Clinical Trial Protocol

A Randomized, Double-Blind, Multi-Dose, Single-Site, Placebo- and Active-Controlled, Efficacy, Tolerability, Safety and Pharmacokinetic Study of Two Different Dosing Regimens of Acetaminophen [redacted] in Post-Surgical Dental Pain.

Protocol Number: CP-NVK009-0002, Version 3.0, Amendment 3

Dated: 15-April-2019

ClinicalTrials.gov Identifier: 2015-002926-38

Sponsor: Nevakar, Inc. NJ 08807

NEVAKAR, INC.

1. STUDY PROTOCOL SUMMARY

Title:	A Randomized, Double-Blind, Multi-Dose, Single-Site, Placebo- and Active-Controlled, Efficacy, Tolerability, Safety and Pharmacokinetic Study of Two Different Dosing Regimens of Acetaminophen [redacted] in Post-Surgical Dental Pain.
Test Drugs:	[redacted] ([redacted] acetaminophen [redacted] [redacted] ([redacted] acetaminophen [redacted] Placebo [redacted]
Methods:	After undergoing surgical removal of two or more impacted third molars, 110 eligible, consenting patients will be randomized 2:2:1 to receive one of three analgesia regimens: A. Acetaminophen [redacted] every 8 hours B. Acetaminophen [redacted] every 6 hours C. [redacted] placebo After surgery, all patients that meet randomization criteria will receive either APAP [redacted] every 8 hours or APAP [redacted] every 6 hours or placebo. To maintain double-blind conditions, after dose 1 patients will receive either a [redacted] or the active study medication every 2 hours (± 10 minutes) over the first 18 hours over the course of a 24-hour evaluation period. Patients will assess Pain Intensity (PI) and Pain Relief (PR) at regularly scheduled intervals, Time to First Perceptible Pain Relief (FPR), and Time to Meaningful Pain Relief (MPR) using a two-stopwatch technique, and a global evaluation of analgesia efficacy. Use of rescue medications will be evaluated and spontaneous adverse events will be documented as they occur.
Sponsor Name and Address:	Nevakar, Inc. [redacted] [redacted] NJ 08807
Protocol Identification:	CP-NVK009-0002
Phase II:	Dental Impaction Pain Model
Company/Sponsor Representative:	[redacted] MD [redacted]
Name and Title of Principal Investigator	[redacted], M.D. [redacted] JBR Clinical Research
Clinical Research Organization	[redacted]

[redacted], CA 91105

PK Laboratory [redacted] IN 47906

Compliance Statement: The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and with standards of current Good Clinical Practice, as defined by the International Conference on Harmonization and all applicable FDA regulations.

Confidential Information

The information contained within this report is confidential and may not be used, divulged, published, or otherwise disclosed without the prior written consent of Nevakar, Inc.

Date	Version	Comment(s)	Author
January 15, 2019	1.0	N/A	[redacted]
March 6, 2019	2.0	Amendment 1	[redacted]
March 25, 2019	2.1	Amendment 2	[redacted]
April 15, 2019	3	Amendment 3	[redacted]

Summary of Protocol Changes (from Version 1 to Version 2)

Change	**Description**	**Location**
Change in number of patients	Decrease in number of participants from 140 to 110 with a 2:2:1 randomization schedule	Synopsis, Section 8
Imputation of data following rescue medication	Clarification that patients who receive rescue medication will have data censored but pain data will still be collected	Synopsis, Section 10.7
Change in Rescue Medication	Change of Rescue Medication to 200 mg ibuprofen	Synopsis, Section 10.7
Change of Efficacy Parameters	Change to SPID and TOPTPAR over a 24-hour period, clarification that Pain Relief will be a 5-Point Categorical Pain Relief Assessment	Synopsis, Section 7.2, Section 12.5
Timing of Patient Global Evaluation	Change to hour 24.25	Synopsis, Section 3, Section 10.2
Consistency in Inclusion/Exclusion Criteria	Corrected lack of consistency in Inclusion/Exclusion Criteria at different places in the protocol	Synopsis, Section 8.1, Section 8.2
Adverse event documentation	Clarify that adverse events will be recorded in the eCRF as they occur during the treatment phase of the study	Synopsis, Section 11.4
Blood volume	Corrected the estimated blood volume required for PK testing	Synopsis, Section 10.5
Formatting	Corrected formatting errors	Multiple locations
Sample size determination	Provided further justification for sample size determination	Synopsis, Section 12.1
Statistical analysis	Provided further detail on planned statistical methods and analysis	Synopsis, Section 12

CRO, vendors and study personnel details	These details have been added	Title Page, synopsis, Section 11.4
Summary of Protocol Changes (from Version 2 to Version 2.1)		
Change in type of vacutainer PK samples collected in	Corrected the type of vacutainer PK samples collected in from K2EDTA to K3EDTA tube	Clinical Protocol Synopsis Pharmacokinetic Assesments (PK):
Addtion of Dosing window time + 10 minutes	Updated dosing time points to reflect a window of dosing of + 10 minutes	Synopsis; Study Design Section 8 Summary of Study Design Section 9.4 Administration of Study Medication and Duration of Evaluation
Summary of Protocol Changes (from Version 2.1 to Version 3)		
Addition of hematology safety labs	Added hematology safety labs to meet exclusion criteria 1	Table 3: Study flow chart, Synopsis, Section 10.2.1: screening assessments Section 10.5: Blood sampling, urine drug screen and pregnancy tests
Administrative Clarification +/- specific added to all PK time points and removal of PK Time point 0 . Total PK samples from 19 to 18	Administrative Clarification +/- specific added to all PK time points and removal of PK Time point 0. Total PK samples from 19 to 18	Synopsis : Pharmacokinetic Assessments (PK) Study Flow Chart: Foot Note #7 Section 10.5: Blood Sampling, Urine Drug Screen and Pregnancy Tests:
Clarification regarding vital sign time points	Administrative clarification around vital sign time points to ensure these completed at screening, priror to surgery and every 4 hours post 1st Dose.	Synopsis: Other Measurements Study Flow Chart: Foot Note #1 Section 10.4: Safety Assessments

Administrative Clarification regarding blood donation	Clarified Whole Blood to Exclusion criteria #9	Synopsis: Inclusion/Exclusion Criteria #9 Section 8.2 Inclusion/Exclusion Criteria #9
Addition of + 10 min window timepoint for PGE Assessment at 24.25	Added +10 min window timepoint for PGE Assessment at 24.25	Section 8.0 Summary of Study Design Section 10.2.3 Postoperative Assessments

Signature Page

Investigator Signature

The signatures of the Principal Investigator and representatives of Nevakar, Inc. (Nevakar/Sponsor) below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations, clinically and administratively, as detailed in the protocol, including all statements as to confidentiality. It is agreed that the conduct and results of this study will be kept confidential and that the Case Report Forms (CRFs) and other pertinent data will become the property of Nevakar.

It is agreed that the protocol contains all necessary information required to conduct the study as outlined in the protocol, and that the study will not be initiated without the approval of an appropriate Institutional Review Board.

It is agreed that all participants in this study will provide written informed consent in accordance with the requirements specified in the FDA Regulations and the Current International Conference on Harmonization Good Clinical Practice Guidelines. All participants will also be informed that their medical records will be kept confidential except for review by representatives of Nevakar, Institutional Review Board and the FDA and/or other international regulatory authorities.

The following have reviewed and approved this protocol:

Principal Investigator's Signature:	
[redacted] M.D.	16 APR 2019 Date

Sponsor Representative's Signature:

[redacted] April 15, 2019
Date

[redacted] Nevakar Inc.

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2. CLINICAL PROTOCOL SYNOPSIS

TITLE:	A Randomized, Double-Blind, Multi-Dose, Single-Site, Placebo- and Active-Controlled, Efficacy, Tolerability, Safety and Pharmacokinetic Study of Two Different Dosing Regimens of Acetaminophen [redacted] in Post-Surgical Dental Pain
SPONSOR	Nevakar, Inc. [redacted] [redacted] NJ 08807
STUDY NUMBER:	CP-NVK009-0002
PRINCIPAL INVESTIGATOR:	[redacted] M.D.
SITE:	JBR Clinical Research [redacted] [redacted] Utah 84124
STUDY OBJECTIVES:	The objective of this study is to assess the safety, tolerability, analgesic efficacy, and pharmacokinetics of acetaminophen [redacted] dosed [redacted] ([redacted] APAP) every eight hours (q8h) relative to placebo and of acetaminophen [redacted] dosed [redacted] every six hours (q6h) relative to placebo over a 24-hour period in participants experiencing moderate to severe pain following surgical third molar removal.
HYPOTHESIS:	[redacted] APAP [redacted] q8h and [redacted] APAP [redacted] q6h have similar safety, tolerability and efficacy profiles when compared with placebo.
STUDY DESIGN:	This will be a randomized, double-blind, single-site, placebo-controlled, parallel-group study to assess similarities in safety, tolerability, efficacy, and pharmacokinetics of [redacted] of [redacted] acetaminophen given in three doses, each 8 hours apart, relative to placebo, and [redacted] of [redacted] acetaminophen given in four doses, each 6 hours apart, relative to placebo over a 24-hour period in patients experiencing moderate to severe postsurgical pain within 7 hours following surgical removal of 2 or more molars. To maintain the double-blind conditions, patients will be receiving either a placebo ([redacted] that looks like study drug) or the active study medication every 2 hours (± 10 minutes) [redacted] over the first 18 hours after Dose 1. Patients will undergo surgical removal of at least two third molars. Maxillary third molars may be removed regardless of impaction level. The mandibular extractions must meet one of the following scenarios and must not result in a trauma rating of severe on the 4-point scale of mild, moderate, moderately severe, or severe:

STUDY DESIGN: ***(cont.)***	• Two full bony impactions • Two partial bony impactions • One full bony impaction in combination with one partial bony impaction Patients who meet the randomization criteria (post-surgical pain of moderate to severe on the 4-point Categorical Pain Intensity scale, and at least a score of 5 on the 11-point [0-10] pain intensity numerical pain rating scale [PI-NPRS] at baseline within 7 hours of last stitch from dental extractions) will be randomly assigned to one of three treatment groups in a 2:2:1 ratio of active to placebo treatments. Approximately 110 patients will receive either [redacted] APAP [redacted] three doses, each in [redacted] of total volume, 8 hours apart **OR** [redacted] APAP [redacted] four doses, each in [redacted] of total volume, 6 hours apart **OR** placebo, [redacted] total volume of [redacted] in a 2:2:1 allocation ratio. No less than approximately 30% of randomized patients will be either male or female. In addition, no more than approximately 30% of patients will be 17 years of age at the time of screening. [redacted] of the first dose of study medication will begin within 10 minutes of randomization. As a result of the different schedules for active drug administration (q6h versus q8h) and in order to maintain the double-blind conditions, every two hours thereafter randomized patients will receive either active drug or placebo [redacted] through Hour 18. The maximum number of doses for an active drug will be 4 doses of [redacted] of acetaminophen or 3 doses of [redacted] of acetaminophen. The maximum dose of acetaminophen over a 24-hour period will be 4 grams. Self-reported pain intensity will be collected using a 11-point [0-10] PI-NPRS at baseline (time 0). NPRS and pain relief (PR) will be collected at 0.5, 0.75, 1, 1.25, 1.75, 2.25 Hours (± 5 minutes), hourly from 3.25 through 12.25 Hours (± 5 minutes), then every two hours from 14.25 through 24.25 hours (± 10 minutes) after the [redacted] of the first dose of study medication is initiated (T0). In addition, efficacy scores (NPRS and PR) will be collected prior to each use of rescue (if applicable). Time to perceptible pain relief and time to meaningful pain relief will be collected using the double-stopwatch methodology as follows: For each randomized patient, two stopwatches will be started immediately upon initiation of the first study dose [redacted] The first stopwatch will be given to each patient with the instructions to stop the watch when they first perceive pain relief to occur (time to perceptible relief). Once the first stopwatch is stopped, the second stopwatch will be given to the patient with the instruction to stop the watch when they are first experiencing meaningful pain relief (time to meaningful relief). Time to perceptible pain relief is confirmed only if the patient experiences meaningful relief. Rescue medication will consist of one ibuprofen 200 mg tablet taken orally with at least 4 ounces of water. Prior to each dose of rescue medication, 11-

STUDY DESIGN: ***(cont.)***	point Pain Intensity (via 0-10 Numerical Pain Rating Scale) and Pain Relief (via 5-Point Categorical Pain Relief Assessment) measurements will be performed. For statistical purposes, pain assessments performed after any dose of rescue will be censored and imputed. The method of imputation will be described in the SAP, which will be finalized prior to unblinding of clinical trial subjects. Any subject requiring additional rescue medication may again receive ibuprofen 200mg and their data will be similarly censored and imputed. Pain scores and safety data will continue to be collected for the 24-hour observation period. Rescue medication will not exceed ibuprofen 200 mg q3h or 2400 mg in a 24-hour period. Patient Global Evaluation of the study medication will be collected at Hour 24.25 or at the time of patient withdrawal (if applicable), whichever occurs first, using a 0-4 rating scale: (0) poor, (1) fair, (2) good, (3) very good, and (4) excellent.
EFFICACY MEASUREMENTS:	• Categorical Pain Intensity: (only at Baseline to determine study eligibility) Appendix 3 None (0) Mild (1) Moderate (2) Severe (3) • Numerical Rating Scale Pain Intensity: (PI-NRS) Appendix 3 (0 = no pain and 10 = worst imaginable pain) • Pain Relief Appendix 3 (5-Point Categorical Pain Relief Assessment) • Stop Watches: First Perceptible and Meaningful Relief Appendix 3 (FPR= First Perceptible Relief-, MPR = Meaningful Pain Relief and FPR-C = FPR that is confirmed by MPR) • Global Evaluation: Appendix 3 Poor (0) Fair (1) Good (2) Very Good (3) Excellent (4) **Efficacy Parameters:** • Time Weighted Sum of Pain Intensity Difference from 0 to 24hours (SPID24); • Time Weighted Sum of Pain Relief from 0 to 24 hours (TOTPAR24); • Time to Perceptible Pain Relief Confirmed (FPR-C); • Time to Meaningful Pain Relief (MPR); • Cumulative proportion of patients with pain half gone over time;

EFFICACY MEASUREMENTS: ***(cont.)***	• Patient Global Evaluation of the study medication will be collected at Hour 24.25, or at the time of patient withdrawal (if applicable), whichever occurs first; • Pain Intensity Difference Rating (PID): scored on the 0-10 PI-NRS at each observation time after Dose 1 administration; • Pain Intensity Rating (PI): scored on the 0-10 PI-NRS at each observation time after Dose 1 administration; • Pain Relief Rating (PR): scored on a 5-point scale at each observation time after Dose 1 administration; • Time to treatment failure (i.e. time to first dose of rescue medication after Dose 1 or withdrawal from the study due to lack of efficacy prior to rescue); • Cumulative % of patients with onset of First Perceptible Relief Confirmed after Dose 1; • Cumulative % of patients with Meaningful Pain Relief after Dose 1; • The cumulative proportion of treatment failures over time after Dose 1 administration (failure defined as requiring rescue analgesic medication or withdraw from the study due to lack of efficacy).
OTHER MEASUREMENTS:	Following signing of the informed consent form (ICF) and/or assent until the completion of the study, patients will be monitored for safety. Vital signs will be collected at screening, prior to surgery, and at Hours 4, 8, 12, 16, 20 and 24 following T0 (±10 min). Patients will continue to be periodically monitored throughout the 24-hour stay at the CRU. All adverse events spontaneously reported by the patients or observed by the research coordinators will be recorded.
PHARMACOKINETIC ASSESSMENTS (PK):	Prior to surgery, patients will have two indwelling catheters placed in the largest available arm veins - one catheter for PK draws [redacted] administration of the study medication. At pre-set time points, a blood sample of approximately 6 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: **Prior to Dose 1:** An initial baseline PK blood sample will be collected at least 5 minutes before administering Dose 1 of study medication. The time of initiation of Dose 1 will be designated as T0.

PHARMACOKINETIC ASSESSMENTS (PK): ***(cont.)***	**Post Dose 1:** To be drawn at 0.25 hr.±3 min (end of [redacted] 0.5 hr. ±3 min, 0.75 hr. ± 3 min, 1 hr. ± 5 min, 2 hr. ± 5min , 4 hr.± 5 min, 6 hr.- 5 min (prior to the next planned [redacted] 6.25 hr. ± 3 min (end of the [redacted] 8hr. - 5 min (prior to the next scheduled [redacted] 8.25 hr. ± 3min (end of the [redacted] 12 hr. - 5 min (prior to the next scheduled [redacted] 12.25 hr. ± 3 min (end of the [redacted] 16 hr. - 5 min (prior to the next scheduled [redacted] 16.25 hr. ±3 min(end of the [redacted] 18 hr. - 5 min (prior to the next scheduled [redacted] 18.25 hr. ± 3min (end of the [redacted] and at 24.25 hr.± 15 min (after starting the very first [redacted] If a scheduled pain assessment and a scheduled PK sampling are at the same time point, the pain assessment should precede the PK sampling, but every attempt should be made to obtain the PK sample within the designated time window. The total amount of blood drawn for PK sampling is approximately 108 mL (18 blood samples of approximately 6 mL). The bioanalytical laboratory will perform the pharmacokinetic (PK) analysis on collected blood samples and provide a report on the plasma levels of acetaminophen. Actual sample collection time will be used for calculating the pharmacokinetic parameters. 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 (AUC0-t) will be calculated by the linear trapezoidal method. AUC0-∞ will be extrapolated if allowed by the data. The PK Collection Lab Manual Guidelines for the site will be provided by the PK Lab.
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 7-day ± 2-day follow-up period. The approximate maximum number of days totals 40 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 the study will be completed within 4 months of the first patient entry.
NUMBER OF PATIENTS:	A sufficient number of male and female patients will be screened to enroll up to 110 patients that meet the American Society of Anesthesiologists (ASA) Category I (healthy) or Category II (mild systemic disease) guidelines.

