Clinical Trial Protocol
HS-16-555

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Enriched-Enrollment Withdrawal, Multicenter Study to Evaluate the Efficacy and Safety of a Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Subjects with Moderate to Severe Chronic Low Back Pain Currently Treated with Daily Opioids

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BRAEBURN PHARMACEUTICALS:
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1. SPONSOR AND KEY PERSONNEL CONTACT INFORMATION

ROLE IN STUDY	NAME	CONTACT INFORMATION
Study Sponsor	Braeburn Pharmaceuticals, Inc.	47 Hulfish Street, Suite 441 Princeton, NJ 08542
Medical Monitor	Robert Allen, MD	rallen@braeburnpharma.com 610-393-1303
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2. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Braeburn Pharmaceuticals

Name of Investigational Products:

CAM2038 6.25 mg/mL (buprenorphine FluidCrystal® once-weekly subcutaneous injection depot)*
CAM2038 50 mg/mL q1w (buprenorphine FluidCrystal once-weekly subcutaneous injection depot)
CAM2038 356 mg/mL q4w (buprenorphine FluidCrystal once-monthly subcutaneous injection depot)

** CAM2038 6.25 mg/mL has been interchangeably referred to as CAM2048 during its development. The active ingredient is the same as for CAM2038 q1w. It also has the same excipients, as the CAM2038 q1w. For the purposes of this protocol, all reference to CAM2048 shall be considered to refer to and interchangeable with CAM2038 q1w.*

Name of Active Ingredient: Buprenorphine

Study Title:

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Enriched-Enrollment Withdrawal, Multicenter Study to Evaluate the Efficacy and Safety of a Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Subjects with Moderate to Severe Chronic Low Back Pain Currently Treated with Daily Opioids

Objectives:

Primary Objective:

The primary objective of this study is to evaluate the efficacy of long-acting subcutaneous (SC) injectable depots of buprenorphine (BPN) (CAM2038 once-weekly [q1w] and CAM2038 once-monthly [q4w]) compared to placebo on average pain intensity (API) scores, as measured on an 11-point, numerical rating scale (NRS-11) in subjects currently taking daily opioids for moderate to severe chronic low back pain (CLBP).

Secondary Objectives:

The secondary objectives of the study are:

- Change from baseline in the weekly average of daily worst pain intensity (WAWPI) scores at Week 12 of the Double-Blind Phase based on the NRS-11.
- To evaluate the safety and tolerability of treatment with CAM2038 q1w and CAM2038 q4w in subjects currently taking opioids for moderate to severe CLBP.

Open Label Safety Extension Objectives

Primary Objectives of Open Label Safety Extension

The primary objective of the open label extension phase is:

- To evaluate the safety and tolerability of treatment with CAM2038 q1w and CAM2038 q4w up to 52 weeks in subjects with moderate to severe chronic pain requiring daily treatment with opioids.

Secondary Objectives of Open Label Safety Extension

The secondary objectives of the open label extension phase are:

- Evaluate the steady-state pharmacokinetics of BPN for CAM2038 q1w and CAM2038 q4w in subjects with moderate to severe chronic pain requiring daily treatment with

opioids
- Evaluate the efficacy and safety of CAM2038 q1w and CAM2038 q4w administration for up to 52 weeks in the treatment of subjects with moderate to severe chronic pain requiring daily treatment with opioids.

Methodology:
This is a Phase III, placebo-controlled, multicenter study with an enriched-enrollment withdrawal (EEW) design to evaluate the efficacy and safety of CAM2038 in opioid-experienced subjects with moderate to severe CLBP that requires continuous, around-the-clock (ATC) opioid treatment ≥ 40 mg morphine equivalent dose (MED). The study includes 5 phases: A Screening Phase (up to 2 weeks), a Transition Phase (up to 2 weeks), an Open-Label Titration Phase (up to 10 weeks), a Double-Blind Treatment Phase including a Final Study Visit (12 weeks), and a Follow-up Phase (4 weeks). The overall duration of participation in the core phase of the study (randomized Double-Blind Phase) is up to 30 weeks, from the Screening Phase through the Follow-up Phase.

Subjects will record their API at Screening and prior to the test dose on a paper diary at the site. Throughout the study, after subjects receive their first CAM2038 injection, they will record their WPI and API using the NRS-11 in an electronic diary. Subjects will be instructed to record their WPI and API once daily between 18:00 and 23:59 (i.e., 6:00 pm and 11:59 pm). Subjects will be instructed to make all attempts to record their pain scores at the same time of day throughout the study. In addition, subjects will be instructed to record their pain intensity in the electronic diary on the NRS-11 "at that moment" prior to taking rescue medication. Rescue medication use will also be recorded in the electronic diary.

Following screening and confirmation of eligibility, subjects will enter a Transition Phase of up to 2 weeks during which their current opioid dose will be down-titrated by approximately 25% per day to:

- ≤80 mg/day MED (for subjects whose opioid dose at screening is > 80 mg/day MED)
- or to ≤40mg/day MED (for subjects whose opioid dose at screening is between 40 mg/day and 79 mg/day MED).

Following the down titration, subjects will be transitioned to an immediate-release (IR) morphine for at least 2 days before they enter the Open-Label Titration Phase, as follows:

- 15 mg 4 times daily [QID] for subjects whose MED at screening was ≥ 80 mg/day
- 15 mg 3 times daily (TID) for subjects whose MED at screening was 40-79 mg/day.

Subjects who were previously on BPN prior to Screening will not need to participate in the morphine IR phase. However, subjects who were previously on BPN will be required to refrain from taking BPN for 12-24 hours as a washout prior to starting open label titration on CAM2038.

Following the morphine IR treatment, subjects will enter the Titration Phase. On Day 1 of the Titration Phase, subjects will return to the clinic after a washout of at least 12 hours from their last morphine IR dose, or 12-24 hours from their last BPN dose. Subjects who report a CLBP of ≥5 on the API scale and have a Clinical Opiate Withdrawal Scale (COWS) score of ≥5, will receive a BPN test dose (Buprenex®0.30 mg intramuscular [IM] injection) at the clinical site. After the Buprenex test dose, subjects will be assessed for any changes in QTcF (Fridericia's corrected QTc) and withdrawal. Subjects who tolerate the BPN test dose, do not show an increase >30 ms in

QTcF within 1 hour after the test dose, and have a COWS score of <5 within 15 minutes after the test dose will receive the first dose of SC CAM2038 q1w within 4 hours (+30 minutes) after the test dose (4 mg CAM2038 for subjects whose screening MED was between 40 mg/day and 79 mg/day; and 8 mg CAM2038 for subjects whose screening MED was ≥80 mg/day).

During the first week of the Titration Phase, subjects who experience significant pain may, at the discretion of the investigator, receive an additional dose at their corresponding CAM2038 q1w dosing level (4 mg or 8 mg respectively) on Day 3, 4 or 5. Subjects will then attend clinic visits every week for dosage adjustment. Dose adjustments will be made by increasing the dose level of CAM2038 q1w at the scheduled weekly visits (doses of 4 mg, 8 mg, 12 mg, 16 mg, 24 mg, or 32 mg per week). Subjects who require doses >32 mg/week will be discontinued from the study.

Rescue medication, consisting of hydrocodone/acetaminophen 5 mg/325 mg every 4 to 6 hours (q4-6h), may be taken during the Titration Phase as needed (prn), up to 15 mg/975 mg/day (3 tablets) for subjects whose MED at screening was 40-79 mg/day or up to 30 mg/1950 mg/day (6 tablets) for subjects whose MED at screening was ≥80 mg/day). The goal of the Titration Phase is to reach a stable dose of CAM2038 q1w that produces analgesia, by the end of the 10–week period.

Eligible subjects will receive CAM2038 titrated to a dose that meets the following criteria:

- Provides analgesia (i.e., 7-day mean API≤4)
- The API is at least 2 points below the value at the start of CAM2038 titration
- The dose of CAM2038 is well-tolerated for 7 days before randomization (no adverse effects that require a change in study dosing or interruption)
- Subject does not require, on average, more than one dose of rescue medication per day over the 7 days before randomization.

Subjects who are stabilized and responding to their CAM2038 q1w dose (4, 8, 12, 16, 24, or 32 mg) at the end of the Titration Phase and who fulfill the pre-defined randomization criteria will be randomized to one of two treatment groups in the 12-week Double-Blind Phase:

- Group 1: CAM2038 (q1w or q4w) SC injections
- Group 2: Placebo (q1w or q4w) SC injections

During the Double-Blind Phase, all subjects who are receiving 4, 8 or 12 mg CAM2038 q1w at the end of the Titration Phase will be randomized to continue their respective CAM2038 q1w dosing (4 mg, 8 mg or 12 mg) or matching placebo q1w for a total treatment duration of 12 weeks. Subjects who are receiving 16 mg, 24 mg or 32 mg CAM2038 q1w at the end of the Titration Phase will be randomized to CAM2038 q4w 64 mg, 96 mg or 128 mg, respectively or to matching placebo q4w for a total treatment duration of 12 weeks.

Rescue medication, hydrocodone/acetaminophen 5 mg/325 mg q4-6h prn, will be allowed during the Double-Blind Phase (up to three tablets or 15 mg/975 mg/day for subjects whose MED at screening was between 40-79 mg/day and up to six tablets or 30 mg/1950 mg/day for subjects whose MED at screening was ≥80 mg/day). Whenever subjects take rescue medication, they must record their pain intensity "at that moment" prior to taking rescue medication in the electronic diary. A Final Study Visit will take place 1 week after the last CAM2038/placebo q1w dose or 4 weeks after the last CAM2038/placebo q4w dose.

At the Final Study Visit (or early termination), subjects will be transitioned back to standard care or to their treatment prior to study entry. Subjects will then be contacted at Follow-up, within 4 weeks after the Final Study Visit, to assess adverse events (AE) and concomitant medications.

Open Label Safety Extension

Subjects who complete the Double-Blind Treatment Study Phase will be offered an opportunity to continue treatment in an open label safety extension for up to 60 weeks. Enrollment in the open label safety extension will continue until a sufficient number of subjects have been recruited to obtain at least 52 weeks of safety information in approximately 100 subjects. Subjects who sign the informed consent for the safety extension will not be required to participate in the post-Double-Blind follow-up period and may proceed directly into the safety extension phase.

Once the required number of subjects for the Double-Blind phase of the trial has been recruited, enrollment for the Double-Blind phase will be closed, and remaining subjects offered the opportunity to proceed directly to the long-term safety extension without having to participate in a double-blind treatment phase. However, to be eligible to proceed to the safety extension, subjects must meet the following criteria:

- Have CAM2038 titrated to a dose that provides analgesia (i.e., 7-day mean API≤4)
- The dose of CAM2038 is well-tolerated for 7 days before randomization (no adverse effects that require a change in study dosing or interruption)
- Subject does not require, on average, more than one dose of rescue medication per day over the previous 7 days

The opening of recruitment of subjects for the safety extension is to ensure that a sufficient number of subjects are enrolled to provide required long-term safety data to support the clinical development of CAM2038 for the indication of chronic pain requiring daily treatment with opioids.

These so called "de novo" subjects may have CLBP or other severe chronic pain disorders (such as osteoarthritis) and will not be required to participate in the Double-Blind Phase. The de novo subjects will undergo the same screening procedures, down titration, morphine IR, and CAM2038 up-titration as required for subjects going through the Double-Blind phase of the study. The CAM2038 dosing titration and rescue medication requirements for the safety extension for subjects whose opioid doses at screening are ≥ 80 mg/day MED, and 40-79 mg/day MED respectively shall be the same as described for the subjects participating in the Double-Blind Randomization phase.

Pharmacokinetics: Subjects in the safety extension will return to the study clinic for their regular weekly or monthly CAM2038 injections until the end of the study. Starting at the Month-4 safety extension visit (Visit Week 23 for De Novo subjects and Visit Weeks 35-36 for subjects transitioned

from randomized Double-Blind Phase), PK sampling for CAM2038 steady state pharmacokinetics will be performed on all subjects who provide additional consent for the pharmacokinetic sampling. PK sample can be done at any visit timepoint after the subject has stabilized but no later than 4 week prior to EOT. Blood samples will be collected prior to administration (within 45 minutes); and at approximately 2 hours, 6 hours, 24 hours, 72 hours, 168 hours, 336 hours, and 672 hours post administration to measure plasma levels of BPN and norbuprenorphine (norBPN) for subjects receiving both CAM2038 qlw and CAM2038 q4w treatments. Actual dates and times of dosing of IMP during the safety extension phase as well as blood sampling for PK measurement will be recorded.

Number of Subjects (Planned):

Approximately 875 subjects will be screened in order to obtain approximately 340 randomized subjects (170 subjects per treatment group) in the core study. The core study comprises two treatment arms: a group of approximately 170 subjects receiving SC CAM2038 q1w or CAM2038 q4w and a group of approximately 170 subjects receiving SC placebo q1w or q4w. Approximately 85 study sites in the United States will be utilized.

Subjects who discontinue prematurely may be replaced at the discretion of the Medical Monitor and the Principal Investigator, in order to maintain study power. Enrollment in the open label safety extension will continue until a sufficient number of subjects have been recruited to obtain at least 52 weeks of exposure safety information in approximately 100 subjects.

Study Population and Main Criteria for Inclusion (Core or Randomized Double-Blind Phase of the Study):

The study population will consist of adult males and females with moderate to severe CLBP currently treated with daily opioids ≥ 40 mg MED.

Inclusion Criteria:

1. Written informed consent provided prior to the conduct of any study-related procedures.
2. Male or non-pregnant, non-lactating female subject, greater than or equal to 18 years old.
3. Body mass index (BMI) between 18 and 38 kg/m^2, inclusive.
4. Treated with daily opioids for moderate to severe CLBP for a minimum of 3 months prior to Screening.
5. On a stable dose of ≥40 mg/day of oral morphine or MED during the 14 days prior to Screening.
6. Systolic blood pressure ≥100 mmHg and diastolic blood pressure ≥60 mmHg.
7. Female subject of childbearing potential who is willing to use a reliable method of contraception during the entire study (Screening Visit to final Follow-up). To be considered not of childbearing potential, female subjects must be surgically sterile (hysterectomy or bilateral oophorectomy, or bilateral tubal ligation with surgery at least 6 weeks before Screening).
8. Male subject who is willing to use reliable contraception
9. Willing and able to comply with all study procedures and requirements.

Exclusion Criteria:

1. Positive for hepatitis B surface antigen, hepatitis C viral RNA, or antibodies to human immunodeficiency virus (HIV).
2. Clinically significant symptoms, medical conditions, or other circumstances which, in the opinion of the investigator, would preclude compliance with the protocol, adequate cooperation in the study, or obtaining informed consent, or may prevent the subject from safely participating in the study, including the following:
    a) Severe respiratory insufficiency, respiratory depression, airway obstruction, gastrointestinal motility disorders, biliary tract disease, severe hepatic insufficiency, or planned surgery.
    b) Bipolar disorder
3. Current diagnosis of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition–defined moderate to severe substance use disorder (including alcohol), other than caffeine or nicotine.
4. Female subject planning to become pregnant during the study.
5. Surgical procedure(s) for CLBP within 6 months prior to Screening.
6. Concomitant disease(s) that could prolong the QTcF interval, such as autonomic neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, Long QT Syndrome, or family history of Long QT Syndrome.
7. QTcF >450 ms for males and >470 ms for females, or clinically significant electrocardiogram (ECG) abnormality at Screening, at the investigator's discretion.
8. Currently taking medications that have the potential to prolong the QTcF interval or may require such medications during the course of the study (Appendix 1) and has clinically significant abnormalities on screening ECG readings, as determined by the investigator.
9. A nerve or plexus block, including epidural steroid injections or facet blocks, within 1 month prior to Screening or botulinum toxin injection in the lower back region within 3 months of Screening.
10. History of chemotherapy or confirmed malignancy (except basal cell carcinoma) within the past 2 years.
11. Any other acute or chronic pain condition that could interfere with the subject's ability to report their CLBP accurately and consistently and/or interfere with the study staff's ability to assess the subjects CLBP.
12. An active or pending workman's compensation, insurance claim, or litigation related to back pain (i.e., primary claim is back pain).
13. Clinically significant history, in the opinion of the investigator, of suicidal ideation or current evidence that the subject is actively suicidal.
14. Clinically significant history of major depressive disorder that is poorly controlled with medication, per investigator judgment.
15. Hypersensitivity or allergy to BPN, other opioids, or excipients of CAM2038.
16. Hypersensitivity or allergy to acetaminophen.
17. Use of strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4), such as some azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., clarithromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir) within the 30 days prior to Screening,
18. Use or planned use of natural supplements that can affect CYP3A4, such as St. John's Wort, throughout the study.
19. Has a major bleeding disorder, such as hemophilia, or treated with high levels of anticoagulants per the investigator's discretion.
20. Current or confirmed past diagnosis of Sphincter of Oddi dysfunction.

21. Has a significant hepatic disease, as indicated by Screening clinical laboratory assessment results (aspartate aminotransferase, alanine aminotransferase, or lactate dehydrogenase values ≥3 × the upper limit of normal [ULN]) or has a creatinine value ≥1.5 × ULN).
22. Is an employee of the investigator or the trial site, with direct involvement in the proposed trial or other studies under the direction of the investigator or trial site or is a family member of the investigator or of an employee of the investigator.
23. Has any pending legal action that could prohibit participation or compliance in the study.

Criteria for Entry into the Titration Phase:

1. After at least a 12-hour washout from the last IR morphine dose, subject must have a COWS ≥5 and an API pain score over the past 24 hours ≥5 in order to receive a test dose of Buprenex.
2. Passed all baseline criteria, including a normal QTcF, had no change in QTcF >30 ms at 1 hour after the test dose with Buprenex, and had a COWS score <5 after the test dose with Buprenex.

Note:

- Subjects on BPN at Screening are required to participate in the down titration and will undergo a washout period prior to the test dose and first on-study treatment. Subjects entering the study on BPN will not transition to IR Morphine, but will refrain from taking their BPN for 12 -24 hours prior to the test dose to achieve the desired washout period.
- Subjects on BPN at Screening are still required to follow the same Day 1 procedures (e.g., confirmation of pain scores, COWS assessment and Buprenex test dose) as non-BPN subjects.

Criteria for Randomization into the Double-Blind Phase:

1. Been on a stable dose of CAM2038 q1w for at least 2 consecutive weeks.
2. CAM2038 titrated to a dose that provides analgesia (i.e., 7-day API score of ≤4 and at least 2 points below the value at the start of Titration Phase) and is well tolerated for 7 days before randomization.
3. Requires no more than an average of one hydrocodone/acetaminophen 5 mg/325 mg/day during the last 7 days prior to randomization.
4. Demonstrated study medication (CAM2038) compliance ≥80% during the previous 14 days.
5. Demonstrated daily compliance with pain intensity scoring for ≥11 of the previous 14 days, including the last 3 days prior to randomization.

Inclusion Criteria for Open Label Extension

For Subjects Continuing from The Randomized Double-Blind Phase.

Subjects must have:

1. Completed Double Blind Phase of the study
2. Signed Informed Consent for Safety Extension

Subjects completing the double-blind phase will be enrolled directly into the open label extension at their respective dose level of CAM2038. They will not be required to participate in a Buprenex treatment test dosing or participate in a titration phase.

For De Novo Subjects (New Subjects Recruited Directly into The Open Label Extension)

Subjects who are not participating in the Double-Blind Phase of the Study must meet all of the following inclusion criteria in order to be eligible for participation in the study:

1. Written informed consent provided prior to the conduct of any study-related procedures.
2. Male or non-pregnant and non-lactating female subject, greater than or equal to 18 years old.
3. BMI between 18 and 38 kg/m^2, inclusive.
4. Treated with daily opioids for moderate to severe chronic pain disorder such as CLBP or osteoarthritis for a minimum of 3 months prior to Screening.
5. On a stable dose of >40 mg/day of oral morphine or MED during the 14 days prior to Screening.
6. Systolic blood pressure ≥100 mmHg and diastolic blood pressure ≥60 mmHg.
7. Female subject of childbearing potential who is willing to use a reliable method of contraception during the entire study (Screening Visit to final Follow-up). To be considered not of childbearing potential, female subjects must be surgically sterile (hysterectomy or bilateral oophorectomy, or bilateral tubal ligation with surgery at least 6 weeks before Screening).
8. Male subject who is willing to use reliable contraception
9. Willing and able to comply with all study procedures and requirements.

Exclusion Criteria for Subjects Continuing from The Randomized Double-Blind Phase

1. Clinically significant symptoms, medical conditions, or other circumstances which, in the opinion of the investigator, would preclude compliance with the protocol, adequate cooperation in the study, or obtaining informed consent, or may prevent the subject from safely participating in the study.

Exclusion Criteria for De Novo Subjects only:

Same exclusion criteria as for subjects participating in the Randomized Double-Blind Treatment Phase.

Criteria for Entry into the Titration Phase (for De novo subjects):

1. After at least a 12-hour washout from the last IR morphine dose, subject should have a COWS ≥5 and an API pain score over the past 24 hours ≥5 in order to receive a test dose of Buprenex.
2. Passed all baseline criteria, including a normal QTcF, had no change in QTcF >30 ms at 1 hour after the test dose with Buprenex, and had a COWS score <5 after the test dose with Buprenex.

Note:

- Subjects on BPN at Screening are required to participate in the down titration and will undergo a washout period prior to the test dose and first on-study treatment. Subjects entering the study on BPN will not transition to IR Morphine, but will refrain from taking their BPN for 12 -24 hours prior to the test dose to achieve the desired washout period.

- However, subjects on BPN at Screening are still required to follow the same Day 1 procedures (e.g., confirmation of pain scores, COWS assessment and Buprenex test dose) as non-BPN subjects.

Criteria for Enrolment into the Open Label Treatment Phase (for de Novo subjects):

1. Been on a stable dose of CAM2038 q1w for at least 2 consecutive weeks.
2. CAM2038 titrated to a dose that provides analgesia (i.e., 7-day API score of ≤4 and at least 2 points below the value at the start of Titration Phase) and is well tolerated for 7 days before randomization.
3. Requires no more than an average of one hydrocodone/acetaminophen 5 mg/325 mg/day during the last 7 days prior to randomization.

Investigational Product, Dosage, and Mode of Administration:

CAM2038 in the Titration Phase:

CAM2038 6.25 mg/mL q1w (BPN FluidCrystal (FC) q1w SC injection depot) at a dose of 4 mg (0.64 mL). CAM2038 50 mg/mL q1w (BPN FC q1w SC injection depot) at doses of 8 mg, 12 mg, 16 mg, 24 mg, or 32 mg (0.16, 0.24, 0.32, 0.48, and 0.64 mL).

During the first week of the Titration Phase, subjects may receive one titration dose of 4 or 8 mg CAM2038 q1w on Day 1. During the first week of the Titration Phase, subjects who experience significant pain may, at the discretion of the investigator, receive a second dose of their CAM2038 on Day 3, 4, or 5 (4 mg CAM2038 q1w for subjects whose screening MED was 40-79 mg/day; 8 mg CAM2038 q1w for subjects whose screening MED was ≥80 mg/day).

CAM2038 in the Double-Blind Phase and Open Label Extension Phase:

CAM2038 6.25 mg/mL q1w (BPN FC q1w SC injection depot) at a dose of 4 mg (0.64 mL).
CAM2038 50 mg/mL q1w (BPN FCq1w SC injection depot) at doses of 8 mg, 12 mg, 16 mg, 24 mg, or 32 mg (0.16, 0.24, 0.32, 0.48, and 0.64 mL).
CAM2038 356 mg/mL q4w (BPN FC q4w SC injection depot) at doses of 64 mg, 96 mg, or 128 mg (0.18, 0.27, or 0.36 mL).

