Clinical Study Protocol
HS-15-549

A Phase II, Open-label, Partially Randomized, Three Treatment Groups, Multi-site Study Assessing Pharmacokinetics after Administration of the Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) at Different Injection Sites in Opioid-Dependent Subjects with Chronic Pain

CAM2038 q1w (50 mg/mL buprenorphine FluidCrystal® once-weekly subcutaneous injection depot)

CAM2038 q4w (356 mg/mL buprenorphine FluidCrystal® once-monthly subcutaneous injection depot)

Original Protocol: 1.0, 15 NOV 2015

Amendment 1: 2.0, 08 DEC 2015

Amendment 2: 3.0, 11 MAY 2016

Amendment 3: 4.0, 31 MAY 2016

Amendment 4: 5.0, 05 OCT 2016

BRAEBURN PHARMACEUTICALS:

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Summary of Changes and Justification
For HS-15-549
Amendment 4

Change and Location Within the Protocol	Rationale
Changed version and protocol date throughout.	Version was changed from 4.0 to 5.0 and protocol date from 31 MAY 2016 to 05 OCT 2016.
Updated Project Manager information. Section 1, Sponsor and Key Personnel	Updated to reflect change in personnel.
Protocol updated to include Group 3, including Group-specific inclusion criterion, treatment, assessments, and planned analysis. Updated throughout entire document, including study title.	Addition of Group 3 (n=16 subjects) and associated treatment and assessments. Subjects in Group 3 will receive 24 mg SL BPN for 7 days, followed by repeated administration of 160 mg CAM2038 q4w injections. To be eligible, subjects must be taking SL BPN ≥24 mg daily for at least 30 days prior to Screening, as BPN exposure following administration of CAM2038 q4w 160 mg is similar to SL BPN 26 mg to 32 mg.
Duration of participation for subjects in Group 1. Section 2, Synopsis	Updated to be consistent with body of protocol.
Subjects who discontinue from the study early will undergo End of Treatment visit assessments, including PK sampling and urine toxicology. Section 7, Investigational Plan Section 8.3, Removal of Subjects from Therapy or Assessment Section 10, Table 2 and Table 3: Schedule of Assessments	Clarification of assessments to be conducted for subjects who discontinue early.
Subjects in Group 1 and Group 2 who choose not to enter the open-label extension phase will undergo EOT procedures and transition back to standard therapy on Day 50 and Day 113, respectively. Section 2, Synopsis Section 7, Investigational Plan Section 10, Table 1 and Table 2: Schedule of Assessments	Clarification of transition to standard therapy and differentiation of EOT for subjects not entering the open-label extension phase and those entering the open-label extension phase (OLE-EOT).
Addition made to specify that a third party could be hired to locate subjects who are lost to follow-up. Section 8.3, Removal of Subjects from Therapy or Assessment	In the event a subject is lost to follow-up, a third party could be hired to locate the subject to ensure safety and collect relevant safety information.

Change and Location Within the Protocol	Rationale
Day 91 (now Day 92; Group 1) and Day 155 (Group 2) designated as in-clinic visits only, with no dosing to occur. Section 10, Table 1 and Table 2: Schedule of Assessments	The schedule of assessments was updated to reflect that dosing of CAM2038 on Day 91 (Group 1) and Day 155 (Group 2) will not occur; these study days are in-clinic visits where no dosing will occur.
In-clinic visits for subjects in Group 1 who enter the extension phase were updated to Days 85 and 92, instead of Days 84 and 91. Section 10, Table 1: Schedule of Assessments	The schedule of assessments was updated to reflect the correct in-clinic visit days for subjects in Group 1 who enter the extension phase.
Follow up visit was updated to be a phone call, and scheduled to occur on Day 99 for Group 1. Section 10, Table 1 and Table 2: Schedule of Assessments	The follow-up visit in the schedule of assessments was updated to be a follow up phone call to be consistent with the body of the protocol, and to occur on Day 99 (Group 1) to reflect the 7 day interval between the EOT visit and call.
Addition of Table 3 for Group 3 (160 mg CAM2038 q4w) Section 10, Table 3: Schedule of Assessments	Addition of visits and procedures for Group 3.
Addition of Group 3 PK blood volume. Section 10.3.1.1, Sample Collection, Preparation and Handling	To describe blood volumes required for PK sampling in Group 3.
Update to total blood volume to be drawn for each subject, by Group. Section 10.5.3, Clinical Laboratory Assessments	Addition of open-label extension clinical laboratory assessment blood volumes for Groups 1 and 2, and addition of blood volumes for Group 3.
Addition of non-identifying photographs of injection site reactions. Section 10.5.7, Injection Site Examinations	To augment documentation of injection site reactions.
Minor typographical and formatting errors and hyperlinking revisions. Updated throughout entire document.	Clarity and consistency.

