Clinical Trial Protocol

A Phase 2, Randomized, Double-Blind, Placebo- and Comparator-Controlled Trial to Evaluate the Safety and Efficacy of Combination [redacted] Pregabalin and Acetaminophen Compared to Acetaminophen and Placebo in Subjects Undergoing Bunionectomy

Protocol Number: CP-NVK009-0005, Version 2.0, Amendment 02

Dated: 08-June-2020

ClinicalTrials.gov Identifier: NCT04495283

Sponsor: Nevakar, Inc. NJ 08807

3. SYNOPSIS

Name of Sponsor/Company:
Nevakar, Inc.

Name of Investigational Product:
NVK009, a combination of pregabalin (PGB) [redacted] and [redacted] (acetaminophen [APAP] [redacted] administered [redacted] ([redacted] The final dose of PGB is determined by the CP-NVK009-0004 study.

Name of Active Ingredients:
Pregabalin (PGB) and acetaminophen (APAP)

Protocol Number:
CP-NVK009-0005

Title of Study:
A Phase 2, Randomized, Double-Blind, Placebo- and Comparator-Controlled Trial to Evaluate the Safety and Efficacy of Combination [redacted] Pregabalin and Acetaminophen Compared to Acetaminophen and Placebo in Subjects Undergoing Bunionectomy

Study Center(s):
1 to 3 study centers (US)

Studied Period (3 months):	**Phase of Development:**
Estimated date first subject enrolled: July 2020 Estimated date last subject completed: September 2020	Phase 2

Objectives:

Primary:

- To evaluate the efficacy of combination PGB [redacted] and APAP [redacted] administered [redacted] vs. placebo for pain control in subjects undergoing bunionectomy.

Secondary:

- To evaluate the efficacy of combination PGB [redacted] and APAP [redacted] administered [redacted] vs. comparator (APAP [redacted] alone) for pain control in subjects undergoing bunionectomy.
- To evaluate the safety and tolerability of a combination of PGB [redacted] and APAP [redacted] administered [redacted] in a postoperative population.

Outcome Measures:

Primary Endpoint:

- Summed pain intensity (SPI) measured by the numeric rating scale (NRS) (Appendix 1) compared between a combination of PGB [redacted] and APAP [redacted] administered [redacted] and placebo from Hour 0 to Hour 48 (SPI_{0-48}).

Secondary Endpoints:

- SPI compared between a combination of PGB [redacted] and APAP [redacted] administered [redacted] and comparator (APAP [redacted] alone) from Hour 0 to Hour 48 (SPI_{0-48});
- SPI compared between a combination of PGB [redacted] and APAP [redacted] administered [redacted] comparator (APAP [redacted] alone), and placebo for the following time intervals:
  - 0–12 hours;
  - 12–24 hours;

- 12–48 hours.

- Percentages of subjects who are opioid free over time (12-24 hours and 12-48 hours);
- Percentages of subjects who do not take opioid rescue (are opioid free) over various time periods (12-24 hours and 12-48 hours);
- The total consumption of opioid rescue analgesia through 24 hours and through 48 hours;
- The total consumption of rescue analgesia;
- Time to first use of rescue medication from Hour 0;
- Percentage of subjects using rescue medication;
- Patient Global Assessment (PGA) of pain control at 48 hours (Appendix 2);
- SPI over time.

The safety outcomes of the study are:

- The incidence and severity of treatment-emergent adverse events (TEAEs), including clinically significant vital signs, electrocardiograms (ECGs), and clinical laboratory test results data.
- The incidence and severity of somnolence and dizziness as determined by the Readiness for Discharge Modified Aldrete Scoring System (Appendix 3), including Activity, Respiration, Circulation, Consciousness, Oxygenation, and Dizziness (Appendix 4) questionnaires.

The PK outcomes of the study are:

The plasma PK endpoints for PGB and APAP, to be calculated from samples taken prior to and after each [redacted] including:

- Maximum observed concentration (C_{max});
- Minimum observed concentration (C_{min}).