Subjects who are receiving either 4 mg, 8 mg, or 12 mg CAM2038 q1w at the end of the Titration Phase will be randomized to continue their respective CAM2038 q1w SC dosing (4 mg, 8 mg, or 12 mg), or to corresponding placebo q1w for a total treatment duration of 12 weeks (12 injections in the Double-Blind Phase). Subjects who are receiving 16 mg, 24 mg or 32 mg CAM2038 q1w SC at the end of the Titration Phase will be randomized to CAM2038 q4w (64 mg, 96 mg or 128 mg, respectively) or to corresponding placebo q4w for a total treatment duration of 12 weeks (3 injections in the Double-Blind Phase).

Reference Therapy, Dosage and Mode of Administration:

Placebo in the Double-Blind Phase:

Subjects randomized to Group 1 who are on 4 mg, 8 mg, or 12 mg CAM2038 q1w after the Titration Phase will receive 12 weekly SC CAM2038 placebo injections with matching or near-matching volumes to CAM2038 (0.64 mL) or CAM2038 q1w (0.16, 0.24 mL). Subjects randomized to Group 2 who are on 16 mg, 24 mg, or 32 mg CAM2038 q1w after the Titration Phase will receive 3 monthly SC CAM2038 placebo injections with matching or near-matching volumes to CAM2038

q4w (0.18, 0.27, or 0.36 mL).

Buprenex Test Dose in the Titration Phase

On Day 1 of the Titration Phase, subjects will receive a test dose consisting of an IM injection of Buprenex 0.30 mg (1.0 mL).

Rescue Medication in the Titration and Double-Blind Phases and Open Label Extension Phase:

Oral hydrocodone/acetaminophen, 5 mg/325 mg tablets, q4-6 h prn. The maximum daily dose is 15 mg/975 mg/day (three tablets) for subjects whose screening MED was 40-79 mg/day or 30 mg/1950 mg/day (six tablets) for subjects whose screening MED was ≥ 80 mg/day. Subjects cannot take more than an average of one rescue tablet per day, in the week prior to randomization.

Criteria for Evaluation:

Primary Efficacy Endpoint:

The primary efficacy endpoint is the change from baseline in WAAPI and the primary timepoint will be Week 12 of the Double-Blind Phase.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints are as follows:

- Change from baseline in the WAWPI scores at Week 12 of the Double-Blind Phase, based on an NRS-11.
- Percentage of subjects with a 30% or greater decrease in API from baseline to Week 12 of the Double-Blind Phase.
- Rescue medication usage (number of days used and total dose) during the Double-Blind Phase.
- Change from baseline to Week 12 of the Double-Blind Phase in EuroQoL Group 5-dimension 5-level self-report questionnaire (EQ-5D-5L) score.
- Change from baseline to Week 12 of the Double-Blind Phase in Work Productivity and Activity Impairment (WPAI) score.
- Time to loss of efficacy, defined as discontinuation of study drug for lack of efficacy.

Safety Endpoints:

- Occurrence of AEs throughout the study.
- Concomitant medication usage throughout the study.

Exploratory Endpoints:

- Change from baseline to Week 12 of the Double-Blind Phase in Clinical Global Impression of Improvement (CGI-I) scale (as assessed by the Investigator).
- Change from baseline to Week 12 of the Double-Blind Phase in Patient Global Impression of Improvement (PGI-I) scale (as assessed by the subject

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3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition of Term
AE	Adverse event
API	Average pain intensity
ATC	Around-the-clock
BMI	Body mass index
BPN	Buprenorphine
C-SSRS	Columbia-Suicide Severity Rating Scale
CGI-I	Clinical Global Impression of Improvement scale
CFR	Code of Federal Regulations
CI	Confidence interval
CLBP	Chronic low back pain
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form (may include electronic data capture systems or paper forms)
CS	Clinically significant
CSA	Clinical Study Agreement
$C_{ss,av}$	Average concentration during a dosage interval at steady state
$C_{ss,trough}$	Trough concentration during a dosage interval at steady state
CYP3A4	Cytochrome P450 3A4
ECG	Electrocardiogram
EDC	Electronic data capture
EEW	Enriched-enrollment withdrawal
EQ-5D-5L	EuroQoL Group 5-dimension 5-level self-report questionnaire
FC	FluidCrystal
FDA	Food and Drug Administration
G	Gauge
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IFU	Instructions for user
IM	Intramuscular
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IR	Immediate-release
IRB	Institutional Review Board
ITT	Intent-to-Treat

Abbreviation	Definition of Term
IV	Intravenous
MED	Morphine equivalent dose
MMRM	Mixed Model Repeated Measures
Ms	milliseconds
NCS	Not clinically significant
norBPN	Norbuprenorphine
NRS-11	11-Point numerical rating scale
PGI-I	Patient Global Impression of Improvement scale
PK	Pharmacokinetic
Prn	As needed
q1w	Once weekly
q4-6h	Every 4 to 6 hours
q4w	Once monthly
QID	Four times daily
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SL	Sublingual
SOC	System Organ Class
SOWS	Subjective Opiate Withdrawal Scale
TID	Three time daily
ULN	Upper limit of normal
US	United States
WAAPI	Weekly Average of (Daily) Average Pain Intensity
WAWPI	Weekly Average of (Daily) Worst Pain Intensity
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment
WPI	Worst pain intensity

4. INTRODUCTION

4.1. Background

Opioids are recommended for the management of moderate to severe pain that cannot be well-controlled using non-opioid analgesics or other interventions (American Academy of Pain Medicine, 2013; Chou et al, 2009). Buprenorphine (BPN) is an opioid with mixed agonist-antagonist properties that is currently available in injectable and buccal formulations to treat moderate to severe (acute) pain (e.g., Buprenex) and transdermal and buccal formulations to treat chronic pain (e.g., BuTrans® and Belbuca™). CAM2038 (buprenorphine FluidCrystal [FC] subcutaneous [SC] injection depot) once weekly (q1w) and once monthly (q4w), hereafter referred to as CAM2038 q1w and CAM2038 q4w, respectively, are ready-to-use, extended-release BPN products with a target of q1w or q4w SC dosing posology, respectively.

CAM2038 q1w and CAM2038 q4w were developed using the proprietary lipid-based and ambient responsive FC Injection depot technology. The principle behind the FC Injection depot is a liquid-to-gel phase transition, occurring immediately as the lipid-based FC system is exposed to *in vivo* conditions of SC tissue. The phase transition proceeds from the outside towards the center of the injected FC by absorption of minute quantities of water. Thus, injection of CAM2038 q1w or CAM2038 q4w into SC tissue results in an immediate and spontaneous formation of controlled BPN release matrix providing long-acting release *in vivo* with a minimum initial burst release. The dual nature of the FC system (i.e., a true liquid drug product *in vitro* before injection and stable gel *in vivo* after injection) enables a ready-to-use drug product in a prefilled syringe.

CAM2038 q1w and q4w are designed for convenient and safe SC injection using a prefilled syringe including a needle safety device and with no need for mixing or temperature adjustment from ambient temperature prior to administration. In addition, the injection volumes for CAM2038 q1w and q4w are relatively low (from 0.15 to 0.64 mL volume, depending on dose and product) and can be administered using a fine gauge needle (23 G). Overall, CAM2038 depots have been designed with a focus on enabling easy administration, dosing flexibility, and, importantly, minimizing risks of misuse, diversion, and poor patient compliance.

4.1.1. CAM2038 q1w (Once Weekly)

SC CAM2038 q1w has so far been investigated after single and repeated doses in 7 clinical trials in opioid-dependent subjects and healthy volunteers. An initial Phase 1/2 study assessed pharmacokinetics (PK), pharmacodynamics, and safety in opioid-dependent subjects (Study HS-07-307). The results showed that CAM2038 q1w was well tolerated, both locally and systemically. Importantly, no treatment-emergent serious adverse events (SAEs) were observed and drug-related local tolerability findings were limited to 4 of 42 subjects (9.5%). Three subjects experienced mild injection site pain and 1 patient exhibited transient injection site inflammation (mild) and injection site pruritus (moderate).

Two additional clinical Phase 1 studies were subsequently performed in healthy volunteers (under naltrexone blockade) to assess the PK and bioavailability of single and repeat doses of CAM2038 q1w versus repeated doses of sublingual (SL) BPN (i.e., at steady state) and single dose of intravenous (IV) BPN (Studies HS-11-426 and HS-13-487). These two studies demonstrated that after administration of the studied doses of CAM2038 q1w, the plasma concentrations corresponded to those obtained after administration of SL BPN at approved doses (i.e., 8 mg, 16 mg, or 24 mg doses). The BPN levels after administration of CAM2038 q1w were furthermore similar in healthy volunteers and subjects with opioid dependence. The systemic tolerability of CAM2038 q1w was good in both studies and similar to the reference products, IV and SL BPN. Local tolerability was very good with no adverse events (AEs)

reported in Study HS-11-426 (N_{safety}=60) related to injection site tolerability. Similarly, local tolerability of CAM2038 q1w was also very good in Study HS-13-487, featuring 4 repeat injections of CAM2038 q1w into the buttock site (1 subject reported 1 AE of injection site pain).

Based on these studies, the following main conclusions were drawn regarding the clinical properties of CAM2038 q1w:

- Extended BPN release over one week
- Dose proportionality and flexible/multiple dosing options
- Six- to 8-fold higher bioavailability versus SL BPN
- BPN plasma concentrations over 7 days within ranges of those produced by corresponding SL BPN doses at steady state (i.e., approved 8 mg, 16 mg or 24 mg doses)
- Less peak/trough fluctuation compared to SL BPN
- Repeated-dose administration suggest time-independent PK
- Good safety and systemic tolerability in subjects
- Safety in healthy volunteers comparable to IV and SL BPN treatments
- Good local tolerability in subjects and healthy volunteers

The clinical PK profile and good systemic and local tolerability of CAM2038 q1w evidenced in subjects in these 3 studies is also supported by a large body of data generated in non-clinical PK and toxicology studies in the dog, mini-pig, and rat of single and repeat SC doses of CAM2038 q1w, including repeat weekly doses of the FC vehicle formulation for 6 months. SC administration of CAM2038 q1w has been shown to be well tolerated both systemically and locally in the non-clinical studies. The treatment-related findings have been limited to clinical observations in agreement with, and considered related to, known pharmacological effects of the drug substance BPN, and to reversible, local inflammatory reactions at the SC site of injection. The latter findings were similar to the physiological response to a foreign body. The FC-related injection site findings appeared to be reversible and self-limiting, and only apparent at the immediate vicinity of test article deposition. In summary, non-clinical data have indicated no systemic toxicity associated with CAM2038 q1w or the FC injection depot vehicle.

4.1.2. CAM2038 q4w (Once Monthly)

SC CAM2038 q4w has been investigated in 5 studies, including one bridging clinical Phase 1 PK study in healthy volunteers versus repeat dose CAM2038 q1w (i.e., at steady state), repeat dose SL BPN (i.e., at steady state), and a single dose of IV BPN (Study HS-13-487). The following conclusions can be drawn regarding the clinical properties of CAM2038 q4w:

- Extended BPN release over 4 weeks
- Six- to 8-fold higher bioavailability versus SL BPN, comparable to CAM2038 q1w
- BPN plasma concentrations over 4 weeks comparable to CAM2038 q1w over one week, and to SL BPN over 24 hours at steady state (i.e., for approved 8 mg, 16 mg, or 24 mg doses)
- Predicted average concentration during a dosage interval at steady state ($C_{ss,av}$) and trough concentration during a dosage interval at steady state ($C_{ss,trough}$) values for CAM2038 q4w similar to CAM2038 q1w
- Safety profile comparable to IV and SL BPN treatments
- Good local tolerability

The most commonly reported drug-related AEs after CAM2038 q1w and CAM2038 q4w administration in Study HS-13-487 were nausea (63% of subjects), dizziness (54% of subjects), and vomiting (39% of subjects). The local tolerability was good, with 9 subjects experiencing 10 AEs that were assessed as related to CAM2038 q4w (injection site reactions, injection site pain, injection site induration, and application site bruise). Two SAEs were reported by 2 subjects after treatment with 192 mg CAM2038 q4w. The first SAE was an event of withdrawal reaction and the second SAE was an event of dehydration due to nausea and vomiting. Both SAEs were assessed as related to CAM2038 q4w (withdrawal reaction was also assessed as related to the concomitant treatment with naltrexone) and the event of withdrawal reaction qualified for reporting as a suspected unexpected serious adverse reaction. There were no deaths or any other significant AEs, and most of the AEs were mild and transient. Analysis of clinical chemistry, hematology, and urinalysis parameters did not suggest any significant safety issues for CAM2038 q4w.

The non-clinical assessment of CAM2038 q4w and the FC vehicle, supported by publicly available data for the drug substance BPN, and for the components of the vehicle, suggests safe use of CAM2038 q4w for the proposed clinical development. This conclusion is further supported by results from non-clinical and clinical studies of CAM2038 q1w, comprising the same active substance and functional lipid components.

Additional information about CAM2038 can be found in the current version of the Investigator's Brochure.

4.1.3. Completed CAM2038 Phase 2 and Phase 3 Studies

There are four completed Phase 2 and Phase 3 clinical studies of CAM2038, HS-11-421, HS-13-478, HS-15-549 and HS-14-499. Please refer to the Investigator's Brochure for more detailed investigative study and safety information.

HS-11-421 (completed)

This was a randomized, double-blind, double-dummy, active-controlled, parallel group, multicenter study, designed to evaluate the non-inferiority of CAM2038 compared to an existing standard of care (SL BPN/naloxone [NX]) in initiation and maintenance treatment with BPN in subjects with opioid use disorder. The study involved 4 phases: Screening, Phase 1 (weekly visits, for 12 weeks), Phase 2 (monthly visits, for 3 months), and Follow-up.

A total of 428 subjects were randomized in the study, whereof 213 subjects were treated with CAM2038 and 215 subjects with SL BPN/NX. The study has been completed with no significant unusual or unexpected safety signals or concerns reported.

HS-15-549 (completed)

This was a Phase 2, open-label, partially randomized, 3-treatment group study designed to evaluate the steady state PK of BPN and norbuprenorphine (norBPN) following multiple weekly SC administrations of CAM2038 q1w at different injection sites (Group 1), following multiple monthly SC administrations of CAM2038 q4w (Group 2) in opioid-dependent subjects with a history of chronic non-cancer pain and following multiple monthly SC administrations of CAM2038 q4w (Group 3) in opioid-dependent subjects with a history of chronic non-cancer pain who were currently taking 24 mg of SL BPN daily. The trial involved up to 4 phases: Screening, Treatment, Follow- up and Open Label Safety Extension. Approximately 55 subjects were to be enrolled. The study has been completed and there were no unusual safety signals or concerns identified.

HS-13-478 (completed)

This was a Phase 2 multi-site, randomized, double-blind, repeat-dose Phase 2 study to evaluate the degree and duration of action of multiple doses of CAM2038 q1w in blocking the effects of a mu opioid receptor agonist (hydromorphone) in subjects with moderate or severe opioid use disorder. The study involved 4 phases: Screening, Qualification, Treatment, and Follow-up. In the treatment Phase, subjects received one of the following treatments (based on a randomization in a 1:1 ratio, stratified by gender and blinded): Group A received CAM2038 q1w 24 mg SC injection (22 subjects) and Group B received CAM2038 q1w 32 mg SC injection (25 subjects).

Each of the Hydromorphone Challenge Sessions in the Qualification Phase and Treatment Phase consisted of the injection of 3 doses of IM hydromorphone (0 mg [placebo], 6 mg and 18 mg) administered once daily over 3 consecutive days in randomized blinded order. Subjects were randomized in a 1:1:1:1:1:1 ratio to 1 of 6 treatment sequences according to two 3 × 3 William squares.

HS-14-499 (completed)

This was a Phase 3, open-label, multicenter, 12-month (48-week) safety study in subjects with opioid use disorder, consistent with standard practice for long-term safety studies. This safety study utilized CAM2038 q1w and CAM2038 q4w and had 3 phases: Screening, Treatment, and Follow-up. The trial is completed and ended when at least 100 subjects have been exposed to CAM2038 for 48 weeks. There were no unusual safety signals or concerns identified in the study.

4.2. Study Rationale

Chronic low back pain (CLBP) is a significant cause of pain and disability costs worldwide (Volinn et al, 2009; Vos et al, 2012). While most subjects with CLBP show significant improvements within 3 months, a proportion of subjects experience persistent pain (≥3 months) and may have limited quality of life and physical function (Shekelle et al, 1995; Thomas et al, 1999). Management of CLBP may be achieved through several modalities, including opioid pharmacotherapy. Despite their proven efficacy, the use of opioids is often limited due to concerns regarding safety and tolerability and concerns pertaining to drug abuse and diversion that may arise with long-term therapy for treatment of persistent pain. However, for many subjects with CLBP, opioid therapy may be the only effective treatment. BPN is an effective analgesic with a potency 25 to 50 times that of morphine (Jasinski et al, 1978; Cowan et al, 1977). Dose-dependent analgesia has been observed with intramuscular (IM) doses up to 10 mg. Respiratory depression is minimized due to the well-characterized ceiling effect at higher doses (Hans and Robert, 2009). Clinically, there is also a less marked effect of BPN on gastrointestinal transit times, with a lower incidence of constipation relative to full mu-opioid receptor agonists (Mercadente, 2009). In addition, the slow dissociation of BPN from receptors results in a long duration of effect and minimizes withdrawal symptoms upon discontinuation (Sittl et al, 2005). Transdermal BPN has proven effective in subjects with chronic cancer and non-cancer pain, with a reduction in the need for additional oral analgesics and improved quality of life (Mercadente, 2009; Dahan et al, 2005; and Griessinger et al, 2005).

A number of treatment goals have been proposed for improved patient therapy, many of which are based on World Health Organization (WHO) recommendations, including providing a stable plasma drug concentration to ensure long lasting and effective pain relief, formulations that provide a long duration of action, and an improved quality of life. By using the transdermal formulation of BPN, the rate of drug delivery can be controlled and stable plasma concentrations achieved. However, transdermal BPN may still be subject to abuse and diversion, as the patches may be swallowed or the BPN may be extracted from the patches and injected or ingested, including improperly disposed patches (Tompkins et al, 2014; Belbuca™ Prescribing Information, October 2015). Transdermal systems may also be accidently ingested, particularly by children. Traditional opioid therapies intended for the treatment of chronic pain (e.g., modified or extended-release formulations of full μ-opioid receptor agonists such as morphine,

oxycodone, hydrocodone, and hydromorphone) are even more subject to diversion and abuse, resulting in significant public health concerns (Sittl et al, 2005 and Likar et al, 2003).

The sustained and stable BPN plasma concentration associated with administration of CAM2038 q1w and q4w may provide an ideal treatment modality for many CLBP subjects. The PK profile of CAM2038 q1w indicates that a rapid and long-acting release of BPN should lead to rapid and smooth onset of action, in combination with a prolonged and stable treatment effect for at least 7 days following a single dose of CAM2038 q1w or up to 4 weeks following a single dose of CAM2038 q4w. Thus, the PK profiles of CAM2038 q1w may help to improve tolerability during initiation of treatment. Like transdermal formulations, CAM2038 may also be suitable for those subjects with difficulty swallowing.
The profiles of CAM2038 provide an alternative to existing oral opioid medications, with the potential added benefit of obtaining consistent and stable plasma levels of BPN. This profile removes the need to take daily medications and helps to prevent diversion and accidental pediatric exposures, which continue to be important public health goals of the Food and Drug Administration (FDA) and Center for Disease Control and Prevention (Frieden and Houry, 2016). Furthermore, the route of administration (i.e., depot injection) of CAM2038 may reduce the risks of diversion and abuse, even when compared to transdermal opioid formulations.

While the efficacy of transdermal and transmucosal BPN in managing pain and improving function has previously been demonstrated in subjects with CLBP (Salinas et al, 2012; Rauck et al, 2016), the anesthetic efficacy of BPN administered as CAM2038 q1w or CAM2038 q4w SC injections has not yet been evaluated. The present study will be conducted to evaluate the efficacy and safety of CAM2038 compared to placebo in subjects with moderate to severe CLBP over a period of 12 weeks during the Double-Blind Phase. In addition, the safety of CAM2038 will be evaluated from the Open-Label Titration Phase and throughout the Open Label Safety Extension Phase.

4.3. Dose Rationale

The 4-mg weekly starting dose of CAM2038 q1w correspond to a daily morphine equivalent dose (MED) of 28.5 mg, using a more conservative conversion factor of 50 from BPN to morphine; thus, representing safe and suitable starting doses for subjects receiving ≥30 mg of morphine daily. In this study, subjects will be titrated to effect. An indicative a priori transition from daily morphine dose to weekly CAM2038 doses and monthly CAM2038 dose is given in Table 1 and Table 2 below, respectively:

Table 1: Conversion from Daily Morphine to Once Weekly CAM2038 Doses

Daily Morphine Dose (mg)	Daily Titration Morphine Dose, 75 % (mg)	Starting Once Weekly Dose
40 to <80	30 to 60	4 mg CAM2038
80 to 120	60 to 90	8 mg CAM2038
>120 to 160	90 to 120	16 mg CAM2038
>160 to 320	120 to 240	24 mg CAM2038
>320	>240	32 mg CAM2038

Table 2: Conversion from Once Weekly CAM2038 to Once Monthly CAM2038 Dose

Once Weekly Dose	Corresponding Once Monthly CAM2038 Dose
4 mg CAM2038	No corresponding monthly dose. Subjects will be kept on CAM2038 once weekly.
8 mg CAM2038	No corresponding monthly dose. Subjects will be kept on CAM2038 once weekly.
12 mg CAM2038	No corresponding monthly dose. Subjects will be kept on CAM2038 once weekly.
16 mg CAM2038	64 mg CAM2038
24 mg CAM2038	96 mg CAM2038
32 mg CAM2038	128 mg CAM2038

The MED will be calculated using the conversion factor for each opioid as described in Table 3 (McPherson, 2009). Subjects taking methadone are allowed to screen; however, the down titration process should be discussed with the Medical Monitor.

Table 3: Opioid Conversion to Morphine Equivalent Dose

Equianalgesic Opioid Dosing			
Drug	**Equianalgesic Doses (mg)**		
	Parenteral	**Oral**	**Sublingual**
Sublingual Buprenorphine	NA	NA	1.5
Belbuca™ buccal film	NA	0.3	NA
Morphine	10	30	NA
Codeine	100	200	NA
Hydrocodone	NA	30	NA
Hydromorphone	1.5	7.5	NA
Meperidine	100	300	NA
Oxycodone	10*	20	NA
Oxymorphone	1	10	NA
Tramadol	100*	120	NA
		Morphine (PO) Equivalents	
*Fentanyl Patch 25mcg/hr (One patch q3 days)	NA	60 mg / d	NA
Butrans patch 10mcg/hr (One patch q week)	NA	80 mg / d	NA
*Methadone 20 mg PO qd	NA	40 mg / d	NA

* Contact Medical Monitor to discuss

4.3.1. Rationale for repeat-site injections

A 9-month study in beagle dogs has been conducted to characterize the chronic systemic toxicity of CAM2038 q1w and CAM2038 q4w SC administration in beagle dogs. Assessments included evaluation of local injection site tolerability and toxicokinetic evaluation at steady-state. Corresponding vehicle placebos and saline were used as controls. A total of 8 injection sites on the back were used. Injection sites were rotated as follows:

- For the q1w: CAM2038 q1w (32 mg/injection), vehicle placebo and saline injections were administered once every week. The injection sites were rotated so that each site was re-used once every eighth week over the course of the study.
- For the q4w: CAM2038 q4w (128, 160 or 192 mg/injection), vehicle placebo and saline. Injections were administered once every 4 weeks. The injection sites were rotated so that each site was used once, except for the last three-monthly injections which were all administered at one site.