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
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Principal Investigator	Greg Sullivan, MD	dgregs@gmail.com 205.815.5000 - office

2 PROTOCOL SYNOPSIS

Name of Sponsor/Company: Braeburn Pharmaceuticals Inc.

Name of Investigational Products:
CAM2038 q1w (50 mg/mL buprenorphine FluidCrystal® once-weekly subcutaneous injection depot); CAM2038 q4w (356 mg/mL buprenorphine FluidCrystal® once-monthly subcutaneous injection depot)

Name of Active Ingredient: Buprenorphine

Study Title:
A Phase II, Open-label, Partially Randomized, Three Treatment Groups, Multi-site Study Assessing Pharmacokinetics after Administration of the Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) at Different Injection Sites in Opioid-Dependent Subjects with Chronic Pain

Objectives:

Primary objectives of the study are:

- To evaluate the steady state pharmacokinetics (PK) of buprenorphine (BPN) and norbuprenorphine (norBPN) following repeated subcutaneous (SC) administration of CAM2038 q1w (50 mg/mL) at 4 different injection sites in adult opioid-dependent subjects with chronic pain.
- To evaluate steady state PK of BPN and norBPN following repeated SC administration of CAM2038 q4w (356 mg/mL) with the buttock as the injection site in adult opioid-dependent subjects with chronic pain.

The secondary objectives of the study are:

- To evaluate the safety and tolerability of CAM2038 q1w and CAM2038 q4w in adult opioid-dependent subjects with chronic pain.
- To assess relative bioavailability of BPN at steady state following repeated SC administration of 160 mg CAM2038 q4w compared with repeated sublingual (SL) administration of 24 mg BPN in adult opioid-dependent subjects with chronic pain.

The exploratory objectives of the study are:

- To evaluate maintenance of treatment efficacy when transferring adult opioid-dependent subjects from SL BPN to CAM2038 q1w and q4w, as determined by urine toxicology.
- To evaluate subject-rated worst daily pain and average daily pain, using an 11-point numerical rating scale (NRS), following repeated SC administration of CAM2038 q1w and CAM2038 q4w in adult opioid-dependent subjects.

Methodology:

This is a Phase II, open-label, partially randomized, 3-treatment group, multi-site study designed to evaluate the steady state PK of BPN and norBPN following repeated SC administration of CAM2038 q1w (Group 1) at different injection sites, to evaluate the steady state PK of BPN and norBPN after repeated SC administration of CAM2038 q4w (Group 2 and Group 3), and to evaluate relative bioavailability of BPN following SC administration of 160 mg CAM2038 q4w as compared with 24 mg SL BPN (Group 3) in opioid-dependent

subjects with a history of chronic non-cancer pain. The study will involve 4 phases: Screening, Treatment, open label safety extension and Follow-up.

Within 21 days of a medical Screening visit and confirmation of eligibility, subjects will be randomized to 1 of 2 treatment groups (Group 1 or Group 2; refer to Section 10.2, Eligibility Review and Randomization, for more detail):

- Group 1: 3 single weekly SC injections of 32 mg CAM2038 q1w (50 mg/mL) administered in the buttock to reach steady state, rotating between right and left buttock and injection site, followed by 4 single weekly SC injections of 32 mg CAM2038 q1w administered in the buttock (reference), abdomen, thigh, and back of upper arm in a randomized, crossover manner, with injection site sequence allocated using a randomized crossover design.
- Group 2: 4 monthly SC injections of 128 mg CAM2038 q4w (356 mg/mL) administered in the buttock, rotating between right and left buttock and injection site.

An additional group, to which subjects will not be randomized, was added following completion of randomization to Groups 1 and 2, in order to evaluate a higher dose of CAM2038 q4w (i.e., 160 mg) and compare resultant BPN exposure with SL BPN treatment:

- Group 3: 7 consecutive single daily doses of 24 mg SL BPN, followed by 4 monthly SC injections of 160 mg CAM2038 q4w (356 mg/mL) administered in the buttock, rotating between right and left buttock.