Methodology:

This is a phase 2, multi--center, randomized, double-blind, parallel-group, placebo- and comparator-controlled study.

Subjects will undergo a Screening Visit (Day -42 to Day -2). Pre-operative assessments will be conducted within 24 hours prior to surgery (on either Day -1 or Day 1 prior to surgery) and prior to any dosing. Subjects scheduled for bunionectomy surgery who meet all of the inclusion criteria and none of the exclusion criteria stated below will be enrolled and randomized (Day 1). Subjects and all study staff performing study assessments will be blinded to treatment allocation.

On Day 1, the first dose of study drug or placebo will be administered approximately 30 to 90 minutes before surgery (pre-Surgery [redacted] #1) when the subject is in the pre-operative area. [redacted] are approximately 15 minutes. Surgery will be performed approximately within the next hour, with end of surgery (i.e., completion of last suture) designated as Hour 0. The second dose of study drug or placebo will be administered in the post-anesthesia care unit (PACU) at +30 minutes (±30 minutes) from Hour 0 (post-surgery [redacted] #2). Study drug or placebo will be administered every 8 hours (±2 minutes) relative to pre-surgery [redacted] #1 and every 6 hours (±2 minutes) relative to post-surgery [redacted] #2 continuing through 48 hours. The APAP dose in the combination [redacted] given every 8 hours and the APAP dose alone given every 6h must not exceed 4000 mg in a 24-hour period. ([redacted] [redacted] Package Insert, 2018). The Schedule of [redacted] is presented in Table 4. Subjects will remain in the research unit for at least 48 hours post-surgery (discharge) as long as they are no longer sedated, and all assessments are completed. Subjects will be requested to return to the clinical research unit (CRU) on Day 7 (±1 day) for a follow-up safety visit. If an AE related to study drug is reported or is ongoing at the Follow-up/End of Study (EOS) visit on Day 7, a subject should be followed until appropriate resolution of the AE(s) as described in the protocol (Section 10.7).

Surgical and Anesthetic Protocol:

Subjects will undergo primary, unilateral, first metatarsal Austin bunionectomy. The surgical procedure should be limited to a maximum duration of 120 minutes with a target duration ≤90 minutes. The end of surgery (Hour 0) will be defined as completion of the last suture.

The surgery will be performed under regional anesthesia via a local Mayo block, with IV propofol for sedation.

Midazolam 1 mg IV may be administered pre-operatively for anxiolysis.

A small dose of lidocaine (up to 5 mL of 1% lidocaine without epinephrine) may be administered prior to administration of propofol to reduce venous irritation [redacted].

Propofol induction (dose per discretion of anesthesiologist) will be given as an initial bolus followed by a continuous infusion of up to 250 mcg/kg/min for intraoperative sedation.

Intraoperatively, all subjects will be given 50 mcg of fentanyl IV around the time of induction with propofol.

Once sedated, a Mayo block of the first metatarsal will be performed using 2% lidocaine without epinephrine; administered volume can range from 5–20 mL.

A pneumatic ankle tourniquet inflated between 150 mmHg and 250 mmHg will be applied to achieve hemostasis.

This standardized anesthetic regimen is a guide that should be followed to minimize interpatient variability to the greatest extent possible; however, it is understood that hemodynamic fluctuations and other intraoperative events may necessitate some deviation from this standard regimen. Anesthetic doses and times as detailed in the current protocol are suggested guidelines to be followed by the anesthesiologist caring for the subject. The actual doses and times administered are at the discretion of the anesthesiologist, based on the clinical status of the subject and will not be protocol deviations if not given exactly as described in the protocol.

In the event that a standard of care rescue medication or anesthetic listed in this protocol is not available due to supply/procurement issues, a medically acceptable alternative may be used after review and approval by the medical monitor, and this will not be a protocol deviation.

