Official Title: A Randomized, Double-Blind, Placebo- and Active-Controlled Study to Determine the Efficacy and Safety of CL-108 5 mg (hydrocodone 5 mg/acetaminophen 325 mg/ promethazine 12.5 mg) as a Treatment for Moderate-to-Severe Acute Pain and the Prevention of Opioid-Induced Nausea and Vomiting (OINV) following Orthopedic Surgery

NCT Number: NCT03657810

Applicant/MAH: Charleston Laboratories Inc.

Version Date: 17 August 2017

16. APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Protocol Amendment 02 Version 3.0 dated 17 August 2017

CHARLESTON LABORATORIES, INC.

Protocol No. CLCT-018

IND 78,609

Protocol No. CLCT-018

A Randomized, Double-Blind, Placebo- and Active-Controlled Study to Determine the Efficacy and Safety of CL-108 5 mg (Hydrocodone 5 mg/Acetaminophen 325 mg/Promethazine 12.5 mg) as a Treatment for Moderate-to-Severe Acute Pain and the Prevention of Opioid-Induced Nausea and Vomiting (OINV) Following Orthopedic Surgery

Amendment 02

Version 3.0

17 August 2017

The confidential information in the following document is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and applicable Institutional Review Board. By accepting this document, you agree that the information contained herein will not be disclosed to others without written authorization from Charleston Laboratories, Inc., except to the extent necessary to obtain informed consent from those persons to whom the drug will be administered.

Approved by:

PI

PI MD

Chief Scientific Office

PI

Date

CHARLESTON LABORATORIES, INC.

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List of Abbreviations

˚F	degrees Fahrenheit
APAP	acetaminophen
BOCF	baseline observation carried forward
CL	Charleston Laboratories, Inc.
CL-108	hydrocodone 7.5 mg/APAP 325 mg/promethazine 12.5 mg
CL-108 5 mg	hydrocodone 5 mg/APAP 325 mg/promethazine 12.5 mg
CRO	Contract Research Organization
eCRF	Electronic CRF
ESAS	Edmonton Symptom Assessment Scales
DMC	Data Monitoring Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HC/APAP	hydrocodone 5 mg/APAP 325 mg
HCG	human chorionic gonadotropin
hr	hour
ICF	informed consent form
IRB	Institutional Review Board
ITT	intent-to-treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mo	month
Norco®	hydrocodone 5 mg/APAP 325 mg
NS	Nausea Scale
NNT	Number-needed to treat
NPQ	Nausea-Prone Questionnaire
OINV	opioid-induced nausea and vomiting
OSS	Opioid Symptoms Scales
PI-CAT	categorical pain intensity rating scale
PI-NRS	numerical pain intensity rating scale
PID	pain intensity difference
SAE	serious adverse event
SAP	statistical analysis plan
$SPID_{24}$	summed pain intensity differences over 24 hours
$SPID_{48}$	summed pain intensity differences over 48 hours
SDS	Symptoms Distress Scale
US	United States
VFS	Vomiting Frequency Scale
WHO-DD	World Health Organization-Drug Dictionary
WOCF	Worst observation carried forward

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Protocol No. CLCT-018

1 SYNOPSIS

1.1 Title

A Randomized, Double-Blind, Placebo- and Active-Controlled Study to Determine the Efficacy and Safety of CL-108 5 mg (hydrocodone 5 mg/acetaminophen 325 mg/ promethazine 12.5 mg) as a Treatment for Moderate-to-Severe Acute Pain and the Prevention of Opioid-Induced Nausea and Vomiting (OINV) following Orthopedic Surgery.

1.2 Objectives

To determine the analgesic efficacy of CL-108 5 mg by comparison with placebo and the anti-emetic efficacy of CL-108 5 mg by comparison with hydrocodone 5 mg/acetaminophen 325 mg (HC/APAP).

1.3 Study design

This is a phase 3, randomized, double-blind, multiple-dose, multi-site controlled study of CL-108 5 mg (hydrocodone 5 mg/APAP 325 mg/promethazine 12.5 mg) compared to placebo and to a standard formulation of hydrocodone 5 mg/APAP 325 mg (Norco®) in patients with moderate-to-severe pain following unilateral first metatarsal bunionectomy (with osteotomy and internal fixation) without collateral procedures.

Adults 18 years at time of consent of age and older who have a bunion on the foot which they want removed and who are possibly at risk for OINV will have a Screening Visit (**Visit 1**) when a foot x-ray will be obtained (if not in possession of a foot x-ray within the past 6 months) and reviewed by the surgeon (between Visit 1 and Visit 2 prior to surgery). Admission criteria will be reviewed, a screening physical examination will be performed, urine will be collected (for drug screening and cotinine on all patients) and pregnancy testing (for all female patients regardless of childbearing potential).

The medical history will be obtained, including a Nausea-Prone Questionnaire (NPQ). This instrument was developed for previous Phase 3 studies to increase assay sensitivity by enriching the study sample with patients who, by history, are assumed to be at risk of developing OINV according to accepted criteria (e.g., by a history of previous OINV, nausea/vomiting after a surgical procedure or operation, exposure to an opioid, or motion sickness).[1-3,6-8] patients whom the Investigators consider possibly at risk of OINV according to their responses on the NPQ will be scheduled for surgery within 3 months.

Urine pregnancy tests will be performed on all female patients and urine drug screening tests and urine cotinine test will be performed on all patients prior to surgery at **Visit 2**. After sedation (midazolam and/or propofol) is achieved, regional anesthesia will be established with a popliteal sciatic nerve block (PSB), after which patients will undergo primary, unilateral, first metatarsal bunionectomy surgery (osteotomy and internal fixation) without collateral procedures. Surgery will be performed under regional anesthesia and propofol sedation. If the PSB is not sufficient to provide

adequate anesthesia, a standard Mayo block may be established. Prophylactic or post-operative anti-emetic or analgesic medications other than protocol-defined medications will not be permitted (see Section 5.2).

After surgery the regional anesthesia will be continued via a continuous anesthetic infusion until approximately 3 am of the morning after surgery (see Section 6.3.3). Supplementary analgesic medication (IV or IM ketorolac) may be administered as needed for breakthrough pain. Patients will be observed in the research center for up to 9 hours after the PSB is discontinued to observe if they report the presence of moderate or severe pain by a rating of 2 or 3 on a 0-3 categorical pain intensity scale (PI-CAT).

Baseline pain intensity must be confirmed by a rating ≥4 on a 0-10 numerical rating scale (PI-NRS) in order to be eligible for randomization.

Temperature (aural), pulse, respiratory rate, systolic and diastolic blood pressure (semi-recumbent for 5 minutes) will be obtained at Baseline.

To determine if nausea and vomiting or other symptoms associated with opioids (e.g., drowsiness, dizziness, ability to concentrate, itch, constipation) are present before exposure to study medication, patients will then complete these measures of patient-reported outcomes:

- Nausea Scale (NS), a binary scale to assess the presence/absence of nausea

- Vomiting Frequency Scale (VFS), a 0-to-3 ordinal scale to assess the occurrence of vomiting over the past hour (not at all, 1 time, 2 times, 3 or more times)

- Opioid Symptoms Scales (OSS), derived from the Symptom Distress Scales,[4] to assess the presence and severity of other opioid-related side effects (e.g., drowsiness, dizziness, ability to concentrate, itch, constipation)

Qualifying patients (n=330) will be assigned a randomization number and randomized under double-blind conditions to one of the three treatment groups: CL-108 5 mg, hydrocodone 5 mg/APAP 325 mg (HC/APAP), or placebo. All randomized patients will remain at the research site for the primary initial 48-hour treatment observation period when the same assigned study medication will be administered on schedule for a total of 10 doses. Subjects should be awoken for dosing, as needed to remain on the dosing schedule.

In the Clinic Diary, after baseline assessments, pain intensity (on the PI-NRS) and nausea (on the NS) will be assessed every 30 minutes over the next 12 hours (while awake).

Beginning at 1 hour through 12 hours after the first dose, the VFS will be completed hourly to assess the occurrence and frequency of retching and/or vomiting.

After 12 hours, the patient will complete the PI-NRS, NS and VFS every hour (if awake) until 48 hours.

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To provide evaluations of other opioid-related side effects after multiple doses of study medication over the first and second day of therapy, patients will repeat the OSS at 24 hours and 48 hours.

In addition to these actively solicited assessments of nausea, vomiting and other opioid side effects, the Study Coordinator will also observe the patient's status on an hourly basis throughout the entire initial 48-hour treatment observation period in the clinic. At these hourly intervals during the day and at night (if the patient is awake) patients will also be asked how they are feeling and to report any other adverse events. The Investigator will rate the severity of all side effects on a 3-category severity scale (mild, moderate, severe) and determine relationship of the adverse event to study drug. These data will be documented on the AE page of the eCRF. Subjects should be awoken for dosing, as needed to remain on the dosing schedule.

Temperature (aural), pulse, respiratory rate, systolic and diastolic blood pressure (semi-recumbent for 5 minutes) will be obtained every 6 hours (if awake) until 24 hours post-dosing and at 48 hours.

Patients may take supplementary (rescue) analgesic medication, ibuprofen 400 mg, as needed at any time according to label directions (every 4-6 hours, up to 2,400 mg over 24 hours), but they will be encouraged to wait at least 2 hours after the initial dose of study medication, if possible, to allow time for evaluation of only the study medication.

Anti-emetic (rescue) medication (prescribed by the Investigator according to standard clinical practice) is permitted any time after the initial dose of study medication.

No other post-operative medications are permitted.

Throughout the entire initial 48-hour treatment observation period, scheduled dosing of study medication will not be interrupted by use(s) of rescue medication. As a result, all patients will receive 5 doses of study medication during each 24-hour period (for a total of 10 doses over 48 hours).

At the completion of the 48-hour assessments, patients will be discharged as outpatients for Days 3-7 of the study. They will receive instructions for routine post-op care and for self-dosing with the same assigned study medication as needed for pain every 4-6 hours (for a maximum of 6 doses in a 24-hour period), documenting the date and time of each dosing with study medication in an Outpatient Diary.

Patients will also use the Outpatient Diary to record the date and time of taking (rescue) supplemental analgesic medication (ibuprofen 400 mg) and/or prescribed anti-emetic medication and any adverse events they experienced over the past 24 hours.

Approximately 24 hours after the patient is discharged from the clinic after Visit 2, the Study Coordinator will telephone the patient to inquire about his/her post-op status, adverse events, uses of study medication and (rescue) supplemental medications, and use of the Diary and to confirm the follow-up appointment.

Approximately 8 (± 2) days after surgery, patients will return to the clinic for **Visit 3**, when the patient's Outpatient Diary, use of study medication and supplemental medications, and all adverse events will be reviewed. Vital signs will be measured for all patients, and a third urine cotinine test will be performed on all patients and urine pregnancy test will be performed on all female patients. All patients will then be discharged from the study. Routine post-op care will be provided according to standard clinical practice, with telephone follow-up for any ongoing side effects until resolution or stabilization.

1.4 Endpoints

1.4.1 Co-Primary Endpoints

- Occurrence of opioid-induced nausea and vomiting (OINV*) over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg

  * *OINV defined as a 2-component endpoint: any vomiting or use of anti-emetic medication (indicative of nausea)*

- Relief of moderate to severe acute pain over 48 hours ($SPID_{48}$), comparing CL-108 5 mg to placebo

1.4.2 Key Secondary Endpoints

1) Absence of any nausea, any vomiting, or any use of anti-emetic medication over 48 hours (complete absence of OINV), comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg

2) Percentage of patients without any vomiting over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg

3) Percentage of patients without any nausea over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg

4) Percentage of patients without any nausea or vomiting 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg

1.5 Setting and Patients

Approximately three hundred and thirty (330) patients undergoing a primary, unilateral metatarsal bunionectomy (osteotomy and internal fixation without collateral procedures) will be randomized to study medication at different research centers in the US.

Males and non-pregnant, non-lactating females aged 18 years and older that experience moderate or severe acute pain will be eligible to participate in the randomized, double-blind clinical trial.

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1.6 Study Treatments

All study treatments appear identical.

Each study medication dose will consist of one over-encapsulated tablet containing either:

- CL-108 5 mg (hydrocodone 5 mg/APAP 325 mg/promethazine 12.5 mg);
- hydrocodone 5 mg/APAP 325 mg (Norco®); or
- placebo.

1.7 Sample Size

The study is sized to determine the occurrence of vomiting or the use of anti-emetics(opioid-induced nausea and vomiting, or OINV) of CL-108 5 mg compared to hydrocodone 5 mg/APAP 325 mg over 48 hours (Section 7.4.2 below).

Approximately three hundred and thirty (330) patients will be enrolled so that three hundred (300) completed patients can be evaluated within three treatment groups: CL-108 5 mg (n = 120), hydrocodone 5 mg/APAP 325 mg (n = 120), placebo (n = 60).

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1.8 STUDY FLOW CHART

	V1 Screen	V2 (≤3 mo)	0	0.5 hr - 12 hrs	13-24 hrs	24-48 hrs	Day 3-7	V3 (±2 d)
Informed Consent	X							
Medical History	X	X						
Nausea Prone Questionnaire (NPQ) Health Questionnaire	X							
Foot X-ray[6]	X	X						
Physical Examination	X	X[10]						
Urine Drug Screen [11]	X	X						
Urine cotinine test	X	X						X
Urine Pregnancy Test[7]	X	X						X
Vitals Signs (aural temp, HR, BP, RR)[8]	X	X	X	X	X	X		X
Height and weight (BMI)	X							
Surgical Procedure		X						
Pain Intensity Categorical Scale (PI-CAT)			X					
Pain Intensity Numerical Rating Scale (PI-NRS)[1,2]			X	X	X			
Nausea Scale (NS)[1,2]			X	X	X			
Vomiting Frequency Scale (VFS)[3]			X	X	X			
Opioid Symptom Scales (OSS)[4]			X			X		
Administration of Study Medication[9]			X	X	X	X	X	
Follow-up Telephone Call[5]							X	
Adverse Events				X	X		X	X
Use of Rescue and other Concomitant Medications	X	X		X	X		X	X
Suture Removal								X
Return Diary, Medication Bottle								X

[1] PI-NRS and NS administered half-hourly (scheduled time) from 30 mins - 12 hrs.
[2] PI-NRS and NS (with VFS) administered hourly from 13 - 48 hrs (when the patient is awake).
[3] VFS administered hourly from 1-48 hrs (when the patient is awake).
[4] OSS administered at baseline, 24 hrs and 48 hrs.
[5] The Study Coordinator will telephone the patient approximately 24 hours (+2 days) after discharge from the study.
[6] The Investigator will examine a foot x-ray before surgery at Visit 2 if not completed at Visit 1 (e.g., if the x-ray was not obtained in the last 6 months of Visit 1 or is unavailable).
[7] All female patients (regardless of childbearing potential) will undergo urine pregnancy testing at the beginning of Visits 1, 2 and 3.
[8] At screening (Visit 1), body temperature (aural), heart rate, blood pressure and respiratory rate will be measured while semi-recumbent for at least 5 minutes. The same measurements will also be performed (semi-recumbent for at least 5 minutes) before surgery, at Baseline, at 6 hours, at 12 hours, at 18 hours, at 24 hours, at 48 hours, and at Visit 3 before discharge.
[9] Each patient should receive 1 dose of study medication at 4-hour intervals (for a total of 5 doses of study medication) over the initial 24 hours of the study and 1 dose of study medication at 4-hour intervals (for a total of 5 doses of study medication) over the final 24 hours of the study while in-clinic (for a total of 10 doses over 48 hours). On Days 3-7 each patient may self-dose with study medication every 4-6 hours as needed.
[10] A brief physical exam will be performed at V2 prior to surgery.
[11] A positive urine drug screen will exclude the subject from participating in the study.

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2 Background and Rationale for the Study

CL-108 is a bi-layered tablet (containing hydrocodone 7.5 mg/APAP 325 mg in one layer, rapid-release promethazine 12.5 mg in the other layer) formulated to provide pain relief and to prevent or reduce opioid-induced nausea and vomiting (OINV). Because of its direct action on the receptors of the nausea-trigger zone (NTZ) in the brain stem which are stimulated by opioids, promethazine is well-suited as anti-emetic treatment of OINV. (Promethazine is approved for the prevention and treatment of nausea and vomiting as tablets, each containing 12.5 mg, 25 mg, or 50 mg, with directions for using 1-2 tablets every 4-6 hours.) Two randomized, double-blind, placebo-controlled Phase 3 trials (CLCT-002, CLCT-003) have been conducted demonstrating significant effects on pain by CL-108 compared to placebo and on OINV compared to the active control (hydrocodone 7.5 mg/APAP 325 mg).

Other hydrocodone/APAP products (such as Norco®) are approved that contain hydrocodone 5 mg with APAP 325 mg per tablet.

The purpose of the current study is to demonstrate the efficacy and safety of a 5-mg version of CL-108: CL-108 5 mg is a bi-layered tablet containing hydrocodone 5 mg/ APAP 325 mg in one layer, rapid-release promethazine 12.5 mg in the other layer.

The design of the current trial is consistent with the study designs developed for previous randomized controlled trials on CL-108. Included in the current trial, for example, is a Nausea-Prone Questionnaire, or NPQ, an enrichment instrument that was used in both previous Phase 3 trials to improve assay sensitivity by identifying patients who are possibly likely to develop OINV according to accepted risk criteria (e.g., a history of previous OINV, nausea/vomiting after a surgical procedure or operation, exposure to an opioid, or motion sickness). [1-3, 6-8]

The co-primary OINV objective of the current Phase 3 trial (CLCT-018) is to demonstrate the prevention of OINV by comparing the occurrence of OINV over 48 hours in patients treated with CL-108 5 mg and those treated with hydrocodone 5 mg/APAP 325 mg (Norco®). There are two components of the OINV endpoint: the occurrence of any vomiting or use of anti-emetic medication (indicative of nausea) over 48 hours. The occurrence and frequency of vomiting will be measured on a 0-3 Vomiting Frequency Scale, the occurrence of nausea will be measured on a binary Nausea Scale, and the use of anti-emetic medication will be documented in diaries.