The beagle dogs tolerated 39 weekly SC doses of CAM2038 q1w drug product at 32 mg/dose or the CAM2038 q1w placebo control, or 10 doses given once every 4-weeks of CAM2038 q4w drug products at 128, 160, or 192 mg/dose or the CAM2038 q4w placebo control. The CAM2038 drug products and placebo controls had no discernible effect on dermal irritation (erythema, or eschar), overall food consumption, ophthalmologic parameters, clinical pathology endpoints (hematology, coagulation, clinical chemistry, and urinalysis), or organ weights.

Injection site reactions were limited to the presence of Grade 1 edema/swelling, which was considered to represent the injection depot matrix (IDM). Most animals given the BPN-containing CAM2038 drug product formulations or the corresponding placebo controls had Grade 1 (“very slight”) IDM at the sites of injection following dosing. There were no observed differences noted between the sites dosed with BPN-containing CAM2038 drug products and placebo controls.

Additionally, there was no apparent increase in the severity of IDM swelling with repeated injections at the same injection site. Discernable swelling associated with the IDM generally resolved between 60 and 144 days after dosing administration.

This study demonstrated that repeat injections could be safely performed at the same site every 4 weeks with the highest volumes and doses of CAM2038, without any associated deleterious effects.

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of long-acting SC injectable depots of BPN (CAM2038 once-weekly [q1w] and CAM2038 once- monthly [q4w]) compared to placebo on average pain intensity (API) scores, as measured on an 11-point, numerical rating scale (NRS-11) in subjects currently taking daily opioids for moderate to severe CLBP.

5.2. Secondary Objectives

The secondary objectives of the study are:

- Change from baseline in the weekly average of daily worst pain intensity (WAWPI) scores at Week 12 of the Double-Blind Phase based on the NRS-11.
- To evaluate the safety and tolerability of treatment with CAM2038 q1w and CAM2038 q4w in subjects currently taking opioids for moderate to severe CLBP.

5.3. Open Label Safety Extension Objectives

5.3.1. Primary Objectives of Open Label Safety Extension

The primary objective of the open label extension phase is:

- To evaluate the safety and tolerability of treatment with CAM2038 q1w and CAM2038 q4w up to 52 weeks in subjects with moderate to severe chronic pain requiring daily treatment with opioids.

5.3.2. Secondary Objectives of Open Label Safety Extension

The secondary objectives of the open label extension phase are:

- Evaluate the steady-state PK of BPN for CAM2038 q1w and CAM2038 q4w in subjects with moderate to severe chronic pain requiring daily treatment with opioids
- Evaluate the efficacy and safety of CAM2038 q1w and CAM2038 q4w administration for up to 52 weeks in the treatment of subjects with moderate to severe chronic pain requiring daily treatment with opioids.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan

This is a Phase III, placebo-controlled, multicenter study with an enriched-enrollment withdrawal (EEW) design to evaluate the efficacy and safety of CAM2038 in opioid-experienced subjects with moderate to severe CLBP that requires continuous, around-the-clock (ATC) opioid treatment ≥ 40 mg MED. An overview of the study design is provided in Figure 1. The study includes 5 phases: A Screening Phase (up to 2 weeks), a Transition Phase (up to 2 weeks), an Open Label Titration Phase (up to 10 weeks), a Double-Blind Treatment Phase including a Final Study Visit (12 weeks), and a Follow-up Phase (4 weeks) The overall duration of participation of the core phase is up to 30 weeks, from the Screening Phase through the Follow-up Phase. Subjects who complete the Double-Blind Treatment Phase will be offered the opportunity to continue treatment in an Open Label Safety Extension Phase for up to 60 weeks. In addition, so called "de novo" subjects may be enrolled in the Open Label Safety Extension Phase. These subjects may proceed directly from the Open Label Titration Phase to the Open Label Safety Extension Phase without participating in the Double-Blind Treatment Phase.

Subjects will record their API at Screening and prior to the test dose on a paper diary at the site. Throughout the study, after subjects receive their first CAM2038 injection, they will record their WPI and API using the NRS-11 in an electronic diary. Subjects will be instructed to record their WPI and API once daily between 18:00 and 23:59 (i.e., 6:00 pm and 11:59 pm). Subjects will be instructed to make all attempts to record their pain scores at the same time of day throughout the study. In addition, subjects will be instructed to record their pain intensity in the electronic diary on the NRS-11 "at that moment" prior to taking rescue medication. Rescue medication use will also be recorded in the electronic diary.

Table 5, Table 6, and Table 7 provide additional information on the baseline, efficacy, and safety assessments included in the study. Efficacy endpoints and statistical analyses are described further in Section 9.6 and Section 11.3, respectively.

6.1.1. Transition Phase

Following Screening and confirmation of eligibility, subjects will enter a Transition Phase of up to 2 weeks during which their current opioid dose will be down-titrated by approximately 25% per day to:

- ≤80 mg/day MED (for subjects whose opioid dose at screening is > 80 mg MED)
- or to ≤40 mg/day MED (for subjects whose opioid dose at screening is between 40-79 mg/day MED).

Following the down titration, subjects will be transitioned to an immediate-release (IR) morphine for at least 2 days before they enter the Open-Label Titration Phase, as follows:

- 15 mg 4 times daily [QID] for subjects whose screening MED was ≥80 mg/day
- 15 mg 3 times daily [TID] for subjects whose screening MED was 40-79 mg/day.

Subjects who were previously on BPN prior to Screening will not need to participate in the morphine IR phase. However, subjects who were previously on BPN will be required to refrain from taking BPN for

12-24 hours as a washout prior to starting open label titration on CAM2038.

6.1.2. Open Label Titration Phase

Following the morphine IR treatment, subjects will enter the Titration Phase. On Day 1 of the Titration Phase, subjects will return to the clinic after a washout of at least a 12-hour from their last morphine IR dose, or 12-24 hours from their last BPN dose. Subjects who report a CLBP of ≥5 on the API scale and have a Clinical Opiate Withdrawal Scale (COWS) score of ≥5, will receive a BPN test dose (Buprenex 0.30 mg IM injection) at the clinical site. After the Buprenex test dose, subjects will be assessed for any changes in QTcF (Fridericia's corrected QTc) and withdrawal. Subjects who tolerate the BPN test dose, do not show an increase >30 ms in QTcF within 1 hour after the test dose, and have a COWS score of <5 within 15 minutes after the test dose will receive the first dose of SC CAM2038 q1w within 4 hours (+30 minutes) after the test dose (4 mg CAM2038 for subjects whose screening MED was between 40 mg/day and 79 mg/day; and 8 mg CAM2038 for subjects whose screening MED was ≥80 mg/day).

During the first week of the Titration Phase, subjects who experience significant pain may, at the discretion of the investigator, receive an additional 4 mg (for subjects whose screening MED was 40-79 mg/day) or 8 mg CAM2038 (for subjects whose screening MED was ≥80 mg/day), on Day 3, 4 or 5. Dose adjustments will be made by increasing or decreasing the dose level of CAM2038 q1w at the scheduled weekly visits (doses of 4 mg, 8 mg, 12 mg, 16 mg, 24 mg, or 32 mg per week). Subjects who require doses >32 mg/week will be discontinued from the study.

Rescue medication, consisting of hydrocodone/acetaminophen 5 mg/325 mg every 4 to 6 hours (q4-6h), may be taken as needed (prn) up to 15 mg/975 mg/day (three tablets) for subjects whose screening opioid dose was between 40 and 79 mg/day MED or 30 mg/1950 mg/day (six tablets) for subjects whose screening opioid dose was ≥80 mg/day MED. The goal of the Titration Phase is to achieve a stable dose of CAM2038 q1w that produces analgesia, by the end of the 10–week period.

Eligible subjects will receive CAM2038 titrated to a dose that meets the following criteria (see also Section 7.4):

- Provides analgesia (i.e., 7-day mean API≤4)
- The API is at least 2 points below the value at the start of CAM2038 titration
- The dose of CAM2038 is well-tolerated for 7 days before randomization (no adverse effects that require a change in study dosing or interruption)
- Subject does not require, on average, more than one dose of rescue medication per day over the 7 days before randomization

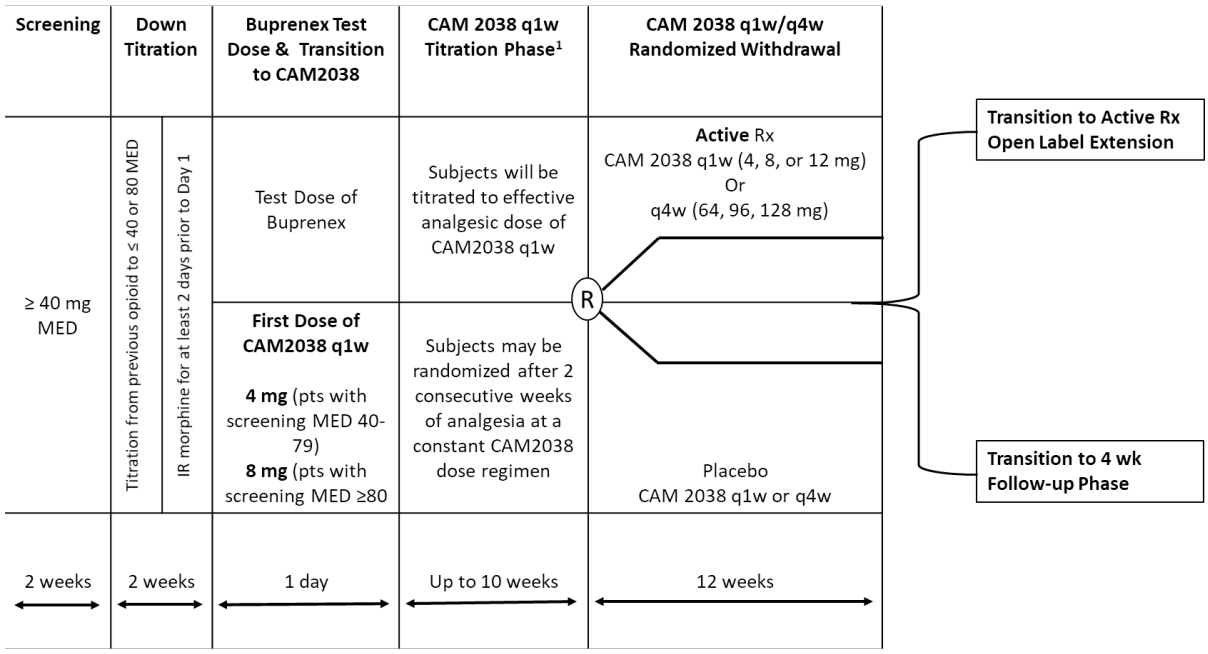
6.1.3. Double-Blind Phase

Subjects who are stabilized and responding to their CAM2038 q1w dose (4, 8, 12, 16, 24, or 32 mg/week) at the end of the Titration Phase and who fulfill the pre-defined randomization criteria will be randomized to one of two treatment groups in the 12-week Double-Blind Phase:

- Group 1: CAM2038 q1w or CAM2038 q4w SC injections
- Group 2: placebo q1w or placebo q4w SC injections

During the Double-Blind Phase, all subjects who are receiving 4, 8 or 12 mg CAM2038 q1w at the end of the Titration Phase will be randomized to continue their respective CAM2038 q1w dosing of 4 mg, 8 mg or 12 mg CAM2038, or to matching placebo q1w for a total treatment duration of 12 weeks. Subjects who are receiving 16 mg, 24 mg or 32 mg CAM2038 q1w at the end of the Titration Phase will be randomized to CAM2038 q4w (64 mg, 96 mg or 128 mg, respectively) or to matching placebo q4w for a total treatment duration of 12 weeks.

Figure 1: Overview of Study Design



[1]One booster is allowed on Day 3-5 after the first CAM2038, 4 or 8 mg injection. If booster is taken, the next dose on week 2 will be 8 or 12 mg, otherwise stay at 8 mg. Then titration is weekly up to 10 weeks. Final Study Visit is 1 week after the last CAM2038 q1w dose for q1w subjects and 4 weeks after the last q4w dose for q4w subjects. Follow-up is within 4 weeks after the Final study visit.
IR = immediate release; MED=morphine equivalent dose; q1w=once weekly; q4w=once monthly; R= randomization. There will be a Final Study Visit or Early Termination and one Follow-up Call.

Rescue medication, hydrocodone/acetaminophen 5 mg/325 mg q4-6h prn, will be allowed during the Double-Blind Phase (up to three tablets or 15 mg/975 mg/day for subjects whose MED at screening was between 40-79 mg/day and up to six tablets or 30 mg/1950 mg/day for subjects whose MED at screening was ≥80 mg/day).Whenever subjects take rescue medication, they must record their pain intensity “at that moment” prior to taking rescue medication in the electronic diary.

6.1.4. Follow-up Phase for Subjects Not Transitioning to the Open Label Safety Extension Phase

A Final Study Visit will take place 1 week after the last CAM2038/placebo q1w dose or 4 weeks after the last CAM2038/placebo q4w dose. At the Final Study Visit (or early termination), subjects will be transitioned back to standard care or to their treatment prior to study entry. Subjects will then be contacted

at Follow-up, within 4 weeks after the Final Study Visit, to assess AEs and concomitant medications.

Subjects transitioning from the Randomized Double-Blind Phase to the Open Label Safety Extension Phase are encouraged to do so at the Final Study Visit of the randomized Double-Blind Phase or as soon as possible thereafter.

6.1.5. Open Label Safety Extension

Subjects who complete the Double-Blind Phase will be offered the opportunity to continue treatment in an open label safety extension for a total duration of up to 60 weeks. Subjects who consent to the Open Label Extension will not be required to participate in the post-double-blind Follow-up Phase but will be transitioned at their Final Study Visit or as soon as possible thereafter, to open label active treatment, in the Open Label Extension. With the Open Label Safety Extension Phase, total duration of exposure to CAM2038 is up to 60 weeks. Enrollment in the Open Label Safety Extension Phase will continue until a sufficient number of subjects have been recruited to obtain at least 52 weeks of safety information in approximately 100 subjects. Due to the double-blind design, all subjects will need to receive at least 1 week of CAM2038 q1w before proceeding to the Open Label Safety Extension Phase.

Subjects completing the Double-Blind Phase on 4 mg, 8 mg or 12 mg CAM2038/placebo q1w will continue on the same dose of active treatment (open-label CAM2038) without need for titration. Subjects completing the Double-Blind Phase on 64 mg, 96 mg or 128mg CAM2038/placebo q4w will begin open-label treatment at the corresponding equivalent weekly dose last received by the subject prior to transition to the monthly dosing regimen. The subject may transition to monthly dosing upon return to the clinic in 1 week following the initial dose. At the Investigator's discretion, the transition period may be extended or the patient down-titrated, in case of poor tolerability. The subjects will continue in the Open Label Safety Extension Phase until the total exposure to CAM2038 (including the Titration and Double-Blind Phases) is at least 52 weeks.

Once the required number of subjects for the Double-Blind phase of the trial has been recruited, enrollment for the Double-Blind phase will be closed, and remaining subjects offered the opportunity to proceed directly to the long-term safety extension without having to participate in a double-blind treatment phase. However, to be eligible to proceed to the safety extension, subjects must meet the following criteria:

- Have CAM2038 titrated to a dose that provides analgesia (i.e., 7-day mean API $\leq$4)
- The dose of CAM2038 is well-tolerated for 7 days before randomization (no adverse effects that require a change in study dosing or interruption)
- Subject does not require, on average, more than one dose of rescue medication per day over the previous 7 days

The opening of recruitment of subjects for the safety extension is to ensure that a sufficient number of subjects are enrolled to provide required long-term safety data to support the clinical development of CAM2038 for the indication of chronic pain requiring daily treatment with opioids.

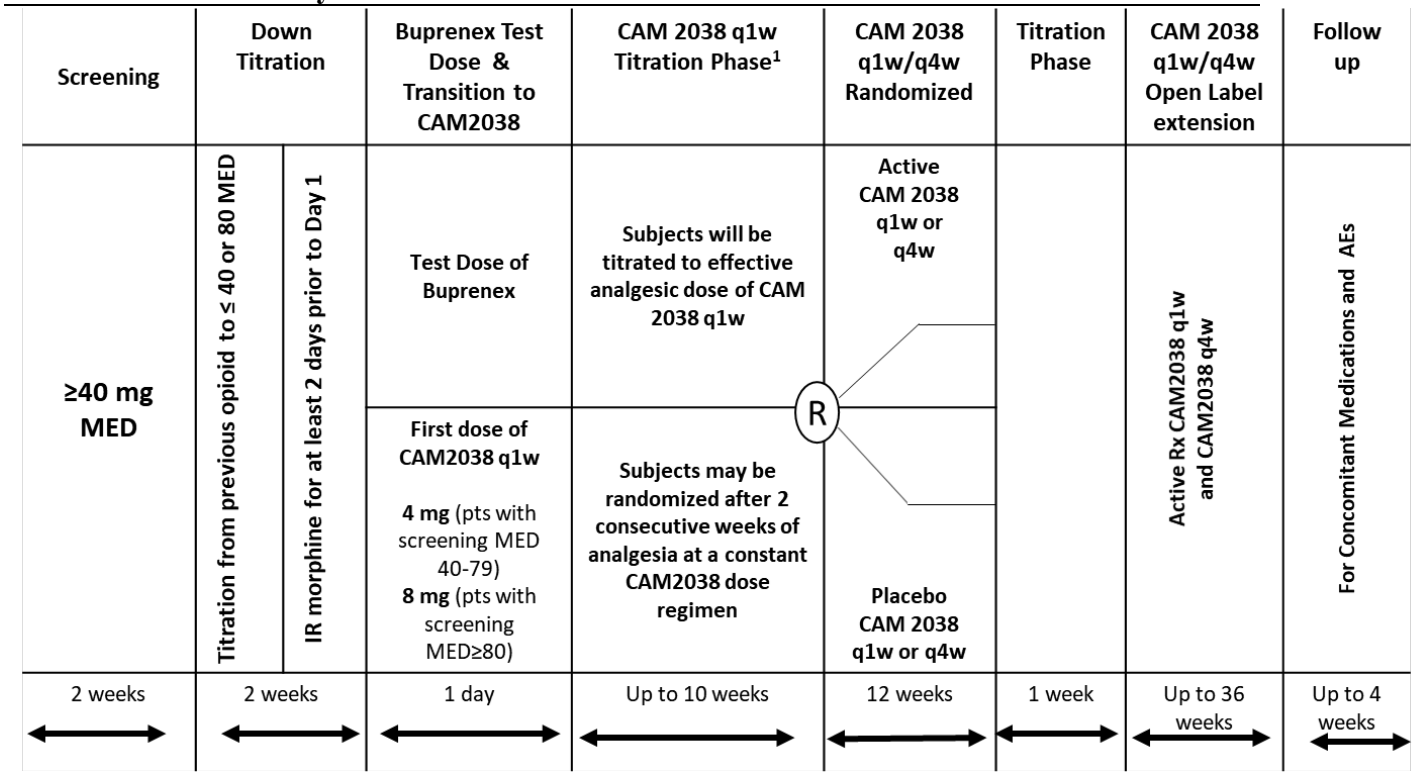
These so called "de novo" subjects may have CLBP or other severe chronic pain disorders (such as osteoarthritis) and will not be required to participate in the Double-Blind Phase. The de novo subjects will undergo the same screening procedures, down titration, morphine IR and CAM2038 up-titration as required for subjects going through the Double-Blind Phase of the study. The CAM2038 dosing titration and rescue medication requirements for the safety extension for subjects whose opioid doses at screening

are > 80 mg/day MED, and 40-79 mg/day MED, respectively, shall be the same as described for the subjects participating in the Double-Blind Phase. De novo subjects may also be subjects who have completed the core study more than 28 days ago or newly identified subjects with a chronic pain indication treated with daily opioids.

Subjects in the Open Label Safety Extension Phase will return to the study clinic for their regular weekly or monthly CAM2038 injections until the end of the study. At the Month-4 safety extension visit (Visit Week 23 for de novo subjects and Visit Weeks 35-36 for subjects transitioned from randomized Double-Blind Phase), PK sampling for CAM2038 steady state PK will be performed on all subjects who provide additional consent for the PK sampling. Blood samples will be collected prior to administration (within 45 minutes); and at approximately 2 hours, 6 hours, 24 hours, 72 hours, 168 hours, 336 hours, and 672 hours after administration to measure plasma levels of BPN and norBPN for subjects receiving both CAM2038 qlw and CAM2038 q4w treatments. Actual dates and times of dosing of IMP during the safety extension phase, as well as, blood sampling for PK measurement will be recorded.

The study design schematics for the Open Label Safety Extension Phase are presented in **Error! Reference source not found.** and Figure 3 below.

Figure 2: Overview of Open-Label Extension for Subjects Continuing from Double-Blind Phase Study[2]



[1] One booster is allowed at the discretion of the investigator, on Day 3-5 after the first 4 or 8 mg injection CAM2038 for subjects experiencing significant pain. Then titration is weekly up to 10 weeks. Follow up is within 4 weeks after the Open Label Treatment Phase

[2] Figure 2 represents entire participation of subjects, who continue on from the randomized double blind of the study through the extension. However, subjects will not be required to participate in the Double-Blind Phase follow-up period and may proceed directly into the Open-Label Safety Extension Phase. A maximum gap of 28 days is allowed between the end of the Double-Blind Phase and the start of the Open-Label Safety

Extension Phase

Figure 3: Overview of Open Label Extension for De Novo Subjects

<table>
<tr><th>Screening</th><th colspan="2">Down Titration & IR Morphine</th><th>Buprenex Test Dose</th><th>Transition to CAM2038 First Dose</th><th>CAM 2038 q1w UP-Titration Phase[1]</th><th>CAM 2038 q1w or q4w Active Open Label Treatment</th><th>Follow up</th></tr>
<tr><td rowspan="2">Subjects on 40-79 mg MED

Subjects on > 80 mg MED</td><td rowspan="2">Titrate from previous opioid to ≤ 40 or 80 MED</td><td rowspan="2">IR morphine for at least 2 days prior to Day 1</td><td rowspan="2">Test Dose of Buprenex</td><td>4 mg CAM2038
-For subjects with opioid MED of 40-79 mg at screening</td><td rowspan="2">Subjects will be titrated to an effective analgesic dose of CAM2038 q1w

Subjects may be enrolled into Open Label Extension after 2 consecutive weeks of analgesia at a constant dose regimen</td><td rowspan="2">CAM2038 q1w
(4, 8, or 12 mg)

OR

CAM2038 q4w
q4w (64, 96, 128 mg)</td><td rowspan="2">Safety follow-up for AEs & ConMeds</td></tr>
<tr><td>8 mg CAM2038
-For subjects with opioid MED ≥80 mg at screening</td></tr>
<tr><td>2 weeks</td><td colspan="2">2 weeks</td><td colspan="2">1 day</td><td>Up to 10 weeks</td><td>Up to 50 weeks</td><td>up to 4 weeks</td></tr>
</table>

[1]One booster is allowed at the discretion of the investigator, on Day 3-5 after the first 4 or 8 mg injection CAM2038 for subjects experiencing significant pain. Then titration is weekly up to 10 weeks. Follow up is within 4 weeks after the Open Label Treatment Phase.