Rescue Medication:

The following rescue medications are available to subjects and may be administered for moderate to severe breakthrough pain measured by the NRS (Appendix 1) during the inpatient period:

- In the first 6 hours after surgery, IV morphine, not to exceed 10 mg in a 2-hour period for severe pain (NRS ≥7).In the first 12 hours after surgery, PO oxycodone 5 mg q2h PRN for moderate or severe pain (≥4) as reported by subjects via a standard 11-point NRS.
- From 12 hours after surgery to discharge, PO oxycodone 5 mg q4h PRN for moderate or severe pain (NRS ≥4).

Oxycodone should be used as the primary rescue medication whenever possible. Subjects will be encouraged to rescue only for moderate or greater pain scores (≥4), however rescue may be requested at any time and medication will be provided when requested per protocol timing above.

Study staff will record the exact time, medication, and dose for each administration of rescue.

Note: the NRS pain assessment must be performed within 15 minutes prior to the administration of rescue medication.

Number of Subjects (Planned):

Up to 80 subjects will be randomized (32 in each active treatment group, 16 placebo).

Randomization Procedure:

Eligible subjects will be randomized on Day 1 in a 2:2:1 ratio to receive either a combination of PGB [redacted] and APAP [redacted] administered [redacted] (Group A), APAP [redacted] (Group B), or [redacted] placebo [redacted] (Group C). Randomized subjects will receive either drug or placebo per their treatment allocation (see treatment groups below). All subjects will receive [redacted] of either study drug or placebo every 8 hours (±2 minutes) relative to [redacted] #1 and every 6 hours (±2 minutes) relative to [redacted] #2.The Schedule of [redacted] is presented in Table 4. To maintain blinding, all [redacted] for all study arms will be of identical volume.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

To be eligible for this study, a subject must meet ***all*** the following inclusion criteria:

1. Provide informed consent by signing the informed consent form (ICF) approved by the Institutional Review Board (IRB);
2. Be male or female aged 18-65 years;
3. Be scheduled to undergo unilateral first metatarsal bunionectomy;
4. Be in good health and capable of undergoing a bunionectomy under anesthesia as described in the study surgical and anesthetic protocol;
5. Weigh between 50 and 100 kg (body mass index [BMI] <32 kg/m^2);
6. Have no additional planned surgeries other than bunionectomy during the course of the study;
7. Have negative urine drug screen for drugs indicative of illicit drug use (unless results can be explained by a current prescription or acceptable over-the-counter medication at screening as determined by the investigator) and no detectable results on the alcohol test (breath or saliva) indicative of alcohol abuse at screening, and/or prior to surgery (may be repeated if the Investigator suspects a false-positive result).
   Note: *For those subjects who test positive for tetrahydrocannabinol (THC), if they are willing to abstain from use or consumption of THC-containing products from screening through end of the subject's participation in the study, they may be allowed to participate in the study.*
8. Biological female subjects must be non-lactating, sterile (bilateral tubal ligation, bilateral salpingectomy, or hysterectomy), post-menopausal for at least 2 years, have a partner that is sterile, be abstinent, use a highly effective double- contraception method (hormonal protection is insufficient), or use an FDA-approved contraceptive for greater than 2 months prior to the screening visit and commit to an acceptable form of birth control for the duration of the study and for 30 days after completion of the study;
9. Be willing and able to complete the study procedures and pain scales and communicate meaningfully in English with study personnel.

Exclusion Criteria:

A subject who meets ***any*** of the following exclusion criteria must be excluded from the study:

1. **Have a medical condition or history** that in the Investigator's opinion could adversely impact the subject's participation or safety or the conduct of the study, or interfere with the pain assessments, including the following:

   a. Serious breathing difficulties or respiratory risk factors (including use of opioid pain medicines and other drugs that depress the central nervous system), and conditions such as chronic obstructive pulmonary disease that reduce lung function.