The other co-primary endpoint of this trial is the relief of moderate to severe pain. Summed pain intensity differences over 48 hours ($SPID_{48}$) will be compared for patients treated with CL-108 5 mg and those treated with placebo. Pain intensity will be measured on a 0-10 Pain Intensity Numerical Rating Scale.

A standard pain model, the bunionectomy pain model that was used in CLCT-003, was selected for this multiple-dose, randomized, double-blind, placebo- and active-controlled trial.

The study will be conducted in compliance with the protocol, Good Clinical Practice Guidelines

(GCP), and all applicable regulatory requirements.

3 Objectives of the Study

- To compare CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg in terms of the occurrence of OINV (any vomiting or use of anti-emetic) over 48 hours
- To compare CL-108 5 mg to placebo in terms of pain reduction over 48 hours ($SPID_{48}$)

4 Trial Design

This is a Phase 3, double-blind, randomized, placebo- and active-controlled, multiple-dose study conducted at different research centers in the U.S. comparing CL-108 5 mg, hydrocodone 5 mg/APAP 325 mg, and placebo in patients after first metatarsal bunionectomy (osteotomy with fixation of the head of the first metatarsal bone).

4.1 Visit 1

Patients who have called the research center (spontaneously, by referral or in response to local advertisements or notification from the center) to have a bunion on the big toe removed and who are potentially qualified according to a pre-screen questionnaire will be scheduled for this screening visit. After patients sign an Informed Consent Form at Visit 1, a foot x-ray will be taken and reviewed by the surgeon between Visit 1 and Visit 2 prior to surgery (unless an x-ray was obtained within the past 6 months of Visit 1 another foot x-ray will be obtained). The patient's Medical History will be obtained and a physical examination will be performed. Height and weight will be measured (to calculate BMI). After the patient has been resting in the semi-recumbent position for a minimum of 5 minutes, vital signs will be measured including temperature, pulse, respiratory rate, blood pressure. A urine drug screen and urine cotinine test will be performed on all patients. A urine pregnancy test will be performed on each female patient regardless of childbearing potential. Inclusion and exclusion criteria will be reviewed to determine eligibility.

To identify the patient's nausea-prone status as suggested on the pre-screen questionnaire, each patient will complete the Nausea-Prone Questionnaire (NPQ), documenting previous medical and non-medical conditions associated with the development of nausea, including exposure to opiates, motion sickness, cigarette smoking, etc. By reviewing responses on the NPQ and using specific criteria (Section 6.3.2 below), the Investigator will determine if the patient could be considered at risk (or not) of opioid- induced nausea and vomiting. Patients who are not considered possibly at risk for OINV or whose nausea-prone status is uncertain or unknown will not be admitted to the trial. Patients who meet other admission criteria and whom the Investigator considers possibly at risk of OINV will progress to Visit 2.

Prior to leaving the clinic patients will be scheduled for surgery at Visit 2 within 3 months. They will take nothing by mouth after midnight on the night before surgery (including, in particular,

no analgesic or anti-emetic medication, although antibiotic prophylaxis for endocarditis may be prescribed, if indicated).

All patient entries in the Clinic Diary from Visit 1 will be entered onto the electronic case report forms (eCRFs) by site personnel.

4.2 Visit 2

On the day of surgery (Baseline/Treatment Visit) prior to surgery, the medical history will be reviewed, including pre-admission entry criteria, and a brief preoperative physical examination will be performed with vital signs, which include body temperature (aural), respiratory rate, pulse, and blood pressure (reclining for 5 minutes). A urine drug screen and urine continue test will be performed on all patients and a urine pregnancy test on all female patients.

Midazolam will be administered according to standard practice pre-operatively (and intra-operatively, if necessary). Regional anesthesia will be established using intravenous propofol and a popliteal sciatic nerve block (PSB) using 0.5% ropivacaine. Patients will undergo primary, unilateral, first metatarsal bunionectomy surgery (osteotomy and internal fixation) with no additional collateral procedures. If the PSB is not sufficient to provide adequate intraoperative anesthesia, a standard Mayo block may be established using short-acting lidocaine 1% or 2% (plain). Preoperative antibiotic (e.g., cephalexin) will be administered to all patients; if there are signs of post-operative infection, a patient may receive additional post-op antibiotic (which will be documented). Prophylactic antibiotic for endocarditis, ASA ≤ 325 mg for cardiovascular prophylaxis and chronic medications that are not contraindicated (Section 4.2 below) are also permitted. Except as permitted by protocol, other medications (in particular, opioid, anti-emetic) are not permitted during or after surgery.

The PSB will be continuous until approximately 3 am (± 15 minutes) of the morning after surgery. Patients will also receive IM or IV ketorolac 15 or 30 mg (by body weight) at the conclusion of surgery, then every 6 hours as needed for breakthrough pain until 1:30 am on the morning after surgery (see Section 6.3.3).

Patients will be observed in the research center for 9 hours after the popliteal sciatic block is discontinued to determine if they develop moderate or severe pain as measured on a categorical pain intensity rating scale (PI-CAT).

Moderate or severe baseline pain intensity must be confirmed on a 0-10 numerical rating scale (PI-NRS) in order to be eligible for randomization. Patients who do not report baseline PI-NRS ≥ 4 are screen failures.

Patients who do not qualify on the PI-CAT and the PI-NRS within 9 hours after discontinuation of the PSB will be discharged from the study with routine care.

All patients with at least moderate pain assessments on the PI-CAT and PI-NRS will complete

scales measuring different opioid side effects, including:

- a conventional binary Nausea Scale (NS) to document the presence/absence of nausea;
- a Vomiting Frequency Scale (VFS) to document episodes of vomiting, a measurement instrument which was used in CLCT-002;
- Opioid Symptoms Scales (OSS), derived from the Symptom Distress Scale to identify other opioid effects,[4] which were used in CLCT-002 and CLCT-003

Study medication will be allocated to qualifying patients based on a computer-generated randomization code: CL-108 5 mg (n = 120), hydrocodone 5 mg/APAP 325 mg (HC/APAP, n = 120), or placebo (n = 60). Study medication will be administered to patients under double-blind conditions.

Following the initial dose of study medication, patients will remain in the clinic for the entire 48-hour treatment observation period. The Study Coordinator will impress on the Patients the importance of using a Clinic Diary correctly, completing all assessments for the initial 12 hours and, when awake, for the remaining 36 hours of the 48-hour primary treatment observation period.

Vital signs, including temperature (aural), pulse, respiratory rate and blood pressure (semi-recumbent for at least 5 minutes) will be measured at Baseline immediately prior to dosing, then every 6 hours until 24 hours post-dosing. During the initial 12 hours of the treatment evaluation period, patients will record assessments every 30 minutes for pain intensity (on the PI-NRS) and the presence/absence of nausea (on the NS).

During the initial 12 hours (beginning at 1 hour) of the treatment evaluation period, at hourly intervals patients will use the VFS to assess the occurrence and frequency of vomiting over the past hour.

During the remaining 36 hours of the 48-hour primary treatment evaluation period (i.e., at hours 13-48), when awake, patients will record hourly assessments on the PI-NRS, NS and VFS.

To provide evaluations of other opioid-related side effects after multiple doses of study medication taken over 48 hours, patients will repeat the OSS at 24 hours and 48 hours while in the research center.

In order to document side effects and any other changes in his/her medical condition during the 48 hours after surgery (including nighttime), the Study Coordinator will make hourly observations of the patient's status. All patient reports of adverse events will be documented on the AE page of the eCRF.

In order to assure that all patients assigned to CL-108 5 mg and HC/APAP receive the same total

amount of hydrocodone/APAP during the primary 48-hour treatment observation period, patients will be dosed on a fixed schedule. To comply with label directions for HC/APAP to not dose more frequently than every 4 hours as treatment for moderate/severe acute pain, the Study Coordinator will give the patient the second dose of study medication 4 hours after the initial dose and the 3rd, 4th and 5th doses also at 4-hour intervals. As a result, all patients will receive 5 doses of study medication over the initial 24-hour treatment period (i.e., midway between 4 and 6 total daily doses that are permitted for hydrocodone/APAP). Dosing every 4 hours for 5 additional doses during the final 24-hour treatment period will assure that all patients are exposed to the same total amount of analgesic (in particular, hydrocodone) over 48 hours, contributing to the co-primary $SPID_{48}$ and OINV endpoints of the study. Subjects should be awoken for dosing, as needed to remain on the dosing schedule.

Patients may take supplementary (rescue) medication for pain (ibuprofen 400 mg) as needed at any time after taking the initial dose of study medication (every 4-6 hours, up to 2,400 mg over 24 hours), but they will be encouraged to wait at least 2 hours after the initial dose of study medication to allow sufficient time for evaluation of only the study drug.

Similarly, patients will be encouraged to take a subsequent scheduled dose of study medication rather than ibuprofen if the next dose of study medication is due within 1 hour. However, a patient will receive supplementary (rescue) medication for pain any time it is required.

Anti-emetic rescue medication (prescribed by the Investigator according to standard clinical practice) is permitted any time after the initial dose of study medication.

The date(s) and time(s) of taking rescue medications will be recorded in the eCRF.

Patients will be instructed to provide ratings on the PI-NRS, NS and VFS prior to each time they take rescue medication(s) over the initial 48-hour treatment observation period unless rescue medication is taken within 5 minutes after regularly scheduled 30- or 60-minute assessments.

Similarly, if a patient who used rescue medication has provided ratings on the PI-NRS, NS and VFS within 5 minutes before regularly scheduled PI-NRS, NS and VFS assessments, these regularly-scheduled assessments do not need to be repeated then.

At all other times regularly scheduled PI-NRS, NS, and VFS assessments will not be interrupted by the time of using rescue medication.

If a patient vomits, reports nausea, or takes a dose of analgesic or an anti-emetic rescue medication and then falls asleep, the patient will be awakened for the next scheduled assessments.

Scheduled dosing of study medication will also not be interrupted by the use(s) of rescue medication throughout the 48-hour treatment observation period. All patients should take all 10 doses of study medication over 48 hours.

Patients who take supplemental medication for pain and/or for nausea/vomiting are expected to document all evaluations and side effects throughout the initial 48-hour treatment evaluation period in the clinic (and for the remainder of the 7-day study as an outpatient).

Patients should continue to use study medication throughout the study in addition to supplemental medication needed for pain or nausea/vomiting.

At the completion of the 48-hour PI-NRS, NS, VFS and OSS assessments, vital signs will be repeated in the semi-recumbent position, adverse events will be reviewed, and patients will receive instructions for routine post-op care according to standard clinical practice.

They will be instructed as outpatients for Study Days 3-7 to self-dose with the same assigned study medication *as needed* for pain every 4-6 hours (for a maximum of 6 doses in a 24-hour period), documenting the date and time of each dosing with study medication (and rescue analgesic and anti-emetic medications) in an Outpatient Diary. All patients will receive a bottle of ibuprofen tablets (analgesic rescue medication) and a prescription for an anti-emetic of the investigator's choice (anti-emetic rescue medication) to be used as needed during Study Days 3-7.

At the conclusion of Visit 2 patients will be discharged from the clinic with a responsible adult.

All patient efficacy and safety entries in the Clinic Diary from Visit 2 will be entered onto the electronic case report forms (eCRFs) by site personnel.

4.3 Outpatient Phase (Days 3-7)

Patients will use an Outpatient Diary each day to document the dose, date and time of each self-dosing with study medication, each self-dosing with rescue analgesic medication (ibuprofen 400 mg) and/or prescribed rescue anti-emetic medication, and any other permitted medication (e.g., chronic medication).

Whether or not they used study medication or rescue medication each day, patients will use the Outpatient Diary on Days 3-7 to document any symptoms (adverse events) they experienced.

The Study Coordinator will telephone the patient approximately 24 hours after discharge from the clinic after Visit 2 (+2 days, to allow for weekends) to inquire about his/her post-op status, in particular, adverse events and uses of pain medication and (rescue) supplemental medications, and use of the Outpatient Diary, and to confirm the follow-up appointment.

4.4 Visit 3

Approximately 8 days (± 2) after surgery, patients will return to the clinic for a final visit, when the patient's Outpatient Diary, uses of study medication, supplemental/rescue medications and concomitant medications, and all adverse events will be reviewed.

Vital signs will be measured for all patients (aural temperature, pulse, respiratory rate), and blood

pressure (semi-recumbent for 5 minutes), and a third urine pregnancy test will be performed on all female patients and a urine cotinine test will be performed on all patients. All patients will then be discharged from the study. Routine post-op care will be provided according to standard clinical practice, with telephone follow-up for any ongoing side effects until resolution.

All patient safety entries in the Outpatient Diary will be entered onto the electronic case report forms (eCRFs) by site personnel.

Routine post-operative care will be provided after discharge from the study. For any continuing side effects, the Study Coordinator will call the patient every 48 hours (or routine follow-up) until the resolution or stabilization of the side effect.

5 Patient Selection and Withdrawal

5.1 Inclusion Criteria

A patient will be eligible for inclusion in this study if all of the following criteria apply:

1.	Informed consent	Signed informed consent form obtained at screening prior to any procedures being performed.
2.	Gender	Male or non-pregnant and non-lactating female. A female of child-bearing potential is eligible to participate in this study if she has a negative urine pregnancy test and is using an acceptable method of birth control (i.e., hormonal, transdermal, or implanted contraceptives, intrauterine device, diaphragm, condom, abstain from heterosexual sex, or surgical sterilization). See Section 5.3.
3.	Age	18 years or older at time of consent.
4.	OINV status	Determined by the Investigator as possibly at risk of opioid-induced nausea and vomiting according to accepted criteria, as documented on the Nausea Prone Questionnaire.
5.	Foot condition	Primary unilateral first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures.
6.	Pain Severity	Presence of moderate or severe pain (rating of 2 or 3) on the 0-3 categorical pain intensity scale (PI-CAT) at

		Baseline.
7.	Pain Confirmation	Rating ≥ 4 on the 0-10 numerical pain intensity scale (PI-NRS) at Baseline.
8.	Diary Completion	Be willing and able to record safety and efficacy ratings in the Diaries.
9.	Safe Transportation Home	Patient must have arrangements for transportation home from the research center accompanied by a responsible adult.

5.2 Exclusion Criteria

A patient will not be eligible for this study if one or more of the following apply:

1.	Medical condition	Presence of a serious medical condition (e.g., poorly controlled hypertension or diabetes, neurological disease including Parkinson's or other condition associated with a movement disorder, chronic pain, significantly impaired cardiac, renal, hepatic, respiratory, or thyroid function), intolerance to NSAIDs (e.g., dyspepsia), or any other medical condition which, in the opinion of the Investigator, makes the patient unsuitable for participation.
2.	Infection	Acute infection of the surgical site at the time of surgery that could confound post-surgical evaluation.
3.	Drug Allergy	History of hypersensitivity (i.e., allergy[1]) to an opioid drug (such as hydrocodone), promethazine, acetaminophen, NSAID (such as ibuprofen or aspirin), midazolam, propofol, mepivacaine, ropivacaine or ketorolac or history of a dystonic/dyskinetic reaction to anti-emetic or anti-psychotic medication.
4.	Confounding and	Other than protocol-permitted medications administered

[1] Because this is a study on opioid-induced nausea and vomiting (OINV), patients with a history of these opioid effects will not be excluded from the study. In fact, "nausea-prone" patients (especially those with a history of OINV) are sought in order to enrich enrollment in this study. Thus, for example, if patients erroneously consider themselves "allergic" to a narcotic, such as codeine, because they felt nauseated or "sick to my stomach" after using a cough medicine, they are admissible. Only medically-defined allergic reactions to an opioid (e.g., rash, hives) should prevent a patient from being admitted into this study.

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	Contraindicated Drugs	pre-operatively or during surgery: use within 14 days before or during the surgical procedure of any systemic corticosteroid or use within 24 hours or during the surgical procedure of any confounding prescription or non-prescription drug (e.g., analgesic, anti-emetic, sedating antihistamine, sedative, alcohol, or CNS/ psychotropic agent, including sleep aides, benzodiazepines, performance/attention enhancers, marijuana, anti-depressants) or any drug contraindicated with hydrocodone, acetaminophen, or promethazine. [Note: Antibiotic for endocarditis prophylaxis (except if known to cause nausea) and aspirin (ASA) ≤ 325 mg for cardiovascular prophylaxis are permitted during the study.] History of consuming more than 2 alcoholic drinks per day every day for the last month or a positive urine test for opiates, benzodiazepines, barbiturates, THC, methamphetamines, cocaine, oxycodone, cotinine at screening or the morning of surgery will exclude the patient from the trial.
5.	Caffeine Use	Ingestion of any caffeine-containing beverage or chocolate since midnight on the night before surgery.
6.	Nicotine Use	Use of any nicotine-containing product (cigarettes, e-cigarettes, patches, etc.) within the past 30 days.
7.	Investigational Drug Use	Use of an investigational drug within the past 30 days.
8.	Participated in Study	Previous participation in this study.
9.	Pregnancy, Lactation	Women who are pregnant or lactating.
10.	Compliance	Inability to swallow capsules whole.
11.	Participant relationship	Employee at the research center, employee of the Principal Investigator, Sub-Investigators, Charleston Laboratories or Daiichi Sankyo or relative of the Investigator, Sub-Investigators or research staff who is involved in this study.