SAMPLE SIZE DETERMINATION:	The sample size was determined from past experience with the Dental Impaction Pain Model (DIPM) and analysis of the results from a previous Phase 2 study comparing the safety and efficacy of [redacted] APAP in combination with oral pregabalin (Nevakar Protocol CP-NVK-009-0001). SPID 24 data for [redacted] APAP in that study suggested that a sample size of 44 patients per active group and 22 patients in the placebo group should be adequate to evaluate similarities between the two active dose regimens vs placebo.
INCLUSION CRITERIA: **INCLUSION CRITERIA:** ***(cont.)***	1. Patients must be capable of reading, comprehending, and signing the informed consent/assent form; 2. Male and female patients between 17-55 years of age; 3. Body Mass Index (BMI) $\leq$35.0 kg/m^2 4. Body weight of >50 kg 5. Patients are ASA Category I or II and are in good physical health as judged by a thorough history and physical examination; 6. Patients without infections in the area of the impacted teeth; 7. Patients must agree to refrain from ingesting any systemic or applying any topical analgesic medication for 3 days or 5 half-lives of the drug prior to and during the study; 8. No alcohol for a minimum of 24 hours prior to the surgery; 9. 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 screening and urine on day of surgery 1) pregnancy test and not be breastfeeding; 10. Patients must have a negative urine drug screen for drugs of abuse at Screening and on the day of surgery. At the discretion of the Principal Investigator, a positive drug screen result may be permitted if the patient has been on a stable dose of an allowed medication for >30 days; 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 Principal Investigator 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 with a history of any type of malignancy within the past 5 years other than minor skin related cancers; 3. Patients with a history of alcohol or substance abuse in the past three years according to DSM V and who do not satisfy Inclusion Criteria 10 (including a positive urine drug screen test); 4. Patients with a known allergy or hypersensitivity to any local anesthetic drug, acetaminophen, ibuprofen, or other NSAIDS; 5. Patients who are taking any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative hypnotics or any analgesics taken within three days or five times of their elimination half-lives, whichever is longer. Selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) are permitted if the patient has been on a stable dose for at least 30 days prior to screening; 6. Patients who have smoked or chewed tobacco-containing substances within 48 hours prior to the day of surgery;
EXCLUSION CRITERIA: ***(cont.)***	7. Patients judged by the Principal Investigator to be unable or unwilling to comply with the requirements of the protocol; 8. Patients who have used an investigational drug within 30 days prior to the screening day or have previously participated in any Nevakar trial; 9. Patients who have donated blood within 3 months prior to the screening day; 10. Patients who are employees or relatives of employees of JBR Clinical Research or Nevakar, Inc.

	11. Patients with liver function tests (ALT, AST) that are above the normal reference range.
SAFETY EVALUATION:	All potential patients will undergo a urine drug screen, hematology, serology testing for HIV, Hepatitis B and Hepatitis C, and serum liver function testing at the screening visit. In addition, females will have a serum pregnancy test. Prior to Hour 24 (±30 minutes), liver function testing will be repeated. All of the study and rescue medications being evaluated in this study are marketed products in the United States.
SAFETY EVALUATION: ***(cont.)***	Adverse events (AEs) will be assessed and recorded in the eCRF. This information will be collected as they occur or are reported at screening and during the treatment and post treatment phase of the study patient regardless of severity or potential association with the study medication or study procedures. AEs will also be assessed and recorded in the eCRF at the time of follow-up telephone call at Day 7 (± 2 days) after discharge from the Clinical Research Unit. This follow-up telephone call designates that the patient has completed the study. In addition, patients/caregivers will be encouraged to report AEs of concern at any time in the interval between discharge and the follow-up call. Treatment-emergent AEs (TEAEs) will be summarized by incidence and severity and reported in the eCRF. 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 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:	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 $p \leq 0.10$ (one-sided), and no adjustments for multiple comparisons/end points will be performed. All confidence intervals will be one-sided 90% confidence intervals. The between-treatment comparisons that will be performed are: • [redacted] APAP [redacted] q8h versus Placebo • [redacted] APAP [redacted] q6h versus Placebo Descriptive statistics for numerical variables will include n (number of patients involved), mean, standard deviation, median, minimum, and maximum values. Categorical variables will be described by number and percent. Treatment of missing data will be described in a statistical analysis plan and finalized prior to database lock.

STATISTICAL ANALYSIS: ***(cont.)***	**Efficacy Data:** Sum of Pain Intensity Difference (SPID) and Total Pain Relief (TOTPAR) from 0 to 24 hours will be analyzed using an analysis of variance (ANOVA) model with treatment group as a fixed effect and baseline pain intensity a covariate. Other covariates may be explored and the final model will be described in the Statistical Analysis Plan (SAP). Actual times will be used for calculating SPIDs and TOTPARs. In addition, sensitivity analyses will be performed and will be described in the Statistical Analysis Plan. Time to Perceptible Pain Relief Confirmed (FPR-C, confirmed by achieving Meaningful Pain Relief), Time to Meaningful Pain Relief (MPR), and Time to Treatment Failure will each be analyzed using a log-rank test; the log rank test may be stratified by baseline pain intensity score (moderate / severe) or other variables as appropriate. In addition, Kaplan-Meier curves will be presented by treatment group. The cumulative percentage of patients with pain at half gone over the 24-hour evaluation period will be summarized descriptively and plotted over time by treatment group. The Patient Global Evaluation at 24.25 hours or patient withdrawal (if applicable) whichever is first, will be analyzed using a model similar to the primary analysis model. Pain Intensity (PI), Pain Intensity Difference (PID), and Pain Relief (PR) Ratings at each observation time following Dose 1 administration will be summarized descriptively and plotted over time by treatment group. The cumulative percentage of patients with onset of FPR-C after Dose 1, MPR after Dose 1, and treatment failure after Dose 1 will each be summarized descriptively and plotted over time by treatment group. A detailed methodology for the statistical analyses of the data collected in this study will be documented in a SAP, which will be signed off prior to the database lock. The SAP may modify the plans outlined in the protocol and in cases where the documents are discrepant, the SAP shall be considered as correct; however, any major modifications to the primary endpoint definition will also be reflected in a protocol amendment. The SAP will be detailed in an addendum to the protocol. The SAP will be finalized and included in the addendum prior to unblinding of the study. **Safety Data:** Tables of descriptive statistics by treatment group and listings will be presented for the actual values and the changes from Baseline for Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Respiratory Rate (RR), and Heart Rate (HR) at Baseline and at 4-hour intervals post surgically. Liver function tests will be compared from baseline to post treatment.

	Analysis of the incidence and severity of all adverse events will also be performed.
RESCUE ANALGESIC: **RESCUE ANALGESIC:** ***(cont.)***	Rescue medication will consist of one ibuprofen 200 mg tablet taken orally with at least 4 ounces of water. Prior to each dose of rescue medication, 11-Point Pain Intensity (via 0-10 Numerical Pain Rating Scale) and Pain Relief (via 5-Point Categorical Pain Relief Assessment) measurements will be performed. For statistical purposes, pain assessments performed after any dose of rescue will be censored and imputed. The method of imputation will be described in the SAP, which will be finalized prior to unblinding of clinical trial subjects. Any subject requiring additional rescue medication may again receive ibuprofen 200 mg and their data will be similarly censored and imputed. Pain scores and safety data will continue to be collected for the 24-hour observation period. Rescue medication will not exceed ibuprofen 200 mg q3h or 2400 mg in a 24-hour period.

3. STUDY FLOW CHART (schedule of activities)

	Screening	Day of Surgery	Post-Op	Follow Up Post-Surgery Call
Procedures	**Day -30 to 0**	**Day 1**	**Day 2**	**Day 7 (±2 day)**
Written informed consent and/or assent	X			
Demography: Age, height, weight & BMI	X			
Inclusion / Exclusion assessment	X	X		
Significant medical history	X	X		
Physical Exam	X			
Vital signs (BP, heart rate, respiratory rate, temperature)[1]	X	X	X	
Serum pregnancy test for females	X			
Serology testing for HIV, Hep B and Hep C	X			
Serum liver function panel[2]	X		X	
Hematology	X			
Urine pregnancy test for females (dipstick)		X		
Urine drug testing (dipstick)	X	X		
Patient Assessment Training	X	X		
Dental Surgery & Randomization Criteria		X		
Study medication administration		X		
[redacted] Catheter Placement		X		
4-Point Categorical PI and 11-point PI-NPRS at Baseline[3]		X		
11-Point Pain Intensity (PI-NPRS) and Pain Relief (PR)[4]		X	X	
Perceptible & Meaningful Stopwatches 1 & 2 after Dose 1		X		
Rescue therapy if needed		X	X	
Patient Global Evaluation[5]			X	
Prior and Concomitant Therapy[6]	X	X	X	X
Patient Safety monitoring	X	X	X	X
PK Blood Draws[7]		X	X	
Discharge			X	

Follow-up interview				X

[1] Vital Signs will be obtained at screening, prior to surgery andhat Hours 4, 8, 12, 16, 20 and 24 following T0 (±10 min)

[2] Liver function panel includes alanine aminotransferase; albumin, serum; alkaline phosphatase, serum; aspartate aminotransferase; bilirubin, direct; bilirubin, total; protein, total

[3] Baseline = when patients report pain ≥5 on PI-NPRS & at least Moderate on 4-point categorical PI scale after surgery

[4] Follow-up pain measurements will be taken at the following times after initiation of Dose 1 (T0): 0, 0.5, 0.75, 1, 1.25, 1.75, 2.25, 3.25, 4.25, 5.25, 6.25, 7.25, 8.25, 9.25, 10.25, 11.25 and 12.25 Hours (±5 min), then at 14.25, 16.25, 18.25, 20.25, 22.25 and 24.25 Hours (±10 min)

[5] At 24.25 hours post-Dose 1 or patient withdrawal (if applicable), whichever is first

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

An initial pharmacokinetic (PK) blood sample will be collected at least 5 minutes before Dose 1 (T0) and then To be drawn at 0.25 hr.±3 min (end of [redacted] 0.5 hr. ±3 min, 0.75 hr. ± 3 min, 1 hr. ± 5 min, 2 hr. ± 5min , 4 hr.± 5 min, 6 hr.- 5 min (prior to the next planned [redacted] 6.25 hr. ± 3 min (end of the [redacted] 8hr. - 5 min (prior to the next scheduled [redacted] 8.25 hr. ± 3min (end of the [redacted] 12 hr. - 5 min (prior to the next scheduled [redacted] 12.25 hr. ± 3 min (end of the [redacted] 16 hr. - 5 min (prior to the next scheduled [redacted] 16.25 hr. ±3 min(end of the [redacted] 18 hr. - 5 min (prior to the next scheduled [redacted] 18.25 hr. ± 3min (end of the [redacted] and at 24.25 hr.± 15 min (after starting the very first [redacted]

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Term	Definition
AE	Adverse Event
ALT	Alanine Transaminase
ANOVA	Analysis of varianceVariance
APAP	Acetaminophen (acetyl-para-aminophenol)
ASA	American Society of Anesthesiologists
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CFR	Code of Federal Regulations
CNS	Central Nervous System
eCRF	Electronic Case Report Form
CRU	Clinical Research Unit
DBP	Diastolic Blood Pressure
DIPM	Dental Impaction Pain Model
DSM V	Diagnostic and Statistical Manual of Mental Disorders
EDC	Electronic Data Capture
EIU	Exposure in Utero
FDA	Food and Drug Administration
FPR	First Perceptible Relief
FPRC	First Perceptible Relief Confirmed
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
HR	Heart Rate
IBU	Ibuprofen
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IDRS	Impaction Difficulty Rating Scale

Abbreviation/Term	Definition
IND	Investigational New Drug
[redacted]	[redacted]
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD/IUS	Intrauterine Device/ Intrauterine System
MedDRA	Medical Dictionary for Regulatory Activities
mg and mg/d	Milligrams and milligrams per day
mL	Milliliter
MPR	Meaningful Pain Relief
NNT	Number Needed to Treat
NPRS	Numerical Pain Relief Scale
NPO	Nil Per Os (nothing by mouth)
NRS	Numerical Rating Scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
OTC	Over the counter
PBO	Placebo
PI	Pain Intensity
PID	Pain Intensity Difference
PK	Pharmacokinetics
PO	Per Os (by mouth)
PR	Pain Relief
PI-NPRS	Pain Intensity-Numerical Pain Relief Scale
RR	Respiratory Rate
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SAE	Serious Adverse Event
SOC	System Organs Class
SPI	Time Weighted Sum Pain Intensity
SPID	Time Weighted Sum Pain Intensity Difference

Abbreviation/Term	Definition
TEAE	Treatment Emergent Adverse Events
TESS	Treatment Emergent Signs and Symptoms
TMF	Trial Master File
TOTPAR	Time Weighted Total Pain Relief
US	United States
USP	United States Pharmacopeia

5. ETHICS

5.1. Institutional Review Board

This protocol, informed consent form, and any amendments will be submitted to institutional review boards (IRBs) for review and approval. A copy of the written approval or vote must be available and sent to the Sponsor (Nevakar, Inc.) before study initiation. Any amendment made to the approved protocol must be forwarded to and approved by the same IRBs before its implementation. Any required regulatory authority notifications will also be in place and fully documented prior to study initiation.

The Principal Investigator and appropriate representatives from the Sponsor will sign the protocol to document their willingness to adhere to this protocol and to conduct the study in accordance with the FDA guidelines and the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP).

5.2. Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and consistent with good clinical practice (GCP) as described by the United States Code of Federal Regulations (21CFR parts 50, 54, 56, and 312) and by the ICH Guidelines E6 (R2).

5.3. Patient Information and Consent

Written informed consent form (ICF), in accordance with local clinical investigation regulations (21 CFR Part 50 Protection of Human Patients), must be obtained from all patients prior to participation in the study. In addition, patients under 18 years of age also must have written parental or guardian consent. The Principal Investigator or his appropriate designee must provide a description of the study treatment (including any potential and possible hazards) and the study procedures to the study patients. Information must be given both in oral and written form. The patient information provided will be in English and may not include any language that appears to waive any of the patient's legal rights, or appears to release the Investigators, the Sponsor, the Sponsor's representative, or the institution, from liability or negligence.

The Principal Investigator or his appropriate designee will provide the prospective study patient sufficient time to consider whether or not to participate, minimizing the possibility of coercion or undue influence, and will discuss any questions the patients may have. The Principal Investigator or his appropriate designee will explain to the patient that withdrawal from the study is possible at any time without detriment to care. The Principal Investigator or his appropriate designee will then ask the patient to give consent in writing.

The consent must include acknowledgment that medical records and medical data derived from the study may be forwarded to the Sponsor, to the Sponsor's representative, to the FDA or other

regulatory authorities. The informed consent will follow the FDA Regulations and ICH Guidelines E6 (R2).

6. INTRODUCTION

6.1. Study Rationale

[redacted]

6.2. Background

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

7. OBJECTIVES, OUTCOMES, AND HYPOTHESIS

7.1. Objectives

This study is designed to assess the safety, tolerability, efficacy, and pharmacokinetics of [redacted] of [redacted] acetaminophen dosed three times daily and [redacted] acetaminophen [redacted] dosed four times daily, each compared to placebo.

7.2. Outcomes

7.2.1. Efficacy Outcome Measures

- Time Weighted Sum of Pain Intensity Difference from 0 to 24 hours (SPID24)
- Time Weighted Sum of Pain Relief from 0 to 24 hours (TOTPAR24)
- Time to Perceptible Pain Relief Confirmed (FPR-C)
- Time to Meaningful Pain Relief (MPR)
- Cumulative proportion of patients with pain half gone over time
- Patient Global Evaluation of the study medication will be collected at Hour 24.25, or at the time of patient withdrawal (if applicable), whichever occurs first
- Pain Intensity Difference Rating (PID): scored on the 0-10 PI-NRS at each observation time after Dose 1 administration
- Pain Intensity Rating (PI): scored on the 0-10 PI-NRS at each observation time after Dose 1 administration
- Pain Relief Rating (PR): scored on a 5-Point Categorical Pain Relief Assessment at each observation time after Dose 1 administration
- Time to treatment failure (i.e. time to first dose of rescue medication after Dose 1 or withdraw from the study due to lack of efficacy prior to rescue)
- Cumulative % of patients with onset of First Perceptible Relief Confirmed
- Cumulative % of patients with Meaningful Pain Relief after Dose 1
- The cumulative proportion of treatment failures over time after Dose 1 administration (failure defined as requiring rescue analgesic medication or withdraw from the study due to lack of efficacy).

7.3. Hypothesis

[redacted] acetaminophen [redacted] dosed three times daily and [redacted] acetaminophen [redacted] dosed four times daily have similar safety, tolerability, and efficacy profiles when compared to placebo.

8. SUMMARY OF STUDY DESIGN

This will be a double-blind, parallel group, single-center, placebo-controlled study. To maintain the double-blind conditions, patients will be receiving either a placebo ([redacted] that looks like study drug) or the active study medication every 2 hours (± 10 minutes) ([redacted]) for the first 18 hours after Dose 1. Patients will undergo surgical removal of at least two third molars. Patients will be evaluated after the first dose of study medication for a 24-hour period and there will be three treatment groups. Treatments will be randomized in a 2:2:1 ratio. The targeted number of patients to be randomized will be 44 for each active treatment group and 22 for placebo for a total of 110 patients.

Patients 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 removal of up to four third molars, of which two must be impacted mandibular third molars both of which must have a "4" or "5" rating on the Impaction Difficulty Rating Scale (IDRS - Appendix 1). During surgery, patients will be administered a short acting local anesthetic (lidocaine or mepivacaine with vasoconstrictor) by both mandibular block and local infiltration. Nitrous oxide may be used at the discretion of the oral surgeon. Topical anesthetics may also be used prior to the administration of the short acting local anesthetic. Long duration local anesthetics such as bupivacaine are not permitted. No other perioperative analgesic, anesthetic agents or corticosteroids are permitted. Prior to the surgical procedure, patients will have two indwelling catheters placed in the largest available arm veins. One catheter will be used for blood draws [redacted] administration of the study medication.

Following surgery, when patients report at least moderate pain on the 4-point categorical pain intentsity scale and a score of ≥5 on 0-10 PI-NPRS they will be randomized to receive study medication. Patients who do not have at least moderate pain on the 4-point categorical pain intensity scale and a score of ≥5 on 0-10 PI-NPRS 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 study medications, but can receive rescue medication upon request. Subsequent to Dose 1, all patients can request rescue analgesic if and when their pain returns to baseline levels. Patients have the right to withdraw from the study at any time.

After the initiation of Dose 1 (T0), Pain Intensity (PI-NPRS) and Pain Relief (PR) will be collected 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, 7.25, 8.25, 9.25, 10.25, 11.25, and 12.25 (± 5 minutes) then at hours 14.25, 16.25, 18.25, 20.25, 22.25, and 24.25 (± 10 minutes).