b. Hypertension (uncontrolled), cardiovascular disease, or history of cerebrovascular events. Hypertension must be controlled without known end organ damage.
c. Concurrent painful conditions that may require analgesic treatment during the study period.
d. History of significantly reduced hepatic or renal function, angle closure glaucoma, or convulsive disorder.
e. Recent history of urinary retention.
f. Opioid tolerant, i.e., the subject is currently taking or has taken a chronic opioid at a dose greater than or equal to 20 mg morphine milligram equivalents (MME) per day (more than 30 consecutive days of daily use) for pain in the 2 months prior to surgery.
g. Active cutaneous disease, or other disease, at the surgical site.
h. Peripheral vascular disease, sickle cell disease, vascular grafts, or vasospastic disorders.
i. Known bleeding disorder or is taking agents affecting coagulation preoperatively. Deep venous thrombosis (DVT) prophylaxis of the surgeon's choice is permitted postoperatively.
j. Diabetes mellitus (uncontrolled). Diabetes mellitus must be controlled without known end organ damage.
k. History of malignancy in the past 2 years with the exception of squamous cell carcinoma or basal cell carcinoma.
l. Prior bunionectomy on the index foot or other foot surgery on the index foot that could impact the surgery or data collection endpoints.

2. **Use of disallowed medications** including the following:

a. Pain medication (opioids, NSAIDs, COX-2 inhibitors, tramadol, ketamine, clonidine, gabapentin, pregabalin, or cannabinoids) within 2 days prior to Day 1.
b. Central nervous system (CNS) active drugs such as benzodiazepines, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors (SNRIs), or selective serotonin reuptake inhibitors (SSRIs) for pain within seven days prior to Day 1. These drugs are permitted for non-pain indications if the dose has been stable for at least 30 days prior to Day 1 and is planned to remain stable throughout the study. The use of lorazepam and other sleep medications, except those containing analgesic properties, is permitted.
c. Use of parenteral or oral corticosteroid(s) within 14 days prior to Day 1.
d. Antihypertensive agent or diabetic regimen at a dose that has not been stable for at least 30 days, or which is not expected to remain stable throughout the study.
e. Digoxin, warfarin (see exception below), lithium, theophylline preparations, aminoglycosides, and all antiarrhythmics except beta-blockers, and use of anticonvulsants except benzodiazepines within 7 days prior to Day 1 and throughout the study.

- Use of warfarin is allowed, at the investigator's discretion, for DVT prophylaxis after the surgery.

3. Significant history of allergic reactions or known intolerance to pregabalin or any gabapentinoid, to APAP, to any rescue medication used in the study, or any medication used in the surgical and anesthetic protocol.
4. Female subjects (biological females only) who are pregnant or lactating, who plan to get pregnant, or who have a positive serum pregnancy test at Screening or a positive urine pregnancy test at either Day -1 or Day 1 prior to surgery.

5. Participated in another clinical trial within 30 days, or previously participated in a clinical study with a similar investigational product.

Investigational Product, Dosage and Mode of Administration:

All subjects will receive [redacted] of matching volume every 8 hours (±2 minutes) relative to pre-surgery [redacted] #1 and every 6 hours (±2 minutes) relative to post-surgery [redacted] #2.

A. The investigational product (IP) is a combination of PGB [redacted] and APAP [redacted] administered [redacted] administered q 8 hours (32 subjects). **Note: The final dose of PGB is determined by the CP-NVK009-0004 study.**
   - Treatment Group A will receive a combination of PGB [redacted] and APAP [redacted] administered [redacted] every 8 hours (±2 minutes) relative to pre-surgery [redacted] #1, and [redacted] placebo for [redacted] every 6 hours (±2 minutes) relative to post-surgery [redacted] #2.

The Schedule of [redacted] is presented in Table 4.

Reference Therapy, Dosage and Mode of Administration:

The reference therapies are the active comparator APAP [redacted] and [redacted] (placebo).

B. APAP [redacted] via [redacted] administered every 6 hours (±2 minutes) (32 subjects).
   - Treatment Group B will receive APAP [redacted] via [redacted] every 6 hours (±2 minutes) relative to post-surgery [redacted] #2, and [redacted] placebo via [redacted] every 8 hours (±2 minutes) relative to pre-surgery [redacted] #1.