6.2. Discussion of Study Design

Chronic pain may result from a number of different conditions with different underlying etiologies; however, to increase sensitivity of the study, eligible subjects will be subjects with moderate to severe CLBP who require ATC opioid treatment. The design selected to meet the objectives of the study is a 12-week randomized, double-blind, placebo-controlled, EEW study in subjects with moderate to severe CLBP that requires continuous, ATC opioid treatment and, despite prior dose escalation, did not receive adequate pain relief.

The overall design is consistent with previous studies of modified-release opioid analgesics, Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations (Weaver and Schnoll, 2002; Yarlas et al, 2013 and Dworkin et al, 2005), and the FDA Guidance for Industry – *Analgesic Indications: Developing Drug and Biological Products* (2014) (Dworkin et al, 2008). The Double-Blind Phase will be 12 weeks in duration, which is consistent with FDA guidance and previous studies demonstrating efficacy of opioid formulations. The frequency of visits is considered to be adequate for dosing, monitoring subject's compliance with study requirements, and not overly burdensome for subjects.

CAM2038 is being evaluated for the management of pain severe enough to require daily, ATC, long-term opioid treatment and for which alternative treatment options are inadequate. Two dosage formulations are being studied (4 mg, 8 mg and 12 mg q1w) and (16 mg, 24 mg and 32 mg q4w).

The study will utilize an EEW approach as an enrichment strategy to enhance the probability of including "responders" and to minimize early discontinuations due to AEs (Dworkin et al, 2012 and FDA CDER, 2014). According to FDA guidance (2014), an enrichment design may be particularly well suited for demonstrating efficacy of alternative dosage forms of an established analgesic. In addition, according to FDA guidance, the titrate-to-effect design may improve subject retention and provide a more realistic picture of efficacy and safety (Dworkin et al, 2012). The use of fixed opioid doses may permit a more rigorous assessment of dose-response, but the limited number of doses may reduce success of the trial, as they are not optimized to meet the subjects' needs.

During the Titration Phase, subjects will be dosed with CAM2038 q1w until a stabilized dose and adequate analgesic effect has been achieved for at least 2 consecutive weeks prior to randomization to the Double-Blind Phase, in accordance with pre-defined randomization criteria. Subjects whose pain is controlled on 4 mg, 8 mg or 12 mg CAM2038 q1w during the Titration Phase, will be maintained on 4 mg, 8 or 12 mg CAM2038 q1w, or corresponding placebo during the Double-Blind Phase. Subjects whose pain is controlled on 16 mg CAM2038 q1w or higher during the Titration Phase will be transitioned to CAM2038 q4w/placebo during the Double- Blind Phase.

Although there are inherent differences in the PK profiles for weekly and monthly administered products, the CAM2038 q1w and q4w formulations are similar with respect to steady state maximum plasma concentration and trough plasma concentration of BPN. Based on these similarities, the CAM2038 products are expected to be interchangeable when subjects go from weekly to monthly dosing regimens.

Rescue medication, hydrocodone/acetaminophen 5 mg/325 mg, will be provided to help minimize opioid withdrawal symptoms in subjects during the Titration Phase and the Double-Blind Phase (particularly in subjects randomized to placebo). Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment, as well as to minimize subject and investigator bias. Double-blinded treatment in the Double-Blind Phase will be used to reduce potential bias of subjects and investigators during data collection and evaluation of clinical endpoints.

During the Double-Blind Phase, the pharmacist will be unblinded to the randomization code to permit dispensation of the CAM2038 or placebo q1w and CAM2038 or placebo q4w syringes to an unblinded staff member who will perform the injections. All other site study personnel, including the investigator and study coordinator, as well as the subjects, will remain blinded to treatment during the Double-Blind Phase of the study. The unblinded staff member will be instructed not to discuss the trial with the blinded staff to ensure the blind is maintained.

The opening of recruitment of subjects for the safety extension is to ensure that a sufficient number of subjects are enrolled to provide required long-term safety data to support the clinical development of CAM2038 for the indication of chronic pain requiring daily treatment with opioids.

7. SELECTION OF STUDY POPULATION

Approximately 875 subjects will be screened to obtain approximately 340 randomized subjects (170 subjects per treatment group). The study comprises two treatment arms: a group of approximately 170 subjects receiving SC CAM2038 q1w or CAM2038 q4w and a group of approximately 170 subjects receiving SC placebo q1w or q4w. Approximately 85 study sites in the United States will be utilized.

Subjects who discontinue prematurely may be replaced at the discretion of the Medical Monitor and the Principal Investigator, in order to maintain study power.

The study population will consist of adult males and females with moderate to severe CLBP currently requiring treatment with daily opioids ≥ 40 mg MED.

For the extension phase, approximately 140 subjects will be enrolled to obtain 100 completed subjects.

7.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria in order to be eligible for participation in the study:

1. Written informed consent provided prior to the conduct of any study-related procedures.
2. Male or non-pregnant, non-lactating female subject, greater than or equal to 18 years old.
3. Body mass index (BMI) between 18 and 38 kg/m^2, inclusive.
4. Treated with daily opioids for moderate to severe CLBP for a minimum of 3 months prior to Screening.
5. On a stable dose of ≥40 mg/day of oral morphine or MED during the 14 days prior to Screening.
6. Systolic blood pressure ≥100 mmHg and diastolic blood pressure ≥60 mmHg.
7. Female subject of childbearing potential who is willing to use a reliable method of contraception during the entire study (Screening Visit to final Follow-up; see Section 9.1.5). To be considered not of childbearing potential, female subjects must be surgically sterile (hysterectomy or bilateral oophorectomy, or bilateral tubal ligation with surgery at least 6 weeks before Screening).
8. Male subject who is willing to use reliable contraception.
9. Willing and able to comply with all study procedures and requirements.

7.2. Exclusion Criteria

Subjects will not be eligible for participation in the study if any of the following exclusion criteria are met:

1. Positive for hepatitis B surface antigen, hepatitis C RNA, or antibodies to human immunodeficiency virus (HIV).

2. Clinically significant symptoms, medical conditions, or other circumstances which, in the opinion of the investigator, would preclude compliance with the protocol, adequate cooperation in the study, or obtaining informed consent, or may prevent the subject from safely participating in the study, including the following:

    a) Severe respiratory insufficiency, respiratory depression, airway obstruction, gastrointestinal motility disorders, biliary tract disease, severe hepatic insufficiency, or planned surgery.

    b) Bipolar disorder

3. Current diagnosis of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition– defined moderate to severe substance use disorder (including alcohol), other than caffeine or nicotine.

4. Female subject planning to become pregnant during the study.

5. Surgical procedure(s) for CLBP within 6 months prior to Screening.

6. Concomitant disease(s) that could prolong the QTcF interval, such as autonomic neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, Long QT Syndrome, or family history of Long QT Syndrome.

7. QTcF >450 ms for males and >470 ms for females, or clinically significant electrocardiogram (ECG) abnormality at Screening, at the investigator's discretion.

8. Currently taking medications that have the potential to prolong the QTcF interval or may require such medications during the course of the study (Appendix 1) and has clinically significant abnormalities on screening ECG readings, as determined by the investigator.

9. A nerve or plexus block, including epidural steroid injections or facet blocks, within 1 month prior to Screening or botulinum toxin injection in the lower back region within 3 months of Screening.

10. History of chemotherapy or confirmed malignancy (except basal cell carcinoma) within the past 2 years.

11. Any other acute or chronic pain condition that could interfere with the subject's ability to report their CLBP accurately and consistently and/or interfere with the study staff's ability to assess the subjects CLBP.

12. An active or pending workman's compensation, insurance claim, or litigation related to back pain (i.e., primary claim is back pain).

13. Clinically significant history, in the opinion of the investigator, of suicidal ideation or current evidence that the subject is actively suicidal.

14. Clinically significant history of major depressive disorder that is poorly controlled with medication, per investigator judgment.

15. Hypersensitivity or allergy to BPN, other opioids, or excipients of CAM2038.

16. Hypersensitivity or allergy to acetaminophen.

17. Use of strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4), such as some azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., clarithromycin), or protease inhibitors

(e.g., ritonavir, indinavir, and saquinavir) within the 30 days prior to Screening,

18. Use or planned use of natural supplements that can affect CYP3A4, such as St. John's Wort, throughout the study.
19. Has a major bleeding disorder, such as hemophilia, or treated with high levels of anticoagulants per the investigator's discretion
20. Current or confirmed past diagnosis of Sphincter of Oddi dysfunction.
21. Has a significant hepatic disease, as indicated by Screening clinical laboratory assessment results (aspartate aminotransferase, alanine aminotransferase, or lactate dehydrogenase values ≥3 × the upper limit of normal [ULN]) or has a creatinine value >1.5 × ULN).
22. Is an employee of the investigator or the trial site, with direct involvement in the proposed trial or other studies under the direction of the investigator or trial site or is a family member of the investigator or of an employee of the investigator.
23. Has any pending legal action that could prohibit participation or compliance in the study.

7.3. Criteria for Entry into the Open-Label Titration Phase

In order to be entered into the Titration Phase, subjects must meet the following criteria:

1. After at least a 12-hour washout from the last IR morphine dose, subject must have a COWS ≥5 and an API pain score over the past 24 hours ≥5 in order to receive a test dose of Buprenex.
2. Passed all baseline criteria, including a normal QTcF, had no change in QTcF >30 ms at 1 hour after the test dose with Buprenex, and had a COWS score >5 after the test dose with Buprenex.

Note:

- Subjects on BPN at Screening are required to participate in the down titration and will undergo a washout period prior to the test dose and first on-study treatment. Subjects entering the study on BPN will not transition to IR Morphine, but will refrain from taking their BPN for 12 -24 hours prior to the test dose to achieve the desired washout period.
- Subjects on BPN at Screening are still required to follow the same Day 1 procedures (e.g., confirmation of pain scores, COWS assessment and Buprenex test dose) as non-BPN subjects.

7.4. Criteria for Randomization into the Double-Blind Phase

For randomization into the Double-Blind Phase, subjects must meet the following criteria at the completion of the Open Label Titration Phase:

1. Been on a stable dose of CAM2038 q1w for at least 2 consecutive weeks.
2. CAM2038 titrated to a dose that provides analgesia (i.e., 7-day API score of ≤4 and at least 2 points below the value at the start of Titration Phase) and is well tolerated for 7 days before randomization.
3. Requires no more than an average of one hydrocodone/acetaminophen 5 mg/325 mg/day during the last 7 days prior to randomization.

4. Demonstrated study medication (CAM2038) compliance ≥80% during the previous 14 days.

5. Demonstrated daily compliance with pain intensity scoring for ≥11 of the previous 14 days, including the last 3 days prior to randomization.

7.5. Inclusion and Exclusion Criteria for Open Label Safety Extension (For Subjects Continuing from the Randomized Double-Blind Phase)

7.5.1. Inclusion Criteria for Existing Subjects Entering from The Randomized Double-Blind Phase

Subjects who are participating in the Double-Blind Phase of the Study must meet all of the following inclusion criteria in order to be eligible for participation in the Open Label Safety Extension Phase:

1. Completed Double-Blind Phase of the study

2. Signed Informed Consent for Safety Extension

7.5.2. Exclusion Criteria for Existing Subjects Entering from The Randomized Double-blind Phase

1. Clinically significant symptoms, medical conditions, or other circumstances which, in the opinion of the investigator, would preclude compliance with the protocol, adequate cooperation in the study, or obtaining informed consent, or may prevent the subject from safely participating in the study.

7.6. Inclusion and Exclusion Criteria for Open Label Safety Extension (De Novo Subjects)

7.6.1. Inclusion Criteria for De Novo Subjects

Subjects who are not participating in the Double-Blind Phase of the study must meet all of the following inclusion criteria in order to be eligible for participation in the study:

1. Written informed consent provided prior to the conduct of any study-related procedures.

2. Male or non-pregnant, non-lactating female subject, greater than or equal to 18 years old.

3. BMI between 18 and 38 kg/m^2, inclusive.

4. Treated with daily opioids for moderate to severe chronic pain disorder such as CLBP or osteoarthritis for a minimum of 3 months prior to Screening.

5. On a stable dose of ≥40 mg/day of oral morphine or MED during the 14 days prior to Screening.

6. Systolic blood pressure ≥100 mmHg and diastolic blood pressure ≥60 mmHg.

7. Female subject of childbearing potential who is willing to use a reliable method of contraception during the entire study (Screening Visit to final Follow-up; see Section 9.1.5). To be considered not of childbearing potential, female subjects must be surgically sterile (hysterectomy or bilateral

oophorectomy, or bilateral tubal ligation with surgery at least 6 weeks before Screening).

8. Male subject who is willing to use reliable contraception.
9. Willing and able to comply with all study procedures and requirements.

7.6.2. Exclusion Criteria for De Novo Subjects

Same exclusion criteria as for subjects participating in the randomized Double-Blind Treatment Phase (see Section 7.2).

7.6.3. Criteria for Entry into the Titration Phase (for De Novo subjects)

1. After at least a 12-hour washout from the last IR morphine dose, subject should have a COWS ≥ 5 and an API pain score over the past 24 hours ≥ 5 in order to receive a test dose of Buprenex.
2. Passed all baseline criteria, including a normal QTcF, had no change in QTcF >30 ms at 1 hour after the test dose with Buprenex, and had a COWS score <5 after the test dose with Buprenex.

Note:

- Subjects on BPN at Screening are required to participate in the down titration and will undergo a washout period prior to the test dose and first on-study treatment. Subjects entering the study on BPN will not transition to IR Morphine, but will refrain from taking their BPN for 12 -24 hours prior to the test dose to achieve the desired washout period.
- Subjects on BPN at Screening are still required to follow the same Day 1 procedures (e.g., confirmation of pain scores, COWS assessment and Buprenex test dose) as non-BPN subjects.

7.6.4. Criteria for Enrollment into the Open Label Treatment Phase (for De Novo subjects)

1. Been on a stable dose of CAM2038 q1w for at least 2 consecutive weeks.
2. CAM2038 titrated to a dose that provides analgesia (i.e., 7-day API score of ≤4 and at least 2 points below the value at the start of Titration Phase) and is well tolerated for 7 days before randomization.
3. Requires no more than an average of one hydrocodone/acetaminophen 5 mg/325 mg/day during the last 7 days prior to randomization.

7.7. Removal of Subjects from Therapy or Assessment

A subject is free to withdraw his/her consent and discontinue participation in the study at any time for any reason. A subject's participation must therefore be terminated immediately upon his/her request, and the reason(s) for discontinuation appropriately documented.

A subject must be discontinued from the study, including the Titration, Double-Blind Phases, and Open-Label Safety Extension Phase, for any of the following reasons:

- Safety reasons, including AEs or significant concomitant illness, injury or urgent surgeries/procedures that would, in the judgment of the investigator, affect assessments of clinical status to a significant extent, require discontinuation of study drug, or both
    - Every attempt should be made to collect samples for a urine toxicology test and BPN blood concentration if a subject experiences a SAE or is discontinued from the study due to an AE. The investigator will remain blinded to the results until the study blind is broken.

- At the request of the Sponsor, regulatory agency, or Institutional Review Board (IRB)
- Subject is lost to follow-up
- Subject treatment allocation is unblinded
- Death of subject

A subject may also be discontinued from the study, at the discretion of the investigator and/or Sponsor, for any of the following reasons:

- Lack of efficacy
- Subject refuses or is unable to adhere to the study protocol visits and procedure
- Major protocol violation
- Pregnancy
- Use of unacceptable concomitant medication(s)
- It is not considered in the best interest of the subject to continue
- Administrative reasons (e.g., termination of enrollment or study)

The investigator must maintain a record of all subjects who discontinue from the study prior to completion. The reason(s) for study discontinuation will be documented. In the event that a subject chooses to withdraw from the study, the Investigator should make a reasonable attempt to obtain and record the reason(s) for withdrawal in as much detail as possible, although the subject is not obligated to provide such reason(s).

In the event that a subject is discontinued while at the clinical site, the early termination procedures shown in the Schedule of Assessments (Table 6 , Table 7, Table 8, and Table 10) should be performed prior to discharge from the clinical site. For any case of early discontinuation, whether or not the subject is at the clinical site, the investigator should ask the subject to return for the early termination procedures, provided that the subject has not withdrawn consent for those procedures. If the subject has not withdrawn consent for procedures, the sponsor can hire a third-party vendor to locate the subject so that the early termination procedures can be performed. If subject refuses to complete early termination procedures, this information will be recorded.

8. TREATMENTS

8.1. Treatment Administration

8.1.1. Transition Phase (after Screening to test dose/Day 1)

Following Screening and confirmation of eligibility, subjects will enter a Transition Phase of up to 2 weeks during which their current opioid dose will be down-titrated by approximately 25% per day to ≤80 mg/day MED for subject whose screening MED was ≥80 mg/day; or to ≤40 mg/day MED for subject whose screening MED was between 40 mg and 79 mg/day. With exception to subjects down-titrating their BPN dosing, subjects will be transitioned to an IR morphine (15 mg QID or 15 mg TID, respectively) for at least 2 days before they enter the Open Label Titration Phase. Following the morphine IR treatment, subjects will enter the Titration Phase. Subjects who were previously on BPN prior to Screening will not need to participate in the morphine-IR phase, but will refrain from taking BPN for 12-24 hours as a washout phase.

8.1.2. Test Dose (Day 1 of Titration)

Subjects are required to refrain from their previous IR morphine treatment for at least 12 hours in order to receive the Buprenex test dose at the clinical site (i.e., Day 1 of the Titration Phase). Subjects will be required to have an API score over the previous 24 hours ≥ 5, recorded on a paper diary and a COWS score ≥ 5 in order to receive the test dose of Buprenex. The COWS assessment can be performed up to 48 hours after the initial COWS assessment. At that time, subjects will receive an IM injection of 0.30 mg (1.0 mL) Buprenex and will be assessed for any changes in QTcF or withdrawal. ECGs will be taken 15 minutes before and 15 minutes and 1 hour after the test dose. COWS will be assessed at 15 minutes after the test dose.

8.1.3. Titration Phase

After administration of the Buprenex test dose on Day 1, subjects who tolerate the test dose, do not show an increase of > 30 ms in QTcF within 1 hour, and have a COWS score of < 5 within 15 minutes after the test dose will receive their first dose of CAM2038 q1w within 4 hours (+ 30 minutes) after the test dose. Subjects whose screening opioid dose was between 40 mg and 79 mg/day MED will be started on 4 mg CAM2038 q1w. Subjects whose screening opioid dose was ≥80 mg/day MED will be started on 8 mg CAM2038 q1w. During the first week of the Titration Phase, subjects who experience significant pain may, at the discretion of the investigator receive a second dose of CAM2038 at their respective dose (4 mg for subjects whose screening MED was 40-79 mg/day; 4 or 8 mg CAM2038 q1w for subjects whose screening Med was ≥80 mg/day) on Day 3, 4, or 5. Subjects will then attend clinic visits every week for dosage adjustment. Dose adjustments will be made by increasing or decreasing the dose level of CAM2038 q1w at the scheduled weekly visits (doses of 4 mg, 8 mg, 12 mg, 16 mg, 24 mg, or 32 mg per week).

The maximum dose within a 7-day period cannot exceed 32 mg. Subjects who require doses higher than 32 mg/week will be discontinued from the study. The dosing of CAM2038 q1w will be titrated with the purpose of achieving a stable dose of CAM2038 q1w by the end of the 10-week Titration Phase.

8.1.4. Double-Blind Phase

Subjects who are receiving 4, 8 or 12 mg CAM2038 q1w at the end of the Titration Phase will be randomized to continue their respective 4 mg, 8 mg or 12 mg CAM2038 q1w dosing, or to corresponding placebo q1w for a total treatment duration of 12 weeks (12 injections in the Double-Blind Phase). Subjects who are receiving 16 mg, 24 mg or 32 mg CAM2038 q1w at the end of the Titration Phase will be randomized to CAM2038 q4w (64 mg, 96 mg or 128 mg, respectively) or to corresponding placebo q4w for a total treatment duration of 12 weeks (3 injections in the Double-Blind Phase).

The dose conversions between CAM2038 q1w and CAM2038 q4w are shown below.

- 4 mg CAM2038 q1w = 4 mg CAM2038 q1w or placebo q1w
- 8 mg CAM2038 q1w = 8 mg CAM2038 q1w or placebo q1w
- 12 mg CAM2038 q1w = 12 mg CAM2038 q1w or placebo q1w
- 16 mg CAM2038 q1w = 64 mg CAM2038 q4w or placebo q4w
- 24 mg CAM2038 q1w = 96 mg CAM2038 q4w or placebo q4w
- 32 mg CAM2038 q1w = 128 mg CAM2038 q4w or placebo q4w

CAM2038/placebo q1w must not be administered into a previously injected site for at least 4 weeks. CAM2038/placebo q4w must not be administered in a site previously injected with CAM2038/placebo q4w or with CAM2038/placebo q1w.

During the entire Double-Blind Phase, subjects will be instructed to record their pain intensity ratings before taking rescue medication. Rescue medication will consist of hydrocodone/acetaminophen 5 mg/325 mg tablets, q4-6h prn, not to exceed a total of 6 tablets or a total dosage of hydrocodone/acetaminophen 30 mg/1950 mg/day for subjects whose screening opioid dose was ≥80 mg/day. For subjects whose screening opioid dose was between 40 and 79 mg/day MED, the maximum allowable rescue medication will be 15 mg/975 mg/day (three tablets). This dosage limit will provide analgesic rescue medication at a maximum dose to prevent liver toxicity.

In addition, at any time during the Double-Blind Phase, if the subject requires rescue medication above the maximum allowable (hydrocodone/acetaminophen 30 mg/1950 mg/day (six tablets) for subjects whose screening MED was ≥80 mg/day; or 15mg/975 mg/day (three tablets) for subjects whose screening MED was between 40 and 79 mg/day), the subject should be asked if they want to continue with the maximum dose of rescue medication or would like to withdraw from the study. If circumstances surrounding discontinuation or withdrawal are unclear, the Medical Monitor should be consulted. If the subject decides to withdraw, the subject should have a final on-treatment visit and then have procedures and assessments completed for any remaining study visits, as specified in the protocol.

Telephone or other contacts made by the site are allowed throughout the course of the study. Subjects should return to the study center according to the schedule specified in this protocol.

One week after the last dose of CAM2038/placebo q1w or 4 weeks after the last dose of CAM2038/placebo q4w, the subjects will attend a Final Study Visit. At the Final Study Visit (or early termination), subjects will be transitioned back to standard care or their treatment prior to study entry. Within 4 weeks after the Final Study Visit, subjects will be contacted by phone to assess AEs and review concomitant medications.

8.1.5. Subjects Randomized to Placebo in the Double-Blind Phase

At the start of the Double-Blind Phase, approximately half of the subjects (170) will be randomized to placebo. These subjects may experience increases in their pain scores and require rescue medication. Sites are encouraged to keep these subjects in the study as long as possible. However, subjects may withdraw consent for participation at any time and for any reason. Subjects who discontinue prematurely may be replaced at the discretion of the Medical Monitor and the Principal investigator, in order to maintain study power.