5.3 Use in Females

The use of any drug in women who are of childbearing potential, pregnant, lactating requires that the potential benefit of the drug is weighed against the possible hazard to the mother and child. In view of these considerations, female patients are only eligible to participate in this study if they demonstrate a negative urine beta HCG test result at Visit 1 and prior to surgery at Visit 2 (confirmed at Visit 3).

5.4 Pregnancy Occurring During a Clinical Trial

If any female patient becomes pregnant while enrolled in this study (as confirmed by a positive urine beta HCG test result at Visit 3), she should notify the Investigator immediately and be withdrawn from the study. If applicable, all study-supplied supplemental (rescue) medications must be returned by the patient. If any female becomes pregnant (as confirmed by a positive urine pregnancy test at follow-up) and has taken study medication, the Investigator must notify INC's Pharmacovigilance Hotline at PI **or Email at** PI within 24 hours of learning about the pregnancy. Within the following 2 weeks, the Investigator must complete the Pregnancy Notification form. The Investigator will be required to follow the patient until delivery or termination of the pregnancy, providing necessary updated information using the Pregnancy Notification Follow-Up form.

5.5 Use of Supplemental (Rescue) Medication

There are two types of supplemental (rescue) medication, analgesic medication and anti-emetic medication. If patients experience post-operative pain that requires supplemental (rescue) analgesic medication, they may take ibuprofen 400 mg (which will be supplied) every 4-6 hours, up to 2,400 mg over 24 hours.

If possible, to allow sufficient time for evaluation of the study medication alone, patients will be encouraged to wait at least 2 hours after receiving the initial dose of study medication before taking supplemental analgesic. Similarly, between subsequent doses of study medication, patients will be encouraged to wait until the next scheduled dose of study medication. However, patients may take supplemental analgesic medication anytime. If a patient's pain cannot be controlled during the study, the patient will be discontinued from the study and treated according to conventional standard of care.

If a patient requires supplemental (rescue) analgesic after the 10th dose of study medication while in the clinic, another dose of ibuprofen 400 mg may be taken (provided the total daily dose of ibuprofen does not exceed 2,400 mg over 24 hours).

If additional analgesia is required at the end of the initial 48-hour treatment period, the Investigator may provide an IV dose of a non-opioid, non-APAP-containing analgesic (e.g., ketorolac 15 or 30 mg IV by body weight) according to package instructions.

If a patient requires anti-emetic rescue medication, the Investigator will prescribe an anti-emetic

at his/her own professional discretion according to standard clinical practice with dosing according to labelled directions for use.

Every time a patient receives a supplemental (rescue) analgesic or anti-emetic, the medication name, date, time, and dose of supplemental medication will be recorded in the source document and in the eCRF.

During the initial 48-hour treatment period patients will be instructed to record ratings on the PI-NRS, NS and VFS prior to each time they take rescue medication(s).

If a rescue time is within 5 minutes *before* the time for any regularly scheduled PI-NRS, NS and VFS assessments, the regularly scheduled assessments do not need to be completed in addition to the assessments at the time of taking an analgesic or anti-emetic rescue medication. If a rescue time is within 5 minutes *after* the time of recording any regularly scheduled PI-NRS, NS and VFS assessments, assessments at the time of rescue do not need to be repeated

At all other times during the initial 48-hour treatment period regularly scheduled PI-NRS, NS, and VFS assessments will not be interrupted by the time of using rescue medication.

To assure that all patients in the CL-108 5 mg and the hydrocodone 5 mg/APAP 325 mg treatment groups receive the same amount of analgesic medication (10 doses) over 48 hours, the schedule for the administration of study medication will not be interrupted by use(s) of any rescue/supplementary analgesic or anti-emetic medication.

After discharge from the clinic, if patients require anti-emetic treatment during Days 3-7 they may take the anti-emetic medication which the Investigator has prescribed according to local practice in addition to their study medication for pain. Every time a patient takes an anti-emetic medication on Days 3-7, he/she will be required to record the name, date(s) and time(s) of taking each dose in the Outpatient Diary.

Patients who use anti-emetic medication during Days 3-7 should continue to use study medication if needed for pain. If supplemental/rescue analgesic is needed on Days 3-7, the patient may take ibuprofen 400 as needed at any time according to label directions (every 4-6 hours, up to 2,400 mg over 24 hours). Every time a patient takes rescue analgesic medication on Days 3-7, he/she will be required to record the name, date(s) and time(s) of taking each dose in the Outpatient Diary.

Patients who take supplemental/rescue medication for pain and/or for nausea/vomiting on Days 3-7 are expected to document any side effects experienced each day in the Outpatient Diary.

5.6 Withdrawal

Patients may withdraw from the study or withdraw his or her consent at any time without penalty of loss of clinical care or patient rights to which they are entitled.

If a patient drops out of the study during the initial 48 hours of the study, he/she will be asked to record on the PI-NRS, NS, VFS and OSS at that time, and the date and time will be recorded on a separate CRF page. Instructions for using these scales at the time of withdrawal are:

> For the PI-NRS – On a scale of 0 to 10, where 0 is "no pain" and 10 is "severe pain," circle the number that best describes your pain *now*.
>
> For the NS - Over the past half-hour, have you had any nausea (feeling like you wanted to throw up)?
>
> For the VFS – How many times did you vomit (throw up) *over the past hour*?
>
> For the OSS - Circle the number that best describes each symptom you've had *since you began taking study medication.*

The Investigator should also perform the following evaluations and procedures before discharge from Visit 2:

- Pregnancy test (in females)
- Clinical adverse event assessment (which will be followed until resolution in consultation with the Medical Monitor)
- Review of use of concomitant medications
- Review of use of study medication
- Review of use of rescue medications
- Review of completeness of diary entries

5.6.1 Investigator's Reasons for Patient Withdrawal

The Investigator may withdraw a patient from the study if:

- a patient is unable to understand or use any of the rating scales;
- a patient has an exclusion criterion after study enrollment (e.g., positive urine pregnancy test, cotinine test, or drug screening test prior to surgery);
- continuing to participate in the study would, in the opinion of the Investigator, pose a risk to the safety and welfare of the patient.

The Investigator will also withdraw a patient upon request of Charleston Laboratories or if Charleston Laboratories terminates the study.

Upon occurrence of a serious or intolerable adverse event, the Investigator or designee will confer immediately with the Medical Monitor. Serious adverse events will be reported to Charleston Laboratories within 24 hours of determination. If a patient is discontinued due to an adverse event, the event will be followed until resolved or stabilized.

5.6.2 Handling of Withdrawals

If a patient withdraws or is withdrawn from the study because of a serious or intolerable adverse event after Visit 2, the Investigator must make every effort to perform the following evaluations and procedures at a follow-up visit:

- Pregnancy test (in females)
- Clinical adverse event assessment (which will be followed until resolution in consultation with the Medical Monitor)
- Review of use of concomitant medications
- Review of use of study medication
- Review of use of rescue medications
- Review of completeness of diary entries

These data are to be entered into the case report form and comprise an essential safety evaluation, which should be completed before discharge from the study.

If a patient withdraws from the study at any time prior to completion at the patient's request or the Investigator's discretion, the reason(s) for withdrawal shall be recorded by the Investigator on the appropriate electronic case report form (eCRF). If possible at a follow-up visit, all patients who withdraw from the study after dosing for non-adverse event-related reasons will undergo all procedures and assessments listed above at that time.

Patients who withdraw from treatment because of an adverse event or a serious adverse event after dosing will be followed until resolution.

6 Study Procedures

6.1 Evaluations of Safety and Eligibility

Safety evaluations will include the following to determine eligibility to participate in the study and to detect any changes from baseline:

Medical history and physical examination: At the screening visit a medical history, including medication history, will be obtained from the patient, and a limited pre-surgery physical examination will be performed to determine that the patient qualifies for the study (e.g., without medical or concurrent pharmacologic contraindications).

Vital Signs: At screening, body temperature (aural), heart rate, blood pressure and respiratory rate will be measured after the patient has been in the semi-recumbent position for at least 5 minutes, and height and weight (to determine BMI). The same measurements will also be performed (with the patient semi-recumbent for 5 minutes): before surgery at Visit 2; at Baseline; every 6 hours (± 10 minutes) following dosing for 24 hours post initial dose if the patient is awake; at 48 hours (± 10 minutes); and at Visit 3, before discharge from the study.

Drug Screen: A urine toxicology screen test (including opiates, benzodiazepines, barbiturates, THC, methamphetamines, cocaine, and oxycodone) will be performed on each patient at the Screening Visit and on the morning before surgery. A positive result will exclude the patient from participating in the trial.

Cotinine Test: A urine cotinine test will be performed on each patient at the Screening Visit and on the morning before surgery. A positive result will exclude the patient from participating in the trial. A urine cotinine test will also be performed at Visit 3. A positive result will indicate that the patient used nicotine during the trial.

Pregnancy Test: All females regardless of childbearing potential must have a urine beta HCG pregnancy test performed at screening and on the morning before surgery. A positive result will exclude the patient from participating in the trial.

A repeat beta HCG urine pregnancy test will be performed at follow-up Visit 3.

Pain Assessments: Patients will be asked to record their level of post-operative pain on the 0-to-3 (no pain, mild pain, moderate pain, severe pain) categorical pain intensity scale, or PI-CAT. Only patients with moderate or severe pain ratings (2 or 3) are eligible for the trial.

Confirmation of at least moderate pain is required on the 0-to-10 numerical pain intensity scale, or PI-NRS (i.e., a Baseline rating ≥ 4).

Clinical adverse event assessment: All adverse events will be recorded by the Study Coordinator or designee in the electronic case report form (eCRF) according to Section 9.1 of this protocol. All adverse events will be followed until resolution or stabilization.

6.2 Evaluations of Efficacy and Safety (See Appendices for Sample Indices)

6.2.1 Categorical Pain Intensity Scale (PI-CAT)

(called "Pain" in the Clinic Diary)

The patient will be asked at baseline to "Circle the number that best describes your pain now" on a 0-to-4 Likert scale. (No Pain/Mild Pain/Moderate Pain/ Severe Pain)

6.2.2 Numerical Pain Intensity Rating Scale (PI-NRS)

(called "Pain Severity" in the Clinic Diary)

The patient will be asked at baseline and at every post treatment assessment time to "Circle the number that best describes your pain now" on a 0-to-10 Likert scale.

The Numerical Pain Intensity Rating Scale is the measurement instrument for the co-primary analgesia endpoint.

6.2.3 Nausea Scale (NS)

(called "Nausea" in the Clinic Diary)

Nausea will be defined for each patient at baseline ("Nausea is feeling like you want to throw up").

At baseline and every 30 minutes after initial treatment until 12 hours, the patient will be asked "*Over the past half-hour, have you had any nausea (feeling like you wanted to throw u*p)?" using a binary scale (no nausea, nausea).

The patient will use the Nausea Scale every 60 minutes from 13 hours through 48 hours (when the patient is awake) in response to the question: *"Over the past hour, Have you had any nausea (feeling like you wanted to throw up)?"*

The Nausea Scale is the measurement instrument for documenting the occurrence (or absence) of nausea.

6.2.4 Vomiting Frequency Scale (VFS)

(called "Vomiting" in the Clinic Diary)

The patient will be instructed at baseline and every hour post treatment over the initial 48 hours after dosing: "How often did you vomit (throw up) over the past hour?" using an ordinal scale (not at all, one time, two times, three or more times).

The Vomiting Frequency Scale is the measurement instrument for documenting the occurrence of vomiting in the co-primary OINV endpoint, as in CLCT-002.

6.2.5 Opioid Symptom Scales (OSS) (from the Symptom Distress Scale)[4]

(called "Other Symptoms" in the Clinic Diary)

To document each of 9 other symptoms commonly experienced by patients using opioids

(dizziness, drowsiness, constipation, difficulty voiding, confusion, headache, itch, difficulty concentrating, dry mouth), at Baseline, at 24 hours, and at 48 hours the patient will be instructed "For each symptom you've had over the past 24 hours, circle the number that describes how severe it was for you" using an 11-point numerical rating scale for each symptom.

The Opioid Symptom Scales are measurement instruments for documenting the occurrence and severity of each other opioid-related symptom, as in CLCT-002 and CLCT-003.

6.2.6 Uses of Supplemental (Rescue) Analgesic Medication

The date, time, name (ibuprofen), and dose (400 mg) of each use of supplemental (rescue) medication for pain will be recorded in the eCRF.

6.2.7 Uses of Anti-emetic (Rescue) Medication

The date, time, name, and dose of each use of anti-emetic medication prescribed by the Investigator will be recorded in the eCRF.

6.2.8 Patient Reports of Adverse Events (Elicited and Volunteered)

Patients will be asked how they are feeling on an hourly basis throughout the initial in-clinic 48-hour treatment evaluation period (when they are awake). The Investigator will rate each side effect on a 1-3 scale (mild, moderate, severe). All ratings of adverse events, their relationship to study medication, remedial treatments, etc. will be documented and entered on the Adverse Events page of the eCRF.

Expected post-operative side effects (i.e., side effects such as localized erythema and numbness that the investigator considers related to the surgery) will not be recorded as AEs.

6.3 Study Conduct

6.3.1 Pre-Screening Procedures

Patients who respond to local advertisements or who are otherwise recruited to the research center (by social media, patient rosters at the clinic, etc.) will be pre-screened over the telephone or in person as potential patients for the study using a screening questionnaire. In addition to routine demographic questions, patients who want to have a bunion removed will also be asked questions to determine if they are possibly at risk for OINV (e.g., any allergy to a medication, including pain-killers; any reactions such as nausea or vomiting after surgery; any history of motion sickness; current smoking status/use of nicotine-containing products) and asked about their willingness to comply with study requirements (e.g., 3 visits, use of a diary) if they are accepted into the study.

Patients who appear to qualify for the study will receive appointments for Visit 1 within the next month.

6.3.2 Screening Procedures (Visit 1)

Patients 18 years of age and older who request a bunionectomy will be evaluated at the Screening Visit. After the informed consent form has been signed, the following procedures will be completed in order to assure eligibility according to the admission criteria:

- Urine drug screen on all patients
- Urine cotinine test on all patients
- Urine pregnancy test on all female patients (regardless of child-bearing potential)
- Physical examination, height and weight (to calculate BMI), vital signs (semi-recumbent for 5 minutes) including temperature (aural), pulse, respiratory rate, systolic and diastolic blood pressure
- Evaluation of a foot x-ray taken within the past 6 months prior to screening visit. If a patient does not have a foot x-ray taken within the past 6 months, it will be obtained and reviewed by the surgeon (to confirm the diagnosis of a first metatarsal bunion) at Visit 1 and/or prior to surgery at Visit 2
- Medical History including admission criteria, gender, smoking status/use of nicotine-containing products, and medications taken in the past 30 days
- Nausea-Prone Questionnaire (NPQ) (See Appendix 3)

As part of medical-history taking, patients will be asked to complete a "Health Questionnaire" which contains more than the Medical History and is designed to identify patients who are possibly at risk of opioid-induced nausea and vomiting (OINV). Patients will be asked a series of questions about different conditions associated with nausea (e.g., previous OINV, nausea after a post-op medication, nausea/vomiting after Vicodin, "allergy" to cough medicines, previous exposure to an opioid medication, sea sickness, other types of motion sickness) based on risk factors identified by Apfel et al[1-3] and Gan et al.[6-8]

Responses on the NPQ will be used by the Investigator to qualify a patient as being possibly at risk for OINV according to pre-determined criteria (A-D):

Criterion A: Any one of the following 5 responses to Questions 4-5, 7, 8 on the NPQ will be interpreted as meaning the patient is possibly at risk of OINV:

- Reports being "allergic" to an opioid-containing drug and the symptoms reported are determined to be nausea or vomiting (Q 4-5)
- Has taken an opioid-containing drug and became nauseated or vomited (Q 4-5)
- Has taken an unknown medication after an operation or surgical procedure and became nauseated or vomited (Q7-8)
- Reports being "allergic" to cough medicine and the symptoms reported are determined to be nausea or vomiting (Q4-5)
- Has taken a cough medicine (naming the opioid in it or not) and became nauseated or vomited (Q4-5)

Criterion B: If a patient has at least one of the following 5 responses to Questions 26-27, 30, 32-34, (relating to motion sickness) on the NPQ, the patient will be considered possibly at risk of OINV:

- Easily becomes nauseated when riding in a car (or requires an open window when riding in a car) (Q26-27)
- Easily becomes nauseated when riding backwards in a train (Q30)
- Easily becomes nauseated when on a roller-coaster (Q32)
- Easily becomes nauseated when spun around (Q33)Easily becomes nauseated when bending over (Q34)

Criterion C: Any rating ≥ 3 on Question 43 of the NPQ (which is a 0-10 Nausea-Prone Scale) will also be interpreted as meaning the patient is possibly at risk of OINV.

Criterion D: If Criteria A-C does not qualify a patient, the Investigator may consider a patient possibly at risk of OINV based on other responses on the NPQ (which the Investigator will identify, such as Questions 16-18, 21, 25, 28, 31, 39, gender, smoking status). The Investigator may thus use "clinical judgment" to admit up to approximately 10% of the total number of qualifying patients at his/her research center.

In sum, as a result of using the NPQ the Investigator will admit patients with a history suggestive of a predisposition for developing OINV, thus providing an enriched group of patients for evaluation at Visit 2.

The Investigator will cite each question on the NPQ that led to his/her determination that

the patient is possibly at risk for OINV.

Admission criteria will be reviewed to assure eligibility to the study. Patients who qualify will be scheduled for surgery within 90 days.

Patients who do not qualify will have their reason(s) for "screen failure" documented in the eCRF and will not progress in the study.