C. [redacted] placebo for [redacted] (16 subjects).
   - Treatment Group C will receive [redacted] placebo for [redacted] every 6 hours relative to post-surgery [redacted] #2 and every 8 hours (±2 minutes) relative to pre-surgery [redacted] #1.

The Schedule of [redacted] is presented in Table 4.

Duration of Treatment:

Up to 48 hours.

Criteria for Evaluation:

Efficacy:

- NRS (Appendix 1) at the following time points post-Hour 0 (note these times are from last suture of surgery, not end of initial study drug [redacted] : 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 hours (±15 minutes), then every 4 hours (±15 minutes) until discharge or early termination. Note: Every effort will be made to ensure two consecutive NRS assessments are not missed or skipped. However, should two NRS assessments be missed due to normal sleeping hours, a deviation will not be incurred. Pain assessments should always be performed 5 to 10 minutes after the end of [redacted] and PK sampling and/or safety blood draws to avoid overlap with any pain associated with blood draws.
- Patient-reported NRS prior to each use of opioid rescue medication.
- PGA at 48 hours or at Early Termination (ET) (Appendix 2).

Criteria for Evaluation (continued):

Safety:

- Monitoring of AEs and SAEs, including clinically significant clinical laboratory findings (hematology, biochemistry, and urinalysis/urine microscopy), physical examination findings, vital signs, and 12-lead ECGs.
- Monitoring of the Modified Aldrete Scoring System (Appendix 3) including Activity, Respiration, Circulation, Consciousness, and Oxygenation.

Pharmacokinetics:

Determination of plasma concentrations of PGB and APAP prior to dosing (C_{min}) and at the end of each dosing (C_{max}).

Statistical Methods:

Sample Size

All hypothesis tests will be performed at a one-sided 10% level of significance. The sample size of 80 evaluable subjects (32 subjects: a combination of PGB [redacted] and APAP [redacted] administered [redacted] 32 subjects: APAP [redacted] alone, and 16 subjects: placebo) will provide 81% power to detect a standardized effect size of 0.54 between the combination of PGB [redacted] and APAP [redacted] administered [redacted] and APAP [redacted] alone treatment groups, and 80% power to detect a standardized effect size of 0.66 between the combination of PGB [redacted] and APAP [redacted] administered [redacted] and placebo treatment groups.

General Considerations

Statistical methods will be further outlined in a Statistical Analysis Plan (SAP). Procedures outlined in the SAP will supersede protocol-specified statistical methods in the event of divergence.

Data presentations 'by treatment group' outlined below are taken to be defined as by treatment group (a combination of PGB [redacted] and APAP [redacted] administered [redacted] APAP [redacted] for [redacted] or placebo for [redacted]

All hypothesis tests will be one-sided and performed at the 10% level of significance. All confidence intervals will be one-sided 90% confidence intervals.

Descriptive statistics (arithmetic mean, standard deviation [SD], median, minimum and maximum) will be calculated for continuous data as well as for the difference from baseline for each applicable visit, when appropriate. Descriptive statistics will be provided by treatment group. Frequency counts and percentages will be calculated for categorical data.

Analysis Sets

The Full Analysis Set (FAS) is defined as all randomized subjects who received at least one dose of study drug. Patients will be analyzed according to the treatment group to which they were randomized.

The Safety Analysis Set is defined as all subjects who received study drug. Subjects will be analyzed according to the actual treatment they received.

Per-Protocol (PP) Analysis Set is defined as the subset of FAS subjects who have no major protocol violations that could potentially impact the interpretation of their efficacy data. Subjects will be analyzed according to the actual treatment they received.

The PK Analysis Set is defined as all randomized subjects who received any amount of APAP and PGB, had no protocol deviations affecting the PK variables, and had sufficient data to allow evaluation of least one PK parameter, which are C_{min} and C_{max}.

Statistical Methods (continued):

Protocol violations will be reviewed and categorized prior to database lock and the PP Analysis Set will also be identified at that time. The subset of the list of major protocol deviations that result in exclusion of a subject from the PP Analysis Set will be documented prior to unblinding the study treatment allocation codes.