Upon initiation of the [redacted] of Dose 1, two stopwatches will be started. The patients will first be given stopwatch #1 and asked to press the stopwatch if and when they first perceive any relief (FPR). At this time, patients will be given the 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 1, the time of rescue as well as PI-NPRS and PR will be collected at that time and collection of stopwatch data will cease. Patients who do not experience any pain relief after Dose 1 will be encouraged, but not required, to wait at least 1 hour before using rescue therapy. Patient Global Evaluation (PGE) of the study medication will be collected at Hour 24.25 ($\pm$ 10 min) 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.

A randomization code will be generated that will randomly assign patients to treatment groups.

A sufficient number of male and female patients will be screened to enroll up to 110 patients that fit the American Society of Anesthesiologists (ASA) Category I (healthy) or Category II (mild systemic disease) classification.

8.1. Inclusion Criteria

Individuals may be included in the study provided they meet all of the following inclusion criteria:

1. Patients must be capable of reading, comprehending, and signing the informed consent form;
2. Male and female patients between 17-55 years of age;
3. Body Mass Index (BMI) $\leq$35.0 kg/m^2;
4. Body weight of >50 kg;
5. Patients are ASA Category I or II and are in good physical health as judged by thorough history and physical examinations;
6. Patients without infections in the area of the impacted teeth;
7. Patients must agree to refrain from ingesting any systemic or applying any topical analgesic medication for 3 days or 5 half-lives of the drug prior to and during the study;
8. No alcohol for a minimum of 24 hours prior to the surgery;
9. 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 Screening and urine on Day 1) pregnancy test and not be breastfeeding;

10. Patients must have a negative urine drug screen for drugs of abuse at Screening and at the day of surgery. At the discretion of the Principal Investigator, a positive drug screen result may be permitted if the patient has been on a stable dose of an allowed medication for >30 days;
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.

8.2. Exclusion Criteria

Individuals are not eligible for participation in the study if any of the following are noted:

1. Patients with a history of any significant medical condition that, in the opinion of the Principal Investigator 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 with a history of any type of malignancy within the past 5 years other than minor skin related cancers;
3. Patients with a history of alcohol or substance abuse in the past three years according to DSM V and who do not satisfy inclusion criteria 10 (including a positive urine drug screen test);
4. Patients with a known allergy or hypersensitivity to any local anesthetic drug, acetaminophen, ibuprofen, or other NSAIDs;
5. Patients who are taking any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative hypnotics or any analgesics taken within three days or five times of their elimination half-lives, whichever is longer. Selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) are permitted if the patient has been on a stable dose for at least 30 days prior to screening;

6. Patients who have smoked or chewed tobacco-containing substances within 48 hours prior to the initiation of surgery;
7. Patients judged by the Principal Investigator to be unable or unwilling to comply with the requirements of the protocol;
8. Patients who have used an investigational drug within 30 days prior to the screening day or have participated in any previous Nevakar trial;
9. Patients who have donated whole blood within 3 months prior to the screening day;
10. Patients who are employees or relatives of employees of JBR Clinical Research or Nevakar, Inc.
11. Patients with liver function tests (ALT, AST) that are above the normal reference range.

9. CLINICAL SUPPLIES

9.1. Study Medications and Dosages

The study medications for administration to patients will be supplied as follows:

Table 1: Study Medications

Study Medication	Supplied By:	Supplied as:
Acetaminophen [redacted]	[redacted]	[redacted]

9.2. Packaging, Labeling and Medication Administration

The study medications for randomized patients will be administered from identical [redacted] solution bags prepared by unblinded CRU staff members. The acetaminophen [redacted] study medication will be prepared as undiluted medication in the original formulation in [redacted] total volume. The acetaminophen [redacted] study medication will be diluted with 30 ml of [redacted] to achieve [redacted] total volume. The placebo [redacted] will be [redacted] of [redacted] Each [redacted] will be identical in appearance to maintain blinded conditions. The randomization schedule will determine which treatment a patient receives.

A randomized listing generated by the Biostatistics Group will be sent to the appropriate party responsible for administering the study medications to the patients.

In addition, a master code will be kept by the by the unblinded CRO team or designee and at the study site. Individually sealed envelopes identifying the study medications each patient received in the study will also be provided in the event of a medical emergency. The study medications for an individual patient may be unblinded in the event of an emergency and only if medically necessary without breaking the code for any other patient. Procedures to be followed for unblinding, notification responsibilities, and regulatory requirements are detailed in Section 11.4.5.

The patients will be administered the [redacted] study medications, either acetaminophen or [redacted] at the designated dosing time points and continue as 15-minute [redacted] via a [redacted]

9.3. Assignment of Study Medication

Treatment assignments will be determined by a computer-generated randomization schedule created by the Biostatistics Group.

The randomization schedule will randomly assign one of the three treatments to the patients. The randomization numbers will be assigned to each patient in a sequential order as they

qualify. The randomization number assigned to the patient will be recorded in the Case Report Form (eCRF).

9.4. Administration of Study Medication and Duration of Evaluation

Dose 1 will be given post-surgically when patients report at least moderate pain on the 4-point categorical pain intensity scale of none (0), mild (1), moderate (2) or severe (3) and also a score of ≥5 on 0-10 PI-NRS. Patient who do not have at least moderate pain on the categorical pain intensity 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 study medications, but can receive rescue medication upon request. Every two hours (± 10 minutes) following Dose 1 through hour 18, patients will receive either active study drug or placebo [redacted] according to the randomization schedule. At each dosing timepoint, patients not scheduled to receive active study drug will receive placebo. Each [redacted] will be [redacted] via a [redacted] over a 15-minute duration. Subsequent to Dose 1, patients can request rescue analgesic if and when their pain returns to baseline levels.

Whenever possible, the blood draws will be taken from a separate indwelling catheter [redacted] of study medication. In the event of failure of the PK [redacted] catheter and inability to achieve additional [redacted] access, [redacted], provided at least three minutes have passed since the completion of study drug dosing and at least 10 ml of blood is aspirated from the catheter and discarded immediately prior to the blood draw. Every effort should be made to ensure that patients have two functioning IVs whenever possible.

Patients 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 will last approximately 24 hours after Dose 1 and patients will be monitored for safety for approximately 24 hours after Dose 1. A team of blinded coordinators and/or investigators will conduct all the evaluations.

9.5. Study Medication Accountability

9.5.1. Storage

The unblinded CRU representative will ensure that study medications are stored in a secured area with controlled access under required storage conditions. Study medication should be stored in the container in which it was supplied to the unblinded CRU team and in accordance with labels. An unblinded monitor will inspect the study medication storage area and perform drug accountability and record keeping. The blinded Principal Investigator will provide oversight for all aspects of the study, including management of study medication as outlined in a separate study blinding plan.

9.5.2. Study Medication Inventory

Upon receipt at the study site, the study medication supplies will be stored in the CRU study medication storage room. At the study initiation, an appropriate unblinded designee, and the unblinded monitor will conduct an inventory and complete the study medication inventory record. The medication inventory record will be sent to the Trial Master File (TMF), and the Principal Investigator at the end of the study, after the study has been unblinded. Any interim shipments will be inventoried by the unblinded designee. For all interim shipments, a study medication inventory record will be completed. The medication inventory record will be returned to TMF by the unblinded monitor and the Principal Investigatorat the end of the study, after the study has been unblinded.

The appropriate unblinded designee, upon dispensing the study medication, must record the information on a study medication dispensing/return log. For accounting purposes and assessing patient compliance, an unblinded monitor will review the study medication dispensing/return log, inventory the study medications, and inspect the storage facility at appropriate time intervals throughout the clinical investigation, depending on the length of the study. The unblinded CRU team must account for any discrepancy and/or deficiency. Study medications will be assigned as described in Section 9.3. The blinded Principal Investigator will provide oversight for all aspects of the study, including management of study medication as outlined in a separate study blinding plan.

9.5.3. Return of Study Supplies

At the conclusion of the study, an appropriate designee, and a representative of the Sponsor (monitor) will inventory all used and unused study medications. The study medication inventory record for returned study medications will then be completed. Both the TMF and the Investigator will retain a copy for his files.

After being inventoried, all unused study medications will either be disposed of by the unblinded CRU or returned to Nevakar, Inc. (as per 21 CFR 312.58), and a Study Medication Inventory Record/certificate of destruction will be sent to the Medical Monitor.

10. STUDY PROCEDURES

10.1. Study Conditions

1. Only patients who satisfy all inclusion and exclusion criteria and provide written informed consent may participate in the trial.
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.

3. After surgery, patients will remain at the study site for up to 31 hours post-surgical monitoring. The evaluation time for efficacy and safety will be 24 hours following Dose 1. (the patient's stay may be longer if there is safety reason to lengthen observation time, or if patient is not stable enough to transport themselves after discharge.)
4. The surgery and post-surgical procedures will be performed at the CRU. Patients will be housed in a private room in the research facility.

10.2. Schedule of Assessments

10.2.1. Screening Assessments

During the screening period, the Principal Investigator or his designee will examine each patient and complete a checklist of the inclusion and exclusion criteria (see Section 8.1 and Section 8.2, respectively) in order to determine the patient's eligibility. The Principal Investigator or designee will enter the pertinent historical information (including any medication taken recently) and clinical findings (including vital signs) in the appropriate section(s) of the source documents.

A Patient Screening Log (provided by the research site) will be maintained in the site central file to document all patients screened for entry into the study. Patients will be screened only once unless otherwise approved by the sponsor. All patients who meet the entrance criteria will be provided with a written informed consent document before participating in the study. Patients are required to read, comprehend, and sign the informed consent. The screening procedure will include:

1. Informed Consent/Assent Form (no procedures can be performed prior to signing);
2. Demography: Age, Height, Weight, and BMI;
3. Inclusion/Exclusion assessment;
4. Medical history;
5. Physical examination;
6. Vital signs (BP, temperature, heart rate, and respiratory rate in supine or reclining position);
7. Urine drug screen (Appendix 2);
8. Serum pregnancy test for females;
9. Hematology
10. Serum liver function tests to include alanine aminotransferase; albumin, serum; alkaline phosphatase, serum; aspartate aminotransferase; bilirubin, direct; bilirubin, total; protein, total;

11. A serum sample will be collected to test for HIV antibody, hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (anti-HCV);
12. Concomitant therapy;
13. Safety monitoring (AEs);
14. Appropriate screening information for eligible patients who are assigned a patient number and receive study medication will be transcribed onto the corresponding sections of the CRF. The surgical procedure must occur within 30 days of the screening visit.

The following will be noted and recorded on the CRF:

- Date of informed consent
- Vital signs obtained
- Date and time the surgery was initiated and completed

10.2.2. Pre-Operative Assessments and Study Drug Administration

- Patients are NPO after midnight the day before surgery.
- Patients will report to the Clinical Research Unit (CRU) the morning of scheduled surgery.
- Patient's continued eligibility to participate in the study is confirmed; any additional medical history since screening will be recorded.
- Vital signs.
- Urine pregnancy test.
- Urine drug test.
- Placement of 2 [redacted] catheters.
- Pre-dose PK sample.
- Dental surgery.
- The assessments and drug administration will be completed in the patient's CRU room.
- The study coordinator will communicate to the unblinded dispenser that requirements for dosing have been met.
- The unblinded dispenser will then assign the next available randomization number.
- The unblinded dispenser will prepare study medication for each patient in a designated dispensing room.

- A second unblinded individual, with no other study involvement, will witness the preparation and dispensing process and confirm the correct study medication assignment.

  (No other study personnel will be present in the designated dispensing room at the time of study drug dispensing).

- A double-blind label with the same randomization number as that assigned to the patient will be affixed respectively to the [redacted] study medication container and the tear-off portion of the label will be attached to the patient's source documents.
- Unblinded dispenser will complete the study drug dispensing record. The study drug dispensing record will remain in a secure and locked area, with access limited to the unblinded third- party dispenser, back-up staff member, and the aforementioned unblinded second dispensing-room witness.
- Unblinded dispenser will dispense study drug to blinded study coordinator for administration to the patient.
- Study coordinator will administer study drug to the patient.
- Recording of concomitant therapy (e.g., anesthesia, etc.).
- Safety monitoring (AE/SAEs).

10.2.3. Post-Operative Assessments

The time points of the post-baseline efficacy assessments are detailed in Section 8 of this protocol. These observations will take place at the initiation of Dose 1. Pain Intensity Numerical Pain Rating Scale (PI-NPRS) and Pain Relief (PR) will be collected 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, 7.25, 8.25, 9.25,10.25, 11.25 and 12.25 (± 5 minutes), then 14.25, 16.25, 18.25, 20.25, 22.25, and 24.25 (± 10 minutes).

Upon initiation of the [redacted] of Dose 1, two stopwatches will be started. The patients will first be given stopwatch #1 and asked to press the stopwatch if and when they first perceive any relief (FPR). At this time, patients will be given the 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 1, the time of rescue as well as PI-NPRS and PR will be collected at that time and collection of stopwatch data will cease.

- Prior to initiation of Dose 1, the Baseline Pain scores on the 4-point categorical pain intensity scale and PI-NPRS will be recorded on the CRF.

- Dose 1 is administered when patients report at least moderate pain on the 4-point categorical pain intensity scale and a score of ≥5 on 0-10 PI-NPRS post-operatively.
- The time at which the 15-minute [redacted] of study medication (or Placebo [redacted] is initiated, will be considered as "Time 0" (T0) for purposes of post-op pain assessments. The FPR and MPR stopwatches are started at this time.
- Any patients who do not report a pain score of at least moderate on the 4-point categorical pain intensity scale and a score of ≥5 on the 0-10 PI-NPRS by Hour 7 post-surgically will be considered to have Insufficient Pain (ISP) and will not be administered any study medications; they may, however, still receive rescue medication upon request.
- Patient Global Evaluation (PGE) at time of patient withdrawal (if applicable) or at 24.25 hours (± 10 min) post-Dose 1; whichever is first).
- Post-dose PK sampling and Liver function Testing.
- Vital Signs.
- Concomitant Therapy.
- Safety Monitoring (AE/SAEs).

10.3. Efficacy Assessments Post Study Medication Administration

10.3.1. Pain Intensity, Pain Relief, Stopwatch, & Global Evaluations

- Pain Intensity (PI-NPRS) Rating Scale at Baseline:
  Moderate or Severe and ≥5 on the 0-10 PI-NPRS
- Pain Intensity Rating at each observation time point: 0-10 PI-NPRS Appendix 3
- Pain Relief (PR) at each observation time point: 5-Point Categorical Pain Relief Assessment Appendix 3
- Stopwatch: First Perceptible Relief (FPR) and Meaningful Pain Relief (MPR) Appendix 3
- Global Evaluation at early termination or at 24.25 hours post-surgery, whichever is first: Appendix 3
  (0) Poor, (1) Fair, (2) Good, (3) Very Good, or (4) Excellent

Patients will evaluate the time to FPR by depressing a stopwatch at the moment they first begin to experience "perceptible" relief and the time to MPR by depressing a second stopwatch at the moment they first begin to experience "meaningful" relief. These times will be recorded by JBR staff up to 24 hours after dosing, or until the time of first rescue medication use, whichever is sooner.

10.4. Safety Assessments

Adverse events will be recorded by JBR staff when they are reported or observed. The AE collection period will begin from the time the patient signs consent and continue for 7 days (±2 day) after the patient's last administration of study medication. Only the Principal Investigator will determine the relationship to study medication for each AE prior to breaking the blind. The information will be recorded on the appropriate study center CRF and outpatient diary. In addition, vital signs (DBP, SBP, temperature, HR, and RR) will be assessed at screening, prior to surgery and at hours 4, 8, 12, 16, 20 and 24 following T0 (±10 min).

10.5. Blood Sampling, Urine Drug Screen, and Pregnancy Tests

For females, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed prior to surgery on the day of surgery. For all patients, a serum sample will be collected to test for HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody (anti-HCV). For both males and females, the urine drug screen will be performed both at Screening and the day of surgery. Serum liver function testing will be at Screening and at Hour 24 (±30 minutes). Hematology will be tested at screening.

An initial pharmacokinetic (PK) blood sample will be collected at least 5 minutes before Dose 1 of study medication. Time 0 (T0) is designated as the initiation of the [redacted] of Dose 1.

Post Dose 1: To be drawn at 0.25 hr.±3 min (end of [redacted] 0.5 hr. ±3 min, 0.75 hr. ± 3 min, 1 hr. ± 5 min, 2 hr. ± 5min , 4 hr.± 5 min, 6 hr.- 5 min (prior to the next planned [redacted] 6.25 hr. ± 3 min (end of the [redacted] 8hr. - 5 min (prior to the next scheduled [redacted] 8.25 hr. ± 3min (end of the [redacted] 12 hr. - 5 min (prior to the next scheduled [redacted] 12.25 hr. ± 3 min (end of the [redacted] 16 hr. - 5 min (prior to the next scheduled [redacted] 16.25 hr. ±3 min(end of the [redacted] 18 hr. - 5 min (prior to the next scheduled [redacted] 18.25 hr. ± 3min (end of the [redacted] and at 24.25 hr.± 15 min (after starting the very first [redacted] The total amount of blood drawn for PK sampling is approximately 108 mL (18 blood samples of approximately 6 mL).The bioanalytical laboratory will perform the PK analysis on collected blood samples and provide a report on the plasma levels of acetaminophen. Actual sample collection time will be used for calculating the pharmacokinetic parameters. The peak concentration will be the observed maximum plasma drug concentration; the time to peak concentration (tmax) 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 CRU will be provided by the PK Lab. For females, a serum pregnancy test will be performed at the screening visit. The urine drug screen will be performed both at screening and the day of surgery. A urine pregnancy test for females will be done on the day of surgery.

10.6. Concomitant Medication

No other medications expected to confound the evaluation of the study medication will be allowed during the study session. This includes, but is not limited to, the use of any systemic analgesics other than the prescribed rescue analgesic. All concomitant medications used during the study will be recorded in the CRF. It is permissible at any time after the surgical procedure for a single dose of 4-8 mg ondansetron (Zofran®) iv, by mouth or sublingual to be administered if a patient experiences nausea.