6.3.3 Surgery Day (Visit 2)

Within 90 days after Visit 1, screened patients who qualify for the study will report in the morning to the center having fasted since midnight.

(Exception: If a subject has consumed a small sip of liquid or small amount of food since midnight, the Investigator will determine if it is safe for the subject to have surgery under local anesthesia.)

Prior to surgery, the following will be performed:

- Documentation of concomitant medications (see Section 5.2, Exclusion #4)
- Urine drug screen
- Urine cotinine test
- Urine pregnancy test for all female patients
- Review of the Medical History
- Vital signs (semi-recumbent for 5 minutes), including temperature (aural), heart rate, respiratory rate and blood pressure (systolic and diastolic)
- Surgeon's assessment of the foot x-ray (at Visit 1, between Visits 1 and 2, or prior to surgery at Visit 2)

Moderate regional anesthesia will be standardized for all patients: patients will receive midazolam and/or propofol for initial sedation at the anesthesiologist's discretion. After adequate sedation is achieved, the anesthesiologist will inject approximately 5 mL lidocaine 1% or 2% (plain) locally to anesthetize the skin and will determine the location of the sciatic nerve for the popliteal sciatic block (PSB) using a nerve stimulator per standard technique. Once the appropriate location is determined and the catheter secured, the anesthesiologist will inject approximately 40 mL of ropivacaine 0.5% to establish the PSB via the catheter. Subsequently, the catheter will remain in place in the proximity of the popliteal sciatic nerve for delivery of postoperative anesthesia.

Patients will undergo primary, unilateral, first metatarsal bunionectomy surgery (osteotomy and internal fixation) with no additional collateral procedures. If the PSB is not sufficient to provide adequate intraoperative anesthesia, a standard Mayo block may be established using short-acting lidocaine 1% or 2% (plain, without epinephrine), not to exceed 25 ml..

Pre-operative antibiotic (e.g., cephalexin) will be administered to all patients; if there are signs of post-operative infection, a patient may receive additional post-op antibiotic (which will be documented).

Prophylactic antibiotic for endocarditis, ASA ≤ 325 mg for cardiovascular prophylaxis and chronic medications that are not contraindicated (see 4.2) are also permitted. Except as permitted by protocol, other medications (in particular, opioid and anti-emetic) and any nicotine-containing product are not permitted during or after surgery.

Patients will receive IM or IV ketorolac 15 or 30 mg (by body weight, per label) at the conclusion of surgery.

Patients who had bunionectomy surgery performed at the research center and patients were transferred to the research center after surgery will stay at the research center for study observations and routine post-surgical care.

The popliteal sciatic block will be maintained until approximately 3 am (± 15 minutes) of the morning after surgery.

Postoperative pain will be controlled by a continuous anesthetic infusion through the catheter previously placed adjacent to the popliteal sciatic nerve. Two methods of continuous anesthetic infusion are permitted. Mepivacaine 0.5% (plain) will be infused starting at 8 mL per hour and not to exceed 14 mL per hour.

During this continuous infusion period, patients may receive supplemental analgesia for breakthrough pain in the following fashion:

- First, bolus of mepivacaine (10 mL boluses injected via the catheter with no more than three 10 mL boluses allowed per hour) and/or increase rate of continuous local anesthetic infusion by 2 mL/hr (up to a maximum rate of 14 mL/hr). All use of mepivacaine will be discontinued at approximately 3 am on the morning following surgery.

Then, ketorolac (patients less than 65 years of age and greater than 50 kg: 30 mg IM or IV every 6 hours as needed with maximum daily dose 120 mg; patients greater than or equal to 65 years of age or less than 50 kg: 15 mg IM or IV every 6 hours as needed with maximum daily dose 60 mg). All use of ketorolac will be discontinued at 1:30 am on the morning following surgery.

Alternatively, postoperative pain will be controlled by a continuous ropivacaine 0.2% infusion via PSB catheter on a PCA pump at a continuous rate of 1 ml/hr. . Up to two, 3 ml boluses of Ropivacaine 0.2% may be given per hr. If pain is not adequately controlled after two boluses, infusion may be increased by 2ml/hr. All use of ropivacaine will be discontinued at approximately 3 am on the morning following surgery.

During this continuous infusion period, patients may receive supplemental analgesia for breakthrough pain (patients less than 65 years of age and greater than 50 kg: ketorolac 30 mg IM or IV every 6 hours as needed with a maximum daily dose of 120 mg; patients greater than or equal to 65 years of age or less than 50 kg: ketorolac 15 mg IM or IV every 6 hours as needed with a maximum daily dose of 60 mg). All use of ketorolac will be discontinued at 1:30 am on the morning following surgery.

If the regional anesthetic infusion and allowed supplemental analgesia do not effectively control the patient's postoperative pain, then the patient will be discontinued from the study.

During this period, the patient will be instructed how to use the rating scales in the In-Clinic Diary.

The patient will remain in the study center for routine post-surgical care (but no topical or systemic analgesic treatment) and for observation for up to 9 hours to observe if the patient develops moderate-to-severe pain after the PSP is discontinued. During this period, the patient will be instructed how to use the rating scales in the Diary.

6.3.4 Post-Surgical Eligibility Assessments and Dosing

During the post-surgical period until 10 minutes pre-dosing, patients may consume non-caffeinated liquids and food (no chocolate). No other treatment is permitted.

When the patient has pain at the surgical site, s/he will be asked to rate his/her pain on a categorical pain intensity scale (PI-CAT). The patient is required to have moderate or severe pain to be eligible for the clinical trial as indicated by a score ≥ 2 on the PI-CAT.

The Study Coordinator will ask patients with moderate or severe pain on the PI-CAT to rate their pain using the PI-NRS pain intensity scale (PI-NRS). The PI-NRS must indicate at least moderate pain (rating ≥ 4) for the patient to be randomized. This qualifying PI-NRS rating constitutes the Baseline pain score, which will be recorded in the eCRF.

If 9 hours have transpired since the popliteal sciatic block was discontinued and the patient does not indicate moderate or severe pain on the PI-CAT and PI-NRS, the patient does not qualify for the study and will be considered a screen failure. These patients will be discharged from the study and routine post-operative care will be provided.

For patients who qualify on the PI-CAT and PI-NRS the Study Coordinator will:

1. Record pulse, respiratory rate, blood pressure (semi-recumbent for 5 minutes), temperature (aural).
2. After defining nausea ("Nausea is feeling like you want to throw up"), administer:
   a) Nausea Scale (NS)
   b) Vomiting Frequency Scale (VFS)
   c) Opioid Symptoms Scales (OSS)
3. Select the next-numbered randomization study medication.
4. Assure that the patient has not had any food or drink for 10 minutes prior to receiving study medication.
5. Administer assigned study medication (1 capsule) to the patient with 4-8 oz. of water. This is the Baseline time.
6. Examine the patient's mouth to assure that the capsule was swallowed.
7. Set the timer for 30 minutes.
8. Record the study treatment number and the date and time of administration in the source and electronic CRF.

For subsequent dosing of study medication, the Study coordinator will administer one dose (1 capsule) of study medication every 4 hours over the initial 12 hours of the treatment period for a total of 4 doses of study medication. The 5th dose of study medication will be administered 4 hours after the 4th dose. Thus each patient will receive the same total amount of study medication, a total of 5 doses over the initial 24 hours (i.e., mid-way between the total per-label amounts of 4-6 doses of hydrocodone/ APAP over 24 hours). Subjects should be awoken for dosing, as needed to remain on the dosing schedule.

The Study Coordinator will follow the same schedule of dosing (every 4 hours (± 10 minutes) for 5 doses) over the final 24 hours of the treatment observation period in the clinic so that all patients receive the same total amount of study medication (10 doses) over 48 hours.

The study treatment number and the date and time of administration of each dose of study medication are to be entered into the eCRF.

When dosing with study medication and assessments of PI-NRS, NS, and VFS are due at the same time, the assessments should be done first, followed by dosing.

Patients are to be in a semi-recumbent position at least 15 minutes prior to each scheduled assessment time.

All doses are to be administered with 4-8 oz. of water, and the study staff should examine patient's mouth to ensure capsule is swallowed.

Patients should not have food or drink 10 minutes prior to receiving study medication or prior to completing assessments. Throughout the 48-hour treatment observation period, patients may consume non-caffeinated liquids and food (no chocolate) during the 20-minute period following any set of assessments (i.e., patients may not receive food or liquids 10 minutes before any scheduled assessment). Use of any nicotine-containing product is also not permitted throughout the 48-hour treatment observation period (or at any time during the 7-day study).

No topical treatments for pain and no other medications will be administered except supplemental (rescue) analgesic and anti-emetic prescribed by the Investigator, if needed.

6.3.5 Study Times Initial 12 Hours Post-Initial Dose

(every 30 minutes over the initial 12 hours: at 30 minutes, 1 hour, 1.5 hours, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5 hours, etc. until 12 hours after the initial administration of study medication)

Every 30 minutes (±5 Minutes) the Study Coordinator will:

1. Instruct the patient to rate pain intensity (PI-NRS).
2. Then instruct the patient to complete the NS.
3. Set the timer for 30 minutes.

Every 60 minutes (±5 Minutes) the Study Coordinator will:

1. Instruct the patient to complete the VFS.
2. Set the timer for 30 minutes.

Throughout this period the Study Coordinator will:

1. Record each use of study medication every 4 hours so that a total of 4 doses of assigned study medication are administered over the initial 12-hour treatment period.

2. Record use(s) of supplemental/rescue analgesic and anti-emetic medication(s).

3. Observe for and record all observed or volunteered adverse events as rated by the Investigator (mild, moderate, severe).

6.3.6 Study Times: 12 Hours Post-Initial Dose through 48 Hours

(every 60 minutes (if awake) over next 36 hours: at 13 hours, 14 hours, 15 hours, etc. until 48 hours after the initial administration of study medication)

Every 60 minutes (±5 Minutes) the Study Coordinator will:

1. Instruct the patient to rate pain intensity (PI-NRS) if the patient is awake.

2. Instruct the patient to rate NS if the patient is awake.

3. Instruct the patient to rate VFS if the patient is awake.

4. Set the timer for 60 minutes.

5. Observe and record patient status (e.g. adverse events) hourly.

6. Record uses of study medication:

   a) 1 dose administered 4 hours after the 4th dose so that a total of 5 doses of study medication are administered over the initial 24-hour treatment period;

   b) 1 dose administered every 4 hours for 5 additional doses during the remaining 24 hours at the research center, so that a total of 10 doses of study medication are administered over the entire 48-hour treatment observation period. Subjects should be awoken for dosing, as needed to remain on the dosing schedule.

7. Record use(s) of supplemental/rescue medication(s) if needed.

8. Record all observed or volunteered adverse events as rated by the Investigator (mild, moderate, severe).

6.3.7 Study Time: Additional Assessments at 24 hours (±15 Minutes)

1. Record OSS (after VFS is obtained).

2. Set timer for 60 minutes.

6.3.8 Study Time: 48 hours (±15 Minutes)

1. Record pain intensity (PI-NRS).
2. Record NS.
3. Record VFS
4. Record OSS.
5. Record temperature (aural), pulse, respiratory rate, blood pressure (after semi-recumbent for 5 minutes).
6. Record use(s) of supplemental/rescue medication(s).
7. Evaluate adverse events (ongoing adverse events will be monitored until resolution).
8. Provide discharge instructions for Study Days 3-7:
    - How to use the Outpatient Diary every day
    - Directions for taking/recording each use of study medication (every 4-6 hours *as needed for pain*, up to 6 doses per 24-hour period)
    - Directions for recording use of supplemental analgesic and/or anti- emetic medications
    - Directions for recording symptoms/adverse experiences
    - Explain study conditions for Days 3-7.

The patient will be reminded that s/he is in a clinical trial and must remain awake until his/her usual bedtime, staying alert in order to record all uses of study medication and rescue medications, if needed, and to document all adverse events on Days 3 - 7.

The patient will be instructed that no caffeine-containing beverage, alcohol, chocolate or nicotine-containing product may be used during the 7-day study period.

The patient will also be reminded that no other treatments for pain (including topical treatments) and no other medications (except the supplemental analgesic prescribed by the Investigator, ibuprofen 400 mg) may be taken if needed for pain.

The patient will be given a prescription for the anti-emetic of the Investigator's choice according to local medical practice, with instructions to how to use this medication for

nausea/vomiting, if needed.

The patient will also be instructed how to document the names and use of these supplemental analgesic and anti-emetic medications, per Section 5.5, above, including the requirement to complete all entries in the Outpatient Diary for 7 days.

The patient will be advised which ongoing medications (e.g. antihypertensive medications) are permitted during the study period and which medications (per exclusion criterion #4) are not permitted.

The patient will also be informed that the Study Coordinator will contact the patient by phone approximately 24 hours after discharge from Visit 2 (or up to 2 days later, to account for weekends) to ask how the patient is feeling, adverse events, and any medications taken, to see how s/he is doing post-op and monitor his/her use of the outpatient diary.

The patient will be discharged from Visit 2 with a bottle containing the remaining study medication capsules, a bottle containing ibuprofen 200 mg tablets (to be used if needed), and a prescription for an anti-emetic(to be used if needed).

The patient will be released from the research facility only when his/her pre- arranged (adult) transportation and escort have arrived.

Patient status and findings will be recorded in the source and eCRF.

6.3.9 Outpatient Activities: Day 3 through Day 7

1. Record the date and times of taking study medication at each time dosed.
2. Record the date and times of taking supplemental analgesic and anti-emetic medication(s) at the time(s) used every day.
3. Record all symptoms (adverse events) experienced over the past 24 hours (even if the patient did not take any study medication on a particular day).

6.3.10 Follow-Up Telephone Call: approximately 24 hours after discharge (+2 days, to account for weekends)

The Study Coordinator will telephone the patient approximately 24 hours after discharge (or up to 2 days after discharge if over a weekend) to inquire about the patient's post-op status (e.g., pain, bleeding, fever, nausea, vomiting, side effects) and uses of medications. Adverse events and concomitant medications will be recorded in the eCRF.

6.3.11 Follow-Up Visit 3 on Day 8 (± 2 days)

The following procedures will be completed at the follow-up visit:

1. Vital signs (aural temperature, pulse, respiratory rate) and blood pressure (semi-recumbent for 5 minutes) will be measured.
2. Retrieve Outpatient Diary, study medication bottle, supplemental pain and anti-emetic medication bottles.
3. Count remaining study medication capsules, account for the number of study medication capsules used and compliance.
4. Evaluate adverse events (ongoing adverse events will be monitored until resolved, per Section 9.1, below).
5. Review use of supplemental/rescue medication(s).
6. Review and document all concomitant medications.
7. Perform urine pregnancy test on all female patients.
8. Perform urine cotinine test on all patients
9. Discharge patient from study with instructions for routine post-op care.
10. For any continuing side effects, the Study Coordinator will call the patient every 48 hours (or routine follow-up) until the resolution of the side effect.

6.4 Concomitant Therapy

Any concomitant medication used (e.g., antihypertensive, contraceptive) must be entered into the eCRF.

6.5 Assignment of Numbers

Each patient who has signed an informed consent form in the study will be assigned in sequence the lowest available (3-digit) screening number.

Patients assigned a screening number but who do not meet inclusion/ exclusion criteria (e.g., do not have at least moderate pain on the PI-CAT and PI-NRS) will have the reasons for screen failure entered into the eCRF.

Patients who meet inclusion/exclusion criteria and qualify to receive study medication will be assigned the next available 4-digit randomization number in ascending sequential order at the investigative site. Each randomization number assigns treatment according to an independent computer-generated randomization schedule.

6.6 Treatment

Patients will be randomized to receive over-encapsulated CL-108 5 mg, hydrocodone 5 mg/ APAP 325 mg, or placebo. The randomization number for a bottle of study drug will correspond to the double-blind assignment of study drug assigned for an individual patient.

6.7 Clinical Adverse Events

All adverse events reported until Visit 3 must be recorded in the case report form according to Section 9.1 of this protocol. All Adverse Events will be followed until resolution or clinical stability.

6.8 Risks/Precautions

Hydrocodone combined with acetaminophen is a Schedule II controlled substance that can produce drug dependence of the opioid type. Like other opioids, respiratory depression has been associated with hydrocodone. Deaths have also been reported in association with concomitant administration of hydrocodone with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self-administration of benzodiazepines or other depressants while under treatment with hydrocodone.

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e. g., driving a car or operating machinery). Patients should be warned of these dangers and counseled accordingly. Patients in the study will not be released from the facility unless their prearranged transportation has arrived.

Promethazine is a phenothiazine. Like other phenothiazines, respiratory depression, seizures, and sedation have been associated with promethazine. Dyskinetic reactions may occur in patients with previous dyskinetic reactions to acute or chronic anti-emetic or antipsychotic medications. Because phenothiazines impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e. g. driving a car or operating machinery), patients should be warned of these dangers and counseled accordingly.

Short-term use of acetaminophen at therapeutic doses is rarely associated with side effects, although nausea and vomiting have been reported with its use. Patients who are alcoholics are susceptible to hepatotoxicity, even liver failure, if they consume more than 4 grams of acetaminophen per day.

6.9 Overdosage

The manifestations of overdosage with hydrocodone and promethazine are similar, with the most serious effects being respiratory depression and hypoventilation.

Immediate management of opioid overdose includes ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, ventilatory and circulatory status.

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be administered, if necessary, to reverse opioid-induced respiratory depression. In the presence of hypo-ventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated.