Subjects who receive mixed treatment(s) will be analyzed according to the treatment group they were randomized to for all analysis sets. Membership in the analysis sets will be determined before unblinding any study treatment codes. In general, data listings will include only subjects who receive study treatment (FAS and/or Safety Analysis Set).

Disposition, Enrollment, Demographics, and Medical History

Summary tables using descriptive statistics by treatment group where applicable would be provided for disposition and enrolment data for all randomized subjects, along with subject listings.

Demographics and medical history will be summarized by treatment group using descriptive statistics and listed by subject using the Safety Analysis Set.

Efficacy

The SPI will be calculated using the trapezoidal method as the area under the curve [AUC] of pain intensity as measured using the NRS (Appendix 1) through various time intervals up to 48 hours. The AUC will be calculated using the actual assessment times. For SPI_{0-48} calculation, all available NRS pain intensity scores (scheduled pain intensity, unscheduled pain intensity and pre-rescue pain intensity) from 0 to 48 hours, including any imputed values, will be used in the calculation. A windowed last observation carried forward (wLOCF) imputation using the pre-rescue pain intensity values will be performed for scheduled pain intensity according to the rescue frequency allowed during the scheduled times (e.g., 2 hours for oxycodone PO q2h, 4 hours for oxycodone PO q4h).

The primary efficacy variable, SPI_{0-48}, will be analyzed using a one-way analysis of variance (ANOVA) model with treatment group as the main effect. Summary statistics (n, mean, SD, median, minimum, and maximum) will be presented. Least squares (LS) means and one-sided 90% confidence intervals will be presented along with the p-values from the ANOVA model.

Other SPI and pain intensity endpoints will be presented and analyzed similarly to the primary endpoint and presented graphically as appropriate. The total consumption of opioid rescue analgesia through 24 hours and through 48 hours will be analyzed using the nonparametric Wilcoxon rank sum test IP vs. placebo and active comparator comparison separately.

The total consumption of rescue analgesia results will be presented in a summary table with standard summary statistics as well as Wilcoxon rank sum means, pairwise rank-sum mean differences and p-values and will also be presented graphically.

The percentage of subjects that took rescue, as well as the percentage of subjects who do not require opioid rescue medication will be analyzed using a logistic regression with treatment group as the main effect. The analysis will compare the odds ratios of the proportions of opioid-free subjects between each treatment group and the placebo or active comparator group, respectively. A summary of frequencies as well as odds ratio, 90% confidence intervals and p-values will be presented.

Time to first rescue will be analyzed using Kaplan-Meier techniques. Summary statistics will be presented, and treatment groups compared using a log rank test. A Kaplan Meier graph will also be presented.

The PGA (Appendix 2) results will be presented in a summary table by treatment group using standard summary statistics as well as LS means, pairwise LS mean differences, standard errors, confidence intervals and p-values. P-values will be calculated using an ANOVA with treatment group as the main effect. The number (%) of subjects answering in each category will also be presented by treatment group.

Statistical Methods (continued):

Safety

Adverse events will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA version 22.0 or higher). A subject AE data listing, including verbatim term, preferred term, system organ class (SOC), treatment group, severity, and relationship to study drug, will be provided. The number of subjects experiencing TEAEs and number of individual TEAEs will be summarized by treatment group, SOC, and preferred term. TEAEs will also be summarized by treatment group, severity, and relationship to study drug, where applicable.

Clinical laboratory evaluations and vital signs assessments will be summarized by treatment group at the protocol specified collection time point using descriptive statistics. A summary of change from baseline and counts of number of values out of normal range at each protocol-specified time point by treatment group will also be presented.

Vital signs (blood pressure [systolic and diastolic], heart rate, respiratory rate, oral or temporal body temperature, and pulse oximetry) will be summarized by treatment group. Observed and change from baseline values will be summarized by treatment group at each scheduled visit. Listings will also be provided.

Clinical assessment of ECG (Normal, Abnormal NCS [not clinically significant], Abnormal CS [clinically significant]) will be summarized by treatment group at each scheduled visit, using frequency tabulations.