8.1.6. Rescue Medications

Hydrocodone/acetaminophen 5 mg/325 mg will be used as a rescue medication throughout the study. Rescue medication will be allowed prn during the Open Label Titration Phase and the Double-Blind Phase up to 30 mg/1950 mg/day of hydrocodone (5 mg)/acetaminophen (325 mg). However, the subject may not use, on average, more than one dose of rescue medication per day over the 7 days before randomization. Throughout the study, subjects will be instructed to record their pain intensity "at that moment" on the electronic diary prior to taking rescue medication.

8.1.7. Open Label Safety Extension

Once the required number of subjects for the Double-Blind phase of the trial has been recruited (approximately 340), enrollment for the Double-Blind Phase will be closed and remaining subjects with CLBP will be offered the opportunity to proceed directly to the Open Label Safety Extension Phase without having to participate in the Double-Blind Phase. However, to be eligible to proceed to the Open Label Safety Extension Phase, subjects must meet the following criteria:

- The analgesic dose of CAM2038 is well-tolerated for 7 days before entry into open label study (no adverse effects that require a change in study dosing or interruption)

The opening of recruitment for subjects with CLBP for the safety extension only after enrollment for the randomized Double-Blind Phase of the study is complete, is to ensure that eligible subjects with CLBP are enrolled into the pivotal randomized Double-blind phase first. However, other subjects with chronic pain requiring daily treatment with opioids, who do not qualify for the randomized Double-Blind Phase of the study but are eligible for the safety extension phase may be enrolled directly into the safety extension phase (so called de novo subjects). These subjects will not be required to wait for recruitment for the randomized Double-Blind Phase to be completed prior to enrolling into the safety extension. The purpose of the safety extension is to ensure that sufficient data is obtained, to provide at least 52 weeks of exposure safety information in at least 100 subjects. These long long-term safety data are required to support the clinical development of CAM2038 for the indication of chronic pain requiring daily treatment with opioids.

De novo subjects proceeding directly to the open label extension, will undergo the same screening procedures, down titration, morphine IR, Buprenex test dose, and CAM2038 up-titration similar to the requirement for subjects enrolling into the randomized Double-Blind Phase of the study. The CAM2038 dosing titration and rescue medication requirements for the safety extension for subjects whose opioid doses at screening are > 80 mg/day MED, and 40-79 mg/day MED, respectively, shall be the same as described for the subjects participating in the Double-Blind Phase.

Subjects in the safety extension will return to the study clinic for their regular weekly or monthly CAM2038 injections until the end of the study.

Starting at the fourth monthly safety extension visit, PK sampling for CAM2038 steady state PK will be performed in subjects who have provided additional consent for the PK sampling. PK sample can be done at any visit timepoint after the subject has stabilized but no later than 4 week prior to EOT visit. Effort will be made to ensure that a sufficient number of subjects are included to cover the range of CAM2038 doses in the safety extension phase.

Blood samples will be collected prior to administration (within 45 minutes); and at approximately 2 hours, 6 hours, 24 hours, 72 hours, 168 hours, 336 hours, and 672 hours to measure plasma levels of BPN and norBPN for subjects receiving both CAM2038 qlw and CAM2038 q4w treatments. Actual dates and times of dosing of IMP during the safety extension phase as well as blood sampling for PK measurement will be recorded.

8.1.7.1. Dosing Schedule

The dose titration schedule below provides guidance regarding titration of subject dosing upon enrollment into the open label extension portion of the study following participation in the double-blind randomization.

- All subjects will be started on the weekly CAM2038 regimen during the open label extension.
- Subjects completing the randomized double-blind phase on 4 mg, 8 mg, or 12mg CAM2038/placebo q1w will continue the same dose of active treatment (open label CAM2038) without need for titration.
- Subjects completing the randomized double-blind phase on 64 mg, 96mg, or 128mg CAM2038/placebo q4w will begin open label treatment at the corresponding equivalent weekly dose last received by the subject prior to transition to the monthly dosing regimen. The subject may transition to monthly dosing upon return to the clinic in 1 week following the initial dose. At the investigator's discretion, the transition period may be extended or the patient down-titrated, in case of poor tolerability.
- Additional details are presented in Table 4 below:

Table 4 Open-Label Extension Dose Schedule for Randomized Double-Blind Rollover

Randomized Double-Blind Dose	Titration Schedule
4mg CAM2038 q1w	Remain at 4mg weekly
8mg CAM2038 q1w	Remain at 8mg weekly
2mg CAM2038 q1w	Remain at 12mg weekly
64mg monthly*	Start at 16mg q1w
96mg monthly*	Start at 24mg q1w
128mg monthly*	Start at 32mg q1w

*Please note:

- 16 mg CAM2038 q1w is the dosing equivalent of 64 mg CAM2038 q4w
- 24 mg CAM2038 q1w is the dosing equivalent of 96 mg CAM2038 q4w

- 32 mg CAM2038 q1w is the dosing equivalent of 128 mg CAM2038 q4w

8.2. Identity of Investigational Product(s)

The following treatments will be used during the study:

- CAM2038 (BPN FC Injection depot for q1w administration), 6.25 mg/mL: 4 mg (BPN base), 0.64 mL SC injection.*
- CAM2038 (BPN FC Injection depot for q1w administration), 50 mg/mL: 8 mg, 12 mg, 16 mg, 24 mg, and 32 mg (BPN base), 0.16, 0.24, 0.32, 0.48, and 0.64 mL SC injection.
- CAM2038 (BPN FC Injection depot for q4w administration), 356 mg/mL: 64 mg, 96 mg, and 128 mg (BPN base), 0.18, 0.27, and 0.36 mL SC injection.
- Placebo: 0.16, 0.32, 0.48 and 0.64 mL SC injections for q1w or q4w administration.

  * *CAM2038 6.25 mg/mL has been interchangeably referred to as CAM2048 during its development. The active ingredient is the same as for CAM2038 q1w. It also has the same excipients, as the CAM2038 q1w. For the purposes of this protocol, all reference to CAM2048 shall be considered to refer to and interchangeable with CAM2038 q1w*

8.2.1. Description of CAM2038 q1w, CAM2038 q4w, and Placebo SC Injection Products

CAM2038 q1w will be supplied as a pre-filled syringe with safety device and plunger containing the following: BPN, soybean phosphatidylcholine, glycerol dioleate, and anhydrous ethanol.

CAM2038 q4w will be supplied as a pre-filled syringe with safety device and plunger containing the following: BPN, soybean phosphatidylcholine, glycerol dioleate, and N-Methyl-2- pyrrolidone.

Placebo SC injections will be supplied as matching (for CAM2038 q1w) or nearly matching (by volume and color for CAM2038 q4w) pre-filled syringes with safety devices and plungers containing the following: soybean phosphatidylcholine, glycerol dioleate, and ethanol.

More information regarding the CAM2038 q1w and CAM2038 q4w and matching or nearly matching placebo injections can be found in the Instructions for User (IFU).

8.2.2. Description of the Buprenex Test Dose

Buprenex (BPN hydrochloride) will be sourced centrally and will be given as 1 mL deep IM injection corresponding to 0.3 mg BPN according to the prescribing information.

8.2.3. Description of the IR Morphine

Morphine sulfate IR will be supplied as 15-mg tablets for oral administration.

8.2.4. Description of the Hydrocodone/Acetaminophen

Hydrocodone/Acetaminophen will be supplied as 5 mg/325 mg for oral administration.

8.2.5. Handling, Storage, and Accountability

All study drugs will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions provided to the research site and applicable regulations.

The CAM2038 drug products, IR morphine, Buprenex, and hydrocodone/acetaminophen 5 mg/325 mg as rescue medication should be stored in a secured area at room temperature (59° to 77° F or 15° to 25° C) and in accordance with the product labeling and all applicable laws, regulations and local/institutional requirements.

Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed and the running inventory. The unused quantities will be returned to the Sponsor's drug supply vendor at the end of the trial. All unused supplies will be checked against the drug accountability records during the study and/or at the end of the study. Subjects will be instructed to return all unused study drugs to the clinical site. The investigator or designee must maintain an inventory record of all rescue medications dispensed to subjects.

Mishandling, potential theft, significant loss of clinical supplies at the site, or other suspected diversion must be reported to the Sponsor within 24 hours of first knowledge of the issue. If diversion is confirmed or suspected (e.g., excessive use of rescue medications), the study staff will be required to complete a clinical supply product complaint form, including documenting if a subject sold drug or gave drug to a friend or relative, if there was a discrepancy in drug accountability and suspected diversion, if a subject had drug stolen, or if there was diversion or theft by site staff or others.

BPN (Schedule III), morphine sulfate (Schedule II), and hydrocodone/acetaminophen 5 mg/325 mg (Schedule II) are controlled substances and must be handled and stored strictly in accordance with restrictions related to controlled substances. Study drugs must be kept securely locked with access limited to appropriate study personnel, according to applicable regulations.

8.2.6. Dispensing and Administration

Only eligible subjects participating in the study will receive the study drug. Only authorized research site staff may supply or administer the study drugs. Once dispensed, study drug may not be relabeled or reassigned for use by other subjects.

During the Double-Blind Phase, the pharmacist will be unblinded to the randomization code to permit dispensation of the CAM2038/placebo q1w and CAM2038/placebo q4w syringes to an unblinded staff member who will perform the injections. All other site study personnel, including the investigator and study coordinator, as well as the subjects, will remain blinded to treatment until the study is unblinded by the study sponsor. The unblinded staff member will be instructed not to discuss the trial with the blinded staff to ensure the blind is maintained.

Injections will be administered in different SC sites, to avoid injecting into the same exact site (Appendix 2). Detailed instructions for use will be provided in the IFU.

8.3. Method of Assigning Subjects to Treatment Groups

Randomization will be used to avoid bias in the assignment of subjects to treatments, to increase the likelihood that known and unknown subject attributes (e.g., demographics, baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across

treatment groups.

Subjects who provide written informed consent will be assigned a unique number in the screening process. This number will be used to identify the subject throughout the study.

Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio (Group 1: active CAM2038 SC injections or Group 2: placebo SC injections). Randomization will be stratified based on double blind dosing regimen. Subjects randomized at a titration dose of either 4, 8 or 12 mg will remain on weekly doses. Subjects randomized at a titration dose of 16, 24, or 32 mg will transition to monthly dosing.

Therefore, there will be four different dose types.

- A1 – Active weekly
- B1 – Placebo weekly
- A4 – Active monthly
- B4 – placebo monthly

Due to the size of the study, it is expected that subjects will be balanced for various other baseline factors, including age.

Once any subject number or randomization number is assigned, it cannot be reassigned to any other subject. This study will use central randomization, as described in Section 9.2.

8.4. Selection of Dose

The study will include the following doses based on each subject's individual analgesia needs and tolerability:

- CAM2038 q1w 6.25 mg/mL: 4 mg (BPN base); 0.64 mL SC injection
- CAM2038 q1w 50 mg/mL: 8 mg, 12 mg, 16 mg, 24 mg, and 32 mg (BPN base); 0.16, 0.24, 0.32, 0.48, and 0.64 mL SC injection
- CAM2038 q4w, 356 mg/mL: 64 mg, 96 mg, and 128 mg (BPN base); 0.18, 0.27, and 0.36 mL SC injection.

Dose adjustments will be allowed during the Open Label Titration Phase only.

Rescue medication is oral hydrocodone/acetaminophen, 5 mg/325 mg tablets, q4-6 h prn. The maximum daily dose is 30 mg/1950 mg/day. Subjects cannot take more than one rescue tablet per day, on average, in the week prior to randomization.

On Day 1 of the Titration Phase, subjects will receive a test dose consisting of a single IM injection of 0.30 mg (1.0 mL) Buprenex and will be assessed for any changes in QTcF or withdrawal prior to any administration of CAM2038.

8.5. Selection and Timing of Dose

Subjects will be randomized to receive either CAM2038 or placebo at individualized doses. No fasting or special dietary requirements are required for the study.

8.6. Blinding

In order to reduce the potential for bias in the study, treatment group assignments will be double-blinded during the Double-Blind Phase. The subject, investigational site personnel, Sponsor, and Sponsor designees directly involved in the conduct and/or monitoring of this study will not be aware of the treatment group assignments.

There is a slight difference in color and fill volume between the placebo and active CAM2038 q4w; however, the viscosity is the same. In order to maintain the blind given the differences in color and fill volume, the following will be implemented during the Double-Blind Phase:

- The Injecting Clinician and any other staff involved in the injection process will not participate in subject evaluations, nor discuss any information regarding the injections with the subjects or other study staff.
- To keep the subjects blinded, appropriate steps will be taken to ensure that the subject is unable to view the syringe at any time.
- The study staff will not ask the Injecting Clinician or any other staff involved in the injection process for information regarding subject group assignment that might inadvertently unblind the study staff.

Under normal circumstances, the blind will not be broken until all participants have completed treatment. In case of emergency, and only if the information is required by the investigator to ensure subject's safety in managing a medical condition, the treatment may be unblinded at the site by using a code break module. The code break module will be provided by the Sponsor or designee. If possible, the investigator should contact the Sponsor prior to unblinding and after any actions have been taken. Whenever a treatment sequence is prematurely unblinded, the reason, date, and time of the unblinding and the individual who broke the blind must be documented. Individual code breaks will result in withdrawal of the subject from the study.

8.7. Prior and Concomitant Medications and Therapy

All non-study medications, including prescription, over-the-counter, or herbal therapies, used by the subject will be documented for the 30 days prior to Screening and throughout the study. The investigator will determine if the prior/concomitant medication(s) affect the subject's eligibility to participate or continue to participate in the study. The following restrictions on concomitant medications will be in place during the study:

- Opioid receptors are likely to be occupied by BPN, which may reduce the analgesic effects of an opioid. The dissociation of BPN from the receptors may take up to 2 weeks (for CAM2038 q1w) or at least 2 months (for CAM2038 q4w) following the last CAM2038 injection. Therefore, subjects requiring analgesic emergency treatment or anesthesia for surgery should ideally be treated with a non-opioid analgesic. Opioids may be used with caution, but as higher doses may be required for analgesic effect, there may be a higher potential for toxicity with opioid administration. The clinical course should be carefully evaluated and fully documented for subjects who have a requirement for any opioid analgesic for >7 days continually or general anesthesia for surgery.

  BPN is metabolized via CYP3A4. Because CYP3A4 inhibitors may increase plasma concentrations of BPN, CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir) are prohibited for at least 30 days prior to Screening. Interactions with CYP3A4 inducers have not been investigated; therefore, CYP3A4 inducers (e.g., phenobarbital, carbamazepine, phenytoin, and rifampicin) are prohibited for at least 30 days prior to Screening.

- Concomitant use of other narcotic anesthetics, benzodiazepines, phenothiazines, other tranquilizers, or other central nervous system (CNS) depressants (including alcohol and sedative/hypnotics) may cause respiratory and CNS depression. Use of these substances should be minimized during treatment with CAM2038. If these sedatives are required during the study, the Medical Monitor must be consulted. Subjects should be advised of the danger of concomitant use of sedatives while participating in the study. Subjects should be explicitly advised of the danger of IV abuse of benzodiazepines and abuse of alcohol while under treatment with CAM2038.

The following concomitant medications and therapies may be permitted during the study:

- Nonsteroidal anti-inflammatory drugs will be permitted occasionally for headache, fever, or other indications, aside from CLBP, for no more than 3 consecutive days and no more than the maximum daily recommended dose
- Other non-opioid analgesics are permitted, but subjects must be on a stable dose (±20% dose and timing of administration) for at least 30 days prior to enrollment
- Rescue medication
- Anti-constipation medications
- Aspirin at doses ≤325 mg/day for cardiovascular prophylaxis

The following medications and therapies are permitted, but must remain stable (±20% dose and timing of administration) throughout the duration of the subject's participation in the study:

- Muscle relaxants
- Hypnotics (eszopiclone, zolpidem, zaleplon)
- Antidepressants
- Anticonvulsants
- Physical therapy
- Biofeedback therapy
- Acupuncture therapy
- Herbal remedies (except products that can affect CYP3A4, such as St. John's Wort)

On a case-by-case basis, the investigator is permitted to allow the use of some concomitant medications, for example, to treat an AE, as long as the investigator determines that the medication will not affect the subject's safety or study integrity (e.g., topical medications). Wherever possible, the investigator should obtain approval from the Sponsor's Medical Monitor prior to administering the medication.

8.8. Treatment Compliance and Monitoring Diversion

Because CAM2038 is administered by study personnel, no compliance procedures are necessary. Diversion will be monitored and recorded by reconciling the number of tablets of rescue medication dispensed against the number of tablets returned at each visit and diary entries. Any suspected or confirmed diversion will be documented and reported.

9. STUDY PROCEDURES AND ASSESSMENTS

All study assessments will be performed at the visits and time points outlined in the Schedule of Assessments (Table 5, Table 6, and Table 7). Open-label safety extension assessments for existing subjects enrolled from the randomized Double-Blind Phase is present in Table 8. Table 9 and Table 10 presents the schedule of assessments for de novo subjects in Open Label Safety Extension Phase. The following sections outline the details and procedures associated with the assessments.

Table 5: Schedule of Assessments for Screening, Transition, and Titration Phases

Study Period/Phase:	Screening	Transition Phase[1]		Open-Label Titration Phase[2]									
Week:	W-2 to -1	W0		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10
Day:	D-14 to -1	D1 up to 10-12 days[3]	2 to 4 days										
Informed Consent[4]	X												
Eligibility Criteria Review	X			X[5]									
Demographic Data	X												
Medical and Medication History	X												
Physical Examination[6]	X												
Vital Signs[7]	X			X[8]	X	X	X	X	X	X	X	X	X
ECG	X			X[h]	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments	X			X				X[9]					
Pregnancy Test[10]	X			X		X		X		X		X	
Hepatitis B/C, HIV[11]	X												
Urine Drug Screen	X			X	X	X	X	X	X	X	X	X	X
Dispense Treatment Identification Card				X									
Down-Titrate Opioid Dose		X											

[1] Subjects on BPN at screening will participate in the down titration but will not transition to morphine IR. Subjects will washout and refrain from their BPN treatment for 12-24 hours prior to the test dose on Day 1.
[2] Titration Phase visit window is ±3 days.
[3] Telephone contact.
[4] Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.
[5] Prior to starting the Titration Phase, all Inclusion/Exclusion and other relevant criteria must be met.
[6] A complete physical examination of all major body systems (including height, weight, and BMI) will be performed.
[7] Includes body temperature, blood pressure, pulse rate, pulse oximetry and respiration rate.
[8] Vital signs and ECG will be measured 15 minutes (allowable window up to 60 minutes) before the Buprenex test dose, 15 minutes (allowable window of between 15-30 minutes) and 1 hour (allowable window of between 60-90 minutes) after the test dose, and 1 hour (allowable window of between 60-90 minutes) and 24 hours (allowable window of ±3 hours) after the first CAM2038 q1w dose. Vital signs and ECG will thereafter be assessed weekly during the Titration Phase.
[9] An additional sample for assessment of electrolytes will be taken 4 weeks after the first dose of CAM2038 q1w. Refer to Table 11 for a list of laboratory analytes.
[10] A serum pregnancy test will be performed at Screening. An "in-office" urine pregnancy test will be required every other week during the Titration (for women of childbearing potential).
[11] It is the Investigator's responsibility to understand and comply with the laws and regulations that apply to HIV, Hepatitis B, and Hepatitis C testing of blood samples. Hepatitis B/C and HIV testing is required unless the site's IRB prohibits such testing.

Study Period/Phase:	Screening	Transition Phase[1]		Open-Label Titration Phase[2]									
Week:	W-2 to -1	W0		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10
Day:	D-14 to -1	D1 up to 10-12 days[3]	2 to 4 days										
IR Morphine[12]			X										
Buprenex Test Dose				X[13]									
COWS/SOWS				X[14]	X								
CAM2038 q1w SC Injection[15]				X	X	X	X	X	X	X	X	X	X
Injection Site Examination				X	X	X	X	X	X	X	X	X	X
Dispense, Collect, and Record Rescue Medications				X	X	X	X	X	X	X	X	X	X
Daily Diary Pain Rating (NRS-11)	X			X[16]	Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily	
EQ-5D-5L	X			X				X				X	
WPAI	X			X	X	X	X	X	X	X	X	X	
C-SSRS[17]	X			X		X		X		X		X	
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs[18]	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=Adverse Event; BMI=Body Mass Index; C-SSRS-Columbia Suicide Severity Rating Scale; COWS=Clinical Opiate Withdrawal Scale; D=day; ECG=electrocardiogram; EQ-5D-5L=EuroQoL Group 5-dimension 5-level self-report questionnaire; HIV=Human Immunodeficiency Virus; IM=intramuscular; NRS-11=11-point numerical rating scale; q1w=once weekly; SC=subcutaneous; SOWS=Subjective Opiate Withdrawal Scale; W=week; WPAI=Work Productivity and Activity Impairment.

[12] IR morphine (15 mg QID for subjects with screening MED of ≥80 mg/day; or 15 mg TID for subjects with screening MED between 40 mg and 79 mg/day) for at least 2 days prior to Day 1 of the Titration Phase. A 12-hour washout from the last IR morphine dose is required before the Buprenex test dose is given.
[13] One IM injection of 0.3 mg (1.0 mL) Buprenex.
[14] COWS/SOWS will be assessed before the test dose, 15 min (allowable window of between 15-30 minutes) after the test dose, and 24 hours (allowable window of ±3 hour) after the first 4 mg or 8 mg CAM2038 dose. If COWS score is not ≥5, the COWS can be repeated for up to 48 hours.
[15] The first dose of either 4 mg or 8 mg CAM2038 q1w will be administered within 4 hours (+30 minutes) after the test dose. During the first week of the Titration Phase, subjects who experience significant pain may, at the discretion of the investigator, receive an additional CAM2038 at their respective dose (4mg or 8 mg) on Day 3, 4 or 5. Dose adjustments will be made by increasing or decreasing the dose level of CAM2038 q1w at the scheduled weekly visits (doses of 4 mg, 8 mg, 12 mg, 16 mg, 24 mg, or 32 mg per week). Subjects who require doses >32 mg/week will be discontinued from the study.
[16] Electronic diary dispensed after test dose.
[17] 'Screening' version at Screening and 'Since Last Visit' version every other week during the Titration Phase.
[18] Any spontaneously reported AEs will be recorded after the subject signs the ICF. In addition, AEs will be elicited using a non-leading question each time the subject visits the clinic.

Table 6: Schedule of Assessments for Subjects Randomized to Once Weekly Injections

Study Period/Phase:		Double-Blind Phase[a b]											Final Study Visit[c]	Follow-up Phase[d]
Month:		M4			M5				M6					M7
Week:	11	12	13	14	15	16	17	18	19	20	21	22	23	27
Eligibility Criteria Review	X[e]													
Physical Examination[f]													X	
Vital Signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X[h]	X			X				X				X	
Clinical Laboratory Assessments	X												X	
Pregnancy Test[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	
COWS/SOWS[j]	X	X												
CAM2038/placebo q1w SC Injection[k]	X	X	X	X	X	X	X	X	X	X	X	X		
Injection Site Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense, Collect, and Record Rescue Medications	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	

[a] Double-Blind Phase visit window is ±3 days.
[b] The first day of the Double-Blind Phase is defined as baseline.
[c] This visit is defined as the twelfth week of the Double-Blind Phase in the analyses of data.
[d] Telephone contact only.
[e] Prior to enrollment into the Double-Blind Phase, all Inclusion/Exclusion and other relevant criteria must be met.
[f] A complete physical examination of all major body systems (including height, weight, and BMI) will be performed.
[g] Includes body temperature, blood pressure, pulse rate, pulse oximetry and respiration rate and will be performed at every visit, prior to treatment, and 1-hour post-study treatment (allowable window of 60-90 minutes).
[h] ECGs will be assessed at Week 11, prior to treatment and 1-hour post-dose (allowable window of 60-90 minutes).
[i] A serum pregnancy test will be performed at the Final Study Visit/Early Termination. An "in-office" urine pregnancy test will be required weekly (for women of childbearing potential).
[j] COWS/SOWS will be assessed before dosing.
[k] Subjects who are receiving 4 mg, 8 mg or 12 mg CAM2038 q1w will randomize to CAM2038/placebo q1w with weekly injections throughout the Double-Blind Phase.
[l] Rescue medication will not be dispensed at this visit.