Acetaminophen overdosage can result in hepatotoxicity and acute liver failure. Treatment is aimed at removing the acetaminophen from the body and replacing glutathione. Activated charcoal can be used to decrease absorption of acetaminophen if the patient presents for treatment soon after the overdose. The specific antidote for acetaminophen overdosage, acetylcysteine, (also called N-acetylcysteine or NAC) acts as a precursor for glutathione, helping the body regenerate enough to prevent permanent damage to the liver which, if extensive, may require liver transplantation.

7 Data Collection and Analysis

7.1 Recording of Data

Data will be recorded from clinical source records and patient diaries into electronic case report forms (eCRFs) by site personnel.

All missing data must be accounted for. If a space is blank because the item was not completed, if the item is unknown, or if the item is not applicable to an individual case the computer will flag the blank and the site personnel must add an explanation why the space is blank. If an entry error has been made, the original entry must be corrected. The computer will record the date of the change and the identity of the person making the change.

All patients signing an informed consent form who fail screening or who withdraw before randomization must have the reason(s) entered in the eCRF. All patients who are randomized will have all data entered in the eCRF.

7.2 Control Methods

Patients will be randomly assigned to receive one of three treatments: CL-108 5 mg, hydrocodone 5 mg/APAP 325 mg, or placebo. In case of an emergency the Investigator should treat the patient assuming he/she received hydrocodone/acetaminophen/ promethazine. In an unusual event where the safety of a patient is at risk and unblinding is necessary to treat the patient, the bottom (scratch-off) portion of the tear-off label may be accessed. Diligent attempts should be made to contact the Medical Monitor and sponsor prior to unblinding. The reason for unblinding, the time of sponsor contact, and unblinding procedures followed should be carefully documented.

7.3 Safety Assessments

Verbatim adverse event terms will be coded into standardized system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Because

sleep disturbance and opioid-related adverse events contributing to it are of special interest, sleep disturbance, nausea, retching, vomiting, and headache will be summarized and analyzed for CL-108 5 mg, hydrocodone 5 mg/APAP 325 mg, and placebo.

Adverse events will be summarized for CL-108 5 mg, hydrocodone 5 mg/ APAP 325 mg, and placebo.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD).

7.4 Statistical Analysis

7.4.1 Primary Hypotheses

This study will test two co-primary null hypotheses:

- That CL-108 5 mg has the same occurrence of vomiting and use of anti-emetic(s) as hydrocodone 5 mg/APAP 325 mg
- That CL-108 5 mg has the same analgesic effect as placebo

This study uses two co-primary endpoints, one for the assessment of opioid-induced nausea and vomiting (OINV) and one for the assessment of pain. Both endpoints are defined over the initial 48 hours following randomization

Co-Primary OINV Endpoint:

The co-primary OINV endpoint is a binary assessment of response/no response to a composite index consisting of any vomiting or use of anti-emetic medication (indicative of nausea) over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/ APAP 325 mg

Co-Primary Analgesia Endpoint:

The co-primary analgesia endpoint is the time-weighted sum of pain intensity differences over 48 hours ($SPID_{48}$), comparing CL-108 5 mg to placebo

The $SPID_{48}$ endpoint is calculated from the PI-NRS values at baseline, every 30 minutes until hour 12, then every hour (when awake) until hour 48 as follows:

- Each subsequent PI-NRS value is subtracted from the baseline PI-NRS value.
- Each difference is weighted by the elapsed time from the previous PI-NRS value to the current one
- The weighed differences are summed to yield the $SPID_{48}$

7.4.2 Sample Size Justification

A sample size of 300 completed patients is planned for analysis: 120 patients in the CL-108 5 mg treatment group, 120 patients in the hydrocodone 5 mg/APAP 325 mg treatment group, 60 patients in the placebo treatment group.

The rates of observed OINV (any vomiting or use of anti-emetic) were 11.9% and 45.2% for CL-108 7.5 mg and hydrocodone 7.5 mg/APAP 325 mg, respectively, in a previous 48-hour bunionectomy study (CLCT-003). Based on a reduced per dose exposure to hydrocodone in the present study (CLCT-018), the expected incidence of OINV in the control group (Norco 5 mg) is estimated to be approximately 30% (vs 45% for Norco 7.5 mg in CLCT-003). With an absolute delta of .20, the estimated incidence of OINV in the CL-108 5 mg treatment group is 10%. With a power of 96.4% and a 2-sided 2-sample chi-square test with an alpha of 0.05, approximately 110 patients would be required in each active treatment group.

The observed means of $SPID_{48}$ in CLCT-003 were 118.4 and 53.1 for CL-108 7.5 mg and placebo, respectively, and the pooled standard deviation was 75. Based on a reduction of hydrocodone exposure (from 7.5 to 5 mg per dose), the estimated $SPID_{48}$ is one-third lower for CL-108 5 mg. For $SPID_{48}$, a sample size of 110 patients in the CL-108 5mg treatment group and 55 in the placebo group provides 93.7% power using a 2-sided 2-sample t-test with an alpha of 0.05 for a delta of 43.5 (96.6 vs 53.2) and SD of 75.

The overall power is 90% for the analyses of these 2 co-primary endpoints. Based on the number of patients who do not qualify (eg, because of admission criteria such as low baseline pain) or patients who enroll but do not complete the study, the plan is to enroll approximately 330 patients in order to be able to analyze a total sample size of 300 patients who complete the study.

7.4.3 Key Secondary Endpoints

1. Percentage of patients with complete absence of OINV (no nausea, no vomiting, and no use of anti-emetic medication) over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg

2. Percentage of patients with any vomiting over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg

3. Percentage of patients with any nausea over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg

4. Percentage of patients with any nausea or vomiting over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg

5. Percentage of patients with Post-Discharge Nausea and Vomiting (PDNV) over days 3-7

6. Number of doses of study medication taken over days 3-7

7. Number of doses of study medication taken per day over days 3-7

7.4.4 Labeling Endpoints

Specific endpoints will be presented in sequence to support a label stating that:

1. CL-108 5 mg relieves moderate to severe pain

2. CL-108 5 mg prevents opioid-induced nausea and vomiting (OINV)

3. More patients treated with CL-108 5 mg experience complete absence of OINV than patients treated with a comparable product containing hydrocodone 5 mg/ acetaminophen 325 mg

4. Patients treated with CL-108 5 mg experience less vomiting than patients treated with a comparable product containing hydrocodone 5 mg/ acetaminophen 325 mg

5. Patients treated with CL-108 5 mg experience less nausea than patients treated with a comparable product containing hydrocodone 5 mg/acetaminophen 325 mg

6. Patients treated with CL-108 5 mg experience less nausea and vomiting than patients treated with a comparable product containing hydrocodone 5 mg/acetaminophen 325 mg

7. Patients treated with CL-108 5 mg experience less nausea and vomiting after discharge following surgery than patients treated with a comparable product containing hydrocodone 5 mg/acetaminophen 325 mg

8. Patients treated with CL-108 5 mg take more doses over days 3-7 and have greater reduction in pain and less OINV after discharge following surgery than patients treated with a comparable product containing hydrocodone 5 mg/ acetaminophen 325 mg

9. Patients treated with CL-108 5 mg take more doses each day over days 3-7 and have greater reduction in pain and less OINV after discharge following surgery than patients treated with a comparable product containing hydrocodone 5 mg/ acetaminophen 325 mg.

These labelling endpoints are supported by the co-primary and key secondary endpoints.

7.4.5 Study Populations

Three datasets will be used for analysis: safety, intent-to-treat, and per protocol.

The definition of these populations follows:

- Safety Population: All randomized patients who received at least one dose of study medication comprise the Safety Population.
- Intent-to-Treat (ITT) Population: All randomized patients who took at least one dose of study medication comprise the Intent-to-Treat Population. The ITT Population is the same as the Safety Population.
- Per-Protocol Population: All ITT patients without major protocol violations that significantly affect the efficacy analyses. (Major and minor protocol violations will be defined in the SAP.)

Safety will be analyzed based on the safety population. Efficacy will be analyzed based on the ITT and Per-Protocol populations.

7.4.6 Predefined Subgroups

Analgesia ($SPID_{24}$, $SPID_{48}$) will be analyzed in the subgroups of patients with moderate pain and patients with severe pain. No other subgroup analyses are planned.

7.4.7 Missing Data Conventions

Missing data for PI-NRS, NS, VFS and OSS will be imputed on a patient-by-patient basis as specified in the Statistical Analysis Plan.

7.4.8 Use of Supplemental Medication

After each use of the supplemental medication for pain (ibuprofen) during the 48-hour period of the primary outcome measures, a baseline observation carried forward (BOCF) method will be used to impute PI-NRS and a worst observation carried forward (WOCF) method will be used to impute NS, VFS, and OSS values for the next 6 hours (the duration of action on the label for ibuprofen 400 mg). After the first use of anti-emetic medication, a worst observation carried forward (WOCF) method will be used to impute NS, VFS, and OSS values (because any use of an anti-emetic indicates the presence of OINV, i.e., non-response), and a baseline observation carried forward (BOCF) method will be used to impute PI-NRS values until the next scheduled assessment following the duration of action of the anti-emetic medication.[5,9]

7.4.9 Statistical Analysis

All analyses will follow a prospectively approved statistical analysis plan (SAP). The SAP will be approved before data lock and before any looks at the data. The SAP will include the details of all analyses, all database specifications and conventions, and all tables, listings and figures.

All analyses will be conducted using two-sided tests with a type I error of 0.05.

7.4.10 Descriptive Statistics:

Continuous variables will be summarized as n, mean, standard deviation, minimum, median, and maximum. Asymptotic 95% confidence intervals for means and for mean differences will be provided as specified in the SAP. For variables expected to be skewed, transformations such as log may be specified in the SAP.

Categorical and binary variables will be summarized as percentages, noting the numerator and denominator of the percentage.

7.4.11 Analysis of the OINV Co-Primary Endpoint:

The OINV endpoint will be tested using a logistic regression model with treatment, gender, and investigator as main effects. Treatment will be tested using a type III likelihood ratio test. The test will be performed on the ITT population.

7.4.12 Analysis of Analgesia Co-Primary Endpoint:

The analgesia endpoint will be tested using a general linear model with treatment, investigator and gender as main effects. Treatment will be tested using a type III test. The test will be performed on the ITT population.

The mean difference between treatment groups will be calculated using least squares means, and 95% confidence interval will be calculated.

7.4.13 Sensitivity Analysis of Primary Endpoints

The missing data imputation method has little impact on the event driven OINV endpoint. Therefore, no sensitivity analysis will be performed for the OINV endpoint.

Two sensitivity analyses will be performed on $SPID_{48}$ to evaluate the robustness of the co-primary analgesic efficacy analysis and the impact of missing data on the results for the ITT population.

In the first sensitivity analysis, the method of multiple imputations (MI)[10] will be used to impute post-dose missing pain intensity differences over 48 hours (either due to early

discontinuation, no valid data entry, or use of supplemental medication for pain or use of anti-emetics for the duration of their dosing interval during which the medications were administered) by using Markov chain Monte Carlo (MCMC) method for the non-monotone missing pattern values and then the sample mean pain intensity difference for patients with available data within that treatment group at that time point for the monotone missing pattern values. The method of multiple imputations uses SAS PROC MI to generate multiple complete datasets for the calculation of $SPID_{48}$, and PROC MIXED and MIANALYZE to analyze and combine the results from them. To ensure robustness of results 10 complete datasets will be created with the initial seed value set at '123'. The same general linear model for the co-primary efficacy endpoint will be carried out for the above datasets.

In the second sensitivity analysis, a Pattern Mixture Model,[11] which is based upon an assumption of Missing Not at Random (MNAR) with an approach similar to above multiple imputations, will be used with missing data for Patients at each time point imputed using the available data for Placebo Patients at that time point.

7.4.14 Analyses of Key Secondary Endpoints:

The details of key secondary endpoint analyses will be specified in the SAP.

7.4.15 Statistical Significance:

The two co-primary endpoints will each be tested at the 0.05 using a two-sided test using the ITT population. Both co-primary endpoints must be statistically significant so that no adjustment for multiple comparisons is required.

If both co-primary nausea and pain endpoints are significant, the key secondary endpoints will be tested using Hochberg step-up test procedure for controlling family-wise type 1 error on the ITT population at the 0.05 level. This sequential testing procedure preserves the overall type I error so that no adjustment for multiple tests is required.

7.4.16 Safety

Adverse events will be summarized for each treatment group. Tabulations and listings of values and/or parameters will be presented for the incidence and severity of adverse events (and, separately, for the incidence and severity of nausea, retching, vomiting, emetic episodes, sleep disturbance, headache).

7.4.17 Interim Analyses

An independent Data Monitoring Committee (DMC) will meet to review efficacy and safety endpoints. The DMC will operate under a charter and will make recommendations

to the sponsor. An interim analysis will be performed by the DMC after approximately 66% of the subjects have completed the 300-subject study and there is adequate representation from each of the investigative sites (i.e., approximately 30 completed subjects per site). If it is judged impossible to achieve this de minimis representation at a particular site or sites, the interim analysis will be conducted on the total number of subjects completed (i.e., approximately 200 subjects). Since the DMC will review efficacy data, formal sequential boundaries for efficacy and futility will be declared in the DMC's Statistical Analysis Plan.

7.4.18 Protocol Deviations

No patients will be excluded from the Safety or Intent-to-Treat populations because of protocol violations. Patients who do not meet admission criteria prior to dosing or who have major protocol violations after dosing that could significantly affect efficacy results (e.g., a missed dose of study medication) will be excluded from the Per Protocol population.

Minor protocol deviations that do not bias efficacy results (such as assessments not obtained at scheduled time points during the 48-hour primary treatment evaluation period) will not be noted as deviations.

8 Clinical Supplies

8.1 Packaging

Double-blinded study medication will be provided in 100-mL HDPE bottles, each containing 45 capsules of study medication.

8.2 Label

On the outer cover of each bottle will appear:

Subject Initials/Subject Screening Number:	___ ___ ___ /___ ___ ___
Date Dispensed:	___ ___ ___
Protocol Number:	CLCT-018
Directions:	Take one capsule every 4-6 hours for pain. Do not exceed 6 capsules in a 24-hour period. Keep this out of the sight and reach of children.
Contents:	45 green capsules Store at 20° to 25°C (68^0 to 77^{0}F)
Manufactured for:	Charleston Laboratories 1001 North US Highway 1

CHARLESTON LABORATORIES, INC.

Protocol No. CLCT-018

Jupiter, FL 33477

Date of Manufacture: MM-DD-YYYY

Lot #: vvvvvvv

Caution: **New Drug Limited by Federal Law to Investigational Use Only Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed. Investigational Drug to be used by a Qualified Investigator Only.**

Study Medication #: XXXX

A tear-off label will also be attached to the outer cover of each bottle and will be placed in the source documents. The top section of the tear-off label is open-label:

Subject Initials ___ ___ ___
Subject Screen # ___ ___ ___
Date ___ ___ ___
Study Medication # XXXX

The bottom portion of the tear-off label is scratch-off (blinded, identifying the Study Medication # and the Treatment Group).

9 Investigator Obligations

9.1 Adverse Event Reporting Obligations

An important objective of this study is to assess the safety and tolerability of the drug. Therefore, the Investigator is responsible for recording and reporting adverse events observed during and after study drug treatment.

9.1.1 Definition of an Adverse Event

An adverse event is any reaction, side effect, or other untoward event, regardless of relationship to study drug, including death, experienced by a patient. An adverse event may consist of a disease, an exacerbation of a pre-existing illness, or condition, a recurrence of an intermittent illness or condition, a set of related signs or symptoms, or a single sign or symptom.

Serious and non-serious events occurring after the ICF is signed, but prior to first dose of study drug, will be collected as part of the medical history. Adverse events noted or reported from the first administration of investigational product to Visit 3 will be followed until resolution.

A treatment-emergent adverse event (TEAE) is defined as:

1. Any new medical occurrence not seen before initial study drug administration.

2. A pre-existing medical condition which recurs with increased intensity or increased frequency subsequent to initial study drug administration.

3. A medical condition which is present at the time of study drug administration which exacerbates at any time following initial study drug administration.

A pre-existing condition or signs or symptoms present at the time of study drug administration are not considered an adverse event unless criterion #2 or #3 above applies. Signs or symptoms associated with the disease or medical condition being evaluated (e.g., pain) should not be recorded as adverse events.

Standard symptoms expected in patients who have recently undergone first metatarsal bunionectomy will not be recorded as adverse events unless they are of greater severity and/or intensity than would be expected. The events considered standard in this study are: pain, erythema, numbness, swelling, bruising, bleeding, and decreased range of motion of the affected foot. Investigators will use their clinical judgment in determining whether these symptoms are of greater severity than usual.

9.1.2 Definition of a Serious Adverse Event (SAE)

Each of the following adverse events is defined as serious:

1. Death

2. Life-threatening event

   A "life-threatening" event is present when the patient was, in the view of the Investigator, at immediate risk of death from the event as it occurred. Note that this definition does not include an event that, had it occurred in a more serious form, might have caused death.

3. Inpatient hospitalization or prolongation of existing hospitalization

   Note that elective hospitalization for treatment of a pre-existing condition that did not worsen/exacerbate during the study is not considered a serious adverse event. Complications, which occur during any hospitalization, are adverse events and if such complication(s) prolongs the hospitalization, the event is a serious adverse event. These conditions should be recorded on the physical examination section of the eCRF.

4. A persistent or significant disability / incapacity

5. Any congenital anomaly / birth defect

6. Important medical events that may not be immediately life-threatening or result in death or hospitalization may be considered a serious adverse event (SAE) when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE above.

   Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.1.3 Recording and Documenting Adverse Events

Patient-reported adverse events will be captured from the initial time of dosing with study medication, through the time of discharge from the study. Serious adverse events will be captured from the initial time of dosing with study medication until 30 days after the last time of dosing with study medication.