10.7. Rescue Analgesic

Rescue medication will consist of one ibuprofen 200 mg tablet taken orally with at least 4 ounces of water. Prior to each dose of rescue medication, 11-Point Pain Intensity (via 0-10 Numerical Rating Scale) and Pain Relief (via 5-Point Categorical Pain Relief Assessment) measurements will be performed. For statistical purposes, pain assessments performed after any dose of rescue will be censored and imputed. The method of imputation will be described in the SAP, which will be finalized prior to unblinding of clinical trial subjects. Any subject requiring additional rescue medication may again receive ibuprofen 200 mg and their data will be similarly censored and imputed. Pain scores and safety data will continue to be collected for the 24-hour observation period. Rescue medication will not exceed ibuprofen 200 mg q3h or 2400 mg in a 24-hour period.

10.8. Study Participant Discontinuation

A patient will be considered discontinued from the study at any time under the following circumstances:

1. Any patient who violates any condition of the entrance criteria after having been entered into the study;
2. Any patient who develops a confounding concomitant illness (as determined by the patient, research coordinator or Principal Investigator), serious adverse event, or a hypersensitivity to the study medication;
3. Any patient who becomes uncooperative, does not adhere to the requirements of the study protocol, or refuses to complete the study;
4. Any patient who requires any concomitant medication during the course of the study that could confound the study results.

If necessary, additional study medications will be provided to the study site for additional patients. A representative of the Sponsor or the Data Management Group will provide the additional number(s) to the study site.

All discontinued patients will record no further assessments after their time of discontinuation, and any recorded efficacy data will be included in the Evaluable Population. All patients taking study medications with follow-up safety data will be included in the safety analysis. Details of

the reason(s) why a patient has been discontinued from the study should be recorded in the appropriate section of the CRF.

11. SAFETY

11.1. Patient Examinations

To ensure the safety and well-being of each patient entered into the study, the patient must first be examined by the Principal Investigator or Sub-Investigator and medically cleared to participate as required by the protocol. Each patient will be observed for adverse events (AEs) and will be required to report any adverse events that develop during the course of the study and for 15 days post-drug treatment. If at any time during the study, the patient has a serious adverse event (SAE) or abnormality, the patient must be withdrawn from the study and appropriate care should be initiated.

11.2. Patient Safety Information

In accordance with the US regulatory requirements regarding informed consent (21 CFR Part 50, Protection of Human Patients), the patient will receive a copy of the informed consent form (ICF) when discharged from the clinic. The ICF will include the information needed to contact the Principal Investigator, along with a description of the study medications the patient may have received.

11.3. Availability of Investigator

Either the Principal Investigator or an appropriate designee will be available to the patient at all times during the study and names and phone numbers of the Principal Investigator and/or appropriate designee will be listed on the informed consent form.

11.4. Adverse Events

11.4.1. Definitions

Adverse Event

An adverse event (AE) will be defined as any untoward medical occurrence in a patient after the informed consent is signed. The adverse event does not necessarily have to have a causal relationship with the study medication. An AE can therefore be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, which is a change from baseline and is temporally associated with the use of the study medication, whether or not it is considered related to the study medication.

Severity

The following definitions will be used for grading severity of adverse events:

Mild - Either asymptomatic or patient is aware of the sign, symptom or event, but it is easily tolerated.

Moderate - Discomfort enough to cause interference with usual activity and may warrant intervention.

Severe - Incapacitating with inability to do usual activities.

Causal Assessment

The causal relationship between an AE and the study medication will be determined by the Principal Investigator on the basis of his clinical judgment and the following definitions:

- Associated: There is a reasonable possibility that the AE may have been caused by the study medication. This definition applies to those AEs that are considered definitely, probably, and possibly related to the use of the study medication.
  a. Definitely Related: An AE that:
     - follows a reasonable temporal sequence from administration of the study medication;
     - follows a known response pattern to the study medication;
     - and, when appropriate to the protocol, is confirmed by improvement after stopping the study medication (positive de-challenge) and by reappearance of the reaction after repeat exposure (positive re-challenge);
     - and cannot be reasonably explained by known characteristics of the patient's clinical state or by other therapies;
  b. Probably Related: An AE that:
     - follows a reasonable temporal sequence from administration of the study medication;
     - follows a known response pattern to the study medication;
     - and, when appropriate to the protocol, is confirmed by improvement after de-challenge;
     - and cannot be reasonably explained by the known characteristics of the patient's clinical state or by other therapies;
  c. Possibly Related: An AE that: follows a reasonable temporal sequence from administration of the study medication and follows a known response pattern to the study medication but could have been produced by the patient's clinical state or by other therapies.

- Not Associated:
    d. Unlikely: An AE that does not follow a reasonable temporal relationship after administration of the study medication or could have been produced by the patient's clinical state or other therapies;
    e. Not related: An AE for which sufficient information exists to indicate that the etiology is unrelated to the study medication. Two or more of the following variables apply;
        – The AE does not follow a reasonable temporal sequence after administration of the study medication;
        – The AE is readily explained by the patient's clinical state or other therapies;
        – Negative de-challenge—the AE does not abate upon dose reduction or cessation of therapy (assuming that it is reasonable to expect abatement of the AE within the observed interval).

Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that occurs at any dose and:

- Results in death;
- Is life threatening;
- Requires inpatient hospitalization or prolongation of an existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is a medically important condition: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, the event(s) may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.4.2. Reporting Adverse Events

Any SAE, regardless of causal relationship, must be reported immediately to the CRO Medical Monitor no later than 24-hours after awareness of the SAE. Initial SAE reports may be made by telephone, and then followed by faxing a completed "Serious Adverse Event Form" and confirming by telephone that the fax was received. Compliance with this time requirement is essential to comply with regulatory obligations. The Principal Investigator also will promptly notify the appropriate Institutional Review Board about the serious adverse event.

Contact:

CRO Medical Monitor:

Name:	[redacted] MD
Address:	[redacted] CA 91105
Telephone:	[redacted]
E-Mail	[redacted]

Follow-up information related to a serious adverse event must be reported to the CRO Medical Monitor within 24 hours of receipt by the Principal Investigator by emailing a completed "Serious Adverse Event Form" to the CRO Medical Monitor and confirming by telephone that the emailed report was received. The patient will be observed and monitored carefully until the condition resolves or stabilizes and its cause is identified. The Principal Investigator also will promptly notify the appropriate Institutional Review Board about the serious adverse event.

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Investigator's brochure (IB) and that the investigator identifies as related to investigational product or procedure. For the purpose of this study, the IB is the United States Prescribing Information (USPI) of each product ([redacted] or Sodium Chloride). SUSARs will be reported to the US FDA in accordance with the requirements detailed in 21 CFR 312.32. The CRO will inform the IRB of the occurrence of any SUSAR.

11.4.3. Other Reportable Events

The following events will be recorded and reported in the same time frame and following the same process as for serious adverse events:

- Overdose or abuse of the study medication with or without adverse events (for this protocol, a total daily dose of acetaminophen exceeding [redacted] day, or ibuprofen exceeding 2400 mg/day);
- Inadvertent or accidental exposure to the study medication with or without an adverse event.

11.4.4. Adverse Event Recording and Reporting

All AEs, whether serious or not, will be recorded on source documents and eCRFs. The recording period for AEs and SAEs starts at the time the patient is screened. The recording period for both AEs and SAEs lasts through 15 days after the patient's last administration of study medication, regardless of the relationship to the study medication. The Principal Investigator must follow up as medically necessary on all AEs, SAEs, and other reportable events until the event has subsided or values have returned to baseline, or in the case of permanent impairment, until the condition stabilizes.

For SAEs, the Principal Investigator will provide all documentation pertaining to the event (*e.g.* additional laboratory tests, consultation reports, discharge summaries, postmortem reports, etc.) to the CRO Medical Monitor in a timely manner. Reports relative to the patient's course must be submitted to the CRO Medical Monitor until the event has subsided or, in the case or permanent impairment, until the condition stabilizes.

Information about all adverse events, serious and non-serious, including the event's severity, start and stop times/dates, chronicity, relatedness to study medication, and any actions taken, must be recorded on the appropriate CRFs. The information recorded will be based on the signs and symptoms detected during the physical examination and clinical evaluation of the patient as well as information recorded in the patient's diary, when applicable.

11.4.5. Breaking the Blind

A set of tamper-proof sealed individual envelopes containing the medication code inside the envelope, will be sent to the investigative site. In the event of a medical emergency that necessitates breaking the code, the sealed envelope containing the medication code may be opened. The seal will only be broken by the Principal or Sub Investigator in the event of an emergency for which knowledge of the patient's double-blind investigational product will have a direct impact on treatment decisions. Every effort will be made to discuss the decision to break the blind with the CRO Medical Monitor in advance.

When the blind is broken, the Principal Investigator will notify the CRO Medical Monitor immediately in order to document the reason and date of the unblinding. The event will also be recorded on the CRF and in the source document. The Principal Investigator will submit a written explanation to the CRO Medical Monitor describing the event within 5 business days.

11.4.6. Discontinuation of Study due to an SAE

The study will be discontinued for safety reasons if a serious adverse event occurs in more than one patient unless it is demonstrated that the serious adverse event is not related (as defined in Section 11.4.1 of this protocol) to study medication, in which case the study will not be required to stop.

The IRB will be notified within 24 hours of any event that results in an SAE or in discontinuation of the study.

12. STATISTICAL METHODS AND DATA HANDLING

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 $p \leq 0.10$ (one-sided), and no adjustments for multiple comparisons/end points will be performed. All confidence intervals will be one-sided 90% confidence intervals.

The between-treatment comparisons that will be performed are:

- [redacted] APAP [redacted] q8h versus Placebo
- [redacted] APAP [redacted] q6h versus Placebo

Descriptive statistics for numerical variables will include n (number of patients involved), mean, standard deviation, median, minimum, and maximum values. Categorical variables will be described by number and percent.

A detailed methodology for the statistical analyses of the data collected in this study will be documented in a SAP, which will be signed off prior to the database lock. The SAP may modify the plans outlined in the protocol and in the cases of discrepancy between the documents, the SAP methodology will be considered as correct; however, any major modifications to the primary endpoint definition will also be reflected in a protocol amendment. The SAP will be detailed in an addendum to the protocol. The SAP will be finalized and included in the addendum prior to unblinding of the study.

12.1. Sample Size Determination

The sample size was determined from past experience with the Dental Impaction Pain Model (DIPM) and analysis of the results from a previous Phase 2 study comparing the safety and efficacy of [redacted] APAP in combination with oral pregabalin (Protocol CP-NVK-009-0001). SPID 24 data for [redacted] APAP in that study suggested that a sample size of 44 patients per active group and 22 patients in the placebo group should be adequate to evaluate similarities between the two active dose regimens vs placebo.

12.2. Analysis Populations

There will be two analysis populations:

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

Evaluable Population: will include all randomized patients who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and; (2) were administered Dose 1. The efficacy analyses will be performed using this population.

12.3. Demographic Data and Baseline Comparability

Quantitative demographic data will be described by summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum). The number and percentage of patients will be presented for categorical variables. No formal statistical comparison between the treatment groups will be performed. Demographic data summary will include age, sex, and race. These data will be presented by treatment group and overall for the Safety Population only, unless the sample sizes for Evaluable Populations are very different from that of Safety Population (differ by more than 5 patients). In this case, demographic data will be presented for that population also. Baseline efficacy assessments will also be presented by treatment group.

12.4. Data Adjustments and Data Censoring

12.4.1. Time Windows

SPID and TOTPAR analyses will be calculated using actual times.

Unless otherwise described in the SAP no windowing will be performed for efficacy or safety endpoint summaries and data will be presented by nominal protocol timepoint.

12.4.2. Data Censoring and Imputation

For statistical purposes, pain assessments performed after any dose of rescue will be censored and imputed. The method of imputation will be described in the SAP, which will be finalized prior to unblinding of clinical trial subjects. Details of the imputation methods for missing efficacy data will be described in the SAP. Missing safety data will not be imputed.

If a subject does not qualify for treatment failure, but prematurely discontinues from the study before 24 hours, then the subject will be censored at the time of discontinuation. If a subject never qualifies as a treatment failure and completes the treatment phase of the study, then the subject will be considered censored at 24 hours.

For the other time to event analyses (FPR-C, MPR) if a subject does not record perceptible/meaningful pain relief and prematurely discontinues from the study prior to 24 hours, then the subject will be censored at 24 hours. If a subject does not record perceptible/meaningful pain relief prior to taking rescue medication, the subject will again be censored at 24 hours.

12.5. Statistical Methods for Efficacy Evaluations

The efficacy analyses will be based on the Evaluable Population.

The efficacy assessments are:

- Numerical Pain Rating Scale Pain Intensity: (PI-NPRS)

  (0 = no pain and 10 = worst imaginable pain)
- Pain Relief (5-Point Categorical Pain Relief Assessment)
- Stopwatches: First Perceptible Relief and Meaningful Relief

  (FPR= First Perceptible Relief-, MPR = Meaningful Pain Relief and FPR-C = FPR that is confirmed by MPR)
- Patient Global Evaluation (PGE):

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

Efficacy Parameters:

- Time Weighted Sum of Pain Intensity Difference from 0 to 24 hours (SPID24)
- Time Weighted Sum of Pain Relief from 0 to 24 hours (TOTPAR24)
- Time to Perceptible Pain Relief Confirmed (FPR-C);
- Time to Meaningful Pain Relief (MPR);
- Cumulative proportion of patients with pain half gone over time;
- Patient Global Evaluation of the study medication will be collected at Hour 24.25 or at the time of patient withdrawal (if applicable), whichever occurs first;
- Pain Intensity Difference Rating (PID): scored on the 0-10 PI-NRS at each observation time after Dose 1 administration;
- Pain Intensity Rating (PI): scored on the 0-10 PI-NRS at each observation time after Dose 1 administration;
- Pain Relief Rating (PR): scored on a 5-Point Categorical Pain Relief Assessmentat each observation time after Dose 1 administration;
- Time to treatment failure (i.e. time to first dose of rescue medication after Dose 1 or withdraw from the study due to lack of efficacy prior to rescue);
- Cumulative % of patients with onset of First Perceptible Relief Confirmed;
- Cumulative % of patients with Meaningful Pain Relief after Dose 1;
- The cumulative proportion of treatment failures over time after Dose 1 administration (failure defined as requiring rescue analgesic medication or withdraw from the study due to lack of efficacy);

Sum of Pain Intensity Difference (SPID) and Total Pain Relief (TOTPAR) from 0 to 24 hours will be analyzed using an analysis of variance (ANOVA) model with treatment group as a fixed effect and baseline pain intensity as a covariate. Other covariates may be explored and the final model will be described in the Statistical Analysis Plan (SAP). Actual times will be used for calculating SPIDs and TOTPARs. In addition, sensitivity analyses, that will be described in the statistical analysis plan (SAP), will be performed.

Time to Perceptible Pain Confirmed (FPR-C, confirmed by achieving Meaningful Pain Relief), Time to Meaningful Pain Relief (MPR), and Time to Treatment Failure will each be analyzed using a log-rank test; the log rank test may be stratified by baseline pain intensity score (moderate / severe) or other variables as appropriate. In addition, Kaplan-Meier curves will be presented by treatment group.

The cumulative percentage of patients with pain at half gone over the 24-hour evaluation period will be summarized descriptively and plotted over time by treatment group.

The Patient Global Evaluation at 24 Hours or at patient withdrawal (if applicable), whichever is first, will be analyzed using an ANOVA model similar to that for the primary endpoint.

Pain Intensity (PI), Pain Intensity Difference (PID), and Pain Relief (PR) Ratings at each observation time following Dose 1 administration will be summarized descriptively and plotted over time by treatment group.

The cumulative percentages of patients with onset of FPR-C after Dose 1, MPR after Dose 1, and treatment failure after Dose 1 will each be summarized descriptively and plotted over time by treatment group.

12.6. Multiple End Points and Multiple Comparisons

There will be no corrections for multiple endpoints or comparisons.

12.7. Safety Analysis

The safety analyses will be based on the Safety Population.

Adverse event (AE) analyses will include all AEs which initially occurred, or worsened following treatment (i.e., treatment emergentadverse events). TEAEs will be summarized by the MedDRA preferred term and by system organ class and classified according to their severity (mild, moderate, or severe) and relationship ("Associated" or "Not Associated") to study medication. For the summary by severity, patients who have multiple occurrences of the same AE they will be classified according to the worst reported severity of the AE. Similarly, for the summary by relationship to the study medication, the patient will be classified according to the most related event.

Tables of descriptive statistics and listings will be presented for the actual values and the changes from Baseline for Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Respiratory Rate (RR), Temperature, and Heart Rate (HR) at Baseline and at 4-hour intervals post surgically. Liver function tests will be compared from baseline to post treatment. Analysis of the incidence and severity of all adverse events will also be performed.

13. STUDY ADMINISTRATION

13.1. Investigator Study Binder

An Investigator Study Binder must be maintained at the study site. Included in this binder will be tabbed sections for maintaining the following: study identification and study site staff signature list, monitoring visit record, protocol and amendments/administrative changes, curricula vitae, Institutional Review Board documentation, informed consent form, product receipt and accountability forms, correspondence, patient screening record, and master patient

log. This binder must be kept current and be available for review by representatives of the Sponsor and any official regulatory body.

13.2. Patient Identification

For purposes of confidentiality and to maintain anonymity, patients will be assigned identification numbers. Patients will be numbered sequentially as they enter the study. Once patients meet the entry criteria, they will be assigned a randomization number corresponding to study medication. Patients should be identified to the Sponsor only by their assigned number, initials and date of birth. The Principal Investigator or his designee will maintain a complete list of all patients enrolled in the study with their current mailing address on the master patient log. This list is necessary should contact of patients be required in the future.

13.3. Case Report Forms

Source Documents provided by CRU will be used to document all patient data and will be typed or printed legibly in black or blue ink. Data will be collected from the study site as eCRFs. Prior to submission to Nevakar, the Principal Investigator will review all eCRFs and sign where necessary. It is important that the eCRFs be completed in a timely manner for each patient evaluation in order that the progress and results of the study may be closely followed by the Sponsor. Corrections to eCRFs must not obscure the original entry; a single line through the original entry is sufficient. All corrections must be initialed and dated by the responsible individual.

eCRFs are to be completed and held for retrieval by a representative of the Sponsor (monitor), unless otherwise directed. All study records must be retained in accordance with Section 13.10. A study site may use forms of their own design, following approval of the form by Nevakar, as source documents only.