Study Period/Phase:		Double-Blind Phase[ab]											Final Study Visit[c]	Follow-up Phase[d]
Month:		M4			M5				M6					M7
Week:	11	12	13	14	15	16	17	18	19	20	21	22	23	27
Daily Electronic Diary Pain Rating (NRS-11)	X	X	X	X	X	X	X	X	X	X	X	X	X	
EQ-5D-5L	X				X				X				X	
WPAI	X				X				X				X	
C-SSRS[m]	X				X				X				X	
CGI-I Scale	X				X				X				X	
PGI-I Scale	X				X				X				X	
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust Opioid Treatment													X[o]	

BMI=Body Mass Index; CGI-I=Clinical Global Impression Improvement; C-SSRS=Columbia Suicide Severity Rating Scale; COWS=Clinical Opiate Withdrawal Scale; ECG=electrocardiogram; EQ-5D-5L=EuroQoL Group 5-dimension 5-level self-report questionnaire; ET=Early Termination; NRS-11=11-point numerical rating scale; PGI-I= Patient Global Impression of Improvement; q1w=once weekly; q4w=once monthly; SC=subcutaneous; SOWS=Subjective Opiate Withdrawal Scale; WPAI=Work Productivity and Activity Impairment.

[m] Since Last Visit' version to be used.

[n] Any spontaneously reported AEs will be recorded after the subject signs the ICF. In addition, AEs will be elicited using a non-leading question each time the subject visits the clinic.

[o] At the Final Study Visit (or ET) subjects will be transitioned back to standard care or their treatment prior to study entry.

Table 7: Schedule of Assessments for Subjects Randomized to Once Monthly Injections

Study Period/Phase:	Double-Blind Phase[a b]			Final Study Visit[c]	Follow- up Phase[d]
Month:	M4	M5	M6		
Week:	11	15	19	23	27
Eligibility Criteria Review	X[e]				
Physical Examination[f]				X	
Vital Signs[g]	X	X	X	X	
ECG[h]	X	X	X	X	
Clinical Laboratory Assessments	X			X	
Pregnancy Test[i]	X	X	X	X	
COWS/SOWS[j]	X				
CAM2038 q4w/placebo SC Injection[k]	X	X	X		
Injection Site Examination	X	X	X	X	
Dispense, Collect, and Record Rescue Medications	X	X	X	X[l]	
Daily Electronic Diary Pain Rating (NRS-11)	X	X	X	X	
EQ-5D-5L	X	X	X	X	
WPAI	X	X	X	X	

[a]Double-Blind Phase ±7 days

[b] The first day of the Double-Blind Phase is defined as baseline.

[c] This visit is defined as the twelfth week of the Double-Blind Phase in the analyses of data.

[d] Telephone contact only.

[e] Prior to enrollment into the Double-Blind Phase, all Inclusion/Exclusion and other relevant criteria must be met.

[f] A complete physical examination of all major body systems (including height, weight and BMI) will be performed.

[g] Includes body temperature, blood pressure, pulse rate pulse oximetry and respiration rate and will be performed at every visit, prior to treatment, 1-hour post-treatment (allowable window of 60-90 minutes) and at 6-10 hours (t_{max}) after the first CAM2038/placebo q4w dose.

[h] ECGs will be assessed at Week 11, prior to treatment and at 6-10 hours (t_{max}) after the first CAM2038/placebo q4w dose.

[i] A serum pregnancy test will be performed at the Final Study Visit/Early Termination. An "in-office" urine pregnancy test will be required monthly (for women of childbearing potential).

[j] COWS/SOWS will be assessed before dosing and 6-10 hours (t_{max}) after the first dose of CAM2038/placebo q4w.

[k] Subjects who are receiving 16, 24, or 32 mg CAM2038 will be randomized to CAM2038/placebo q4w (64, 96, or 128 mg) and receive 3 doses with CAM2038/placebo q4w (Weeks 11, 15 and 19)

[l] Rescue medication will not be dispensed at this visit.

Study Period/Phase:	Double-Blind Phase[ab]			Final Study Visit[c]	Follow- up Phase[d]
Month:	M4	M5	M6		
Week:	11	15	19	23	27
C-SSRS[m]	X	X	X	X	
CGI-I Scale	X	X	X	X	
PGI-I Scale	X	X	X	X	
Concomitant Medications/Procedures	X	X	X	X	X
AEs[n]	X	X	X	X	X
Adjust Opioid Treatment				X[o]	

AE=Adverse Events; BMI=Body Mass Index; CGI-I=Clinical Global Impression Improvement; C-SSRS=Columbia Suicide Severity Rating Scale; COWS=Clinical Opiate Withdrawal Scale; ECG=electrocardiogram; EQ-5D-5L=EuroQoL Group 5-dimenstion 5-level self-report questionnaire; ET=Early Termination; NRS-11=11-point numerical rating scale; PGI-I= Patient Global Impression of Improvement; q1w=once weekly; q4w=once monthly; SC=subcutaneous; SOWS=Subjective Opiate Withdrawal Scale; WPAI=Work Productivity and Activity Impairment.

[m] Since Last Visit' version to be used.

[n] Any spontaneously reported AEs will be recorded after the subject signs the ICF. In addition, AEs will be elicited using a non-leading question each time the subject visits the clinic.

[o] At the Final Study Visit (or ET) subjects will be transitioned back to standard care or their treatment prior to study entry.

Table 8a: Schedule of Assessments for Subjects Enrolled from the Randomized Double-Blind Phase to The Open Label Safety Extension Phase Weekly Dose

Study Phase	**Open Label Extension[a]**										**End of Study**	**Follow-Up Phase[b]**
Month	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**	**M14**	**M15**			
Study Treatment Week:	**W23[c]**	**27**	**31**	**35**	**39**	**43**	**47**	**51**	**55**	**All Other Weekly Treatment Visits[d]**	**EOT[e]**	**Up to 4 weeks after EOT**
Eligibility Criteria Review	X											
Physical Examination[f]											X	
Vital Signs[g]	X	X	X	X	X	X	X	X	X		X	
ECG	X[h]			X			X				X	
Clinical Laboratory Assessments	X			X			X				X	
Pregnancy Test[i]	X	X	X	X	X	X	X	X	X	X	X	
COWS/SOWS[j]	X	X	X	X	X	X	X	X	X		X	
CAM2038 q1w SC Injection[k]	X	X	X	X	X	X	X	X	X	X		
Injection Site Examination	X	X	X	X	X	X	X	X	X	X	X	

[a] Open Label Safety Extension Phase visit window is ±3 days for the CAM2038 q1w visit.
[b] Telephone contact only.
[c] Study treatment may vary depending on subject's titration schedule.
[d] This includes weeks 24, 25, 26, 28, 29, 30, 32, 33, 34, 36, 37, 38, 40, 41, 42, 44, 45, 46, 48, 49, 50, 52, 53, 54, 56, 57, 58, and 59.
[e] EOT is week 60 for weekly subjects.
[f] A complete physical examination of all major body systems (including height, weight, and BMI) will be performed.
[g] Includes body temperature, blood pressure, pulse rate, pulse oximetry and respiration rate and will be performed, prior to treatment during the monthly visit, and 1-hour post-study treatment (allowable window of 60-90 minutes).
[h] ECGs will be assessed quarterly prior to treatment
[i] A serum pregnancy test will be performed at the Final Study Visit/Early Termination. An "in-office" urine pregnancy test will be required weekly (for women of childbearing potential).
[j] COWS/SOWS will be assessed before dosing.
[k] Subjects who are receiving 4 mg, 8 mg or 12 mg CAM2038 q1w at enrollment into the Open Label Safety Extension Phase will return to the study site every week for administration of CAM2038 q1w throughout the Open Label Safety Extension Phase. Exact times when CAM2038 injection is administered must be recorded.

Study Phase	**Open Label Extension[a]**										**End of Study**	**Follow-Up Phase[b]**
Month	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**	**M14**	**M15**	**All Other Weekly Treatment Visits[d]**		
Study Treatment Week:	**W23[c]**	**27**	**31**	**35**	**39**	**43**	**47**	**52**	**56**		**EOT[e]**	**Up to 4 weeks after EOT**
Dispense, Collect, and Record Rescue Medications	X	X	X	X	X	X	X	X	X	X	X[l]	
Daily Electronic Diary Pain Rating (NRS- 11)	X	X	X	X	X	X	X	X	X	X	X	
Steady State PK Sampling[m]				X								
EQ5DL	X			X			X				X	
WPAI	X			X			X				X	
C-SSRS	X			X			X				X	
CGI-I Scale	X			X			X				X	
PGI-I Scale	X			X			X				X	
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X	X	X	X	X
AEs[n]	X	X	X	X	X	X	X	X	X	X	X	X
Adjust Opioid Treatment											X[o]	

[l] Rescue Medication will not be dispensed at this visit

[m] Blood samples will be collected prior to administration (within 45 minutes); and at approximately 2 hours, 6 hours, 24 hours, 72 hours, 168 hours, 336 hours, and 672 hours post administration to measure plasma levels of BPN and norBPN for subjects receiving both CAM2038 qlw and CAM2038 q4w treatments. Actual dates and times of dosing of IMP during the safety extension phase as well as blood sampling for PK measurement will be recorded.

[n] Any spontaneously reported AEs will be recorded after the subject signs the ICF. In addition, AEs will be elicited using a non-leading question each time the subject visits the clinic.

[o] At the Final Study Visit (or EOT) subjects will be transitioned back to standard care or their prior treatment.

Table 8b: Schedule of Assessments for Subjects Enrolled from the Randomized Double-Blind Phase to The Open Label Safety Extension Phase Monthly Dose

Study Phase	**Open Label Extension[a]**									**End of Study**	**Follow-Up Phase[b]**
Month	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**	**M14**	**M15**		
Study Treatment Week:	**W23-24[c]**	**27-28**	**31-32**	**35-36**	**39-40**	**43-44**	**47-48**	**51-52**	**55-56**	**EOT[d]**	**Up to 4 weeks after EOT**
Eligibility Criteria Review	X										
Physical Examination[e]										X	
Vital Signs[f]	X	X	X	X	X	X	X	X	X		
ECG	X[g]			X			X			X	
Clinical Laboratory Assessments	X			X			X			X	
Pregnancy Test[h]	X	X	X	X	X	X	X	X	X	X	
COWS/SOWS[i]	X	X	X	X	X	X	X	X	X	X	
CAM2038 q1w SC Injection[j]	X	X	X	X	X	X	X	X	X		
Injection Site Examination	X	X	X	X	X	X	X	X	X	X	
Dispense, Collect, and Record Rescue Medications	X	X	X	X	X	X	X	X	X	X[k]	
Study Phase	**Open Label Extension[a]**									**End of Study[d]**	**Follow-Up Phase[b]**

[a] Open Label Safety Extension Phase visit window is ±3 days for the CAM2038 q1w visit and ±7 days for the CAM2038 q4w visit.
[b] Telephone contact only.
[c] Study treatment may vary depending on subject's titration schedule. All subjects receive a weekly dose at week 23.
[d] EOT is 4 weeks after the last monthly injection.
[e] A complete physical examination of all major body systems (including height, weight, and BMI) will be performed.
[f] Includes body temperature, blood pressure, pulse rate, pulse oximetry and respiration rate and will be performed, prior to treatment during the monthly visit, and 1-hour post-study treatment (allowable window of 60-90 minutes).
[g] ECGs will be assessed every quarterly prior to treatment
[h] A serum pregnancy test will be performed at the Final Study Visit/Early Termination. An "in-office" urine pregnancy test will be required monthly (for women of childbearing potential).
[i] COWS/SOWS will be assessed before dosing.
[j]Subjects who are receiving 16, 24, or 32 mg CAM2038 at enrollment into the Open Label Treatment Phase will return to the study site every 4 weeks to be administered CAM2038 q4w (64, 96, or 128 mg) throughout the Open Label Safety Extension Phase. Exact times when CAM2038 injection is administered must be recorded.
[k] Rescue Medication will not be dispensed at this visit

Month	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**	**M14**	**M15**		
Study Treatment Week:	**W23-24[l]**	**27-28**	**31-32**	**35-36**	**39-40**	**43-44**	**47-48**	**51-52**	**55-56**	**EOT**	**Up to 4 weeks after EOT**
Daily Electronic Diary Pain Rating (NRS- 11)	X	X	X	X	X	X	X	X	X	X	
Steady State PK Sampling[m]				X							
EQ5DL	X			X			X			X	
WPAI	X			X			X			X	
C-SSRS	X			X			X			X	
CGI-I Scale	X			X			X			X	
PGI-I Scale	X			X			X			X	
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X	X	X	X
AEs[n]	X	X	X	X	X	X	X	X	X	X	X
Adjust Opioid Treatment										X[o]	

[l] Study treatment may vary depending on subject's titration schedule. All subjects receive a weekly dose at week 23.

[m] Blood samples will be collected prior to administration (within 45 minutes); and at approximately 2 hours, 6 hours, 24 hours, 72 hours, 168 hours, 336 hours, and 672 hours post administration to measure plasma levels of BPN and norBPN for subjects receiving both CAM2038 qlw and CAM2038 q4w treatments. Actual dates and times of dosing of IMP during the safety extension phase as well as blood sampling for PK measurement will be recorded.

[n] Any spontaneously reported AEs will be recorded after the subject signs the ICF. In addition, AEs will be elicited using a non-leading question each time the subject visits the clinic.

[o] At the Final Study Visit (or EOT) subjects will be transitioned back to standard care or their prior treatment.

Table 9: Schedule of Assessments for Screening, Transition, and Titration Phases for De Novo Subjects

Study Period/Phase:	Screening	Transition Phase[a]		Open-Label Titration Phase[b]									
Week:	W-2 to -1	W0		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10
Day:	D-14 to -1	D1 up to 12 days[c]	2 to 4 days										
Informed Consent[d]	X												
Eligibility Criteria Review	X			X[e]									
Demographic Data	X												
Medical and Medication History	X												
Physical Examination[f]	X												
Vital Signs[g]	X			X[h]	X	X	X	X	X	X	X	X	X
ECG	X			X[h]	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments	X			X[i]				X					
Pregnancy Test[j]	X			X		X		X		X		X	
Hepatitis B/C, HIV[k]	X												
Urine Drug Screen	X			X	X	X	X	X	X	X	X	X	X

[a] Subjects on BPN at screening will not participate in the down titration and morphine IR phases, but will washout and refrain from their BPN treatment for 12-24 hours prior to the test dose on Day 1.
[b] Titration Phase visit window is ±3 days.
[c] Telephone contact.
[d] Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.
[e] Prior to starting the Titration Phase, all Inclusion/Exclusion and other relevant criteria must be met.
[f] A complete physical examination of all major body systems (including height, weight, and BMI) will be performed.
[g] Includes body temperature, blood pressure, pulse rate, pulse oximetry and respiration rate.
[h] Vital signs and ECG will be measured 15 minutes (allowable window up to 60 minutes) before the Buprenex test dose, 15 minutes (allowable window of between 15-30 minutes) and 1 hour (allowable window of between 60-90 minutes) after the test dose, and 1 hour (allowable window of between 60-90 minutes) and 24 hours (allowable window of±3 hour) after the first CAM2038 q1w dose. Vital signs and ECG will thereafter be assessed weekly during the Titration Phase.
[i] An additional sample for assessment of electrolytes will be taken 4 weeks after the first dose of CAM2038 q1w. Refer to Table 11 for a list of laboratory analytes.
[j] A serum pregnancy test will be performed at Screening. An "in-office" urine pregnancy test will be required every other week during the Titration Phase. (for women of childbearing potential).
[k] It is the investigator's responsibility to understand and comply with the laws and regulations that apply to HIV, Hepatitis B, and Hepatitis C testing of blood samples. Hepatitis B/C and HIV testing is required unless the site's IRB prohibits such testing.

Study Period/Phase:	Screening	Transition Phase[a]		Open-Label Titration Phase[b]									
Week:	W-2 to -1	W0		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10
Day:	D-14 to -1	D1 up to 12 days[c]	2 to 4 days										
Dispense Treatment Identification Card				X									
Down-Titrate Opioid Dose		X											
IR Morphine[l]			X										
Buprenex Test Dose				X[m]									
COWS/SOWS				X[n]	X								
CAM2038 q1w SC Injection[o]				X	X	X	X	X	X	X	X	X	X
Injection Site Examination				X	X	X	X	X	X	X	X	X	X
Dispense, Collect, and Record Rescue Medications				X	X	X	X	X	X	X	X	X	X
Daily Diary Pain Rating (NRS-11)	X			X[p]	Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily	
EQ-5D-5L	X			X				X				X	
WPAI	X			X	X	X	X	X	X	X	X	X	
C-SSRS[q]	X			X		X		X		X		X	
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs[r]	X	X	X	X	X	X	X	X	X	X	X	X	X

[l] IR morphine (15 mg QID for subjects with screening MED of ≥80 mg/day; or 15 mg TID for subjects with screening MED between 40 mg and 79 mg/day) for at least 2 days prior to Day 1 of the Titration Phase. A 12-hour washout from the last IR morphine dose is required before the Buprenex test dose is given.

[m] One IM injection of 0.3 mg (1.0 mL) Buprenex.

[n] COWS/SOWS will be assessed before the test dose, 15 min (allowable window of between 15-30 minutes) after the test dose, and 24 hours (allowable window of ±3 hour) after the first 4 mg or 8 mg CAM2038 dose. If COWS score is not ≥5, the COWS can be repeated for up to 48 hours.

[o] The first dose of either 4 mg or 8 mg CAM2038 q1w will be administered within 4 hours (+30 minutes) after the test dose. During the first week of the Titration Phase, subjects who experience significant pain may, at the discretion of the investigator, receive an additional CAM2038 at their respective dose (4mg or 8 mg) on Day 3,4 or 5. Dose adjustments will be made by increasing or decreasing the dose level of CAM2038 q1w at the scheduled weekly visits (doses of 4 mg, 8 mg, 12 mg, 16 mg, 24 mg, or 32 mg per week). Subjects who require doses >32 mg/week will be discontinued from the study.

[p] Electronic diary dispensed after test dose.

[q] 'Screening' version at Screening and 'Since Last Visit' version every other week during the Titration Phase.

[r] Any spontaneously reported AEs will be recorded after the subject signs the ICF. In addition, AEs will be elicited using a non-leading question each time the subject visits the clinic.

Table 10a: Schedule of Assessments for De Novo Subjects Enrolled in Open Label Extension for Weekly Patients

Study Phase	**Open Label Treatment[a]**													**EOT[b]**	**Follow -up Phase**
Open Label Treatment Week:	**11**	**15**	**19**	**23**	**27**	**31**	**35**	**39**	**43**	**47**	**51**	**55**	**All Other Weekly Treatment Visits[c]**	**EOT**	**Up to 4 weeks after EOT**
Eligibility Criteria Review	X														
Physical Examination[d]														X	
Vital Signs[e]	X	X	X	X	X	X	X	X	X	X	X	X		X	
ECG	X[f]			X			X			X					
Clinical Laboratory Assessments	X			X			X			X				X	
Pregnancy Test[g]	X	X	X	X	X	X	X	X	X	X	X	X		X	
COWS/SOWS[h]	X	X	X	X	X	X	X	X	X	X	X	X		X	
CAM2038 SC Injection[i]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Injection Site Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense, Collect, and Record Rescue Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	

[a] Open Label Safety Extension Phase visit window is ±3 days for theCAM2038 q1w visit and ±7 days for the CAM2038 q4w visit

[b] Telephone contact within 4 weeks after EOT for AEs and Conmeds.

[c] This includes weeks 12, 13, 14, 16, 17, 18, 20, 21, 22, 24, 25, 26, 28, 29, 30, 32, 33, 34, 36, 37, 38, 40, 41, 42, 44, 45, 46, 48, 49, 50, 52, 53, 54, 55, 57, 58 and 59.

[d] A complete physical examination of all major body systems (including height, weight, and BMI) will be performed.

[e] Includes body temperature, blood pressure, pulse rate, pulse oximetry and respiration rate and will be performed prior to treatment at each monthly visit and 1hr post-study treatment (allowable window of between 60-90 minutes).

[f] ECGs will be assessed quarterly prior to treatment

[g] A serum pregnancy test will be performed at the Final Study Visit/Early Termination. An “in-office” urine pregnancy test will be required weekly (for women of childbearing potential).

[h] COWS/SOWS will be assessed before dosing.

[i] Subjects who are receiving 4 mg, 8 mg or 12 mg CAM2038 q1w at enrollment into the Open Label Safety Extension Phase will return to the study site every week for administration of CAM2038 q1w throughout the Open Label Safety Extension Phase. Exact times when CAM2038 injection is administered must be recorded

[j] Rescue Medication will not be dispensed at this visit

Study Phase	**Open Label Treatment[a]**													**EOT[b]**	**Follow -up Phase**
Open Label Treatment Week:	**11**	**15**	**19**	**23**	**27**	**31**	**35**	**39**	**43**	**47**	**51**	**55**	**All Other Weekly Treatment Visits[c]**	**EOT**	**Up to 4 weeks after EOT**
Daily Electronic Diary Pain Rating (NRS-11)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Steady State PK Sampling[k]				X[k]											
EQ5DL	X			X			X			X				X	
WPAI	X			X			X			X				X	
C-SSRS[l]	X			X			X			X				X	
CGI-I Scale	X			X			X			X				X	
PGI-I Scale	X			X			X			X				X	
Concomitant medications / Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust Opioid Treatment														X[n]	

[k] At week 23 or later, PK sample will be done. Blood samples will be collected prior to administration (within 45 minutes); and at approximately 2 hours, 6 hours, 24 hours, 72 hours, 168 hours, 336 hours, and 672 hours post administration to measure plasma levels of BPN and norBPN for subjects receiving both CAM2038 qlw and CAM2038 q4w treatments. Actual dates and times of dosing of IP during the safety extension phase as well as blood sampling for PK measurement will be recorded.

[l] 'Since Last Visit' version to be used.

[m] Any spontaneously reported AEs will be recorded after the subject signs the ICF. In addition, AEs will be elicited using a non-leading question each time the subject visits the clinic.