Each adverse event must be promptly recorded and sufficiently documented by the Investigator in the source document as well as the eCRF, even if the adverse event is assessed by the Investigator as unlikely to be causally related to therapy with study drug. The Investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms.

If the adverse event meets the definition of an SAE, in addition to being documented on the AE page of the eCRF, the SAE form must also be completed. The completeness and accuracy of these forms will be monitored.

When a patient spontaneously mentions any problems or an adverse event is observed, the duration and intensity of each adverse event will be documented as well as any action taken and treatment administered. The investigator will evaluate the adverse event and determine the severity and relationship to (association with) study medication.

Recurrent symptoms of a chronic pre-existing condition are not considered adverse events unless they occur in a worse or unexpected pattern during study drug administration.

9.1.4 Intensity of Adverse Events

The intensity (or severity) of adverse events is characterized as mild, moderate, or severe:

- **Mild** adverse events are usually transient, do not interfere with the patient's daily

activities, and often respond to symptomatic therapy (e.g. rest or distraction).

- **Moderate** adverse events introduce some level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures (e.g. medication to treat the symptom).

- **Severe** adverse events significantly interrupt a patient's usual daily activity and often are not ameliorated by therapeutic drug therapy or other treatment. In addition, the adverse event may require discontinuing or reducing the dose of study medication administration.

When the intensity of an adverse event changes more frequently than once daily, the maximum intensity for the event is recorded. If the intensity changes after a number of days, then these sub-events or changes are recorded separately (i.e., with distinct onset and stop dates).

9.1.5 Relationship to Study Medication

The degree of "relatedness" of the adverse event to the study drug may be described using the following scale:

- **Not related** indicates that the adverse event is definitely not related to the study drug.

- **Unlikely related** indicates that there are other, more likely causes and study drug is not suspected as a cause.

- **Possibly related** indicates that a direct cause and effect relationship between study drug and the adverse event has not been demonstrated but there is a reasonable possibility that the event was caused by the study drug.

- **Probably related** indicates that there probably is a direct cause and effect relationship between the adverse event and the study drug.

It is the sponsor's policy to consider "Probable" and "Possible" causality assessments as positive causality and to consider "Not" and "Unlikely" causality assessments as negative causality.

Assessments will be recorded on the eCRF. The date and time of the last dose of study medication will be recorded on the AE page of the eCRF.

9.1.6 Therapeutic Failure as an Adverse Event

Reports of therapeutic failure need not be recorded or processed as adverse events.

Complications of therapeutic failure should be recorded as adverse events.

9.1.7 Treatment Period

Adverse events occurring from the initial study drug administration to the follow-up Visit 3 discharge should be recorded as adverse events in the eCRF.

All unresolved adverse events observed at the follow-up Visit 3 should be followed by the Investigator until the event(s) are resolved, stabilized, the patient is lost to follow-up, or the event is otherwise explained. Reporting of serious adverse events should follow Section 9.1.6.

9.1.8 Investigator Report of a Serious Adverse Event

For any SAE, the Investigator must first call the INC Medical Monitor**:**

PI , MD at
Office: PI
Cell: PI (cell)
Email: PI

AND fax and/or email the report to INC Safety Department within 24 hours after the Investigator's initial identification of the event:

SAE Reporting Fax Number: PI
Email: PI

If Dr. PI cannot be reached, the Investigator should call PI **MD** at Charleston Laboratories**:**

PI , MD
Cell: PI
Email: PI

Data for the Serious Adverse Events Form, Medical History Form and Concomitant Medication Form must be entered into the eCRF within 24 hours of receipt of the SAE. The sponsor must receive a written SAE report of the event within 1 working day after the Investigator's initial identification of the event. The completed form should be FAXED or Emailed to the INC Safety Department at the numbers list above**.**

The Investigator is responsible for continuing to report to any new or relevant follow-up information on the adverse event as the information becomes known to the Investigator. The Investigator is required to notify the IRB of all SAEs occurring at his/her site within a reasonable time period or as governed by the IRB.

9.1.9 Other Investigations

The Investigator and supporting personnel responsible for patient care should institute any supplementary investigations of serious adverse events based on their clinical judgment of the likely causative factors. This may include seeking a consult by an appropriate specialist. Charleston Laboratories may also request extra tests or follow-up assessment. If a patient dies, any post-mortem findings (including histopathology) must be provided to Charleston Laboratories.

9.1.10 Ethics Committee Notification

The Investigator is responsible for promptly notifying the ethics committee (Institutional Review Board) of all serious adverse events, including any significant follow-up information.

9.1.11 Post-study Serious Adverse Events

The Investigator should notify Charleston Laboratories of any new serious adverse event that occurs within 30 days following the last dose of study drug.

Investigators should notify Charleston Laboratories, or designee, if they become aware of a study participant who is one of the parents of a subsequently conceived child with a congenital anomaly.

9.1.12 Regulatory Aspects

In agreeing to the provisions of this protocol, the legal responsibilities for prompt notification of serious adverse events are accepted by the Investigator.

9.2 Drug Accountability

9.2.1 Storage of Investigational Drug

All study medication for this study must be stored under ambient temperature conditions in a locked area suitable for schedule II controlled substances. The area must also be free of environmental extremes and with a limited access. Before any agreements are concluded between the Principal Investigator and Charleston Laboratories, the drug storage area will be inspected and the drug accountability system discussed.

9.2.2 Receipt of Drug Shipment

No study drug will be shipped prior to receipt of a valid DEA Form 222 by the clinical trial supplier. The Principal Investigator or designee, upon receipt of the drug supplies and accompanying packing list, will conduct an inventory and sign the pro forma invoice and manufacturer shipping checklist and forward one copy to the manufacturer and one

copy to Charleston Laboratories. One copy of all documents contained with the drug supplies must be retained in the Investigator's records.

9.2.3 Materials Control

The Principal Investigator, or his designee, shall record the dispensing of the clinical drug supply to patients and any subsequent returns. These records will be made available to clinical monitoring personnel for the purpose of accounting for the clinical drug supply. A drug supply inspection for inventory purposes and assurance of proper storage will be conducted no less than every 6-8 weeks throughout the clinical investigation. Any significant discrepancy and/or deficiency is to be recorded and immediately reported to Charleston Laboratories and the DEA (according to requirements), and a plan for resolution is to be documented.

Clinical trial material must not be loaned or dispensed by the Principal Investigator to another Investigator or site. Only patients in this clinical trial and eligible for treatment are to receive this clinical trial material.

9.2.4 Return of Drug to Sponsor

At the end of the study, a final inventory will be performed by the Study Monitor and the Principal Investigator or designee. If any supplies are missing, this must be indicated on the Drug Accountability Form together with an explanation of the discrepancy. The Principal Investigator will be instructed to return all unused medication to the manufacturer along with a DEA 222 Form and to return a copy of the Clinical Supplies Return Form to Charleston Laboratories or designee. The Principal Investigator must retain a copy of the Clinical Supplies Return Form and the original Drug Accountability Form. A copy of the Drug Accountability Form must be returned to the Study Monitor/Charleston Laboratories.

9.3 Deviations from Protocol

The Investigator is not permitted to deviate from the protocol. Apart from the regulatory requirements, it is vital to the success of the study that the Investigator adheres to the details of the protocol and thus holds to a minimum the number of cases later classified as "incomplete," "unusable," or "not evaluable."

Charleston Laboratories will not compensate the Investigator for evaluation of cases in which the procedures and evaluations are not conducted as specified in the protocol.

9.4 Disclosure of Data

9.4.1 Confidentiality

The Principal Investigator and all of the Principal Investigator's employees or agents

involved with this study shall not disclose or use for any purposes (other than performance of the Study) any data, records, or other information (hereinafter collectively "Information") disclosed to the Principal Investigator or his employees or agents. Such Information shall remain the confidential and proprietary property of Charleston Laboratories, and shall be disclosed only to the Principal Investigator or his employees or agents.

The obligation of non-disclosure shall not apply to the following:

a. Information after such time that it is or becomes publicly available through no fault of the Principal Investigator or his employees or agents;

b. Information after such time that it is disclosed to the Principal Investigator by a third party entitled to disclose such information; or

c. Information that is already known to the Principal Investigator as shown by his prior written records provided the Principal Investigator so advises Charleston Laboratories within twenty (20) days after disclosure of the Information to the Principal Investigator by Charleston Laboratories.

9.4.2 Publication

All data resulting from this study remain property of Charleston Laboratories. Publication of trial results is discussed in the Clinical Trial Agreement.

9.5 Study Records and Source Documents

Federal regulations and Charleston Laboratories policy require that, following completion of a clinical study, a copy of all records of that study be maintained by the Principal Investigator for at least the shorter of the following two time periods:

- Two years after FDA approval of the drug for the indication for which it was investigated; or

- In situations where no application is to be filed or an application is not approved for such indication, two years after the IND is discontinued and the FDA is notified.

Current electronic data collection should be maintained throughout the conduct of the study. The Investigator must maintain an electronic copy (e. g CDROM) of all data collected for each patient screened and treated. Charleston Laboratories or its representative will provide the electronic copy of the data; paper copies of the completed eCRFs for each patient are not required.

In order to assure the accuracy of data collected in the eCRFs, it is mandatory that representatives of Charleston Laboratories, as well as representatives of the Food and Drug

Administration, have access to original source documents (e.g., patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality.

Charleston Laboratories reserves the right to terminate the study for refusal of the Investigator to supply source documentation of work performed in this clinical trial.

9.6 Investigator Documentation

9.6.1 Patient Consent

Written informed consent of the patient to participate in the study must be obtained in accordance with the Declaration of Helsinki and in accordance with the FDA Regulations set forth in Part 50 of Title 21 of the Code of Federal Regulations.

9.6.2 Ethics Committee Review

This protocol, the Informed Consent Form, and any relevant supporting information must be submitted to the ethics committee (IRB) for review and must be approved before the study is initiated. In addition, all advertising materials must be approved by the IRB. The study will be conducted in accordance with FDA Regulations, applicable national and local health authority, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate.

The Principal Investigator must also keep the IRB informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator Brochure and that are considered by the Investigator to be possibly or probably related to the study drug. Some IRBs may have other specific adverse event requirements to which Investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Charleston Laboratories (e.g. IND safety report, Investigator Brochure, safety amendments and updates, etc.).

The Principal Investigator will forward to Charleston Laboratories a copy of the ethics committee approval of this protocol, amendments, informed consent form and any changes to the informed consent form. A copy of the IRB membership list is to be provided to Charleston Laboratories.

9.6.3 Curriculum Vitae and FDA Form 1572

The Principal Investigator must provide Charleston Laboratories with his/her own current curriculum vitae, a current curriculum vita for each sub-Investigator, and a completed and signed FDA Form 1572.

9.6.4 Financial Disclosure

The Investigator is required to provide Financial Disclosure for each person listed on Form FDA 1572 relating to financial interests held.

9.6.5 Tax ID No. and Form W-9

Prior to payments from any grant-in-aid, Charleston Laboratories must be provided the tax identification number for each grant payee and a completed Form W-9. In addition, the Investigator is required to provide Financial Disclosure for each person listed on Form FDA 1572 relating to financial interests held.

9.6.6 Laboratory Certification and Normal Values

(Not applicable.)

9.6.7 Final Report to the IRB

After completion of the clinical trial, the Investigator will submit a Study Close-Out Report to the IRB.

10 Termination of Study

Charleston Laboratories reserves the right to discontinue this study for administrative reasons at any time. Investigators will be compensated for reasonable expenses incurred, if it is necessary to terminate the study. Charleston Laboratories will not compensate the Investigator for evaluation of cases in which the procedures and evaluations are conducted in a manner other than that specified by the protocol.

11 Investigator's Protocol Agreement

The Investigator's Protocol Agreement (last page of this protocol) must be signed by the Principal Investigator. The original or a copy must be kept on file at Charleston Laboratories or designee, and the Investigator must retain the original or a copy. The completed Investigator's Protocol Agreement signifies review and acceptance of the protocol by the Principal Investigator prior to initiation of the study.

12 References

1. Apfel CC, Greim CA, Haubitz I et al. A risk score to predict the probability of postoperative vomiting in adults. Acta Anaesthesiol Scand 1998;42:495-501.
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4. Apfelbaum JL, Gan TJ, Zhao S, Hanna DB, Chen C. Reliability and validity of the perioperative opioid-related symptom distress scale. Anesth Analg 2004;99:699-709.
5. Center for Drug Evaluation and Research, US Food and Drug Administration. Guidance for Industry. Analgesic Indications: Developing Drug and Biological Products. 2014.
6. Gan T, Meyer T, Apfel C, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2003;97:62–71.
7. Gan TJ. Risk factors for postoperative nausea and vomiting. Anesth Analg 2006;102:1884-98.20.
8. Gan TJ, Meyer T, PONV Consensus Panel: Christian A, Chung F, Davis P, Eubanks S, Kovac A, Philips B, Sessler D, Temo J, Tramer M, Watcha M. A consensus panel identification of risk factors for PONV. Anesth 2002; 97:A19.
9. Panel on Handling Missing Data in Clinical Trials; National Research Council. The Prevention and Treatment of Missing Data in Clinical Trials. National Academies Press. 2010.
10. Ratitch B and O'Kelly M. Implementation of Pattern Mixture Models Using Standard SAS/STAT Procedures. PharmaSug 2011 paper SP04.
11. Little RJA. Pattern-Mixture Models for Multivariate Incomplete Data with Covariates. Biometrics, Vol. 52, No. 1 (Mar., 1996), 98-111

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13 Appendices

13.1 Appendix 1. Analgesic Rating Scales

Numerical Pain Intensity Scale (PI-NRS)

On a scale of 0 to 10, where 0 is "no pain" and 10 is "severe pain," circle the number that best describes your pain *now*.

0 1 2 3 4 5 6 7 8 9 10

Categorical Pain Intensity Scale (PI-CAT)

How would you describe your pain *now*?

(circle one)

NO PAIN	MILD PAIN	MODERATE PAIN	SEVERE PAIN

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13.2 Appendix 2: Nausea/Vomiting Rating Scales

Nausea Scale (NS)

Over the past half-hour (over the past hour),
have you had any nausea
(feeling like you wanted to throw up)?

(circle one)

NO NAUSEA NAUSEA

Vomiting Frequency Scale (VFS)

How often did you vomit (throw up) over the past hour?

(Circle one)

NOT AT ALL	ONE TIME	TWO TIMES	THREE OR MORE TIMES

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13.3 Appendix 3: Opioid Symptoms Scales (OSS)

For each symptom you've had *over the past 24 hours*,
circle the number that describes how severe it was for you:

	NONE										SEVERE
Itchiness	0	1	2	3	4	5	6	7	8	9	10
Constipated	0	1	2	3	4	5	6	7	8	9	10
Dry Mouth	0	1	2	3	4	5	6	7	8	9	10
Drowsy	0	1	2	3	4	5	6	7	8	9	10
Headache	0	1	2	3	4	5	6	7	8	9	10
Lightheaded (Dizzy)	0	1	2	3	4	5	6	7	8	9	10
Difficult To Pass Urine	0	1	2	3	4	5	6	7	8	9	10
Confused	0	1	2	3	4	5	6	7	8	9	10
Difficult To Concentrate	0	1	2	3	4	5	6	7	8	9	10

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13.4 Appendix 4. Nausea Prone Questionnaire (called "Health Questionnaire" in the CRF)

1. What medications have you used over the past week?

Any antihistamines (e.g., Benadryl, Claritin)? Any cough-cold products (e.g., Sudafed, Tussionex)? Any antibiotics (e.g., Cipro, tetracycline)? Any vitamins or nutritional supplements (e.g., vitamin E, calcium)? Any prescription medicines?

List all medications used over the past week*:*

_____

_____

_____

2. Did you have any side effects from any of these medicines? NONE N/A

(Circle all that apply)

a) Nausea
b) Vomiting
c) Problems with urination
d) Diarrhea
e) Constipation
f) Itchy skin
g) Dizziness (light-headed)
h) Difficulty concentrating
i) Feeling confused
j) Drowsiness (difficulty staying awake)
k) Lack of energy (fatigue, weakness)
l) Dry mouth
m) Headache
n) Hives
o) Other: _____
p) Other: _____

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Considering medications you have used in the past (e.g., antihistamines, cough medicines, cold products, antibiotics, nutritional supplements, prescription medicines), have you ever had any side effects from any medicines? **NONE**

(Circle all that apply)

a) Nausea

b) Vomiting

c) Problems with urination

d) Diarrhea

e) Constipation

f) Itchy skin

g) Dizziness (light-headed)

h) Difficulty concentrating

i) Feeling confused

j) Drowsiness (difficulty staying awake)

k) Lack of energy (fatigue, weakness)

l) Dry mouth

m) Headache

n) Hives

o) Other: _____

p) Other: _____

Write the medicine(s) beside each side effect:

For example: Drowsiness – Benadryl, Tylenol with codeine, Vicodin.

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3. Have you ever used a strong pain-killer, a prescription drug such as Vicodin, Oxycontin, Norco, Tylenol with codeine, morphine, Demerol, hydrocodone, Lortab, cough medicine containing codeine, Tussionex? **NO YES**

Which medicine(s)? _____

_____

4. Have you ever had any allergies or side effects from any of these medicines? **NONE N/A**

(Circle all that apply)

a) Nausea

b) Vomiting

c) Problems with urination

d) Diarrhea

e) Constipation

f) Itchy skin

g) Dizziness (light-headed)

h) Difficulty concentrating

i) Feeling confused

j) Drowsiness (difficulty staying awake)

k) Lack of energy (fatigue, weakness)

l) Dry mouth

m) Headache

n) Hives

o) Other: _____

Write in the medicine(s) beside each side effect:

For example: Drowsiness – Tylenol with codeine, Lortab, Vicodin.