Physical examination findings at each visit will be listed.

Prior and concomitant medications will be coded using the most current World Health Organization (WHO) drug dictionary (Version B3 September 2018 Drug Global or higher). Prior and concomitant medications will be summarized by anatomical therapeutic class and preferred name for each treatment group.

Modified Aldrete Scoring System (Appendix 3) including Activity, Respiration, Circulation, Consciousness, and Oxygenation will be summarized by treatment group using descriptive statistics. Subject listings will also be provided.

Pharmacokinetics

Plasma concentration data will be summarized by sampling time and treatment group as appropriate; PK parameters will be summarized by treatment group and scheduled visit as appropriate. All individual plasma concentrations and PK parameter estimates of C_{min} and C_{max} will be listed and summarized. Summary statistics will include number of subjects, number below the limit of quantification (BLQ) (exclusively for concentration summaries), arithmetic mean, SD, co-efficient of variation (CV), median, minimum and maximum. In addition, the geometric mean and geometric CV will be reported. Between-subject variability will be based on geometric mean CV. Mean concentration over time will be presented as graphs for each treatment group on the raw and linear scale.

Statistical Analysis Plan

A Phase 2, Randomized, Double-Blind, Placebo- and Comparator-Controlled Trial to Evaluate the Safety and Efficacy of Combination [redacted] Pregabalin and Acetaminophen Compared to Acetaminophen and Placebo in Subjects Undergoing Bunionectomy

Version 2.0; Dated: 19-November-2020

Protocol number: CP-NVK009-0005

Sponsor: Nevakar, Inc. NJ 08807

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: NVK009, a combination of pregabalin (PGB) [redacted] and [redacted] (acetaminophen [APAP] [redacted] administered [redacted]	**Page:**	
Name of Active Ingredient: Pregabalin (PGB) and acetaminophen (APAP)		
Title Of Study: A Phase 2, Randomized, Double-Blind, Placebo- and Comparator-Controlled Trial to Evaluate the Safety and Efficacy of Combination [redacted] Pregabalin and Acetaminophen Compared to Acetaminophen and Placebo in Subjects Undergoing Bunionectomy		
Investigators: Study Center(s): 1 to 3 study centers (US)		
Studied period (years): Study is expected be completed within 4 months of the first subject entry.	**Phase of development:** Phase 2	

Objectives:

Primary:

• To evaluate the efficacy of combination PGB [redacted] and APAP [redacted] administered [redacted] vs. placebo for pain control in subjects undergoing bunionectomy.

Secondary:

• To evaluate the efficacy of combination PGB [redacted] and APAP [redacted] administered [redacted] vs. comparator (APAP [redacted] alone) for pain control in subjects undergoing bunionectomy.

• To evaluate the safety and tolerability of a combination of PGB [redacted] and APAP [redacted] administered [redacted] in a postoperative population.

Methodology:

CP-NVK009-0005 is a phase 2, multi-center, randomized, double-blind, parallel-group, placebo- and comparator-controlled study.

Subjects will undergo a Screening Visit (Day -42 to Day -2). Pre-operative assessments will be conducted within 24 hours prior to surgery (on either Day -1 or Day 1 prior to surgery) and prior to any dosing. Subjects scheduled for bunionectomy surgery who meet all of the inclusion criteria and none of the exclusion criteria stated below will be enrolled and randomized (Day 1). Subjects and all study staff performing study assessments will be blinded to treatment allocation.