[n] At the Final Study Visit (or EOT) subjects will be transitioned back to standard care or their prior treatment prior to study entry

Table 10b: Schedule of Assessments for De Novo Subjects Enrolled in Open Label Extension for Monthly Patients

Study Phase	**Open Label Treatment[a]**												**EOT[b]**	**Follow-up Phase**
Open Label Treatment Week:	**11**	**15**	**19**	**23**	**27**	**31**	**35**	**39**	**43**	**47**	**51**	**55**	**EOT**	**Up to 4 Weeks after EOT**
Eligibility Criteria Review	X													
Physical Examination[c]													X	
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X[e]			X			X			X				
Clinical Laboratory Assessments	X			X			X			X			X	
Pregnancy Test[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	
COWS/SOWS[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	
CAM2038 SC Injection[h]	X	X	X	X	X	X	X	X	X	X	X	X		
Injection Site Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense, Collect, and Record Rescue Medications	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	
Daily Electronic Diary Pain Rating (NRS-11)	X	X	X	X	X	X	X	X	X	X	X	X	X	

[a] Open Label Safety Extension Phase visit window is ±3 days for the CAM2038 q1w visit and ±7 days for the CAM2038 q4w visit

[b] Telephone contact within 4 weeks after EOT for AEs and Conmeds.

[c] A complete physical examination of all major body systems (including height, weight, and BMI) will be performed.

[d] Includes body temperature, blood pressure, pulse rate, pulse oximetry and respiration rate and will be performed prior to treatment at each monthly visit and 1hr post-study treatment (allowable window of between 60-90 minutes).

[e] ECGs will be assessed quarterly prior to treatment

[f] A serum pregnancy test will be performed at the Final Study Visit/Early Termination. An "in-office" urine pregnancy test will be required monthly (for women of childbearing potential).

[g] COWS/SOWS will be assessed before dosing.

[h] Subjects who are receiving 16, 24, or 32 mg CAM2038 at enrollment into the Open Label Safety Extension Phase will return to the study site every 4 weeks to be administered CAM2038 q4w (64, 96, or 128 mg) throughout the Open Label Safety Extension Phase. Exact times when CAM2038 injection is administered must be recorded

[i] Rescue Medication will not be dispensed at this visit

Study Phase	**Open Label Treatment[a]**												**EOT[b]**	**Follow -up Phase**
Open Label Treatment Week:	**11**	**15**	**19**	**23**	**27**	**31**	**35**	**39**	**43**	**47**	**51**	**55**	**EOT**	**Up to 4 Weeks after EOT**
Steady State PK Sampling[j]				X[j]										
EQ5DL	X			X			X			X			X	
WPAI	X			X			X			X			X	
C-SSRS[k]	X			X			X			X			X	
CGI-I Scale	X			X			X			X			X	
PGI-I Scale	X			X			X			X			X	
Concomitant medications / Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust Opioid Treatment													X[m]	

[j] At week 23 or later but no later than 4 weeks prior to a subject's scheduled EOT visit, PK draws will begin. Blood samples will be collected prior to administration (within 45 minutes); and at approximately 2 hours, 6 hours, 24 hours, 72 hours, 168 hours, 336 hours, and 672 hours post administration to measure plasma levels of BPN and norBPN for subjects receiving both CAM2038 qlw and CAM2038 q4w treatments. Actual dates and times of dosing of IP during the safety extension phase as well as blood sampling for PK measurement will be recorded.

[k] 'Since Last Visit' version to be used

[l] Any spontaneously reported AEs will be recorded after the subject signs the ICF. In addition, AEs will be elicited using a non-leading question each time the subject visits the clinic.

[m] At the Final Study Visit (or EOT) subjects will be transitioned back to standard care or their prior treatment prior to study entry

9.1. Demographics and Other Baseline Characteristics

9.1.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the subject by the investigator or designated study personnel. The subject must voluntarily provide written informed consent on an ethics-approved informed consent form (ICF), prior to performing any study-related procedures. The subject's medical records must document that the consent process has been completed and that written informed consent has been obtained from the subject prior to the initiation of any study-specific procedures. Documentation that the subject was given adequate time to ask the investigator (or designee) questions about their participation in the study and that a signed and dated copy of the ICF was provided to the subject should also be included in the medical records or clinical chart.

9.1.2. Demographics

The following demographics will be recorded: age (birth date), sex, race, and ethnicity. A complete psychosocial history will be obtained including education, employment status, marital/significant other status, residential status, and legal status/arrest history.

9.1.3. Medical History

The complete medical history, up to the previous 5 years, will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems or are the source of the subjects' chronic pain. All findings on medical history will be evaluated by the investigator for clinical significance.

9.1.4. Medication History

All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) taken by the subjects during the 30 days prior to Screening will be recorded in the source documentation as medication history. A brief substance abuse history will also be collected.

9.1.5. Contraceptive Requirements

Female subjects of childbearing potential must be using and willing to continue using medically acceptable contraception during the study from Screening through study completion. Examples of medically acceptable forms of contraception:

- True abstinence (at the discretion of the investigator.
- Intrauterine device in place for at least 3 months.
- Non-surgical permanent sterilization (e.g., Essure procedure) at least 3 months prior to dosing.
- Barrier method (condom or diaphragm) with spermicide for at least 14 days before Screening and through study completion.
- Stable hormonal contraceptive use for at least 3 months prior to dosing and through study completion.

Female subjects of non-childbearing potential are not required to use contraception or undergo pregnancy

tests; however, they must have been surgically sterile (hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy, as determined by subject medical history) or congenitally sterile or must be post-menopausal. Post-menopausal is defined as being amenorrhoeic for at least 2 years without another cause or amenorrhoeic for at least 1 year without another cause and a documented follicle stimulating hormone level ≥50 mIU/mL.

9.2. Eligibility Review and Randomization

At the Screening Visit, the investigator or designee must document that the subject meets all inclusion and no exclusion criteria via a signed note or eligibility and clinical stability checklist. In addition, subjects must fulfill the criteria for entry into the Transition Phase, the Titration Phase, the Double-Blind Phase and the Open Label Safety Extension Phase. Randomization will be accomplished centrally using an Interactive Response Technology managed by the Sponsor.

9.3. Efficacy Assessments

Details regarding primary, secondary, and exploratory endpoints are provided in Section 9.6 and discussed further in Section 11.3 (Statistical Analysis). The following sections provide an overview of the efficacy assessments included in the study.

9.3.1. Numerical Rating Scale (NRS-11)

The NRS-11 is an 11-point scale with anchors at 0 (no pain) and 10 (worst pain imaginable). Subjects will record their API at Screening and test dose Day 1 on paper and their WPI and API scores over the past 24 hours daily in an electronic diary. Subjects should record their "pain at that moment" on their electronic diary immediately prior to taking rescue medication. Study personnel and subjects will undergo training on how to complete this assessment.

9.3.2. Rescue Medications

The number of rescue doses taken per day and proportion of days rescue medication was taken will be recorded using an electronic diary. Subjects will be instructed on the proper use and timing of rescue medication. Subject's pain intensity will be recorded in the electronic diary whenever the subject takes rescue medication.

9.3.3. EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ-5D-5L): Descriptive System

The EuroQoL Group 5-dimension 5-level self-report questionnaire (EQ-5D-5L) descriptive system is a generic, multidimensional, health-related, quality-of-life instrument. The profile allows participants to rate their health state in 5 health domains: mobility, self-care, usual activities, pain/discomfort, and mood using a 5-level scale. These combinations of attributes will be converted into a weighted health-state Index Score according to the United States population-based algorithm, with higher scores indicating better quality of life.

9.3.4. Work Productivity and Activity Impairment (WPAI)

The Work Productivity and Activity Impairment (WPAI) is a self-administered instrument used to measure the effect of general health and symptom severity on work productivity and regular activities, and yields 4 types of scores: Absenteeism (work time missed)=Question (Q)2/(Q2+4))*100);

Presenteeism (impairment at work/reduced on-the-job effectiveness)=(Q5/10)*100); Work Productivity Loss (overall work impairment/absenteeism plus presenteeism)=(Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)])*100); and Activity Impairment=(Q6/10)*100. Scores range from 0 to 1 for each of the above 4 types; higher scores indicate greater impairment.

9.3.5. Clinician Global Impression of Improvement (CGI-I) Scale

The Clinician Global Impression of Improvement (CGI-I) scale is a 7-point scale that requires the clinician to assess how much the subject's CLBP has improved or worsened relative to a baseline state at the beginning of the intervention and rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse (Guy, 1976).

9.3.6. Patient Global Impression of Improvement (PGI-I) Scale

The Patient Global Impression of Improvement (PGI-I) scale is a 7-point scale that requires the subject to assess how much the his/her CLBP has improved or worsened relative to a baseline state at the beginning of the intervention and rated as: 1, much worse; 2, worse; 3, a little worse; 4, no change; 5, a little better; 6, better; or 7, much better.

9.4. Pharmacokinetic assessments

Venous blood samples (6 mL each) will be collected, as indicated in Tables 8 and 10. Samples will be collected, processed, and shipped according to instructions provided in the Study MOP. The actual date and time of each blood sample collection will be recorded.

The plasma concentrations of BPN and norBPN will be summarized descriptively. PK parameters of BPN will be evaluated and reported separately.

9.5. Safety Assessments

Safety monitoring will be performed throughout the study for all subjects. All AEs, regardless of causality or severity, will be recorded on the AE case report form (CRF). CAM2038/placebo injections may be discontinued as clinically indicated.

Opioid-naïve subjects will not be permitted into this study, as the study drug is very potent and the doses for this study have been selected for opioid-experienced subjects. Opioid-experienced subjects are defined as taking ≥40 mg/day of oral morphine or MED, including ATC and rescue medication, for the management of their CLBP for the 14 days prior to Screening.

9.5.1. Adverse Events and Serious Adverse Events

The following definitions, developed in accordance with the US Code of Federal Regulations (CFR) and the International Council for Harmonization (ICH) Clinical Safety Data Management Guidance for Industry, E2A, will be used for the purpose of identifying AEs in this clinical study.

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered

problems, complaints, or symptoms, are to be recorded on the appropriate CRF.

AEs, will be monitored and documented from the time of informed consent until the final Follow-up. AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization. Subjects should be instructed to report any AE that they experience to the investigator. Investigators should make an assessment of AEs at each visit and record the event on the appropriate AE CRF.

Wherever possible, a specific disease or syndrome, rather than individual associated signs and symptoms, should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the CRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure.

Any medical condition already present at Screening should not be reported as an AE, unless the medical condition or signs or symptoms present at Screening changes in severity or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as AEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

9.5.2. Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

9.5.3. Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

9.5.4. Assessment of Adverse Events by the Investigator

The investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of related, possibly related, or not related.

Assessment of Severity:

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality Assessment:
The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Possibly related – An event that follows a reasonable temporal sequence from administration of the study drug, but that may be due to another cause and could also be reasonably explained by the subject's clinical state or other modes of therapy administered to the subject.

Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-
    - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
    - Each report should be evaluated in the context of the natural history and course of the CLBP being treated and any other disease the subject may have.
- Concomitant drug-
- The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug-
    - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
    - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug-
    - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

9.5.5. Serious Adverse Event

An AE or adverse reaction is considered serious if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
    - NOTE: An AE or adverse reaction is considered "life-threatening" if, in view of the

investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalization
    - NOTE: Any hospital admission with at least one overnight stay will be consideredan inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the abilityto conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event

NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed 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 hospitalizations, or the development of drug dependency.

All AEs requiring hospitalization or prolongation of a pre-existing hospitalization should be reported as SAEs, unless they occur after the final Follow-up or 30 days after early termination AND are not considered to be drug-related by the investigator.

Hospitalizations meeting the following criteria will not be reported as an SAE but must be recorded on the appropriate CRF: study specified hospitalization, short-term administrative hospitalization for procedures, tests or treatments of conditions that would not otherwise constitute an SAE, or elective hospitalizations.

9.5.6. Serious Adverse Event Reporting – Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent through Follow-up (or 30 days following early termination) must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). Serious AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at MedPace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE hotline – USA:
Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Facsimile: +1-866-336-5320 or +1-513-579-0444
e-mail: medpace-safetynotification@medpace.com

Follow-Up Reports

The investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

9.5.7. Pregnancy

If the subject becomes pregnant during the study or within 30 days of discontinuing study drug, the investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure In Utero form to the investigator for completion.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The subject should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

9.5.8. Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the FDA, and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA as soon as possible, but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all investigators as required.

9.5.9. Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood and urine samples will be performed at a selected central laboratory, with the exception of urine pregnancy tests that are conducted at the study site. The central laboratory will generate laboratory reports and forward them to the clinical site in a timely manner. It is the responsibility of the investigator to review and sign all laboratory reports expeditiously, in order to document appropriate safety monitoring of study subjects. The investigator should sign and date each laboratory report concurrent with her or his review and should indicate the clinical significance of each abnormal/flagged value by noting “NCS” (not

clinically significant) or "CS" (clinically significant), for example. Notations indicating that a value is clinically significant should also include a brief description of the underlying disease or condition that is associated with the value, e.g., "CS/mild anemia." In general, abnormal, clinically significant laboratory values are expected to be associated with an item recorded in medical history or with an AE.

Blood and urine samples will be collected, processed, and shipped according to instructions from the safety laboratory. Additional laboratory samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety. Specific hematology, coagulation, biochemistry, and urinalysis assessments are listed in Table 11.

Table 11: Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell count Red blood cell morphology Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Total and differential (absolute) white blood cell count Platelets	Sodium Potassium Magnesium Calcium Glucose (random) Bicarbonate Chloride Creatinine Total protein Blood urea nitrogen Albumin Total bilirubin Alanine transferase Aspartate transferase Lactic dehydrogenase Amylase Lipase Gamma-glutamyl transferase Alkaline phosphatase Creatinine phosphokinase Total cholesterol (non-fasting)	Color pH Specific gravity Ketones Protein Glucose Bilirubin Nitrite Urobilinogen Occult blood Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*
Coagulation		
Prothrombin time, International normalized ratio		

In addition to the clinical laboratory tests, a serum pregnancy test will be performed at the Screening Visit and the Final Study Visit/Early Termination for women of childbearing potential. An "in-office" urine pregnancy test will be required every other week during the Titration Phase and weekly/monthly during the Double-Blind Phase (for women of childbearing potential).

A blood sample for a serology panel testing for hepatitis B surface antigen, hepatitis C RNA, and HIV will be performed for all subjects, unless a site's IRB prohibits such testing. It is the investigator's responsibility to understand and comply with all laws and regulations that apply to the testing of blood for HIV and hepatitis B and C. These laws and regulations may include state laws related to written consent, separate from the ICF for this study, and pre- and post-test counseling.

The total blood volume to be taken per subject will be approximately 75 mL, as each blood collection will be approximately 15 mL.

Every attempt should be made to collect samples for a urine toxicology test and BPN blood concentration if a subject experience an SAE or is discontinued from the study due to an AE.

9.5.10. Vital Signs

Vital signs will consist of temperature, blood pressure (systolic and diastolic blood pressure, mmHg), pulse rate (beats per minute), pulse oximetry and respiratory rate (breaths/min) collected while sitting, following a rest period of at least 3 minutes.

9.5.11. 12-Lead Electrocardiogram (ECG)

12-lead ECGs will be performed after the subject has been resting in a recumbent/supine position for at least 3 minutes. The ECG variables will include ventricular heart rate and the PR, QRS, QT, and QTcF intervals. The ECGs will be signed and dated by a medically-qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant. In general, abnormal, clinically significant ECGs are expected to be associated with an item recorded in the medical history or with an AE. ECGs will be performed at the Screening Visit, 15 minutes before and 15 minutes and 1 hour after the Buprenex test dose, 1 and 24 hours, ± 3 hours, after the first CAM2038 q1w dose and then weekly during the Titration Phase Double-Blind Phase. For q1w subjects, ECGs will be performed monthly during the Double-Blind Phase. For q4w subjects, ECGs will be performed at 6-10 hours (tmax) after the first CAM2038/placebo q4w injection in the Double-Blind Phase, then monthly thereafter, quarterly in the Open Label Safety Extension, and at the Final Study Visit/Early Termination.

Male subjects who have a QTcF >450 ms or post-baseline increases ≥60 ms and female subjects who have a QTcF >470 ms or post-baseline increases ≥60 ms will be monitored closely with repeated ECGs until their ECGs return to baseline. Any subjects with QTcF ≥500 ms will have their dose withheld and repeat ECGs until their ECG values return to baseline. In some cases, the subject will need to be discontinued from the study and will not receive any more injections of CAM2038/placebo. The investigator can refer the subject to a cardiologist, if necessary.

9.5.12. Physical Examination

A complete physical examination, including all major body systems (and height, weight, and BMI) will be performed at Screening and at the Final Study Visit/Early Termination.

9.5.13. Injection Site Examination

CAM2038 or placebo injection sites will be examined during each scheduled visit for any signs of adverse site reactions, including erythema, pruritus, edema, pain, etc. The pain scale will be completed by the subjects within 10 minutes after each injection. The new injection site will also be examined within 15 minutes after each injection to determine if any site related AEs have occurred. Additionally, the previous injection site will be examined in the similar fashion as the current injection site. Subjects will also be queried specifically about local tolerability AEs in connection to the examinations. Injection site

examination can only be performed by the blinded site personnel. If an injection site reaction is observed, non-identifying pictures of the injection site, accompanied by a ruler adjacent to the injection site, will be taken and placed in the subject's files.

9.5.14. Treatment Identification Card

Subjects will receive a wallet card indicating that they are receiving BPN as part of the study. This card should be presented to health care providers by the subject in the event of an emergency or if medications such as opioid analgesics are required. Sample wallet cards will be provided for IRB submission.

9.5.15. Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used to assess both behavior and ideation that tracks all suicidal events and provides a summary of suicidal ideation and behavior. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation, and deterrents), all of which are significantly predictive of completed suicide.

Two versions of the C-SSRS will be used in this study: the Screening version (6 months and lifetime history) and the Since Last Visit version. The Screening version of the C-SSRS will be administered at Screening. The Since Last Visit version of the C-SSRS will be administered at all subsequent assessment times.

The C-SSRS is to be administered by the investigator or his/her qualified designee at every visit as indicated in the Schedule of Assessments. Note: Qualified designee is defined as an individual who has completed the C-SSRS training within the last 2 years. The survey should be administered by the same assessor, where possible, throughout the study.

9.5.16. Urine Drug Screen

A 12-panel urine drug screen will test for the following drugs of abuse: tetrahydrocannabinol/marijuana, cocaine, phencyclidine, morphine, methamphetamines, methadone, amphetamines, barbiturates, benzodiazepines, methylenedioxymethamphetamine, oxycodone and tricyclic antidepressants.

9.5.17. Clinical Opiate Withdrawal Scale (COWS)

The study personnel will assess clinical observations indicative of withdrawal using the COWS. This scale consists of 11 common opiate withdrawal signs or symptoms, rated on a numeric scale and based on a timed period of observation of the subject by the rater.

9.5.18. Subjective Opiate Withdrawal Scale (SOWS)

Subjects will complete a self-assessment of withdrawal symptoms using the Subjective Opiate Withdrawal Scale (SOWS). This form contains 16 questions that rate the intensity of withdrawal from 0 ("Not at all") to 4 ("Extremely").

9.5.19. Other Safety Considerations

BPN may impair the mental and physical abilities required for performance of potentially dangerous tasks. Subjects will be instructed to avoid operating heavy machinery during induction and to exercise caution in performing activities requiring alertness, such as driving a car during the first few days after

the beginning of the clinical trial or until such time that they are reasonably certain that their ability to engage in such activities is not adversely affected.

9.6. Efficacy and Safety Variables

9.6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in WAAPI and the primary timepoint will be Week 12 of the Double-Blind Phase.

9.6.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Change from baseline in the WAWPI scores at Week 12 of the Double- Blind Phase, based on an NRS-11.
- Percentage of subjects with a 30% or greater decrease in API from baseline to Week 12 ofthe Double-Blind Phase.
- Rescue medication usage (number of days used and total dose) during the Double-Blind Phase.
- Change from baseline to Week 12 of the Double-Blind Phase in EQ-5D-5L score.
- Change from baseline to Week 12 of the Double-Blind Phase in Work Productivity and WPAI score.
- Time to loss of efficacy, defined as discontinuation of study drug for lack of efficacy.

9.6.3. Safety Endpoints

The safety endpoint are as follows:

- Occurrence of AEs throughout the study.
- Concomitant medication usage throughout the study.

9.6.4. Exploratory Endpoints

The safety endpoint are as follows:

- Change from baseline to Week 12 of the Double-Blind Phase in Clinical Global Impression of Improvement (CGI-I) scale (as assessed by the Investigator).
- Change from baseline to Week 12 of the Double-Blind Phase in Patient Global Impression of Improvement (PGI-I) scale (as assessed by the subject

10. DATA QUALITY ASSURANCE

This study will be conducted under Good Clinical Practice (GCP) and all applicable regulatory requirements. To ensure compliance, the Sponsor or designee may conduct a quality assurance audit, as outlined in Section 10.2.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigator s and appropriate study centers; the review of protocol procedures with the investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use (where applicable); the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as periodic site monitoring by the Sponsor. The Sponsor or designee will review source documents for accuracy and completeness during on-site monitoring visits and after their return to the Sponsor; any discrepancies will be resolved with the investigator, as appropriate.

Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigational site termination and regulatory authority notification.

10.1. Data Collection

Source documents include, but are not limited to, original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, participant diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records. This study will use an EDC system. At a minimum, all data required by the protocol should have supporting source documentation for entries in the EDC system.

All CRFs will be completed by the site staff prior to review by the Sponsor's monitor or designated representative. The Sponsor's monitor or designated representative will review all source records on-site and compare them to the data collected on the CRF. All entries, corrections, and alterations will be made by the investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The EDC system maintains a full audit trail.

10.2. Study Auditing and Monitoring

Monitoring of the study site (including, but not limited to, reviewing CRFs for accuracy and completeness) will be performed by the Sponsor's designated monitor(s). The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. By signing the protocol, the investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority and/or an IRB may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, participant charts, and source documents, as well as other records related to study conduct. The purpose of the Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether the study-related activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, the site's standard operating procedures, GCP guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

11. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

11.1. Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan (SAP), which will be completed prior to unblinding of the study data from the core study. This document will include more detail of analysis populations, summary strategies, and any amendments to the proposed analyses listed here, if necessary. A separate SAP will describe the analyses to be performed for the Open Label Safety Extension Phase. Any changes to the SAP will be outlined in the final study report.

11.2. Analysis Populations

Four analysis populations will be considered for the randomized Double-Blind Phase of the study:

- **Randomized Population:** The Randomized Population will consist of all subjects who have been assigned random treatment.
- **Intent-to-Treat (ITT) Population:** The ITT Population will include all randomized subjects. The primary efficacy analyses will be based on the ITT Population.
- **Safety Population:** The Safety Population will include all subjects who have received any study medication (CAM2038). Analysis based on this population will group subjects according to the treatment they actually received, regardless of the treatment they were randomized to receive. All safety analyses will be based on the Safety Population.
- **Per-Protocol Population:** The Per-Protocol Population will include all ITT subjects with no major protocol violations. Major protocol violation criteria will be established prior to the database lock and included in the protocol deviation plan. Protocol deviations will be presented in the clinical study report. Efficacy analyses may also be performed based on the per protocol population.

Analysis populations for the Open Label Safety Extension Phase will include:

- **Intent-to-Treat (ITT) Population:** The ITT Population will include all subjects enrolled into the Open Label Safety Extension. Efficacy analyses will be based on the ITT Population.
- **Safety Population:** The Safety Population will include all subjects who have received any study drug. All safety analyses will be based on the Safety Population.
- **Per-Protocol Population:** The Per-Protocol Population will include all ITT subjects without major protocol violations. Major protocol violation criteria will be established prior to the database lock.
- **PK population:** The PK population will include all subjects who have received CAM2038 in the treatment phase and from whom at least 1 measurable plasma concentration is obtained.