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6.	Have you ever had an operation or surgical procedure? If yes, type of operation or surgical procedure (e.g., stitches):	**NO**	**YES**	
7.	Were you ever nauseous after taking any medication after the surgery or procedure?	**NO**	**YES**	**N/A**
8.	Did you vomit after taking any medication after the surgery or procedure?	**NO**	**YES**	**N/A**
9.	Do you have anemia or bleeding problems? If yes, medications you are taking:	**NO**	**YES**	
10.	Do you have heart disease or high blood pressure? If yes, medications you are taking:	**NO**	**YES**	
11.	Do you have asthma? If yes, medications you are taking:	**NO**	**YES**	
12.	Do you have any gastro-intestinal disorders (ulcer, colitis, etc.)? If yes, medications you are taking:	**NO**	**YES**	
13.	Do you have arthritis? If yes, medications you are taking:	**NO**	**YES**	
14.	Do you have any endocrine disorder (thyroid disease, diabetes)? If yes, medications you are taking:	**NO**	**YES**	
15.	Do you have any neurologic disease (seizure disorder)? If yes, medications you are taking:	**NO**	**YES**	

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16.	Do you ever get "vertigo" (a sense of motion when you're not moving, a sense of things moving around you, with dizziness, lightheadedness, or loss of balance)?	**NO**	**YES**	
17.	Do you have "Meniere's Disease" (a sense of the room spinning around you, ringing in the ears, hearing loss, ear fullness, with recurrent bouts of dizziness, loss of balance, or unsteadiness)?	**NO**	**YES**	
18.	Are you ever nauseous when you have a Meniere's attack?	**NO**	**YES**	**N/A**
19.	Do you get "migraine headaches"? If yes, medications you are taking: _____	**NO**	**YES**	
20.	Do you ever get headaches that are associated with nausea or vomiting?	**NO**	**YES**	**N/A**
21.	Do you ever get nauseous? If yes, when? _____	**NO**	**YES**	
22.	Do you ever get "a knot in your stomach" when you're nervous or afraid or very worried about something?	**NO**	**YES**	
23.	Did this "knot in your stomach" ever make you feel nauseous?	**NO**	**YES**	**N/A**
24.	Did this "knot in your stomach" ever make you vomit?	**NO**	**YES**	**N/A**

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Following are questions about different <u>situations where some people tend to be nauseous or vomit:</u>

25.	Do you walk slowly or turn slowly to avoid losing your balance?	**NO**	**YES**
26.	Do you get "car sick"?	**NO**	**YES**
27.	Do you need to have the window open when riding in a car?	**NO**	**YES**
28.	Do you get "sea sick"?	**NO**	**YES**
29.	Do you get sick to your stomach or nauseous or even vomit when you gag on something?	**NO**	**YES**
30.	Do you get sick to your stomach or nauseous or even vomit when riding backwards on a train?	**NO**	**YES**
31.	Do you get sick to your stomach or nauseous or even vomit when riding on a plane during turbulence or a sudden turn?	**NO**	**YES**
32.	Do you get sick to your stomach or nauseous or even vomit on roller coasters or other amusement park rides?	**NO**	**YES**
33.	Do you get sick to your stomach or nauseous or even vomit from spinning around?	**NO**	**YES**
34.	Do you get sick to your stomach, nauseous, or vomit sometimes when you bend over?	**NO**	**YES**
35.	Do you get sick to your stomach or nauseous or even vomit from seeing a frightening movie?	**NO**	**YES**
36.	Do you get sick to your stomach or nauseous or even vomit from seeing blood?	**NO**	**YES**
37.	Do you get sick to your stomach or nauseous or even vomit from seeing body parts (such as seeing a horrible accident)?	**NO**	**YES**
38.	Do you get sick to your stomach or nauseous or even vomit from seeing severe malnutrition (such as starving children)?	**NO**	**YES**
39.	Do you get sick to your stomach or nauseous or even vomit from smelling a very bad smell (such as vomit)?	**NO**	**YES**

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40. Do you get sick to your stomach or nauseous or even vomit from seeing someone throw up? **NO** **YES**

41. Do you get sick to your stomach or nauseous or even vomit after eating certain foods? **NO** **YES**

42. Do you get sick to your stomach or nauseous or even vomit just thinking about getting nauseous? **NO** **YES**

43. Think of <u>situations where you tend to get sick to your stomach, nauseous or vomit</u>

    --- such as taking a strong pain-killer or a cough medicine with codeine, gagging, riding a roller coaster, spinning around, turning around suddenly, riding in a car, sitting backwards on a train, riding in a boat, seeing blood, smelling a bad smell.

    In general:

    Do you consider yourself prone (likely) to get nauseous?

    (Circle one number)

0	1	2	3	4	5	6	7	8	9	10
NOT LIKELY										**VERY LIKELY**

44. Is there anyone in your family who has a tendency to get nauseous easily? **NONE**

    Circle all relatives who are likely to get nauseous:

    FATHER MOTHER SISTER BROTHER TWIN

    UNCLE AUNT COUSIN

45. Is there anyone in your family who gets nauseous after taking a strong pain killer (a prescription drug such as Vicodin, OxyContin, Tylenol with codeine, morphine, hydrocodone, Norco, Lortab, cough medicine containing codeine, Tussionex)? **NONE**

    Circle all relatives who are prone to get nauseous after taking a strong pain killer:

    FATHER MOTHER SISTER BROTHER TWIN

    UNCLE AUNT COUSIN

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14 INVESTIGATOR'S PROTOCOL AGREEMENT

PROTOCOL NUMBER	**CLCT-018 (Version 3.0)**
PROTOCOL TITLE	**A Randomized, Double-Blind, Placebo- and Active-Controlled Study to Determine the Efficacy and Safety of CL-108 5 mg (Hydrocodone 5 mg/Acetaminophen 325 mg/Promethazine 12.5 mg) as a Treatment for Moderate-to-Severe Pain and the Prevention of Opioid-Induced Nausea and Vomiting (OINV) following Orthopedic Surgery**

By my signature, I confirm that my staff and I have carefully read and understand this protocol, and agree to comply with the conduct and terms of the study specified herein. In particular, I/we have agreed to:

1. Maintain confidentiality and assure security of Charleston Laboratories, Inc. confidential documents such as the protocol, case report form, Investigator's Brochure, final study reports, manuscript drafts, unpublished data, correspondence, etc.

2. Assure access by Charleston Laboratories, Inc. monitors to original source documents.

3. Retain IRB approval of study, any amendments to the study, and periodic re-approval as required.

4. Keep the IRB informed of serious adverse events. A copy of the Study Close-Out Report will be sent to the IRB upon completion of the study.

5. Obtain written informed consent from each participant or their legal representative.

6. Make prompt reports of serious adverse events to Charleston Laboratories, Inc.

7. Cooperate fully with any study-related GCP audit as performed by the sponsor's quality assurance group.

8. Abide by stipulations in the Disclosure of Data section.

9. Abide by manuscript preparation/authorship guidelines established at the outset of the study.

_____ _____

Principal Investigator Date

CHARLESTON LABORATORIES, INC.

Protocol No. CLCT-018

15 Protocol Amendment 1: Table of Changes

Section Updated	Original Text/Content	Updated Text/Content
Title Page and Footers Dates and Version #	**Original Text** Version 1.0, May 10, 2017	**Updated Text:** Version 2.0, June 16, 2017
Retching Vomiting Index (RVI) Replaced with Vomiting Frequency Scale ((VFS) **Page 5**: Abbreviations **Page 8 and 9**: **Section 1.3**, Study Design **Page 11**: **Section 1.8**, Study Flow Chart **Page 15-17: Section 4.2**, Visit 2 **Page 22**: **Section 5.5** Use of Supplemental (Rescue) Medications, Paragraphs 6-9. **Page 23: Section 5.6**, Withdrawal **Page 26**: **Section 6.2.4**, Retching and Vomiting Index (entire section replaced) **Page 32**: **Section 6.3.4**, Post-Surgical Eligibility Assessments and Dosing, #2 **Page 32-33: Sections 6.3.5, 6.3.6, 6.3.7, 6.3.8** (Time Point Assessments) **Page 43: Section 7.4.7,** Missing Data **Page 43: Section 7.4.8,** Use of Supplemental Medications **Page 62: Section 13.2**, Nausea/Vomiting Rating Scales	**Original Scale** Retching Vomiting Index (RVI) **Section 5.6 Original Text** For the RVI - Did you have these stomach symptoms *over the past hour*?	**Deleted Scale** RVI in all relative locations. **Added Scale** Vomiting Frequency Scale (VFS) **General Changes** -The entire RVI scale was replace with the VFS scale in all referenced sections. -The Acronym "RVI" was replaced with "VFS" in all referenced areas of the protocol. -Timing of assessments of the new VFS scale will occur at the same time points specified for RVI in the original protocol. **Section 5.6 Updated Text** For the ~~R~~VFS~~I~~ – How many times did you vomit (throw up) over the past hour? ~~***Did you have these stomach symptoms** over the past hour*?~~

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Section Updated	Original Text/Content	Updated Text/Content
Nausea Intensity Scale **Page 5**: Abbreviations **Page 7 and 8**: **Section 1.3**, Study Design **Page 11**: **Section 1.8,** Study Flow Chart **Page 15-17**: **Section 4.2**, Visit 2 **Page 22**: **Section 5.5**, Use of Supplemental (Rescue) Medications, Paragraphs 6-9. **Page 23: Section 5.6**, Withdrawal **Page 26**: **Section 6.2.3**: Nausea Intensity Scale **Page 32**: **Section 6.3.4**: Post-Surgical Eligibility Assessments and Dosing, #2 **Page 36-38**: **Sections 6.3.5**, **6.3.6, 6.3.7 and 6.3.8** (Assessment Time points) **Page 59: Section 13.2** Nausea/Vomiting Rating Scales	**Original Name** Nausea Intensity Scale (NIS) **Original Definition** Nausea Intensity Scale (NIS), a 0-10 Likert scale derived from the Edmonton Symptom Assessment Scales,[5,7] to assess the intensity of nausea **Section 5.6 Wording** For the NIS - On a scale of 0 to 10, where 0 is "no nausea" and 10 is "severe nausea," circle the number that best describes the worst nausea you've had *over the past half hour*.	**Update Name of Scale:** Nausea ~~Intensity~~ Scale (N~~I~~S) **Updated Definition**: Nausea ~~Intensity~~ Scale (N~~I~~S), a ~~0-10 Likert~~ binary scale ~~derived from the Edmonton Symptom Assessment Scales,~~[~~5,7~~] to assess the ~~intensity~~ presence/absence of nausea Reference #5 and 7 in original protocol now deleted. **Section 5.6 Updated Language** For the NS - ~~For the NIS - On a scale of 0 to 10, where 0 is "no nausea" and 10 is "severe nausea," circle the number that best describes the worst nausea you've had~~ *Over the past half-hour,* ***have you had any nausea (feeling like you wanted to throw up)?***

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Section Updated	Original Text/Content	Updated Text/Content
Secondary Endpoints **Page 9**: **Section 1.4.2** Key Secondary Endpoints	**Original Text** 1) Severity of opioid-induced nausea over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg	**Updated Text:** 1) Absence of any ~~Severity of opioid induced~~ nausea ***or any use of anti-emetic medication*** over 48 hours, ***(complete absence of OINV)***, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg **Added Secondary End Point #3:** Percentage of patients without any nausea over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg **Added Secondary End Point #4** Percentage of patients without any nausea or vomiting 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg
Secondary Endpoints **Page 42**: **Section 7.4.3** Key Secondary Endpoints	**Original Text** 1. Severity of opioid-induced nausea over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg 2. Percentage of patients with any vomiting over 48 hours, comparing CL-108 5 mg to hydrocodone %5 mg/APAP 325 mg	**Updated Text** 1. ***Percentage of patients with complete absence*** ~~Severity~~ of ***OINV (no nausea, no vomiting, and no use of anti-emetic medication)*** ~~opioid induced nausea~~ over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg 2. Percentage of patients with***out*** any vomiting over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg **ADDED #3** Percentage of patients without

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Section Updated	Original Text/Content	Updated Text/Content
		any nausea over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg **ADDED #4** Percentage of patients without any nausea or vomiting 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg
Rescue Medication Clarification **Page 16: Section 4.2**: Visit 2 **Page17: Section 4.3:** Outpatient	**Original Text** **Section 4.2:** NA	**Added Text** **Section 4.2** ***All patients will receive a bottle of ibuprofen tablets (analgesic rescue medication) and a prescription for an anti-emetic of the investigator's choice (anti-emetic rescue medication) to be used as needed during Study Days 3-7.*** **Section:** The patient will be discharged from Visit 2 with a bottle containing the remaining study medication capsules, a bottle containing ibuprofen 200 mg tablets ***(to be used*** if needed), and a prescription for an anti-emetic(***to be used*** if needed).
Page 17: Section 4.3: Outpatient	**Original Text** to document any symptoms (adverse events) they experienced and any cigarettes smoked over the past 24 hours.	**Deleted Text** to document any symptoms (adverse events) they experienced~~**and any cigarettes smoked over the past 24 hours.**~~

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Section Updated	Original Text/Content	Updated Text/Content
Page 12: Section 2: Background and Rationale	**Original Text:** … the occurrence of any vomiting or use of anti-emetic medication (indicative of nausea) over 48 hours. … 48 hours ($SPID_{48}$) will be compared for patients treated with CL-108 5 mg and those treated with placebo. Opioid Symptoms Scales (OSS), derived from the Symptom Distress Scale to identify other opioid effects,[4]	**Added Text:** ….the occurrence of any vomiting or use of anti-emetic medication (indicative of nausea) over 48 hours. ***The occurrence and frequency of vomiting will be measured on a 0-3 Vomiting Frequency Scale, the occurrence of nausea will be measured on a binary Nausea Scale, and the use of anti-emetic medication will be documented in diaries.*** …. 48 hours ($SPID_{48}$) will be compared for patients treated with CL-108 5 mg and those treated with placebo. ***Pain intensity will be measured on a 0-10 Pain Intensity Numerical Rating Scale.*** Opioid Symptoms Scales (OSS), derived from the Symptom Distress Scale to identify other opioid effects,[4] ***which were used in CLCT-002 and CLCT-003***
Page 18: Inclusion Criteria, #2	**Original Text** …condom, abstinence or surgical sterilization)…	**Updated Text** …condom, ~~**abstinence**~~ ***abstain from heterosexual sex,*** or surgical sterilization)…
Opioid Symptom Scale **Page 27**: **Section 6.2.5:** (OSS) (from the Symptom Distress Scale)[4] **Page 32**: **Section 6.3.4**, Post-Surgical Eligibility Assessments and Dosing, #2, c	**Original Text:** **Page 29**: NA **Page 34**: Opioid symptoms Scales (OSS) over past 24 hours	**Clarification Added**: **Page 29:** ***The Opioid Symptom Scales are measurement instruments for documenting the occurrence and severity of each other opioid-related symptom, as in CLCT-002 and CLCT-003.*** **Page 34**: Opioid symptoms Scales (OSS) ~~over past 24 hours~~
PI-CAT Scale **Page 25: Section 6.1**,	**Original Text** *Pain Assessments:*	**Deleted Text** *Pain Assessments*

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Section Updated	Original Text/Content	Updated Text/Content
Evaluations of Safety and Eligibility, Pain Assessments **Page 25: Section 6.2.1** Categorical Pain Intensity Scale (PI-CAT) **Page 61: Appendix 13.1**	… categorical pain intensity scale, or PI-CAT (which is called a "Pain Severity Scale" in the patient diary). Only patients with moderate or severe pain ratings (2 or 3) are eligible for the trial.	… categorical pain intensity scale, or PI-CAT ~~(which is called a "Pain Severity Scale" in the patient diary).~~ Only patients with moderate or severe pain ratings (2 or 3)… **Section 6.2.1 Updated** ***…(called "Pain" in the Clinic Diary)***
Adverse Event Reporting of Opioid –related Events **Page 8: Section 1.3: Study Design, Paragraph 13** **Page 25: Section 6.1**, Evaluations of Safety and Eligibility, Clinical Adverse Event Assessment	**Original Text:** **Section 1.3: Study Design** The Investigator will rate the severity of these other (i.e., not opioid-related) side effects on a 3-category severity scale **Section 6.1: Adverse event assessment:** All adverse events except for those evaluated by the patient on the NIS, RVI and OSS will be recorded by the Study Coordinator or designee in the electronic case report form (eCRF) according to Section 9.1 of this protocol.	**Updated Text:** **Section 1.3: Study Design** The Investigator will rate the severity of ***all*** ~~these other (i.e., not opioid-related)~~ side effects on a 3-category severity scale **Section 6.1: Clinical adverse event assessment:** All adverse events ~~except for those evaluated by the patient on the NIS, RVI and OSS~~ will be recorded by the Study Coordinator or designee in the electronic case report form (eCRF) according to Section 9.1 of this protocol.
Adverse Event Reporting of Opioid –related Events **Page 27: Section 6.2.8**, Patients Reports of Adverse Events (Elicited and Volunteered.)	**Original Text: Section 6.2.8** The Investigator will rate each non-opioid-related side effect on a 1-3 scale (mild, moderate, severe)… To avoid duplication of AE data entry, the following opioid-related adverse events will not be reported as AEs during the primary 48-hour treatment evaluation period: nausea, retching and vomiting (which are measured as endpoints on the NIS and RVI) and dizziness, drowsiness, constipation, difficulty	**Deleted Text: Section 6.2.8** The Investigator will rate each ~~non-opioid-related~~ side effect on a 1-3 scale (mild, moderate, severe)… ~~To avoid duplication of AE data entry, the following opioid-related adverse events will not be reported as AEs during the primary 48-hour treatment evaluation period: nausea, retching and vomiting (which are measured as endpoints on the NIS and RVI) and dizziness, drowsiness, constipation, difficulty voiding, confusion,~~