13.4. Monitoring of Study

The study will be monitored by representatives of the Sponsor. On-site visits will be made before the study begins, at regular intervals during the conduct of the study, and at the completion of the study. Communication by telephone, mail, and facsimile may also be used to supplement on-site visits.

The Monitor of the Sponsor will inspect all source documents and eCRFs and corresponding portions of the patient's original office and/or hospital records. These inspections are for the purpose of verifying adherence to the protocol and determining the completeness and exactness of the data entered on the eCRF and study medication log.

As a part of monitoring and inspection of this study, the Principal Investigator agrees that Nevakar, its employees or representatives, Institutional Review Board, as well as representatives of the FDA will have the right to inspect and review pertinent medical records relating to this trial. In addition,

informed consent documents signed by study participants will indicate approval to release their medical records for review while maintaining their confidentiality.

13.5. Protocol Modifications and Deviations

As the study progresses, any necessary additions or changes to the protocol will be decided by mutual agreement of the Principal Investigator and the CRO Medical Monitor. An amendment to this effect will be submitted first to Nevakar for review and approval and then to the Institutional Review Board for review and approval prior to implementation. If the protocol change impacts the conduct of the study, the informed consent form will be amended, as appropriate. A protocol change to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the reviewing Institutional Review Board is notified in accordance with 21 CFR 56.104(c). Otherwise, no deviations will be permitted. Approved amendments will become part of the protocol and will be reported to the appropriate regulatory authority prior to implementation.

All protocol deviations will be documented in the eCRFs and reported to the CRO Medical Monitor and Sponsor.

13.6. Discontinuation of Study by Sponsor or Principal Investigator

Nevakar reserves the right to discontinue the study for administrative reasons at any time. All CRFs will then be returned to the Sponsor and study medications properly disposed of.

If the Principal Investigator discontinues the study prematurely, the Principal Investigator will return all study treatment and eCRFs to the Sponsor and provide a written explanation as to why the study was ended.

13.7. Disclosure of Data/Publications

All information obtained during the conduct of the study will be regarded as confidential. Written agreement from Nevakar must be obtained prior to disclosing any information relative to the study.

Upon completion of the study, Nevakar may decide to publish the results with the Principal Investigator in a recognized scientific journal and/or present the results (as a poster or oral presentation) at a meeting of a recognized scientific association. In order to safeguard against disclosure of confidential information, however, Nevakar requires that it has the right to review any manuscript and/or abstract prior to submission. A draft manuscript must be reviewed by Nevakar 60 days prior to submission of the final version to the journal. Abstracts of presentations must be reviewed by Nevakar 15 days prior to submission. Nevakar assures the Principal Investigator that all manuscripts and abstracts will be reviewed promptly.

13.8. Informed Consent

Regulations require that written informed consent and/or assent must be obtained for each patient prior to entry into the study. Informed consent means the knowing consent of an

individual, so situated so as to exercise free power of choice without undue inducement or constraint or coercion. The informed consent form will include all elements required by the FDA. A copy of the consent form will be provided to the patient. For 17-year-old patient, both the patient and either a parent or legal guardian also must provide written assent.

The Investigator will provide Nevakar with a copy of the consent form as approved by the Institutional Review Board used by the study site.

The Principal Investigator will ensure that this study is in full conformance with the principles of the Declaration of Helsinki as well as GCP and ICH guidelines.

13.9. Institutional Review Board

Prior to initiating the study, the protocol and amendments, informed consent form, any advertisement, Principal Investigator's and sub-investigators' curriculum vitae, medical license, financial disclosure forms, questionnaires and investigational product brochure must be reviewed and approved by a properly constituted Institutional Review Board as required by the FDA and the International Conference on Harmonization Guidelines.

The Principal Investigator must certify to Nevakar that the Institutional Review Board meets all the legal requirements as specified by the FDA. The Institutional Review Board must provide a signed and dated statement that the protocol, informed consent form, and other pertinent documents, such as recruitment advertisements (in any medium) have been approved by the Committee. If the study continues longer than one year, re-approval must be obtained from the Institutional Review Board on an annual basis. The Institutional Review Board must be informed of any changes in research activity including amendments to the protocol and/or informed consent form, advertisements, and serious adverse events.

At the conclusion of the study, the Principal Investigator must submit a summary of the study to the Institutional Review Board with a copy forwarded to Nevakar no later than 60 days after the study closeout visit.

13.10. Retention of Records

The Principal Investigator /JBR Clinical Research shall retain the Study Records for the longer of:

1. two (2) years after the FDA approves the New Drug Application (NDA) or Premarket Approval Application (PMA) for the Investigational Product; or
2. two (2) years following the termination or withdrawal of the Investigational New Drug (IND) application or Investigational Device Exemption (IDE) application under which the Study was conducted; or
3. the period required by federal laws and regulations.

The Sponsor shall reimburse the Principal Investigator /JBR Clinical Research for any expense the Principal Investigator /JBR Clinical Research incurs in retaining the Study Records beyond the first five (5) years after the end of the Study at JBR Clinical Research. After the required retention period, the Principal Investigator /JBR Clinical Research shall provide the Sponsor sixty (60) days' written notice before destroying any Study Records.

If at any time the Principal Investigator /JBR Clinical Research is no longer able to maintain the required study records, or if the Principal Investigator relocates or delegates custody of the records to another party, Nevakar must be notified in writing as soon as possible. In any case, Nevakar retains the right to reclaim all study records. If Nevakar reclaims the study records, the master patient log, which contains confidential information identifying and how to contact the study patients, will be provided to Nevakar in a sealed envelope labeled "confidential".

The Principal Investigator assumes the responsibility of retaining the following records:

a. Signed and dated protocol and amendments, written authorization to allow enrollment of potentially ineligible patients or otherwise amend the protocol;

b. Curriculum vitae of the Principal Investigator and sub-investigators;

c. Investigational Product Brochure or full prescribing information, instructions to Principal Investigator, or other information provided by Nevakar for conducting the clinical study;

d. Records of receipt and disposition of all product supplies, including:

   – Dates and amounts of product received from Nevakar

   – Lot numbers or other identification

   – Dates and quantity dispensed and returned for each patient

   – Dates and amounts of product returned to Nevakar

   (For this study, the study medications will be supplied by the study site using a local retail pharmacy.)

e. Institutional Review Board approval, correspondence, interim reports, and final study summary;

f. Documented informed consent for each patient;

g. Completed eCRFs and diaries (if applicable) for each patient including all source documents from which the eCRFs were prepared;

h. Patient screening record indicating disposition of each patient and reason for exclusion when appropriate;

i. Master patient log indicating all patients enrolled in the study with their current mailing address;

j. Detailed medical histories for each patient containing medical history prior to enrollment with basic identifying information linking records to eCRFs, results of all diagnoses made, therapy provided, any other data on patient's physical state;

k. Medical history during the study including documentation of enrollment, concomitant or concurrently administered therapy, observations on patient's condition during the study, any factors that might alter the effects of the test product, adverse event or laboratory abnormality reports and follow-up where appropriate;

l. Copies of tests and/or examinations results required by the protocol, including laboratory normal values and accreditation, if applicable;

m. Copies of interim and final reports issued to the Institutional Review Board or Nevakar;

n. Documentation of contacts between Nevakar and the Principal Investigator and/or other study site personnel, including all correspondence;

o. Copies of any reports on serious adverse events, death, or life-threatening symptoms;

p. Roster of all study personnel with their signatures and signed initials;

q. Monitoring visit record.

13.11. Responsibilities of Principal Investigator

In agreeing to conduct this study, the Principal Investigator assumes certain responsibilities mandated by FDA regulations: an Investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan as defined by the protocol, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator's care; and for the control of the products under investigation. An Investigator will, in accordance with the appropriate regulations, obtain the informed consent of each human patient to whom the study medication is administered. The Investigator will retain all study documents as stipulated in Section 13.10. The Investigator certifies that he/she has not been disbarred by any regulatory agency from conducting clinical trials. The Investigator will comply with the requirements outlined in the CFR final ruling, Financial Disclosure by Clinical Investigators, effective February 2, 1999.

13.12. Filing of Protocol with FDA

This protocol, any amendments made to it, and data from this study will be submitted to the U.S. FDA.

14. TEXT REFERENCES

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APPENDIX 1. IMPACTION DIFFICULTY RATING SCALE

The Impaction Difficulty Rating Score (IDRS) will be used to assess the projected surgical trauma for each impacted mandibular third molar. The oral surgeon will base the difficulty assessment on the radiographic appearance and the intraoral examination. Each mandibular molar will be rated from 1 to 5 using the following criteria:

1= Erupted in tissue

2= Soft tissue impaction

3= Mild partial bony impaction
(>30% erupted through the alveolar bone),

4= Moderate to severe partial bony
(at least 70% impacted in the alveolar bone)

5= Full bony impaction
(no penetration of the bone into the soft tissue).

Only patients whose mandibular impactions are scored a “4” or “5” will be eligible to participate in the study. In addition, if during the surgical procedure extreme trauma or surgical complications arise, then that patient will not be continued in the study.

APPENDIX 2. URINE DRUG SCREEN

APPENDIX 3. PAIN SCALES

CATEGORICAL PAIN INTENSITY

☐	☐	☐	☐
None (0)	**Mild (1)**	**Moderate (2)**	**Severe (3)**

ASSESSMENT OF PAIN INTENSITY- 11-POINT NUMERICAL PAIN RATING SCALE (NPRS)

On a scale of 0-10, please rate your pain by marking an 'X" in the appropriate box that best describes your pain NOW.

☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10
No Pain										***worst pain imaginable***

5-POINT CATEGORICAL PAIN RELIEF ASSESSMENT (PR)

Finish the statement by checking the appropriate box. "My pain relief at this time is:"

- ☐ **No Pain Relief**
- ☐ **A Little Pain Relief**
- ☐ **Some Pain Relief**
- ☐ **A Lot of Pain Relief**
- ☐ **Complete Pain Relief**

TIME TO PAIN RELIEF

Time to perceptible pain relief and time to meaningful pain relief will be collected using the double-stopwatch methodology as follows: For each randomized subject, two stopwatches will be started immediately upon initiation of the first study dose [redacted] The first stopwatch will be given to each subject with the instructions to stop the watch when they first perceive pain relief to occur (time to perceptible relief). Once the first stopwatch is stopped, the second stopwatch will be given to the subject with the instruction to stop the watch when they are first experiencing meaningful pain relief (time to meaningful relief). Time to perceptible pain relief is confirmed only if the subject experiences meaningful relief.
If a subject requires a rescue analgesic after Dose 1, the time of rescue as well as PI and PR assessments will be collected at that time and collection of stopwatch data will cease.

5-POINT PATIENT GLOBAL ASSESSMENT (PGA) OF PAIN CONTROL

The following question will be answered by the subject at hour 24.25 or at the time of subject withdrawal (if applicable), whichever occurs first:

"Overall, please rate how well your pain has been controlled since you received study medication?"

☐ **Poor (0)**

☐ **Fair (1)**

☐ **Good (2)**

☐ **Very Good (3)**

☐ **Excellent (4)**

Statistical Analysis Plan

A Randomized, Double-Blind, Multi-Dose, Single-Site, Placebo- and Active-Controlled, Efficacy, Tolerability, Safety and Pharmacokinetic Study of Two Different Dosing Regimens of Acetaminophen [redacted] in Post-Surgical Dental Pain.

Version 1.0; Dated: 09-AUG-2019

Protocol number: CP-NVK009-0002

Sponsor: Nevakar, Inc. NJ 08807

STATISTICAL ANALYSIS PLAN
PHASE II

VERSION: 1.0

DATE OF PLAN:

09-AUG-2019

BASED ON:

Protocol Version 3.0 Amendment 3 15APR2019 and CRF v3.0 22-MAY-2019

STUDY DRUG:

[redacted] acetaminophen [redacted] OR [redacted] acetaminophen [redacted]

[redacted]

PROTOCOL NUMBER:

CP-NVK009-0002

STUDY TITLE:

A Randomized, Double-Blind, Multi-Dose, Single-Site, Placebo- and Active-Controlled, Efficacy, Tolerability, Safety and Pharmacokinetic Study of Two Different Dosing Regimens of Acetaminophen [redacted] in Post-Surgical Dental Pain.

SPONSOR:

Nevakar, Inc.

[redacted]

[redacted] NJ 08807

[redacted]

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

APPROVALS

Author: [redacted]

09-Aug-19

Date:

Reviewed: [redacted]

09-Aug-19

Date:

Approved: [redacted]

09-Aug-19

Date:

[redacted]
Nevakar, Inc.

TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company Nevakar, Inc.	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Finished Product: [redacted] acetaminophen [redacted] OR [redacted] acetaminophen [redacted] [redacted]	Page:	
Name of Active Ingredient: Acetaminophen		
Title of Study: A Randomized, Double-Blind, Multi-Dose, Single-Site, Placebo- and Active-Controlled, Efficacy, Tolerability, Safety and Pharmacokinetic Study of Two Different Dosing Regimens of Acetaminophen [redacted] in Post-Surgical Dental Pain.		
Investigators: Study Center(s): Single-Site (JBR Clinical Research)		
Studied period (years): Study is expected be completed within 4 months of the first patient entry.	**Phase of development:** II	
Objectives: The objective of this study is to assess the safety, tolerability, analgesic efficacy, and pharmacokinetics of acetaminophen [redacted] dosed [redacted] ([redacted] APAP) every eight hours (q8h) relative to placebo and of acetaminophen [redacted] dosed [redacted] every six hours (q6h) relative to placebo over a 24-hour period in participants experiencing moderate to severe pain following surgical third molar removal.		

Methodology:

This will be a randomized, double-blind, single-site, placebo-controlled, parallel-group study to assess similarities in safety, tolerability, efficacy, and pharmacokinetics of [redacted] of [redacted] acetaminophen given in three doses, each 8 hours apart, relative to placebo, and [redacted] of [redacted] acetaminophen given in four doses, each 6 hours apart, relative to placebo over a 24-hour period in patients experiencing moderate to severe postsurgical pain within 7 hours following surgical removal of 2 or more molars.

To maintain the double-blind conditions, patients will be receiving either a placebo ([redacted] that looks like study drug) or the active study medication every 2 hours (± 10 minutes) [redacted] over the first 18 hours after Dose 1.

Patients who meet the randomization criteria (post-surgical pain of moderate to severe on the 4-point Categorical Pain Intensity scale, and at least a score of 5 on the 11-point [0-10] pain intensity numerical pain rating scale [PI-NPRS] at baseline within 7 hours of last stitch from dental extractions) will be randomly assigned to one of three treatment groups.

Approximately 110 patients will be randomized to receive either [redacted] APAP [redacted] three doses, each in [redacted] of total volume, 8 hours apart **OR** [redacted] APAP [redacted] four doses, each in [redacted] of total volume, 6 hours apart **OR** placebo, [redacted] total volume of normal [redacted] in a 2:2:1 allocation ratio. No less than approximately 30% of randomized patients will be either male or female. In addition, no more than approximately 30% of patients will be 17 years of age at the time of screening.

Number of Subjects (planned and analyzed):

110 (44 subjects per active group and 22 subjects in the placebo group)

Diagnosis and main criteria for inclusion:

Male and female patients between 17-55 years of age will undergo surgical removal of at least two third molars. Maxillary third molars may be removed regardless of impaction level. The mandibular extractions must meet one of the following scenarios and must not result in a trauma rating of severe on the 4-point scale of mild, moderate, moderately severe, or severe:

- Two full bony impactions
- Two partial bony impactions
- One full bony impaction in combination with one partial bony impaction

Patients must have body weight of >50 kg, Body Mass Index (BMI) ≤35.0 kg/m^2, not have infections in the area of the impacted teeth, and must meet the randomization criteria (post-surgical pain of moderate to severe on the 4-point Categorical Pain Intensity scale, and at least a score of 5 on the 11-point [0-10] pain intensity numerical pain rating scale [PINPRS] at baseline within 7 hours of last stitch from dental extractions).

Test product, dose and mode of administration:

Acetaminophen [redacted] dosed [redacted] ([redacted] APAP) every eight hours (q8h) OR

Acetaminophen [redacted] dosed [redacted] ([redacted] APAP) every six hours (q6h)

Duration of treatment:

The study will consist of a screening period of up to 30 days (Day -30 to 0), day of surgery (Day 1), Day of discharge (Post-Op Day 2) and follow-up telephone call (Day 7 ±2 days). Duration of treatment is 24 hours.

Reference therapy, dose and mode of administration:

[redacted] Placebo

Criteria for evaluation (see protocol section 7.2):

Efficacy:

- Time Weighted Sum of Pain Intensity Difference from 0 to 24 hours (SPID24)
- Time Weighted Sum of Pain Relief from 0 to 24 hours (TOTPAR24)
- Time to Perceptible Pain Relief Confirmed (FPR-C)
- Time to Meaningful Pain Relief (MPR)
- Cumulative proportion of patients with pain half gone over time
- Patient Global Evaluation of the study medication will be collected at Hour 24.25, or at the time of patient withdrawal (if applicable), whichever occurs first
- Pain Intensity Difference Rating (PID): scored on the 0-10 PI-NRS at each observation time after Dose 1 administration
- Pain Intensity Rating (PI): scored on the 0-10 PI-NRS at each observation time after Dose 1 administration
- Pain Relief Rating (PR): scored on a 5-Point Categorical Pain Relief Assessment at each observation time after Dose 1 administration
- Time to treatment failure (i.e. time to first dose of rescue medication after Dose 1 or withdraw from the study due to lack of efficacy prior to rescue)
- Cumulative % of patients with onset of First Perceptible Relief Confirmed
- Cumulative % of patients with Meaningful Pain Relief after Dose 1
- The cumulative proportion of treatment failures over time after Dose 1 administration (failure defined as requiring rescue analgesic medication or withdraw from the study due to lack of efficacy).

Safety: Adverse events and vital signs.

Statistical methods: The null for this study is that [redacted] acetaminophen [redacted] dosed three times daily and [redacted] acetaminophen [redacted] dosed four times daily have similar safety, tolerability, and efficacy profiles when compared to placebo.

Since this is a proof-of-concept study, statistically significant treatment differences will be declared if $p \leq 0.10$ (one-sided), and no adjustments for multiple comparisons/end points will be performed. All confidence intervals will be one-sided 90% confidence intervals.