Planned analyses for the Open Label Extension will be detailed in the SAP which will be finalized prior to Database Lock.

11.3. Planned Analyses

11.3.1. Demographics and Baseline Characteristics

A summary of demographics and baseline characteristics will be presented by treatment arm and overall for the ITT, Safety and PK Populations.

Demographic data and baseline clinical characteristics will be summarized.

Tabular summaries and/or listings will be provided for baseline clinical characteristics, such as BMI, type of primary opioid use (e.g., prescription opioid pain relievers, other), medical history, inclusion/exclusion criteria, and medication history.

11.3.2. Primary Efficacy Analysis

The primary analysis will be performed based on the ITT population. The primary efficacy endpoint is the change from baseline in WAAPI and the primary timepoint will be Week 12 of the Double-Blind Phase.

11.3.3. Missing Value Imputation

Unless otherwise stated, all other missing values will not be imputed.

11.3.4. Sensitivity Analysis

Additional sensitivity analyses may be performed as appropriate.

11.3.5. Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- Change from baseline in the WAWPI scores at Week 12 of the Double-Blind Phase based on an NRS-11.
- Percentage of subjects with a 30% or greater decrease in API from baseline to Week 12 of the Double-Blind Phase.
- Rescue medication usage (number of days used and total dose) during the Double-Blind Phase.
- Change from baseline to Week 12 of the Double-Blind Phase in EQ-5D-5L score.
- Change from baseline to Week 12 of the Double-Blind Phase in WPAI score.
- Time to loss of efficacy, defined as discontinuation of study drug for lack of efficacy.

Change from Baseline in Weekly Average of Daily Worst Pain Intensity (WAWPI) over Time

This variable will be analyzed via methods similar to those used to analyze the primary efficacy variable.

Use of Rescue Medication

Percentage of days in the study that rescue medication is used will be calculated for both treatment groups. This variable will be analyzed via an analysis of variance model with treatment effects. The estimated treatment effects, treatment difference and the two-sided 95% CI of the treatment difference will be presented.

Percent of subjects who used rescue medication will also be calculated for both treatment groups. This variable will be analyzed using the Chi-square test. The percentages, the difference of the percentages, and

the two-sided 95% CI of the treatment difference will be presented. The 95% CIs of the treatment difference will be calculated using normal approximation.

Change from Baseline to Week 12 of the Double-Blind Phase in EQ-5D-5L score

This variable will be analyzed via methods similar to those used to analyze the primary efficacy variable.

Change from Baseline to Week 12 of the Double-Blind Phase in WPAI score

This variable will be analyzed via methods similar to those used to analyze the primary efficacy variable.

Time to Loss of Efficacy

Time to loss of efficacy is defined as discontinuation of study drug for lack of efficacy. Time to loss of efficacy will be analyzed via log-rank model with treatment effects. Time to event "survival" curves will be presented using the Kaplan-Meier method. Median time to event and the 95% CI of the median times will be presented, if estimable. In this time to event analyses, subjects who discontinue the study due to any reason other than "lack of efficacy" will be censored at the time they discontinued and subjects who completed the study will be censored at the time they completed the study.

11.3.6. Analysis of Pharmacokinetics

Plasma concentration data of BPN and norbuprenorphine (norBPN) will be listed for the PK Population by analyte, subject and actual time after last dose. Concentrations below the lower limit of quantification (BLQ) will be indicated by BLQ<0.0125 for BPN and BLQ<0.0200 for norBPN in the listings. Individual BPN and norBPN plasma concentration-time data will be displayed graphically on linear and semi-logarithmic scales by analyte and dose.

Plasma concentrations of BPN and norBPN will be summarized descriptively (n, arithmetic mean, standard deviation [SD], geometric mean, geometric CV%, minimum, median and maximum) for the PK Population by analyte, dose and scheduled time after last dose. Mean plasma concentration-time data will be displayed graphically on linear and semi-logarithmic scales by analyte.

Trough concentration during a dosage interval at steady state ($C_{ss,trough}$) of BPN and norBPN will be summarized (n, arithmetic mean, standard deviation [SD], geometric mean, geometric CV%, minimum, median and maximum) for the PK Population by analyte, dose and scheduled time after last dose.

Model predicted PK parameters of BPN will be evaluated by population PK modeling and reported separately.

11.3.7. Analysis of Safety

Exposure will be summarized by treatment group.

AEs will be coded by primary system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities and summarized by number and percent of subjects in each primary SOC and preferred term. Summaries of these AE subsets will be presented for relationship to study drug, intensity, seriousness, AEs or SAEs leading to discontinuation, and AEs occurring in 5% or greater of any treatment group (by preferred term). Frequencies for deaths and hospitalizations will also be summarized

by treatment group and overall.

Data for clinical laboratory tests, ECG, COWS/SOWS, vital signs, injection site reactions, and physical examinations will be summarized using standard descriptive and change from baseline statistics. Shift tables and tabular summaries of abnormalities will be provided, where appropriate.

Medications will be coded using the WHO Drug Dictionary and summarized using descriptive statistics.

By-subject listings will be provided for all safety data.

11.4. Determination of Sample Size

It is estimated that 170 subjects per treatment group will provide 90% power with a 2-sided test at a 5% significance level and standard deviation of API at Week 12 of 2.0 to detect a treatment effect of 0.7 unit (or a standardized effect of 0.35) in change from baseline in the WAAPI scores at Week 12 (Double-Blind Phase). Considering a titration success rate of 60%, this study will enroll approximately 875 subjects to obtain 340 subjects achieving a successful dose in order to be randomly assigned to study drug treatment in the Double-Blind Phase.

Additional statistical details will be outlined in the SAP.

12. STUDY ADMINISTRATION AND INVESTIGATOR RESPONSIBILITIES

12.1. Regulatory and Ethical Considerations

12.1.1. Ethical Conduct of the Study

The investigator will conduct the study in accordance with GCP and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the Sponsor's representatives and/or regulatory authority's representatives at any time.

12.1.2. Ethics Approval

The investigational site's IRB must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB prior to enrolling participants into the study. Written approval from the committee must be received by the Sponsor before drug will be released to the investigator. The investigator is responsible for submitting all protocol or ICF changes and SAE reports to the IRB according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

In accordance with applicable local regulatory requirements, the investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her research site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the Sponsor. The Sponsor will be provided with copies of all notifications sent to the IRB.

All relevant correspondence from the IRB will be forwarded by the respective study site to the Sponsor in a timely fashion.

12.1.3. Subject Informed Consent

The investigator (or authorized designee) will ensure that the participant is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject will receive an IRB-approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided in a language understandable to the participant and must not include any language that waives the participant's legal rights.
Prospective participants must also be informed of their right to withdraw consent without prejudice at any time during the study. If the participant chooses to participate, he/she must sign the ICF before any study-related procedures are performed.

Significant changes to the protocol or product safety information may require a revision of the ICF, which must be reviewed and signed by all applicable study participants.

The time that informed consent is obtained must be documented. The investigator must maintain the original, signed ICF in the participant's source documents. A copy of the signed ICF must be given to the study participant.

12.2. Privacy and Confidentiality

The investigator is responsible for complying with applicable privacy regulations, per his or her jurisdiction. Only information identified in this protocol will be collected. The information collected will only be used for the purposes identified in this protocol.

To ensure anonymity and to limit disclosure, participants will be assigned a unique identifier at their first assessment. This identifier will be cross-referenced in the participant's chart. The identifier will not contain any potentially identifiable information. An identifier log will be maintained, linking each participant's name to the corresponding identifier. This log will be stored at the research site in a secure location.

The knowledge gained through this study is the property of the Sponsor. The Sponsor, representatives and affiliated companies of the Sponsor, the IRB, and regulatory agencies (such as the US FDA) may inspect medical records related to the study to check the validity and accuracy of the data gathered in this study. Participant medical records (with participant's initials and/or date of birth) may be copied. Confidentiality of participant records will be maintained except where release of information is required by law.

The results of this study will be reported in such a manner that participants will not be identifiable in any way. Published reports or presentations will refer to grouped data or coded individual data and not to any identifiable individuals. Study reports sent to the Sponsor or drug regulatory agencies will not include participant names.

By signing the ICF, the participant consents to the collection, access, use, and disclosure of his or her information as described in the ICF document. If a participant withdraws consent, some of the subject's information may still be collected, used, and disclosed by those involved in this study, per applicable laws.

By signing this protocol, the investigator affirms that he or she will maintain in confidence information furnished to him or her by the Sponsor and will divulge such information to his or her respective IRB under an appropriate understanding of confidentiality with such board. All data will be

considered the sole property of the Sponsor. Please refer to the Clinical Study Agreement (CSA) for details.

12.3. Study and Site Closure

Upon completion of the study, all study data will be provided to the Sponsor following review of site study records for completeness, and data clarifications and resolutions. Accounting, reconciliation, and final disposition of used and unused study drugs, treatment codes, and emergency code break envelopes will be performed, as applicable.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the Sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. The Sponsor will promptly inform any other investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons and will inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator will inform the IRB promptly and provide the study participants with the reason for the suspension or termination. If the study is prematurely discontinued, all study data will be returned to the Sponsor.

12.4. Regulatory Documents and Records Retention

The investigator is responsible for creating and/or maintaining all study documentation required by 21 CFR 50, 54, 56 and 312, ICH E6 section 8, as well as any other documentation defined in the protocol or CSA. The investigator must provide key documents to the Sponsor prior to the start of the study. A complete list of required regulatory documents will be supplied by the Sponsor or its representative.

Federal and local regulations require that the investigator retain a copy of all regulatory documents and records that support the data for this study for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.

The Sponsor will notify investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by the Sponsor that the entire clinical investigation (not merely the investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application/Clinical Trial Authorization or request for marketing approval (New Drug Application/Marketing Authorization Application).

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the Sponsor.

12.5. Delegation of Responsibilities and Adequate Resources

The investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study.

The term "investigator" used throughout this protocol refers to the principal investigator and/or qualified sub-investigators. However, the investigator may delegate responsibilities to other investigational site personnel. The investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The investigator is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the investigational site.

12.6. Protocol Amendments

Approval of a protocol amendment by the investigator's IRB must be obtained before implementation of the protocol amendment, unless a change is necessary to eliminate an apparent immediate hazard to the participant or when the change involves logistical or administrative aspects of the study. The protocol amendment must be signed and dated by both the Sponsor and the investigator. The Sponsor or designee will submit protocol amendments to the appropriate regulatory authorities, if required.

12.7. Financial Disclosure

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR § 54.2, a Clinical investigator is a listed or identified investigator or Sub-investigator who is directly involved in the treatment or evaluation of research participants. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

13. SPONSOR APPROVAL PAGE

APhase III, Randomized, Double-Blind, Placebo-Controlled, Enriched-Enrollment Withdrawal, Multicenter Study to Evaluate the Efficacy and Safety of a Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Subjects with Moderate to Severe Chronic Low Back Pain Currently Treated with Daily Opioids

Protocol: Amendment 9 / Version 10.0

Date: 12-Apr-2018

Braeburn Pharmaceuticals

Sponsor
Representative

(please print or type)

Sponsor Representative Signature

Date (DD-MMM-YYYY)

14. INVESTIGATOR PROTOCOL AGREEMENT PAGE

APhase III, Randomized, Double-Blind, Placebo-Controlled, Enriched-Enrollment Withdrawal, Multicenter Study to Evaluate the Efficacy and Safety of a Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Subjects with Moderate to Severe Chronic Low Back Pain Currently Treated with Daily Opioids

Protocol: Amendment 9 / Version 10.0

Date: 12-Apr-2018

Braeburn Pharmaceuticals

I have read this protocol and I agree to conduct the study in accordance with the protocol and with all applicable government regulations and International Conference on Harmonization/Good Clinical Practice guidance's.

Principal Investigator's Name

_____

(please print or type)

_____ _____

Principal Investigator's Signature Date (DD-MMM-YYYY)

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16. APPENDICES

Appendix 1: Agents Associated with Potential QTcF Interval Prolongation

Generic Name	Brand Name (Partial List)	Drug Class
Alfuzosin	Uroxatral®	Alpha1-blocker antiviral
Amantadine	Symmetrel®, Symadine®	Antiviral
Amiodarone	Cordarone®, Pacerone®, Nexterone®, Elavil®, Tryptomer®, Tryptizol®, Laroyxl®, Saroten®, Sarotex®	Antiarrhythmic
Amitriptyline	Lentizol®, Endep®	Antidepressant, tricyclic
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor
Apomorphine	Apokyn®, Ixense®, Spontane®, Uprima®	Dopamine agonist
Aripriprazole	Abilify®, Aripiprex®	Antipsychotic, atypical
Arsenic trioxide	Trisenox®	Anticancer
Artenimol+piperaquine	Eurartesim®	Antimalarial
Atazanavir	Reyataz®	Antiviral
Atomoxetine	Strattera®	Norepinephrine reuptake inhibitor
Azithromycin	Zithromax®, Zmax®	Antibiotic
Bedaquiline	Sirturo®	Proteasome inhibitor
Bortezomib	Velcade®, Bortecad®	Tyrosine kinase inhibitor
Bosutinib	Bosulif®	Kinase inhibitor
Certinib	Zykadia®	Sedative
Chloral hydrate	Aquachloral®, Novo-chlorhydrate®, Somnos®, Noctec®, Somnote®	Antimalarial
Chloroquine	Aralen®	Antipsychotic/Antiemetic
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Phosphodiesterase 3 inhibitor
Cilostazol	Pletal®	Vasodilator

Generic Name	Brand Name (Partial List)	Drug Class
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic
Citalopram	Celexa®, Cipramil®	Antidepressant, selective serotonin reuptake inhibitor (SSRI)
Clarithromycin	Biaxin®, Prevpac®	Antibiotic
Clomipramine	Anafranil®	Antidepressant, tricyclic
Clozapine	Clozaril®, Fazaclo®, Versacloz®	Antipsychotic, atypical
Cocaine	Cocaine	Local anesthetic
Crizotinib	Xalkori®	Kinase inhibitor
Dabrafenib	Tafinlar®	Kinase inhibitor
Dasatinib	Sprycel®	Tyrosine kinase inhibitor
Degarelix	Firmagon®	Gonadotropin releasing hormone agonist/antagonist
Desipramine	Pertofrane®, Norpramine®	Antidepressant, tricyclic
Dexmedetomidine	Precedex®, Dexdor®, Dexdomitor®	Sedative
Diphenhydramine	Benadryl®, Nytol®, Unisom®, Sominex®, Dimedrol®, Daedalon®	Antihistamine
Disopyramide	Norpace®	Antiarrhythmic
Dofetilide	Tikosyn®	Antiarrhythmic
Dolasetron	Anzemet®	Antiemetic
Donepezil	Aricept®	Cholinesterase inhibitor
Doxepin	Sinequan®, Silenor®, Aponal®, Adapine®, Doxal®, Deptran®, Sinquan®	Antidepressant, tricyclic
Dronedarone	Multaq®	Antiarrhythmic
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Antipsychotic/Antiemetic
Eribulin mesylate	Halaven®	Microtubule inhibitor

Generic Name	Brand Name (Partial List)	Drug Class
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	Antibiotic
Escitalopram	Lexapro, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)	SSRI
Famotidine	Pepcid®, Fluxid®, Quamatel®	H2-receptor antagonist
Felbamate	Felbatol®	Anticonvulsant
Fingolimod	Gilenya®	Sphingosine phospate receptor modulator
Flecainide	Flecaine®	Antiarrhythmic
Fluconazole	Diflucan®, Trican®	Antifungal
Fluoxetine	Prozac, Sarafem, Fontex®	Antidepressant SSRI
Foscarnet	Foscavir®	Antiviral
Furosemide	Lasix®, Fusid®, Frumex®	Diuretic
Galantamine	Reminyl®, Nivolin®, Razodyne-ER®	Cholinesterase inhibitor
Gemifloxacin	Factive®	Antibiotic
Granisetron	Kytril®, Sancuso®, Granisol®	Antiemetic
Halofantrine	Halfan®	Antimalarial
Haloperidol	Haldol®, Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol®, Einalon S®, Eukystol®, Halosten®, Keselan®,	Antipsychotic

Generic Name	Brand Name (Partial List)	Drug Class
	Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	
Hydrochlorothiazide	Apo-Hydro®, Aquazide H®, BP Zide®, Dichloride®, Hydrodiuril®, HydroSaluric®, Hydrochlorol®, Microzide®, Esidrex®, Oretic®	Diuretic
Hydroxychloroquine	Plaquenil®, Quineprox®	Antimalarial/Anti-inflammatory
Hydroxzine	Atarax®, Visaril®, Aterax®, Alamon®, Durrax®, Equipose®, Masmoran®, Orgatrax®, Paxistil®, Quiess®, Tran-Q®, Tranquizine®	Antihistamine
Ibutilide	Corvert®	Antiarrhythmic
Iloperidone	Fanapt®, Fanapta®, Zomaril®	Antipsychotic, atypical
Imipramine	Tiofranil®	Antidepressant, tricyclic
Indapamide	Lozol®, Natrilix®, Insig®	Diuretic
Isradipine	Dynacirc®	Antihypertensive
Itraconazole	Sporanox®, Onmel®	Antifungal
Ketoconazole	Nizoral®, Sebizole®, Ketomed®, Keton®	Kinase inhibitor
Lapatinib	Tykerb®, Tyverb®	Tyrosine kinase inhibitor/Antineoplastic agent
Leuprolide	Lupron®, Eligard®, Viadur®, Carcinil®, Enanton®, Leuplin®, Lucrin®, Procren®, Prostap® and others	Gonadotropin receptor agonist/antagonist
Levofloxacin	Levaquin®, Tavanic®	Antibiotic
Lithium	Eskalith®, Lithobid®	Antimania
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®	Opioid agonist
Metoclopramide	Reglan®, Afipran®, Maxolon®, Cerucal®, Clopamon®, Clopra®, Maxeran®,	Antiemetic

Generic Name	Brand Name (Partial List)	Drug Class
	Maxolon®, Metozolv®, Plasil®, Pramin®, Primperan®, Perinorm®	
Metronidazole	Flagyl® and many others	Antibiotic
Mifepristone	Korlym®, Mifeprex®	Progesterone antagonist
Mirabegron	Myrbetriq®	Beta3 adrenergic antagonist
Mirtazapine	Remeron	Antidepressant, Tetracyclic
Moexipril/HCTZ	Uniretic®, Univasc®	Antihypertensive
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic
Nelfinavir	Viracept®	Antiviral
Nicardipine	Cardene®	Antihypertensive
Nilotinib	Tasigna®	Kinase inhibitor
Norfloxacin	Noroxin®, Ambigram®	Antibiotic
Nortriptyline	Pamelor®, Sensoval®, Aventyl®, Norpress®, Allegron®, Noritren®, Nortrilen®	Antidepressant, tricyclic
Ofloxacin	Floxin®	Antibiotic
Olanzapine	Zyprexa®, Zydis®, Relprevv®	Antipsychotic, atypical
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Antiemetic
Oxytocin	Pitocin®, Syntocinon®	Oxytocic
Paliperidone	Invega®, Xepilon®	Antipsychotic, atypical
Panobinostat	Farydak®	Histone deacetylase inhibitor
Pantoprazole	Protonix® and others	Proton pump inhibitor
Papaverine HCl	none	Vasodilator, coronary

Generic Name	Brand Name (Partial List)	Drug Class
Paroxetine	Paxil®, Aropax®, Pexeva®, Seroxat®, Sereupin®	Antidepressant, SSRI
Pasireotide	Signifor®	Somatostatin analog
Pazopanib	Votrient®	Tyrosine kinase inhibitor
Pentamidine	Pentam®	Antifungal
Perflutren lipid microspheres	Definity®	Imaging contrast agent
Pimozide	Orap®	Antipsychotic
Posacoanazole	Noxafil®, Posamol®	Antifungal
Procainamide	Protestyl®, Procan®	Antiarrhythmic
Promethazine	Phenergan®	Antipsychotic/Antiemetic
Propofol	Diprivan®, Propoven®	Anesthetic, general
Quetiapine	Seroquel®	Antipsychotic, atypical
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Antiarrhythmic
Quinine sulfate	Qualaquin®	Antimalarial
Ranolazine	Ranexa®, Ranozex®	Antianginal
Rilpivirine	Edurant®, Complera®, Eviplera®	Antiviral
Risperidone	Risperdal®	Antipsychotic, atypical
Ritonavir	Norvir®	Antiviral
Saquinavir	Invirase® (combo)	Antiviral
Sertraline	Zoloft®, Lustral®, Daxid®, Altruline®, Besitran®, Deprax®, Elrval®, Emergen®, Gladem®, Implicane®, Sedoran®, Sealdin®, SerivoLowfin®, Stimuloton®, Tresleen®, Sertalin Bluefish	Antidepressant, SSRI
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general

Generic Name	Brand Name (Partial List)	Drug Class
Solifenacin	VESIcare®	Muscle relaxant
Sorafenib	Nexavar®	Tyrosine kinase inhibitor
Sotalol	Betapace®, Sotalex®, Sotacor®	Antiarrhythmic
Sunitinib	Sutent®	Kinase inhibitor
Tacrolimus	Prograf®, Advagraf®, Protopic®	Immunosuppressant
Tamoxifen	Nolvadex® (discontinued 6/13), Istubal®, Valodex®	Antiestrogen
Telaprevir	Incivek®, Incivo®	Antiviral
Telavancin	Vibativ®	Antibiotic
Telithromycin	Ketek®	Antibiotic
Tetrabenazine (orphan drug in US)	Nitoman®, Xenazine®	Monoamine transporter inhibitor
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Antipsychotic
Tizanidine	Zanaflex®, Sirdalud®	Muscle relaxant
Tolterodine	Detrol®, Detrusitol®	Muscle relaxant
Toremifene	Fareston®	Estrogen agonist/antagonist
Torsemide	Demadex®, Diuver®, Examide®	Diuretic
Trazodone	Desyrel® (discontinued 6/13), Oleptro®, Beneficat®, Deprax®, Desirel®, Molipaxin®, Thombran®, Trazorel®, Trialodine®, Trittico®, Mesyrel®	Antidepressant/Serotonin Antagonist Reuptake Inhibitor (SARI)
Trimipramine	Surmontil®, Rhotrimine®, Stangyl®	Antidepressant, tricyclic
Vandetanib	Caprelsa®	Anticancer
Vardenafil	Levitra®	Phosphodiesterase 5 inhibitor
Vemurafenib	Zelboraf®	Kinase inhibitor

Generic Name	Brand Name (Partial List)	Drug Class
Venlafaxine	Effexor®, Efexor®	Antidepressant/Serotonin-norepinephrine reuptake inhibitors (SNRI)
Voriconazole	VFend®	Antifungal
Vorinostat	Zolinza®	Histone deacetylase inhibitor
Ziprasidone	Geodon®, Zeldox®	Antipsychotic, atypical

Source: http://www.crediblemeds.org/

Appendix 2: CAM2038 Administration Sites

Thirty-six administration sites have been identified for injection of CAM2038/placebo.

- CAM2038/placebo q1w must not be administered into a previously injected site for at least 4 weeks.
- CAM2038/placebo q4w must not be administered in a sited previously injected with CAM2038/placebo q4w or CAM2038/placebo q1w for at least 4 weeks.

The pictorial below will help record the injection site location. The injection site location will be recorded in the EDC.