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Section Updated	Original Text/Content	Updated Text/Content
	voiding, confusion, headache, itch, difficulty concentrating, and dry mouth (which are 9 other opioid-related side effects measured on the OSS). Observed and reported episodes of retching will be entered on the Adverse Events page of the eCRF.	~~headache, itch, difficulty concentrating, and dry mouth (which are 9 other opioid-related side effects measured on the OSS). Observed and reported episodes of retching will be entered on the Adverse Events page of the eCRF.~~
Adverse Event Reporting and Opioid Symptoms **Page 48, Section 9.1.1** Definition of Adverse Event	**Original Text** Because nausea, retching and vomiting are measured as endpoints on the NIS, WNS and RVI and because 9 other opioid-related symptoms (dizziness, drowsiness, constipation, difficulty voiding, etc.) are measured on the OSS as secondary endpoints, these 12 opioid-related symptoms will not be duplicated as AEs.	**Deleted Text** ~~Because nausea, retching and vomiting are measured as endpoints on the NIS, WNS and RVI and because 9 other opioid-related symptoms (dizziness, drowsiness, constipation, difficulty voiding, etc.) are measured on the OSS as secondary endpoints, these 12 opioid-related symptoms will not be duplicated as AEs~~.
Adverse Event Reporting and Opioid Symptoms **Page 50: Section 9.1.5,** Treatment Period	**Original Text** Adverse events occurring from the initial study drug administration to the follow-up Visit 3 discharge should be recorded as adverse events in the eCRF. However, nausea, retching, vomiting, other opioid symptoms (on the OSS) and the usual post-surgical outcomes of bunionectomy should not be recorded as adverse events.	**Deleted Text** Adverse events occurring from the initial study drug administration to the follow-up Visit 3 discharge should be recorded as adverse events in the eCRF. ~~However, nausea, retching, vomiting, other opioid symptoms (on the OSS) and the usual post-surgical outcomes of bunionectomy should not be recorded as adverse events.~~

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Section Updated	Original Text/Content	Updated Text/Content
NPR Scale **Page 26, Section 6.2.2**, Numerical Pain Intensity Rating Scale (PI-NRS) **Page 58: Appendix 13.1**	**Original Text** Numerical Pain Intensity Rating Scale (PI-NRS) ***(called "Pain Severity Scale" in the Clinic Diary)*** Patients will be asked at baseline and at every post treatment assessment time… This is the measurement instrument for the co-primary analgesia endpoint.	**Original Text** Numerical Pain Intensity Rating Scale (PI-NRS) ***(called "Pain Severity ~~Scale~~" in the Clinic Diary)*** ***The*** patient***s*** will be asked at baseline and at every post treatment assessment time … The ***Numerical Pain Intensity Rating Scal***e ~~is~~ the measurement instrument for the co-primary analgesia endpoint.
Page 28: Section 6.3.2 Screening Procedures	**Original Text** **Criterion D**: If Criteria A-C do not qualify a patient… "clinical judgment" to admit up to ca. 10% ….	**Updated Text** **Criterion D**: If Criteria A-C do***es*** not qualify a patient... "clinical judgment" to admit up to ***approximately*** 10% ….
Surgical Clarification **Page 32: Section 6.3.3** Surgical Day (Visit 2)	**Original Text** …and for observation for up to 9 hours to observe if the patient develops moderate-to-severe pain. During this period, the patient will be instructed how to use the rating scales in the Diary.	**Added Text** …and for observation for up to 9 hours to observe if the patient develops moderate-to-severe pain ***after the PSP is discontinued***. During this period, the patient will be instructed how to use the rating scales in the Diary.
Page 32: Section 6.3.4: Post-Surgical Eligibility	**Original Text** During the post-surgical period until 10 minutes pre-dosing, patients may consume non-caffeinated liquids and soft foods (no chocolate) served at room temperature. No other treatment is permitted. … If 9 hours have transpired since surgery ended and the patient does not indicate…	**Updated Text** During the post-surgical period until 10 minutes pre-dosing, patients may consume non-caffeinated liquids and**~~soft~~** food (no chocolate) **~~served at room temperature.~~** No other treatment is permitted. … If 9 hours have transpired since ***the popliteal sciatic block was discontinued*** **~~ended~~** and the patient does not indicate…

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Section Updated	Original Text/Content	Updated Text/Content
Vital Sign Measurements **Page 32: Section 6.3.4,** Post-Surgical Eligibility	**Original Text** NA	**Added Text** ***Patients are to be in a semi-recumbent position at least 15 minutes prior to each scheduled assessment time.***
Smoking Exclusions **Page 38: Section 6.4** Concomitant Medications	**Original Text** Any concomitant medication used (e.g., antihypertensive, contraceptive) including cigarettes smoked during the study must be entered into the eCRF.	**Deleted Text** Any concomitant medication used (e.g., antihypertensive, contraceptive) ~~including cigarettes smoked during the study~~ must be entered into the eCRF.
Page 42, Section 7.3.4 Key Secondary Endpoints	**Original Text** #2 Percentage of patients without any vomiting over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg #3 Percentage of patients without any nausea over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg #4 Percentage of patients without any nausea or vomiting over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg	**Updated and Added Text** #2 Percentage of patients with~~out~~ any vomiting over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg #3 Percentage of patients with~~out~~ any nausea over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg #4 Percentage of patients with~~out~~ any nausea or vomiting over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg ***#5 Percentage of patients with Post-Discharge Nausea and Vomiting (PDNV) over days 3-7*** ***#6 Number of doses of study medication taken over days 3-7*** ***#7 Number of doses of study medication taken per day over days 3-7***
Labeling Endpoints **Page 42-43: 7.4.4** Labeling Endpoints	**Original Text:** **Number 3:** Patients treated with CL-108 5 mg experience less nausea	**Updated Text** **Number 3:** ***More p***~~P~~atients treated with CL-108 5 mg experience complete

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Section Updated	Original Text/Content	Updated Text/Content
	than patients treated with a comparable product containing hydrocodone 5 mg/ acetaminophen 325 mg	absence of OINV ~~less nausea~~ than patients treated with a comparable product containing hydrocodone 5 mg/ acetaminophen 325 mg **Added # 5 and #6** **#5**: Patients treated with CL-108 5 mg experience less nausea than patients treated with a comparable product containing hydrocodone 5 mg/acetaminophen 325 mg **#6**: Patients treated with CL-108 5 mg experience less nausea and vomiting than patients treated with a comparable product containing hydrocodone 5 mg/acetaminophen 325 mg

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Section Updated	Original Text/Content	Updated Text/Content
Page 45: Section 7.4.16 Safety	**Original Text** …nausea, retching, vomiting, emetic episodes).	**Updated Text** …nausea, retching, vomiting, emetic episodes, ***sleep disturbance, headache).***
Page 46: Section 7.4.18, Protocol Deviations	**Original Text** …could significantly affect efficacy will be excluded…	**Updated Text:** …could significantly affect efficacy results ***(e.g., a missed dose of study medication)*** will be excluded
Urine Cotinine Test Added to the Protocol **Page 6-9: Section 1.3,** Study Design, Paragraphs 2, 3 **Page 11: Section 1.8,** Study Flow Chart: Line for Urine Cotinine Added **Page 13-18: Section 4.1,** Visit 1**, 4.2:** Visit 2 and **4.4:** Visit 3 **Page 19: Section 5.2,** Exclusion Criteria, #4 Confounding and Contraindicated Drugs **Page 23: Section 5.6.1,** Investigator's Reason for Withdrawal **Page 25: Section 6.1:** Evaluations of Efficacy and Safety **Page 30: Section 6.3.3:** Screening Procedures (Visit 1) and 6.3.3: Surgery Day (Visit 2):	**Original Text** Cotinine not included in the original protocol.	**Added Text:** **Section 1.3: Paragraph 2:** …collected (for drug screening ***and cotinine*** on all patients)… **Section 1.3 Paragraph 3;** …and urine drug screening tests ***and urine cotinine test*** will be performed **Section 4.1, 4.2 and 4.4:** ***…and urine cotinine test*** will be performed… **Section 5.2**: …oxycodone, ***cotinine*** at screening…. **Section 5.6:** …pregnancy test, ***cotinine test,*** or drug screening… **Section 6.1** ***Cotinine Test:*** ***A urine cotinine test will be performed on each patient at the Screening Visit and on the morning before surgery. A positive result will exclude the patient from participating in the trial. A urine cotinine test will also be performed at Visit 3. A positive result will indicate that the***

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Section Updated	Original Text/Content	Updated Text/Content
		patient used nicotine during the trial. **Section 6.3.2 and 6.3.3** • ***Urine cotinine test…***
General Updates		General grammatical errors were updated throughout the document.
Page 6: Section 1.3: Study Design	**Original Text:** **Visit 2**. After sedation (midazolam and/or propofol) is achieved, regional anesthesia will be established with a popliteal sciatic nerve block (PSB) using ropivacaine initially, then mepivacaine, after which patients will undergo primary…	**Updated Text:** **Visit 2**. After sedation (midazolam and/or propofol) is achieved, regional anesthesia will be established with a popliteal sciatic nerve block (PSB),~~using ropivacaine, initially then mepivacaine,~~ after which patients will undergo primary…
Page 19: Section 5.2: Exclusion Criteria: #3: Drug Allergy	**Original Text:** …NSAID (such as ibuprofen or aspirin), midazolam, propofol or ketorolac…	**Added Text:** NSAID (such as ibuprofen or aspirin), midazolam, propofol, ***mepivacaine, ropivacaine*** or ketorolac
Page 31: Section 6.3.3: Surgery Day (Visit 2)	**Original Text:** Postoperative pain will be controlled by a continuous anesthetic infusion through the catheter previously placed adjacent to the popliteal sciatic nerve. Mepivacaine 0.5%... All use of mepivacaine will be discontinued at approximately 3 am.	**Added Text:** Postoperative pain will be controlled by a continuous anesthetic infusion through the catheter previously placed adjacent to the popliteal sciatic nerve. ***Two methods of continuous anesthetic infusion are permitted.*** Mepivacaine 0.5%... All use of mepivacaine will be discontinued at approximately 3 am ***on the morning following surgery.***

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Section Updated	Original Text/Content	Updated Text/Content
Page 31: Section 6.3.3: Surgery Day (Visit 2)	**Original Text:** All use of ketorolac will be discontinued at 1:30 am.	**Added Text:** All use of ketorolac will be discontinued at 1:30 am ***on the morning following surgery.***
Page 31: Section 6.3.3: Surgery Day (Visit 2)	**Original Text:** New text	**Added Text:** ***Alternatively, postoperative pain will be controlled by a continuous ropivacaine 0.2% infusion through the catheter previously placed adjacent to the popliteal sciatic nerve. Ropivacaine 0.2 % will be infused starting at 1-2 mL per hour and titrating the rate of infusion as needed up to a maximum rate of 10 mL per hour. All use of ropivacaine will be discontinued at approximately 3 am on the morning following surgery.*** ***During this continuous infusion period, patients may receive supplemental analgesia for breakthrough pain (patients less than 65 years of age and greater than 50 kg: ketorolac 30 mg IM or IV every 6 hours as needed with a maximum daily dose of 120 mg; patients greater than or equal to 65 years of age or less than 50 kg: ketorolac 15 mg IM or IV every 6 hours as needed with a maximum daily dose of 60 mg). All use of ketorolac will be discontinued at 1:30 am on the morning following surgery.***

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16 Protocol Amendment 2: Table of Changes

Section Updated	Original Text/Content	Updated Text/Content
Title Page and Footers Dates and Version #	**Original Text** Version 2.0, June 16, 2017	**Updated Text:** Version **3.0**, **13 August 2017**
Clarifying that positive urine drug screen will result is screen failure of subject. **Page 11: Section 1.8,** Study Flow Chart: Urine Drug Screen Footnote	**Original Text**: None	Added Text: ***11 A positive urine drug screen will exclude the patient from participating in the study.***
Clarifying to awake subjects for scheduled dosing. **Page 7 and 8, Section 1.3**, Study Design **Page 16, Section 4.2**, **Paragraph 14,** Visit 2 **Page 35, Section 6.3.4,** Post-Surgical Eligibility Assessment and Dosing, **Page 37, Section 6.3.6, #6b** Study Times: 12 Hours Post-Initial Dose through 48 Hours	**Original Text**: None	**Added Text**: ***Subjects should be awoken for dosing, as needed to remain on the dosing schedule.***
Clarifying % Lidocaine **Page 14, Section 4.2** Visit 2 **Page 30, Section 6.3.3** Surgery Day (Visit 2)	**Original Text** **Section 4.2: …**short-acting lidocaine 1% (plain). **Section 6.3.3, Paragraph 4:** inject approximately 5 mL lidocaine 2% (plain) locally… **Section 6.3.3, Paragraph 5:** … using short-acting lidocaine 2% (plain, without epinephrine)…	**Updated Text** **Section 4.2: …**short-acting lidocaine 1% ***or 2%*** (plain). **Section 6.3.3, Paragraph 4:** inject approximately 5 mL lidocaine ***1% or*** 2% (plain) locally… **Section 6.3.3 Paragraph 5:** … using short-acting lidocaine ***1% or*** 2% (plain, without epinephrine)…
Page 28, Section 6.3.2,	**Original Text**	**Updated Text**

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Section Updated	Original Text/Content	Updated Text/Content
Screening Procedures (Visit 1), Criterion B	**Criterion B**: If a patient has at least one of the following 5 responses to Questions 26-27, 30, 32-34, or 39 (relating to motion sickness) on the NPQ	**Criterion B**: If a patient has at least one of the following 5 responses to Questions 26-27, 30, 32-34, ~~**or 39**~~ (relating to motion sickness) on the NPQ
Page 30, Section 6.3.3, Surgery Day (Visit 2)	**Original Text** Alternatively, postoperative pain will be controlled by a continuous ropivacaine 0.2% infusion through the catheter previously placed adjacent to the popliteal sciatic nerve. Ropivacaine 0.2 % will be infused starting at 1-2 mL per hour and titrating the rate of infusion as needed up to a maximum rate of 10 mL per hour.	**Updated Text** Alternatively, postoperative pain will be controlled by a continuous ropivacaine 0.2% infusion ~~**through the catheter previously placed adjacent to the popliteal sciatic nerve**~~. ***via PSB catheter on a PCA pump at a continuous rate of 1 ml/hr. Up to two, 3 ml boluses of Ropivacaine 0.2% may be given per hr. If pain is not adequately controlled after two boluses, infusion may be increased by 2ml/hr.*** ~~**Ropivacaine 0.2 % will be infused starting at 1-2 mL per hour and titrating the rate of infusion as needed up to a maximum rate of 10 mL per hour.**~~
Page 42, Section 7.3.4 Key Secondary Endpoints	**Original Text** #2 Percentage of patients without any vomiting over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg #3 Percentage of patients without any nausea over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg #4 Percentage of patients without any nausea or vomiting over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg	**Updated and Added Text** #2 Percentage of patients with~~**out**~~ any vomiting over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg #3 Percentage of patients with~~**out**~~ any nausea over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg #4 Percentage of patients with~~**out**~~ any nausea or vomiting over 48 hours, comparing CL-108 5 mg to hydrocodone 5 mg/APAP 325 mg ***#5 Percentage of patients with Post-Discharge Nausea and Vomiting (PDNV) over days 3-7***

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Section Updated	Original Text/Content	Updated Text/Content
		#6 Number of doses of study medication taken over days 3-7 ***#7 Number of doses of study medication taken per day over days 3-7***
Page 43, Section 7.4.4 Labeling Endpoints	**Original Text** No #7-#9	**Added Text** ***#7. Patients treated with CL-108 5 mg experience less nausea and vomiting after discharge following surgery than patients treated with a comparable product containing hydrocodone 5 mg/acetaminophen 325 mg*** ***#8 Patients treated with CL-108 5 mg take more doses over days 3-7 and have greater reduction in pain and less OINV after discharge following surgery than patients treated with a comparable product containing hydrocodone 5 mg/ acetaminophen 325 mg*** ***#9. Patients treated with CL-108 5 mg take more doses each day over days 3-7 and have greater reduction in pain and less OINV after discharge following surgery than patients treated with a comparable product containing hydrocodone 5 mg/ acetaminophen 325 mg.***
Page 46, Section 7.4.17 Interim Analysis	**Original Text** No Interim Analysis is planned.	**Added Text** ~~**No Interim Analysis is planned**~~. ***An independent Data Monitoring Committee (DMC) will meet to review efficacy and safety endpoints. The DMC will operate under a charter and will make recommendations to the sponsor. An interim analysis will be performed by the DMC after approximately 66% of the subjects have completed the***

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Section Updated	Original Text/Content	Updated Text/Content
		300-subject study and there is adequate representation from each of the investigative sites (i.e., approximately 30 completed subjects per site). If it is judged impossible to achieve this deminimis representation at a particular site or sites, the interim analysis will be conducted on the total number of subjects completed (i.e., approximately 200 subjects). Since the DMC will review efficacy data, formal sequential boundaries for efficacy and futility will be declared in the DMC's Statistical Analysis Plan.
Page 62 , Section 13.4 Appendix 3, Nausea Prone Questionnaire	**Original Text** #20, Responses "Yes" and "No"	**Updated Text** #20, Responses, "Yes", "No" and "**NA**"
Page 71, Appendix 14 Protocol Agreement	**Original Text** Version 2.0	**Updated Text** Version **3.0**