325<rel_time≤385
11	495	385<rel_time≤505
12	615	505<rel_time≤625
13	735	625<rel_time≤745
14	1440	745≤rel_time≤1450

APPENDIX B – PLANNED EFFICACY ANALYSIS

Efficacy Endpoint	Planned Analysis	Treatment Comparison	Imputation/Calculation Rule	Displayed Statistics
SPID	ANCOVA	• GRP D vs. GRP B • GRP C vs. GRP B • GRP C vs. GRP A • GRP B vs. GRP A • GRP D vs. GRP A • GRP D vs. GRP C • GRP E vs. GRP D	Please refer to SAP table 1. Please note: Analysis will be performed for both extrapolation approaches with LOCF being primary analysis and WOCF being supportive. Actual time will be used.	Summary statistics (n, mean, SD, median, min, max), L.S. mean (SE) from ANCOVA, L.S. mean difference (SE) along with one-sided 90% CI for the denoted comparison. P value from treatment comparison will be included in the log and SAS output, but will not be displayed in the table. Bar chart with SE bar will be plotted for each treatment group.
TOTPAR	ANCOVA	• GRP D vs. GRP B • GRP C vs. GRP B • GRP C vs. GRP A • GRP B vs. GRP A • GRP D vs. GRP A • GRP D vs. GRP C • GRP E vs. GRP D	Please refer to SAP table 1. Please note: Analysis will be performed for both extrapolation approaches with LOCF being primary analysis and WOCF being supportive. Actual time will be used.	Summary statistics (n, mean, SD, median, min, max), L.S. mean (SE) from ANCOVA, L.S. mean difference (SE) along with one-sided 90% CI for the denoted comparison. P value from treatment comparison will be included in the log and SAS output, but will not be displayed in the table. Bar chart with SE bar will be plotted

				for each treatment group.
Time from end of surgery (last suture) to Dose 2	Summary by treatment with no statistical analysis planned	Summary by GRP A, B, C, D, E, and A–D combined		Summary statistics (N, median, SD, Min, Max)
SPI	ANCOVA	• GRP D vs. GRP B • GRP C vs. GRP B • GRP C vs. GRP A • GRP B vs. GRP A • GRP D vs. GRP A • GRP D vs. GRP C • GRP E vs. GRP D	Same as SPID, except that observed PI post baseline is summarized. Only LOCF will be used for extrapolation.	Summary statistics (n, mean, SD, median, min, max), L.S. mean (SE) from ANCOVA, L.S. mean difference (SE) along with one-sided 90% CI for the denoted comparison. P value from treatment comparison will be included in the log and SAS output, but will not be displayed in the table.
PI and PID	mixed-effect repeated measures model	• GRP D vs. GRP B • GRP C vs. GRP B • GRP C vs. GRP A • GRP B vs. GRP A • GRP D vs. GRP A • GRP D vs. GRP C • GRP E vs. GRP D	Visit window described in Appendix A is applied. For visit occurred after study discontinuation or first rescue med, imputation rule described in SAP section 9.2 will be used. Otherwise, LOCF will be applied as primary imputation method, and WOCF as supportive method.	For each visit, summary statistics (n, mean, SD, median, min, max), L.S. mean (SE), L.S. mean difference (SE) along with one-sided 90% CI for the denoted comparison. P value from treatment comparison at each visit will be included in the log and SAS output, but will not be displayed in the table Plot of cumulative distribution of pain intensity percent reduction at 6, 8, 12 & 24 hrs post Dose 2 will be provided.

				Pain Intensity scores over all time points will also be plotted for each treatment group.
PR	mixed-effect repeated measures model	• GRP C vs. GRP B • GRP C vs. GRP A • GRP B vs. GRP A • GRP D vs. GRP A • GRP D vs. GRP C • GRP E vs. GRP D	Visit window described in Appendix A is applied. For visit occurred after study discontinuation or first rescue med, imputation rule described in SAP section 9.2 will be used. Otherwise, LOCF will be applied as primary imputation method, and WOCF as supportive method.	For each visit, summary statistics (n, mean, SD, median, min, max), L.S. mean (SE), L.S. mean difference (SE) along with one-sided 90% CI for the denoted comparison. P value from treatment at each visit comparison will be included in the log and SAS output, but will not be displayed in the table Plot of cumulative distribution of pain relief at 6, 8, 12 & 24 hrs post Dose 2 will be provided respectively. Pain relief scores over all time points will also be plotted for each treatment group.
Duration of pain reduction	Time to event analysis	• GRP C vs. GRP B • GRP C vs. GRP A • GRP B vs. GRP A • GRP D vs. GRP A • GRP D vs. GRP C		Summary statistics (N, median, SD, Min, Max), Quartile estimate (median, Q25, Q75) along with CI from Kaplan-Meier method, hazard ratio and its CI from proportional hazards regression model adjusting for treatment group, sex, and baseline

		• GRP E vs. GRP D		pain intensity score as covariates. Binomial proportion of the subjects with treatment failure (Yes/No) at 6, 8 12, and 24 hr post Dose 2. P value from treatment comparison of proportional hazard model will be included in the log and SAS output, but will not be displayed in the table
Cumulative % of patients with onset of First Perceptible Relief (FPR) & First Perceptible Relief – Confirmed (FPR-C)	Summary by treatment with no statistical analysis planned	No treatment comparison	Time collected from the 1st stop watch.	Cumulative plot and table with descriptive statistics by GRP A-E
Cumulative % of patients with onset of Meaningful Pain Relief (MPR) after Dose 2	Summary by treatment with no statistical analysis planned	No treatment comparison	Time collected from 2nd stopwatch	Cumulative plot and table with descriptive statistics by GRP A-E
Patient Global Evaluation at time of first rescue or 12.25 hours post-surgery, whichever is first	Summary by treatment with no statistical analysis planned	No treatment comparison	Please note: Some subjects have two sets of Patient Global Evaluation collected, one at 12.25 hrs post surgery and the other after. For these subjects, please ignore the one collected after 12.25 post surgery.	Summary statistics (n, mean, SD, median, min, max)
Total doses of rescue analgesia	Summary by treatment with no statistical	No treatment comparison		Time to 1st dose of rescue medication: summary statistics (n, mean, SD, median, min, max) for time to 1st dose

	analysis planned			of rescue medication will be provided by treatment group for subjects who took rescue medication during the study. Summary statistics (n, mean, SD, median, min, max) for time to 1st dose of rescue medication will be provided for subjects who used any doses of rescue medication at 6, 8, 12, & 24 hours.