An analysis of covariance (ANCOVA) model with treatment group as a fixed effect and baseline PI-NPRS as a covariate will be used to compare the two active treatments to the placebo group with respect to Time-weighted Sum of Pain Intensity Difference from 0 to 24 hours (SPID24), Time-weighted Total Pain Relief from 0 to 24 hours (TOTPAR24), and Patient Global Evaluation at 24 Hours. The log rank test with Kaplan-Meier curves will be used to analyze and present time to event data by treatment group (FPR-C, MPR, and Time to Treatment Failure). Descriptive summaries and listings will be used for other efficacy and safety data. The two analysis populations that are specified in this study are:

a) Safety Population, which will include all randomized patients who received the study medication. This population will be used for all safety summaries.

b) Evaluable Population, which will include all randomized patients who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and; (2) were administered Dose 1. The efficacy analyses will be performed using this population.

c) PK Evaluable Population, which will include all randomized subject who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and; (2) were administered Dose 1 resulting in an adequate number of quantifiable concentrations to calculate pharmacokinetic parameters.

TABLE OF CONTENTS

LIST OF TABLES

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BMI	Body Mass Index
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
DOB	Date of Birth
DBP	Diastolic Blood Pressure
dy	Days
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FPR	First Perceptible Relief
FPRC	First Perceptible Relief Confirmed
GCP	Good Clinical Practices
HR	Heart Rate
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IRB	Institutional Review Board
[redacted]	[redacted]
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities Terminology
mg and mg/d	Milligrams and milligrams per day
MPR	Meaningful Pain Relief
mL	Milliliter
mo	Months

N	Total Sample Size
NPRS	Numerical Pain Relief Scale
NRS	Numerical Rating Scale
PBO	Placebo
PI	Pain Intensity
PID	Pain Intensity Difference
PK	Pharmacokinetics
PR	Pain Relief
RR	Respiratory Rate
S	Sex
s.d.	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SOC	System Organs Class
SPI	Time Weighted Sum Pain Intensity
SPID	Time Weighted Sum Pain Intensity Difference
SDTM	Study Data Tabulation Model
TEAE	Treatment Emergent Adverse Events
TG	Treatment Group
TLFs	Tables, Listings, and Figures
TOTPAR	Time Weighted Total Pain Relief
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WHO	World Health Organization
wLOCF	windowed Last pain score Carried Forward
yr	Years

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol CP-NVK009-0002. Revisions to the protocol are shown below.

Protocol Revision Chronology:		
Protocol	15-JAN-2019	Original
Amendment 1	06-MAR-2019	Amendment No. 1: The key purposes of this amendment are to: 1) Decrease the number of participants from 140 to 110 with a 2:2:1 randomization schedule 2) Clarification that patients who receive rescue medication will have data censored but pain data will still be collected 3) Change to SPID and TOPTPAR over a 24-hour period, clarification that Pain Relief will be a 5-Point Categorical Pain Relief Assessment 4) Provided further justification for sample size determination 5) Provided further detail on planned statistical methods and analysis
Amendment 2	25-MAR-2019	Amendment No. 2: The key purposes of this amendment are to: 1) Corrected the type of vacutainer PK samples collected in from K2EDTA to K3EDTA tube 2) Updated dosing time points to reflect a window of dosing of ± 10 minutes.
Amendment 3	15-APR-2019	Amendment No. 3: The key purposes of this amendment are to: 1) Added hematology safety labs to meet exclusion criteria 1 2) Administrative Clarification +/- specific added to all PK time points and removal of PK Time Point 0. Total PK samples from 19 to 18 3) Administrative clarification around vital sign time points to ensure these completed at screening, prior to surgery and every 4 hours post 1st Dose. 4) Clarified Whole Blood to Exclusion Criterion #9 5) Added +10 min window timepoint for PGE Assessment at 24.25

This SAP was developed in accordance with ICH E9 guideline. All decisions regarding final analysis, as defined in this SAP document, will be made prior to Database Freeze / unblinding of the study data. Further information can be found in the protocol.

The SAP is based on Protocol No. CP-NVK009-0002, Amendment 3, dated April 15, 2019 and ICH guidelines E4 and E9 (Statistical Principles for Clinical Trials)

The purpose of this document is to provide details on study populations and on how the variables will be derived, how missing data will be handled as well as details on statistical methods to be used to analyze the safety and efficacy data for Study Protocol No. CP-NVK009-0002.

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file before database is locked. Deviations from the final approved plan will be noted in the CSR.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

The objective of this study is to assess the safety, tolerability, analgesic efficacy, and pharmacokinetics of acetaminophen [redacted] dosed [redacted] ([redacted] APAP) every eight hours (q8h) relative to placebo and of acetaminophen [redacted] dosed [redacted] every six hours (q6h) relative to placebo over a 24-hour period in participants experiencing moderate to severe pain following surgical third molar removal.

3.2. Study Endpoints

3.2.1. Efficacy Endpoints

- Time Weighted Sum of Pain Intensity Difference from 0 to 24 hours (SPID24)
- Time Weighted Sum of Pain Relief from 0 to 24 hours (TOTPAR24)
- Time to Perceptible Pain Relief Confirmed (FPR-C)
- Time to Meaningful Pain Relief (MPR)
- Cumulative proportion of patients with pain half gone over time
- Patient Global Evaluation of the study medication will be collected at Hour 24.25, or at the time of patient withdrawal (if applicable), whichever occurs first
- Pain Intensity Difference Rating (PID): scored on the 0-10 PI-NRS at each observation time after Dose 1 administration
- Pain Intensity Rating (PI): scored on the 0-10 PI-NRS at each observation time after Dose 1 administration
- Pain Relief Rating (PR): scored on a 5-Point Categorical Pain Relief Assessment at each observation time after Dose 1 administration
- Time to treatment failure (i.e. time to first dose of rescue medication after Dose 1 or withdraw from the study due to lack of efficacy prior to rescue)
- Cumulative % of patients with onset of First Perceptible Relief Confirmed
- Cumulative % of patients with Meaningful Pain Relief after Dose 1
- The cumulative proportion of treatment failures over time after Dose 1 administration (failure defined as requiring rescue analgesic medication or withdraw from the study due to lack of efficacy).

4. STUDY DESIGN

4.1. Summary of Study Design

This will be a randomized, double-blind, single-site, placebo-controlled, parallel-group study to assess similarities in safety, tolerability, efficacy, and pharmacokinetics of [redacted] of [redacted] acetaminophen given in three doses, each 8 hours apart, relative to placebo, and [redacted] of [redacted] acetaminophen given in four doses, each 6 hours apart, relative to placebo over a 24-hour period in patients experiencing moderate to severe postsurgical pain within 7 hours following surgical removal of 2 or more molars.

To maintain the double-blind conditions, patients will be receiving either a placebo ([redacted] that looks like study drug) or the active study medication every 2 hours (± 10 minutes) (infused [redacted] over the first 18 hours after Dose 1.

Patients who meet the randomization criteria (post-surgical pain of moderate to severe on the 4-point Categorical Pain Intensity scale, and at least a score of 5 on the 11-point [0-10] pain intensity numerical pain rating scale [PI-NPRS] at baseline within 7 hours of last stitch from dental extractions) will be randomly assigned to one of three treatment groups.

Approximately 110 patients will be randomized to receive either [redacted] APAP [redacted] three doses, each in [redacted] of total volume, 8 hours apart **OR** [redacted] APAP [redacted] four doses, each in [redacted] of total volume, 6 hours apart **OR** placebo, [redacted] total volume of normal [redacted] in a 2:2:1 allocation ratio. No less than approximately 30% of randomized patients will be either male or female. In addition, no more than approximately 30% of patients will be 17 years of age at the time of screening.

4.2. Definition of Study Drugs

The Study Drugs consist of either

- [redacted] APAP [redacted] three doses, each in [redacted] of total volume, 8 hours apart **OR**
- [redacted] APAP [redacted] four doses, each in [redacted] of total volume, 6 hours apart **OR**
- Placebo, [redacted] total volume of normal [redacted]

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

The sample size was determined from past experience with the Dental Impaction Pain Model (DIPM) and analysis of the results from a previous Phase 2 study comparing the safety and efficacy of [redacted] APAP in combination with [redacted] pregabalin (Nevakar Protocol CP-NVK-009-0001). SPID 24 data for [redacted] APAP in that study suggested that a sample size of 44 patients per active group and 22 patients in the placebo group should be adequate to evaluate similarities between the two active dose regimens vs placebo.

4.3.2. Sample Size Re-estimation

Sample size re-estimation is not planned for the study.

4.4. Randomization

Treatment assignments will be determined by a computer-generated randomization schedule created by the Biostatistics Group.

The non-stratified randomization schedule with block size of 5 will randomly assign one of the three treatments to the patients. The randomization numbers will be assigned to each patient in a sequential order as they qualify. The randomization number assigned to the patient will be recorded in the Case Report Form (eCRF).

4.5. Clinical Assessments

4.5.1. Demographics and Baseline Characteristics

Demographic variables include age, sex, race, and ethnicity. Baseline characteristics include height (cm), weight (kg), and body mass index (BMI; kg/m^2). These are obtained at the screening visit. Prior to initiation of Dose 1, baseline pain scores on the 4-point categorical pain intensity scale and PI-NPRS are also assessed.

4.5.2. Medical/Surgical History

Medical and Surgical history, as collected at screening and prior to surgery, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 to determine system organ class (SOC) and preferred term (PT).

4.5.3. Physical Examination

A complete physical examination including all major body systems will be performed at the Screening visit. Abnormal or clinically significant physical exam findings will be recorded as AEs.

4.5.4. Vital Signs

Vital signs results including blood pressure (systolic and diastolic; mmHg), heart rate (beats per minute), respiration rate (breaths/min), and temperature in supine or reclining position are obtained at Screening, prior to surgery, and at Hours 4, 8, 12, 16, 20, and 24 following T0 (±10 min).

Baseline for vital signs measurements will be defined as the last evaluation before dosing with study medication.

4.5.5. Urine drug screen

Urine drug test is performed at Screening and Day 1 prior to surgery. Each test result will be defined to be “negative” or “positive”.

4.5.6. Patient Assessment Training

Pain assessment training video and post-video test are completed at screening. Video pain assessment training only is completed prior to surgery.

4.5.7. Qualifying 4-Point Categorical PI and 11-point PI-NPRS at Baseline

This assessment will be done after surgery. Dose 1 will be given only when subjects report at least moderate pain on the 4-point categorical pain intensity scale of none (0), mild (1), moderate (2) or severe (3), and also a score of ≥5 on 0-10 PI-NPRS. This will be the baseline assessment for the 4-Point Categorical PI and 11-point PI-NPRS.

4.5.8. 11-Point Pain Intensity (PI-NPRS)

Follow-up pain intensity (PI) measurements will be taken at the following times after initiation of Dose 1 (T0): 0.5, 0.75, 1, 1.25, 1.75, 2.25, 3.25, 4.25, 5.25, 6.25, 7.25, 8.25, 9.25, 10.25, 11.25 and 12.25 Hours (±5 min), then at 14.25, 16.25, 18.25, 20.25, 22.25 and 24.25 Hours (±10 min).

4.5.9. Pain Relief (PR)

Pain Relief (PR) will be measured using a 5-point categorical scale (0=No Pain Relief, 1=A Little Pain Relief, 2=Some Pain Relief, 3=A Lot of Pain Relief, 4=Complete Pain Relief)

4.5.10. Perceptible & Meaningful Stopwatches 1 & 2 after Dose 1

Upon initiation of the [redacted] of Dose 1, two stopwatches will be started. The subjects will first be given stopwatch #1 and asked to press the stopwatch if and when they first perceive any pain relief (FPR). At this time, patients will be given the 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 1, the time of rescue as well as PI-NPRS and PR will be collected at that time and collection of stopwatch data will cease. The stopwatches will be stopped at 24 hours, if not prior.

4.5.11. Patient Global Evaluation

Patient Global Evaluation (PGE) is assessed on a scale of 0 (Poor), 1 (Fair), 2 (Good), 3(Very Good) and 4 (Excellent) at 24.25 hours post-Dose 1 or at patient withdrawal (if applicable), whichever occurs first.

4.5.12. Pregnancy test for females

Serum pregnancy tests (for female subjects of childbearing potential) are performed at Screening, and urine pregnancy tests (dipstick) are performed pre-surgery.

Each test result will be defined to be “negative” or “positive”.

4.5.13. Serology and liver function tests

Liver Function test will be done at screening and Hour 24, while Serology test for HIV antibody, hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (anti-HCV) will be done at Screening only.

4.5.14. Prior and Concomitant Medications

Medications expected to confound the evaluation of the study medication are not allowed during the study session. This includes, but is not limited to, the use of any systemic analgesics other than the prescribed rescue analgesic. It is permissible at any time after the Day 1 pre-surgery for a single dose of 4-8 mg ondansetron (Zofran®) iv, by mouth or sublingual to be administered if a patient experiences nausea,

Prior medications/therapies are those that stop prior to the start of the study drug administration. Any medication/therapy that stops at or after this time or is ongoing at the time of discontinuation/completion is considered concomitant medication/therapy. Prior and concomitant medications will be collected at Screening through day of discharge and follow-up telephone call. Prior and concomitant medications will be coded using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical (WHO/ATC) classification index version September 1, 2015.

4.5.15. Rescue Medication

Rescue medication will consist of one ibuprofen 200 mg tablet taken orally with at least 4 ounces of water. Prior to each dose of rescue medication, 11-Point Pain Intensity (via 0-10 Numerical Rating Scale) and Pain Relief (via 5-Point Categorical Pain Relief Assessment) measurements will be performed. For statistical purposes, pain assessments performed after any dose of rescue will be censored and imputed for 4 hours. Any subject requiring additional rescue medication may again receive ibuprofen 200 mg and their data will be similarly censored and imputed. Pain scores and safety data will continue to be collected for the 24-hour observation period. Rescue medication will not exceed ibuprofen 200 mg q3h or 2400 mg in a 24-hour period.

4.5.16. Non-Medication Therapies

Non-Medication Therapies will be collected at Screening through day of discharge and follow-up telephone call. These will also be coded using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical (WHO/ATC) classification index version September 1, 2015.

4.5.17. Adverse Events monitoring

Adverse events will be recorded by site staff when they are reported or observed. The recording period for both AEs and SAEs lasts through 15 days after the patient's last administration of study medication, regardless of the relationship to the study medication.

4.5.18. Pharmacokinetic (PK) Assessment

Blood samples for PK assessment are drawn at the following timepoints:

- Prior to Dose 1: An initial baseline PK blood sample will be collected at least 5 minutes before administering Dose 1 of study medication.
- Post Dose 1: To be drawn at 0.25 hr.±3 min (end of [redacted] 0.5 hr. ±3 min, 0.75 hr. ± 3 min, 1 hr. ± 5 min, 2 hr. ± 5min , 4 hr.± 5 min, 6 hr.- 5 min (prior to the next planned [redacted] 6.25 hr. ± 3 min (end of the [redacted] 8hr. - 5 min (prior to the next scheduled [redacted] 8.25 hr. ± 3min (end of the [redacted] 12 hr. - 5 min (prior to the next scheduled [redacted] 12.25 hr. ± 3 min (end of the [redacted] 16 hr. - 5 min (prior to the next scheduled [redacted] 16.25 hr. ±3 min(end of the [redacted] 18 hr. - 5 min (prior to the next scheduled [redacted] 18.25 hr. ± 3min (end of the [redacted] and at 24.25 hr.± 15 min (after starting the very first [redacted]

If a scheduled pain assessment and a scheduled PK sampling are at the same time point, the pain assessment should precede the PK sampling, but every attempt should be made to obtain the PK sample within the designated time window.

5. PLANNED ANALYSES

5.1. Interim Analyses

No interim analyses are planned.

5.2. Final Analyses

Final analyses will occur after all data are entered, cleaned, and the database is locked.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

This section discusses general policies to be employed in the analysis and reporting of the data from the study. Departures from these general policies may be provided in the specific detailed sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

Since this is a proof-of-concept study, statistically significant treatment differences will be declared if $p \leq 0.10$ (one-sided), and no adjustments for multiple comparisons/end points will be performed. All confidence intervals will be one-sided 90% confidence intervals.

The following conventions will be used in the study analysis as needed for intermediate calculations:

- Time 0 (T0) is the time of initiation of study drug administration.
- Assessment visit times are defined relative to T0.
- Duration of an AE will be computed in days for AEs lasting longer than 24 hours, and as hours for AEs lasting less than 24 hours. Duration in hours will be calculated as the stop date/time of the event minus the start date/time. Duration in days will be calculated by using stop date minus the start date +1 if AE occur on or after taking study medication. If AE occurs prior to the study medication, then the duration will be calculated by using stop date minus the start date. If reported as ongoing at the time of database lock, the AE will be listed as ongoing, and the duration will be calculated using the date of the last visit or the last date of any AE for the subject in the database, whichever is later.

6.1. General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings (e.g., post-text tables and individual subject data listings are prepared according to ICH Guideline E3) include a “footer” providing explanatory notes that indicate as a minimum:

1. Date of data extraction.
2. Date of output generation.
3. SAS program name, including the path that generates the output.
4. Any other output specific details that require further elaboration.

Post-text tables also include reference(s) to the subject data listing(s) that supports the summary data. The data extraction date links the output to the archived database that is locked to ensure the replication of the results.

6.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

Post-text tables will be included in Appendix 14 and the individual subject data listings will be in Appendix 16. All post-text tables will have a main number level 14 and the listings 16. The subject accounting and disposition table be first in the first section of the report and numbered Table 14.1. The supportive subject data listing would be Listing 16.1.

Titles of post-text tables and listings will be complete, accurate, and concise. The last line of the title will provide the analysis group being summarized (e.g., Evaluable Subjects or Safety Subjects). If possible, the units of measurement for data contained in the table will appear in parentheses to conserve space in the body of the table and must be specified for all appropriate data.

Variables being summarized and statistics being reported will appear in the left most column of the table. The next columns for treatment groups will report the data from left to right for the investigational drugs, placebo, and (where appropriate) all treated subjects, respectively

Listings will be sorted and presented by treatment group, and subject number. All tables and listings will have explanatory notes that give data extraction date, output generation date, complete program name and path where it was executed.