On Day 1, the first dose of study drug or placebo will be administered approximately 30 to 90 minutes before surgery (pre-Surgery [redacted] #1) when the subject is in the pre-operative area. [redacted] are approximately 15 minutes. Surgery will be performed approximately within the next hour, with end of surgery (i.e., completion of last suture) designated as Hour 0. The second dose of study drug or placebo will be administered in the post-anesthesia care unit (PACU) at +30 minutes (±30 minutes) from Hour 0 (post-surgery [redacted] #2). Study drug or placebo will be administered every 8 hours (±2 minutes) relative to pre-surgery [redacted] #1 and every 6 hours (±2 minutes) relative to post-surgery [redacted] #2 continuing through 48 hours. The APAP dose in the combination [redacted] given every 8 hours and the APAP dose alone given every 6h must not exceed [redacted] in a 24-hour period ([redacted] [redacted] Package Insert, 2018). The Schedule of [redacted] is presented in Table 4 of the protocol. Subjects will remain in the research unit for at least 48 hours post-surgery (discharge) as long as they are no longer sedated, and all assessments are completed. Subjects will be requested to return to the clinical research unit (CRU) on Day 7 (±1 day) for a follow-up safety visit. If an AE related to study drug is reported or is ongoing at the Follow-up/End of Study (EOS) visit on Day 7, a subject should be followed until appropriate resolution of the AE(s) as described in the protocol (Section 10.7).

Number of Subjects (planned and analyzed):

80 subjects (32 per active treatment group, 16 placebo).

Diagnosis and main criteria for inclusion:

Male and female between 18-65 years of age with weigh between 50 and 100 kg (body mass index [BMI] <32 kg/m^2) could participate in the study. Subjects must be in good health and capable of undergoing a bunionectomy under anesthesia as described in the study surgical and anesthetic protocol.

They must be scheduled to undergo unilateral first metatarsal bunionectomy and have no additional planned surgeries other than bunionectomy during the course of the study. Subjects should provide informed consent by signing the informed consent form (ICF) approved by the Institutional Review Board (IRB), be willing and able to complete the study procedures and pain scales and communicate meaningfully in English with study personnel. The inclusion criteria is to have negative urine drug screen for drugs indicative of illicit drug use (unless results can be explained by a current prescription or acceptable over-the-counter medication at screening as determined by the investigator) and no detectable results on the alcohol test (breath or saliva) indicative of alcohol abuse at screening, and/or prior to surgery (may be repeated if the Investigator suspects a false-positive result).
Biological female subjects must be non-lactating, sterile (bilateral tubal ligation, bilateral salpingectomy, or hysterectomy), post-menopausal for at least 2 years, have a partner that is sterile, be abstinent, use a highly effective double- contraception method (hormonal protection is insufficient), or use an FDA-approved contraceptive for greater than 2 months prior to the screening visit and commit to an acceptable form of birth control for the duration of the study and for 30 days after completion of the study.

Test product, dose and mode of administration:

All subjects will receive [redacted] of matching volume every 8 hours (±2 minutes) relative to pre-surgery [redacted] #1 and every 6 hours (±2 minutes) relative to post-surgery [redacted] #2.
Treatment Group A will receive a combination of PGB [redacted] and APAP [redacted] administered [redacted] every 8 hours (±2 minutes) relative to pre-surgery [redacted] #1, and [redacted] placebo for [redacted] every 6 hours (±2 minutes) relative to post-surgery [redacted] #2.
Note: The final dose of PGB is determined by the CP-NVK009-0004 study.
The Schedule of [redacted] is presented in Table 4 of Protocol.

Duration of treatment:

The study will consist of a screening period of up to 40 days (Day -42 to -2), day of admission (Day -1 or Hour -24), day of surgery (Day 1), Day of discharge (Hour 48 relative to Hour 0) and follow-up visit (Day 7 ±1 days). Duration of treatment will be up to 48 hours.

Reference therapy, dose and mode of administration:

The reference therapies are the active comparator APAP [redacted] and [redacted] (placebo):

- Treatment Group B will receive APAP [redacted] via [redacted] every 6 hours (±2 minutes) relative to post-surgery [redacted] #2, and [redacted] placebo via [redacted] every 8 hours (±2 minutes) relative to pre-surgery [redacted] #1.
- Treatment Group C will receive [redacted] placebo for [redacted] every 6 hours (±2 minutes) relative to post-surgery [redacted] #2 and every 8 hours (±2 minutes) relative to pre-surgery [redacted] #1.

The Schedule of [redacted] is presented in Table 4 of Protocol.