6.3. Data Management

All computations will be performed using SAS® version 9.4 (SAS Institute, Cary, NC). For final tables, listings, and figures (TLFs), the domain (Study data tabulation Model [SDTM]) and analysis (Analysis Data Model [ADaM]) data sets will be taken as input to the SAS programs that generate the report ready TLFs. The submission ready SDTM and ADaM data sets will be provided to the sponsor along with display deliveries.

6.4. Data Presentation Conventions

Since this is a proof-of-concept study, statistically significant between-treatment differences will be declared if $p \leq 0.10$ (one-sided), and no adjustments for multiple comparisons/end points will be performed. All confidence intervals will be one-sided 90% confidence intervals.

The following two between-treatment comparisons will be performed:

- [redacted] APAP [redacted] q8h versus Placebo
- [redacted] APAP [redacted] q6h versus Placebo

All continuous study assessments will be summarized by treatment group and time point (as applicable) using the descriptive statistics n, mean, SD, median, minimum, and maximum. All categorical study assessments will be summarized by treatment group and time point (as applicable) using frequency counts and rates of occurrence (%). Changes from baseline for continuous outcomes will be presented as their corresponding continuous measures for post-baseline visits if applicable. Only results from scheduled visit will be used in analysis. For continuous variable, if multiple measurements were done at the same visit, the last one will be used. All study data will be listed by treatment group, subject, and time point (as applicable).

No preliminary rounding will be performed; rounding will only occur after the analysis. To round, consider the digit to the right of the last significant digit: if <5, then round down; if ≥5, then round up. Means and medians will be presented with one more decimal place than the precision of the data. Standard deviations will be presented with two more decimal places than the precision of the data. Percentages will be presented with one decimal place. A percentage of 100% will be reported as 100%. Minimums and maximums will be presented with the same precision as the original data.

Date variables will be formatted as DDMMMYYYY for presentation. Time will be formatted in military time as HH:MM for presentation.

The table and listing shells and table of contents as part of this SAP provide the expected layout and titles of the TLFs. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation. The appropriate listings supporting the tables will be included and are not specified in the individual sections throughout the document.

6.5. Analysis Populations

6.5.1. Safety Population

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

6.5.2. Evaluable Population

The Evaluable Population will include all randomized patients who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and; (2) were administered Dose 1.

The efficacy analyses will be performed using this population.

6.5.3. PK Evaluable Population

The PK Evaluable Population will include all randomized subject who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and; (2) were administered Dose 1 resulting in an adequate number of quantifiable concentrations to calculate pharmacokinetic parameters.

6.6. Baseline Definition

A baseline assessment is defined as the last non-missing result prior to administration of the first dose of study medication.

6.7. Derived and Transformed Data

6.7.1. Baseline Age

Subject's age in years will be calculated based on date of informed consent date using the following formula:

Age (year) = FLOOR((date of informed consent – date of birth)/365.25*12)

where FLOOR( ) function returns the integer part of the result.

6.7.2. Study Day

If the date of interest occurs on or after the first dose/randomization date, then study day will be calculated as (date of interest – date of first dose/randomization) + 1. If the date of interest occurs prior to the first dose/randomization date, then study day will be calculated as (date of interest – date of first dose/randomization). There is no study day 0. Duration of event in hours will be calculated as: [stop date/time of the event minus the start date/time] and displayed with one decimal (e.g., 6.1 hours).

6.7.3. Change from Baseline

Change from baseline will be calculated as (post-baseline result – baseline result). If used, percent change from baseline will be calculated as (change from baseline/baseline result * 100). If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

6.7.4. Visit Windows

Summaries and data listings will be presented by nominal protocol timepoint and no visit windowing will be used for data presentations. Unscheduled visit will be excluded from the summary tables but will be included in the listings. As discussed in Section 6.4, if multiple visits or assessments occur within the same nominal timepoint, the latest will be used for analyses/presentations. The protocol-defined visits with the allowed visit windows are presented in Table 2.

Table 2: Visit Windows (Days)

Visit	Relative Target Day	Visit Window
Visit 1 (Screening)	-7	-30 – 0
Day of Surgery/Dosing	1	n/a
Post-Op	2	n/a
Follow Up Post-Surgery Call	7	±2 day

6.7.5. Multiple Assessments and Uninterpretable values

If duplicate values are obtained at a given visit (e.g., repeated vital sign measurements), the last value will be used unless it is noted that the measurement was in error for that value. Values that compromise interpretation will not be used in summaries (e.g., values that were obtained post-dose will not be summarized as pre-dose values).

6.8. Handling of Missing Data

6.8.1. Missing Efficacy Endpoints

Prior to each dose of rescue medication, 11-Point Pain Intensity (via 0-10 Numerical Rating Scale) and Pain Relief (via 5-Point Categorical Pain Relief Assessment) measurements will be performed. For statistical purposes, pain assessments performed after any dose of rescue will be censored and imputed in the following manner. For subjects who take rescue medication, a windowed last pain score carried forward (wLOCF) will be used for all PI and PR endpoints. The pre-rescue pain score will be used to impute scheduled assessments for 4hrs following the rescue use. Note: if a pre-rescue NRS assessment occurs at the same time as a scheduled NRS assessment, the scheduled assessment will be assumed to happen first, and then the pre-rescue NRS will be assumed to occur afterwards. If a scheduled NRS assessment occurs at the same time as the time of taking a rescue medication, the NRS assessment will be assumed to be a Pre-rescue medication result. For subjects who drop out of the study early, scheduled pain assessments will first be imputed using the worst prior pain score carried forward (WOCF).

For time to treatment failure, if a subject does not qualify for treatment failure, but prematurely discontinues from the study before 24 hours, then the subject will be censored at the time of discontinuation. If a subject never qualifies as a treatment failure and completes the treatment phase of the study, then the subject will be considered censored at 24 hours.

For the other time to event analyses (FPR-C, MPR) if a subject does not record perceptible/meaningful pain relief and prematurely discontinues from the study prior to 24 hours, then the subject will be censored at 24 hours. If a subject does not record perceptible/meaningful pain relief prior to taking rescue medication, the subject will again be censored at 24 hours.

Imputation of non-numerical values reported in the plasma PK data set for acetaminophen will be dealt with, in both PK parameter calculation and calculation of descriptive statistics of the concentration data, as follows:

- Day 1 pre dose sample times will be set equal to zero;
- Values that are below the limit of quantification (BLQ) obtained prior to the first quantifiable concentration post-dose administration will be set equal to zero;
- Values that are BLQ after the first quantifiable concentration post dose administration will be treated as missing for the calculation of PK parameters
- Concentrations that are treated as missing (non-numerical values) will be ignored in the calculation of descriptive statistics for serum concentrations.

No other missing data will be imputed.

6.8.2. Missing Start and Stop Dates for Adverse Events

If a Treatment-emergent AEs (TEAE) is reported as ongoing at the time of database lock, the AE will be shown as ongoing in listings, and the stop date will be imputed for calculations as the date of the last visit or the last date of any event for the subject in the database, whichever is later.

If a TEAE is considered resolved, but the stop date is missing, the last day of the month will be imputed if the month and year are available. If only the year is available, and the year is the same as the year of the last visit, the stop date will be the latest of the last visit date or latest event for the subject in the database.

If the year of the event is prior to the year of the last treatment, the end day and month will be set to 31 December.

For missing or partial start and stop dates/times, the most conservative imputation will be used (AEs will be assumed to be temporally related to the study medication). The original incomplete or missing dates will be presented in the listings, not the imputed dates. Table 4 will be used to impute any missing dates/times:

Table 3: Table of Imputation Rules for Missing AE Start Dates

Missing Date Portion	Prior to Treatment	Same as Treatment Start Date	After Treatment Start Date
Day	Month and Year < Month and Year of Study treatment: Start Day = 1 Stop Day=last day of the month	Month and Year = Month and Year of Study treatment: Start Day = Day of first treatment Stop Day= last day of the month	Month and Year > Month and Year of Study Treatment: Start Day = 1 Stop Day=last day of the month
Day and Month Define Day as above, then:	Year < Year of first treatment: Start Month = July Stop Month = Dec	Year = Year of study treatment: Start Month = Month of study treatment Stop Month = Dec	Year > Year of study treatment: Start Month = January Stop Month = Dec
Day, Month, and Year	To be conservative, completely missing start dates will be imputed using the date of study treatment, Missing end dates will be imputed using date of last study contact with the subject		
Time	Missing start times will be imputed as 00:01 Missing stop times will be imputed as 23:59		

6.8.3. Missing Start and Stop Dates for Prior and Concomitant Medication

Partially missing dates for medications and procedures will be imputed as described in Section 6.8.2 for adverse events.

7. STUDY POPULATION

7.1. Subjects Disposition

All subjects and the populations for which they qualify will be listed. Subjects who are screened and who fail screening, are randomization failures or withdraw consent prior to randomization or are randomized but not treated will be listed and summarized in the disposition summary table. Subjects who are randomized, subject inclusion into each study population, subjects who are treated, subjects who complete follow-up as well as subjects who withdraw early from the study and the reason for withdrawal will be summarized by treatment group and overall in the subject disposition summary table.

7.2. Protocol Deviations

Deviations are categorized as informed consent procedures, inclusion/exclusion criteria, study medication, prohibited medications, study procedures, study drug assignment/treatment, visit or assessment time window, missed visit or assessment and/or other. All protocol deviations will be captured on case report forms (CRFs) and/or documented in site-specific logs throughout the study. Deviations will be categorized and classified as major or minor by the project team and the medical monitor after database lock but before unblinding and will be discussed in the CSR. Subjects with protocol deviations, both minor and major, will be presented in a data listing and will be summarized by type of deviation and major/minor classification for all randomized subjects.

7.3. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized overall and by treatment group using the Safety and Evaluable Populations.

7.4. Listing of Subject Inclusion and Exclusion Criteria

Listing showing subject inclusion/exclusion status (inclusion criteria not met and exclusion criteria met) will be provided.

7.5. Medical History and Medical Conditions Present at Entry

Medical histories will be presented in a by-subject listing. Any events that occur prior to surgical removal of molars will be categorized as medical history .

7.6. Prior Medication History and Medications Present at Entry

All medications and non-medical therapies captured in CRFs will appear in data listings.

8. EFFICACY

8.1. Statement of the Hypothesis

The hypotheses of this study are that [redacted] APAP [redacted] dosed three times daily and [redacted] APAP [redacted] dosed four times daily have similar safety, tolerability, and efficacy profiles when compared to placebo.

8.2. Subgroup Analyses

Time Weighted Sum of Pain Intensity Difference from 0 to 24 hours (SPID24) and Time Weighted Sum of Pain Relief from 0 to 24 hours (TOTPAR24) will be analyzed by age group (<median, >=median) and by sex, using an analysis of covariance (ANCOVA) model with treatment group as a fixed effect and baseline pain intensity PI-NPRS as a covariate. Descriptive summaries, including least square means (lsmeans) and standard errors for each treatment group and confidence intervals will be presented.

8.3. Multiple Comparisons and Multiplicity

No adjustments for multiple comparisons/end points will be performed.

8.4. Analysis of the Efficacy Endpoints

8.4.1. Time Weighted Sum of Pain Intensity Difference from 0 to 24 hours (SPID24)

Pain intensity (PI) is collected at various scheduled timepoints and also prior to each use of rescue medication. SPID is calculated as $\Sigma[T(i) - T(i-1)] \times (PID(i-1) + PID(i))/2$, where $T(0)=0$, T(i) is the scheduled time, and PID(i) is the pain intensity difference (PID) score at time i. At any timepoint, SPID will include all assessments from T0 to the nominal time point. Thus, SPID24 will include all nominal timepoints from T0 to T24.25. The last PI score prior to the use of any rescue medication will be used to impute subsequent PI scores for the subsequent protocol-specified time points for measurement of pain intensity through 4 hours after the time of the dosing of the rescue medication (wLOCF). If a pre-rescue PI assessment occurs at the same time as a scheduled assessment, the schedule PI will be assumed to happen first, and then the pre-rescue PI will be assumed to occur. If a PI assessment occurs at the same time as the time of taking a rescue medication, the PI will be assumed to be a Pre-rescue medication result. If the PI time is the same as the end of time window after taking the rescue medication (end of imputation period), then PI score will be considered as occurring before the 4 hours assessment and will be imputed. Intermittent missing pain scores will not be imputed, and SPID24 will be calculated based on non-missing values. For subjects who drop out of the study early, scheduled assessments will first be imputed using the worst prior pain score carried forward (WOCF).

For calculations of SPID24, the actual dates/times of assessments will be used in calculations. While the PI scores are intended to be collected at the pre-defined protocol scheduled time points, it is recognized that operationally the scores are collected as close to the target times as possible but there is some flexibility in terms of the actual times the scores are collected. Thus, to account for this inherent aspect of data collection, the ACTUAL TIMES will be used for the

calculation of SPID24. The actual times will be based relative to the time of completion of study drug administration.

This will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as a fixed effect and baseline PI-NPRS as a covariate. Descriptive summaries including least square means and standard errors for each treatment group, confidence intervals, and p-values will be presented.

8.4.2. Time Weighted Sum of Pain Relief from 0 to 24 hours (TOTPAR24)

Pain Relief Rating (PR) is scored on a 5-point scale (0=no-, 1= a little-, 2= some-, 3= a lot of-, and 4=complete- PR) at each observation time after Dose 1 administration, TOTPAR24 is derived similarly as SPID24 above, with pain relief at time i (PR(i)) replacing PID(i) in the formula.

This will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as a fixed effect and baseline PI-NPRS as a covariate. Descriptive summaries including least square means and standard errors for each treatment group, confidence intervals, and p-values will be presented.

8.4.3. Time to Perceptible Pain Relief Confirmed (FPR-C) and Cumulative % of patients with onset of First Perceptible Relief Confirmed after Dose 1 administration

This will be analyzed using a log-rank test; the log rank test may be stratified by baseline categorical pain intensity score (moderate / severe) if there are sufficient subjects in each stratum. Number of subjects in the population (N), number of subjects with FPR-C event, number of subjects censored, median time to FPR-C, and p-values from log-rank test will be displayed in a summary table.

In addition, the cumulative percent of subjects achieving perceptible pain relief confirmed after Dose 1 will be presented in Kaplan-Meier curves by treatment group.

If a subject does not record perceptible pain relief and prematurely discontinues from the study prior to 24 hours, then the subject will be censored at time of drop out. If a subject does not record perceptible pain relief prior to taking rescue medication, the subject will be censored at 24 hours.

8.4.4. Time to Meaningful Pain Relief (MPR) and Cumulative % of patients with onset of Meaningful Pain Relief after Dose 1 administration

This will be analyzed using a log-rank test; the log rank test may be stratified by baseline categorical pain intensity score (moderate / severe). Number of subjects in the population (N), number of subjects with MPR event, number of subjects censored, median time to MPR, and p-values from stratified log-rank test will be displayed in a summary table.

In addition, the cumulative percent of subjects achieving meaningful pain relief after Dose 1 will be presented in Kaplan-Meier curves by treatment group.

If a subject does not record meaningful pain relief and prematurely discontinues from the study prior to 24 hours, then the subject will be censored at time of drop out. If a subject does not record meaningful pain relief prior to taking rescue medication, the subject will also be censored at 24 hours.

8.4.5. Cumulative proportion of patients with pain half gone over time

A subject's pain level will be considered half gone at a given assessment time point (Ti) if the percent PID, defined as PPID(i) =(PID(i) / PI(T0) *100, at that assessment time point is less than 50%.

The endpoint will be analyzed using a Kaplan Meier approach to summarize time to first occurrence of 50% improvement. This will count a subject as an event when they first hit 50% pain half gone. If a subject does not record 50% improvement and prematurely discontinues from the study prior to 24 hours, then the subject will be censored at time of drop out. If a subject does not record 50% improvement prior to taking rescue medication, the subject will be censored at 24 hours.

Number of subjects in the population (N), number of subjects that achieve 50% improvement, number of subjects censored, median time to achieving 50% improvement, and p-values from stratified log-rank test will be displayed in a summary table.

In addition, Kaplan-Meier curves will be presented by treatment group.

8.4.6. Patient Global Evaluation of the study medication

The Patient Global Evaluation will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as a fixed effect and baseline PI-NPRS as a covariate. Descriptive summaries including least square means and standard errors by treatment group, confidence intervals, and p-values will be presented.

8.4.7. Pain Intensity Difference (PID) Rating at each observation time after Dose 1 administration

This will be summarized descriptively and plotted over time by treatment group.

8.4.8. Pain Intensity (PI) Ratings at each observation time after Dose 1 administration

This will be summarized descriptively and plotted over time by treatment group.

Compliance with recording NRS is calculated as the number of non-missing NRS scores divided by the number of expected NRS scores. NRS scores recorded prior to rescue medication use are excluded from the calculation. Compliance with recording NRS will also be summarized descriptively by treatment group.

8.4.9. Pain Relief (PR) Ratings at each observation time after Dose 1 administration

This will be summarized descriptively and plotted over time by treatment group.

Compliance with recording PR is calculated as the number of non-missing PR scores divided by the number of expected PR scores. PR scores recorded prior to rescue medication use are

excluded from the calculation. Compliance with recording PR will also be summarized descriptively by treatment group.

8.4.10. Time to treatment failure and Cumulative % of patients with treatment failure

Time to treatment failure is defined in the protocol as the earlier of the time to first dose of rescue medication after Dose 1 or time to withdrawal from the study due to lack of efficacy (if prior to any rescue). Since withdrawal from the study due to lack of efficacy was not collected in the study, this SAP redefines Time to treatment failure as the earlier of the time to first dose of rescue medication after Dose 1 or withdrawal from the study for any reason.

This will be analyzed using a log-rank test; the log rank test may be stratified by baseline categorical pain intensity score (moderate / severe). Number of subjects in the population (N), number of subjects with treatment failure, number of subjects censored, median time to treatment failure, and p-values from stratified log-rank test will be displayed in a summary table.

In addition, the cumulative percent of subjects that fail treatment will be presented in Kaplan-Meier curves by treatment group.

If a subject does not take rescue medication or withdraw from the study prior to 24 hours, the subject will be censored at 24 hours.

8.4.11. Sensitivity Analyses of the Primary Efficacy Results

Interaction between baseline PI-NPRS and treatment group will be tested for statistical significance for SPID24 and TOTPAR24 by including the interaction term in the ANCOVA model utilized for the primary efficacy analyses.

9. SAFETY AND TOLERABILITY

9.1. Overall Summary of Tolerability

All AEs will be listed, but only TEAEs will be summarized. Treatment-emergent AEs are defined as all AEs which initially occurred or worsened following first dose of treatment (T0).

9.2. Adverse Event Preferred Term and Body/Organ System Summary Tables

9.2.1. Summaries of Adverse Event Incidence Rates for All Subjects

For evaluation of causal relatedness to treatment, the categories are definitely related, probably related, possibly related, unlikely related, or not related. For categorization in the summary tables, AEs designated as definitely, probably, or possibly related will be considered related.

For the evaluation of event severity terms, the criteria are mild, moderate, or severe. In addition to a listing of all AEs, treatment associated TEAEs, serious TEAEs, Deaths, and TEAEs leading to premature discontinuation from the study will be provided.

An overall summary will be prepared giving for each treatment group and overall, both the number of TEAEs, and the number of subjects with at least one TEAEs. SAEs, TEAEs associated with treatment and TEAEs leading to premature discontinuation from study will also be included in this overall summary.

The number of subjects with AEs will be summarized for each treatment group and overall by System Organ Class (SOC) and Preferred Term (PT) sorted alphabetically by SOC, and then by PT within SOC. Separate tables will be presented for each of the following TEAE event sets:

- All events
- Treatment-related events
- Serious events
- Events leading to premature discontinuation from study
- Events by maximum severity
- Events by relationship to study drug

If a given subject experiences a TEAE that maps to the same PT/SOC more than once, the subject will be counted only once for the SOC/PT at the greatest severity (i.e., mild, moderate, or severe) and causality (i.e., related).

In summary tables, missing relationship to study drug will be imputed as “Related” and missing Severity as “Severe”. In listings, these will be shown as UNK or Blank,

Duration of a TEAE lasting more than 24 hours will be computed in days as the stop date of the event minus the start date plus 1 and will be reported in days. TEAEs lasting less than 24 hours will be computed as stop date/time minus start date/time and reported in hours. If reported as ongoing at the time of database lock, the date used to calculate duration will be defined as the date/time of the last visit or the last date/time of any event for the subject in the database, whichever is later.

9.2.2. Missing and Partial AE Onset Dates

Missing and partial AE onset dates will be handled as described in Section 6.8.3: Missing Start and Stop Dates for Adverse Events.

9.3. Total Duration of Therapy, Average Daily Dose, Maximum Daily Dose, Final Daily Dose of Study Medication, and Compliance

A listing of study drug administration and exposure data will be provided. [redacted] of drug administered is 1300 (10x130) ml. Percentage of intended dose that was taken by each subject is defined as 100 x 10 x (actual volume administered at each timepoint) / intended volume. A summary table by treatment group of percentage of intended dose that was taken by each subject will be provided.

9.4. Concomitant and Other Medications

9.4.1. All medications and non-medical therapies captured in CRFs will appear in data listings.

Missing and partial concomitant and other medication start and stop dates will be handled as described in Section 6.8.2: Missing Start and Stop Dates for Prior and Concomitant Medication.

9.5. Rescue Medications, and Compliance for Pre-Rescue NRS and Pain Relief

Rescue medication will consist of one ibuprofen 200 mg tablet taken orally with at least 4 ounces of water. Total dose in mg will be derived as number of tablets taken multiplied by 200. Summary statistics will be presented for total dose of rescue medication used, by treatment group.

NPRS and PR assessments should be completed prior to each rescue dose.

Compliance with recording NPRS prior to rescue = 100 x (number of times NPRS are recorded prior to rescue)/(number of rescue doses taken).

Compliance with recording PR prior to rescue = 100 x (number of times PR are recorded prior to rescue)/(number of rescue doses taken).

9.6. Routine Clinical Laboratory Data

Serology test is done at Screening only, while Liver Function Panel is done at Screening and Hour 24. All results will be listed. For each lab test, the raw value will be summarized by treatment group and timepoint.

The number and percentage of subjects who have clinically significant laboratory results will be summarized for overall, and by treatment group.

9.7. Vital Signs

Vital signs results including blood pressure (systolic and diastolic; mmHg), heart rate (beats per minute), respiration rate (breaths/min), and temperature will be listed for individual subjects.

Baseline for vital signs measurements will be defined as the last evaluation before dosing with study medication. Summary statistics, including change from baseline, will be presented for each measure and will be summarized by treatment group and time point.

9.8. Physical Examination

A complete physical examination including all major body systems will be performed at Screening.

Physical examination results will be listed for individual subjects.

9.9. Study Termination Status

A post-text table will be provided that categorizes the status of the subjects at the end of the study by treatment group. The completion status will be summarized with respect to the number of subjects:

1. Completing the entire course of treatment.
2. Discontinuing the trial prematurely.
3. Reason for premature study termination.

The reasons for early study termination are adverse event, protocol violation, screen failure, administrative, lack of efficacy, lost to follow-up, death, subject non-compliance, withdrawal of consent by subject, prohibited medication, sponsor decision, investigator decision, and other.

10. PHAMACOKINETIC EVALUATION

10.1. Pharmacokinetic Objectives

The PK objectives/questions to be addressed in this study are as follows :

1. Is the daily drug exposure from the [redacted] APAP [redacted] q6h dose like that from the [redacted] APAP [redacted] q8h dose?
2. Is there any change in the PK of acetaminophen in going from a single dose of [redacted] APAP [redacted] to a single dose of [redacted] APAP [redacted] ?
3. Is there drug accumulation on multiple dosing with either regimen? If yes, how much?
4. Do we achieve a steady state with either regimen?

10.2. Pharmacokinetic Sample Analysis and Modeling Process

Sampling for Pharmacokinetic (PK) assessments will be done following the schedule discussed in Section 4.5.17 (Pharmacokinetic (PK) Assessment). Samples will be sent to a [redacted] who will measure the concentration of APAP in each sample and return those concentration results to the project team.

Seventh Wave will use the concentration data to perform a Non-Compartmental Analysis (NCA) of the concentrations and produce PK parameters and a stand-alone PK report. PK parameters to be used in evaluating the above objectives will be provided by Seventh Wave, to include:

For the [redacted] q8h regimen:

Dose 1:
1. $AUC_{(0-8)}$
2. $AUC_{(0-inf)}$
3. C_{max}
4. C_{trough}
5. Half-life ($t_{1/2}$)

Dose 2:
1. C_{max}
2. C_{trough}
3. RA_C_{max}_Dose 2

Dose 3:
1. C_{max}
2. C_{trough}
3. RA_C_{max}_Dose 3

Daily Drug Exposure

1. $AUC_{(0-24)}$

For the [redacted] q6h regimen:

Dose 1:

1. $AUC_{(0-6)}$
2. $AUC_{(0-inf)}$
3. C_{max}
4. C_{trough}
5. Half-life ($t_{1/2}$)

Dose 2:

1. C_{max}
2. C_{trough}
3. RA_C_{max}_Dose 2

Dose 3:

1. C_{max}
2. C_{trough}
3. RA_C_{max}_Dose 3

Dose 4:

1. C_{max}
2. C_{trough}
3. RA_C_{max}_Dose 4

Daily Drug Exposure

1. $AUC_{(0-24)}$

10.3. Summary of Pharmacokinetic Concentrations

[redacted] will receive the PK concentrations as provided by [redacted]. PK concentrations will be summarized using descriptive statistics (number of non-missing and missing observations, arithmetic mean, geometric mean, standard deviation (SD), percent coefficient of variation (CV%), minimum , median, and maximum for each treatment group and nominal time point. Figures of the PK concentrations over time for each subject and the mean concentration over time for each treatment group will be presented in both standard and log scale.

10.4. Statistical Analysis of Pharmacokinetic Parameters

[redacted] will receive the PK parameters as derived by Seventh Wave. All analyses that involve AUCs and Cmax's will be analyzed on log scale, and the model estimates will be back-transformed. PK parameters except Tmax will be summarized using descriptive statistics [N, Mean, SD, CV%, minimum, median, maximum, geometric mean (Geom Mean), and geometric CV% (Geom CV%)] for each treatment group, nominal time point and study day. Minimum, median and maximum will be presented for Tmax.

All PK parameters will be summarized with the same number of significant figures as reported.

In addition, the following statistical analysis will be performed to support each of the PK objectives.

10.4.1. Differences in Daily Drug Exposure by Dose Regimen

To evaluate PK objective 1, AUC(0-24) after the [redacted] q8h will be compared with the AUC(0-24) after the [redacted] q6h using an analysis of variance (ANOVA) model with daily drug exposure (AUC(0-24)) as the dependent variable and treatment group as a fixed effect independent variable. The null hypothesis here is that there is no difference between the AUC(0-24) of the two active treatment groups.

Because the overall study is being performed at the 0.10 (one sided) confidence level, eighty percent (80%) confidence intervals, standard errors, lsmeans, and geometric mean ratios (GMR) will be presented.

10.4.2. Differences in Pharmacokinetics by Dose Regimen

Evaluation of PK objective 2 will be accomplished by comparing the dose normalized AUC(0-inf) of the two active treatment groups using an ANOVA model and summarized as described in section 10.4.1 above. The null hypothesis here is that there is no difference between the dose normalized AUC(0-inf) of the two active treatment groups.

10.4.3. Drug Accumulation by Dose

To evaluate PK objective 3, the accumulation for each active treatment group will be evaluated to see if it is significantly different from 1.0.

For the [redacted] q8h regimen, the null hypothesis that RA_Cmax_Dose 3 = 1 will be analyzed using a one sample t-test. For the [redacted] q6h regimen RA_Cmax_Dose 4 will be tested under a similar hypothesis and analysis method. P-values will be presented and are considered significant if < 0.10 (one-sided).

10.4.4. Steady State by Dose

To evaluate PK objective 4 (achievement of a steady state with either active treatment group), differences between absolute values of Cmax (last dose) and Cmax (previous Dose) will be compared for each subject for the last dose. T-test will be used to test the null hypotheses that these differences equal 0 within each treatment regimen. For the [redacted] q8h regimen, the null hypothesis that Cmax from Dose 3 will be comparable to Cmax from Dose 2 will be done using

a one sample t-test of the difference. For the [redacted] q6h regimen Cmax from Dose 4 will be similarly compared to Cmax from Dose 3. P-values will be presented and are considered significant if < 0.10 (one sided). Helmert contrasts may be performed if warranted.

11. REFERENCES

US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583.

US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320.

Guidance for Industry (2014) Analgesic Indications: Developing Drug and Biological Products - Draft Guidance. Department of Health and Human Services: Food and Drug Administration. Center for Drug Evaluation and Research (CDER) February 2014 Clinical/Medical.

12. APPENDIX

12.1. Table of Contents for Data Display Specifications

Tables

Table Number	Title	Analysis Population	Comments
Study Population Section			
14.1.1	Summary of Subject Disposition	All Subjects	Unique
14.1.2	Summary of Analysis Populations	Randomized	Unique
14.1.3	Summary of Reasons for Efficacy Non-Evaluability/Exclusion from Evaluable Population	Safety	Unique
14.1.4.1	Summary of Demographic Characteristics	Safety	Unique
14.1.4.2	Summary of Demographic Characteristics	Evaluable	Repeat 14.1.3.1
14.1.5	Summary of Protocol Deviations	Safety	Unique
14.1.6	Summary of Baseline Vital Signs	Safety	Unique
14.1.7.1	Summary of Subject Compliance for: NRS Diary, Dosing, and Pre-Rescue NRS	Safety	Unique
14.1.7.2	Summary of Subject Compliance for: Pain Relief and Pain Relief at Rescue	Safety	Unique
14.1.8	Incidence and Total Dose of Rescue Medication Use by Treatment Group	Safety	Unique
Efficacy Section			
Figures			
14.2.1	Kaplan-Meier Plot of Time to Perceptible Pain Relief Confirmed (FPR-C)	Evaluable	Unique
14.2.2	Kaplan-Meier Plot of Time to Meaningful Pain Relief (MPR)	Evaluable	Repeat 12.2.3
14.2.3	Kaplan-Meier Plot of Time to Treatment Failure	Evaluable	Repeat 12.2.4
14.2.4	Kaplan-Meier Plot of Time to Pain Half Gone	Evaluable	Repeat 12.2.4
14.2.5	Plot of % Subjects with Pain Half Gone at Each Time Point	Evaluable	Unique
Tables			
14.2.1.1	ANCOVA Analysis of Time Weighted Sum of Pain Intensity Difference from 0 to 24 hours (SPID24) – WOCF	Evaluable	Unique
14.2.1.2	Sensitivity Analysis of Time Weighted Sum of Pain Intensity Difference from 0 to 24 hours (SPID24) – WOCF	Evaluable	Unique

14.2.2.1	ANCOVA Analysis of Time Weighted Sum of Pain Relief from 0 to 24 hours (TOTPAR24) – WOCF	Evaluable	Repeat 14.2.1
12.2.2.2	Sensitivity Analysis of Time Weighted Sum of Pain Relief from 0 to 24 hours (TOTPAR24) – WOCF	Evaluable	Unique
14.2.3	Log-Rank Analysis of Time to Perceptible Pain Relief Confirmed (FPR-C)	Evaluable	Unique
14.2.4	Log-Rank Analysis of Time to Meaningful Pain Relief (MPR)	Evaluable	Repeat 14.2.3
14.2.5	Cumulative Proportion of Patients with Pain Half Gone over Time	Evaluable	Unique
14.2.6	ANCOVA Analysis of Patient Global Evaluation (PGE) of Study Medication	Evaluable	Unique
14.2.7	Summary of Pain Intensity Difference (PID) Rating at Each Observation Time after Dose 1 Administration	Evaluable	Unique
14.2.8	Summary of Pain Intensity (PI) Ratings at Each Observation Time after Dose 1 Administration	Evaluable	Repeat 14.2.7
14.2.9	Summary of Pain Relief (PR) Ratings at Each Observation Time after Dose 1 Administration	Evaluable	Repeat 14.2.7
14.2.10	Log-Rank Analysis of Time to Treatment Failure	Evaluable	Unique
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14.3.1	Overall Summary of Treatment-emergent Adverse Events (TEAEs)	Safety	Unique
14.3.2.1	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety	Unique
14.3.2.2	Summary of Treatment Related Treatment-Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term	Safety	Unique
14.3.2.3	Summary of Death and Serious Adverse Events by System Organ Class and Preferred Term	Safety	Unique
14.3.2.4	Summary of Treatment-Emergent Adverse Events (TEAEs) Leading to Study Discontinuation by System Organ Class and Preferred Term	Safety	Unique
14.3.2.5	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety	Unique
14.3.2.6	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to Study Drug	Safety	Unique
14.3.3	Summary of Clinical Chemistry Data by Treatment Group and Study Time	Safety	Unique
14.3.4	Summary of Actual Values and Changes from Baseline in Vital Signs by Treatment Group and Study Time	Safety	Unique

PK Section			
Tables			
14.4.1	Summary of PK Concentration Data	PK Evaluable Population	Unique
14.4.2	Summary of PK Parameters	PK Evaluable Population	Unique
14.4.3	ANOVA Analysis of Daily Drug Exposure	PK Evaluable Population	Unique
14.4.4	ANOVA Analysis of Dose Normalized AUC	PK Evaluable Population	Unique
14.4.5	One Sample T-Test of Dose Accumulation	PK Evaluable Population	Unique
14.4.6	Analysis of Cmax values to Evaluate Steady State	PK Evaluable Population	Unique
Figures			
14.4.1	PK Concentration-over time by Subject	PK Evaluable Population	Unique
14.4.2	PK Concentration-over time by Subject (Log scale)	PK Evaluable Population	Unique
14.4.3	Mean PK Concentration-over time by Treatment	PK Evaluable Population	Unique
14.4.4	Mean PK Concentration-over time by Treatment (log scale)	PK Evaluable Population	Unique
14.4.5	Mean (SD) trough concentrations vs time by Treatment	PK Evaluable Population	Unique

Listings

Listing Number	Title	Population	Comment
16.2.1.1	Subject Enrollment Information	Enrolled	Unique
16.2.1.2	Subject Disposition	Safety	Unique
16.2.2.1	Subjects who did not Satisfy Inclusion/Exclusion Criteria	**All Subjects**	Unique
16.2.2.2	Protocol Deviations	Safety	Unique
16.2.2.3	Subject Demographic and Baseline Characteristics	Safety	Unique
16.2.2.4	Listing of Medical/Surgical History	Safety	Unique
16.2.2.5	Listing of Physical Exam	Safety	Repeat
16.2.2.6.1	Listing of Concomitant Medications	Safety	Unique
16.2.2.6.2	Listing of Non-Medication Therapies	Safety	Unique
16.2.2.7	Listing of Drug Administration and Compliance	Safety	Unique
16.2.2.8	Listing of Pain Assessment Training	Safety	Unique
16.2.3.1a	Listing of Subject NPRS and NPRS at Rescue Compliance	Safety	Unique
16.2.3.1b	Listing of Subject PR and PR at Rescue Compliance	Safety	Unique
16.2.3.2	Listing of Pain Intensity as measured on 11 – Point Numeric Pain Rating Scale (NPRS)	Safety	Unique
16.2.3.3	Listing of 5-Point Categorical Pain Relief Assessment (PR)	Safety	Unique
16.2.3.4	Listing of Efficacy Endpoints	Safety	Unique
16.2.6.1	Listing of Relationship of Adverse Event Body System, Group Terms, and Verbatim Text	Safety	Unique
16.2.6.2	Listing of All Adverse Events	Safety	Unique
16.2.6.3	Listing of Subjects Withdrawn Due to AEs	Safety	Repeat
16.2.6.4	Listing of Deaths or SAEs	Safety	Repeat

16.2.7.1	Listing of Chemistry Data	Safety	Unique
16.2.7.2	Listing of Hematology Data	Safety	Repeat 16.2.7.1
16.2.7.4	Listing of Serology	Safety	Repeat 16.2.7.1
16.2.8	Listing of Vital Sign Data	Safety	Unique
16.2.9	Listing of Rescue Medication Administration	Safety	Unique
16.2.10	Listing of Pregnancy Test	Safety	Unique
16.2.11	Listing of Surgery	Safety	Unique
16.2.12	Listing of Pharmacokinetic (PK) Concentration (unit) Data	Evaluable	Unique
16.2.13	Listing of Pharmacokinetic (PK) Parameters	Evaluable	Unique

12.2. 7th wave 17-RS-610CL PKAP

Electronic Record and Signature Disclosure created on: [redacted]
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