For subjects in Group 1, the first 3 SC injections of CAM2038 q1w will be administered in the buttock, rotating between right and left buttock on Day 1, Day 8 and Day 15 in order to achieve steady state PK of BPN and norBPN. Subjects will be administered each CAM2038 q1w injection at the clinical research unit (CRU) on an outpatient basis. Following the first administration, subjects will attend an interim visit on Day 2 to evaluate safety and tolerability of the transition from 24 mg SL BPN (Suboxone or equivalent) to CAM2038 q1w. To evaluate steady state PK of BPN and norBPN following CAM2038 q1w administration at various sites, CAM2038 q1w will be administered at 4 different injection sites, i.e., buttock (reference), abdomen, thigh and back of upper arm, on Day 22, Day 29, Day 36 and Day 43, using a randomized crossover design. Subjects will be confined to the CRU for 24 hours while serial PK samples will be collected. Subsequent PK samples will be collected for up to 168 hours post-dose. At the Day 50 (End of Treatment [EOT]) visit, subjects may continue on with the open-label extension phase for up to 6 weeks or transition back to standard care. For those enrolling into the open-label extension, subjects will receive additional CAM2038 q1w injections and will then transition back to standard care on Day 92 (EOT - OLE). At each study visit, including the open-label extension phase, safety and efficacy assessments will be conducted at pre-specified times. Subjects will also be required to record their worst daily pain and average daily pain using an 11-point NRS on an electronic device.

For subjects in Group 2, SC injections of 128 mg CAM2038 q4w will be administered in the buttock, rotating between right and left buttock, on Day 1, Day 29, Day 57 and Day 85, for a total of 4 doses. Following the first administration, subjects will attend an interim visit on Day 2 to evaluate safety and tolerability of the transition from SL BPN 24 mg to CAM2038 q4w. Following administration of the first 3 doses, PK samples will be collected pre-dose and at scheduled times post-dose on an outpatient basis to determine achievement of steady state. To characterize steady state PK of BPN and norBPN, subjects will be confined to the CRU and serial PK samples will be collected for up to 24 hours following the fourth dose, administered on Day 85; subsequent PK samples will be collected up to 28 days' post-dose on an outpatient basis. At each study visit, safety and efficacy assessments will be conducted at pre-specified times. At the Day 113 (EOT) visit, subjects in Group 2 (128 mg CAM2038 q4w) may continue on with the open-label extension phase for up to 6 weeks or transition back to

standard care. For those enrolling into the open-label extension, subjects will be switched to CAM2038 q1w 32 mg on Day 113 and will then transition back to standard care on Day 155 (EOT - OLE). At each study visit, including the open-label extension phase, safety and efficacy assessments will be conducted at pre-specified times. Subjects will also be required to record their worst daily pain and average daily pain using an 11-point NRS on an electronic device.

For subjects in Group 3, single daily doses of 24 mg SL BPN will be administered in the morning on Day 1 through Day 7 for a total of 7 doses. This will be followed by SC injections of 160 mg CAM2038 q4w in the buttock, rotating between right and left buttock, on Day 8, Day 36, Day 64 and Day 92, for a total of 4 doses. Following the first 160 mg CAM2038 q4w administration, subjects will attend an interim visit on Day 9 to evaluate safety and tolerability of the transition from SL BPN 24 mg to CAM2038 q4w. Following administration of the first 3 doses of CAM2038 q4w, PK samples will be collected pre-dose and at scheduled times post-dose on an outpatient basis to determine achievement of steady state. To characterize steady state PK of BPN and norBPN and evaluate relative bioavailability of CAM2038 q4w as compared with SL BPN, subjects will be confined to the CRU and serial PK samples will be collected for up to 24 hours following the seventh dose of SL BPN administered on Day 7, and following the fourth dose of CAM2038 q4w administered on Day 92. Subsequent PK samples will be collected up to 28 days post-dose on an outpatient basis. At the Day 127 (EOT) visit, subjects will be transitioned back to standard care. At each study visit, safety and efficacy assessments will be conducted at pre-specified times. Subjects will also be required to record their worst daily pain and average daily pain using an 11-point NRS on an electronic device.

For all Groups, a follow-up call will be conducted approximately 7 days after the last study visit of the Treatment Phase or open label safety extension phase.

Number of Subjects (Planned):

Up to a total of approximately 40 subjects will be randomized at a 3:2 ratio to Group 1 (32 mg CAM2038 q1w) or Group 2 (128 mg CAM2038 q4w). An additional group (Group 3) of approximately 16 subjects will be assigned to receive 24 mg SL BPN for 7 days followed by 160 mg CAM2038 q4w.
At least 20 subjects, and up to 24 subjects, will be randomized to Group 1 and assigned to 1 of the following 4 injection site sequences: ABDC, BCAD, CDBA, and DACB, where A=buttock (reference), B=abdomen, C=thigh, and D=back of upper arm. For Group 2 (128 mg CAM2038 q4w) and Group 3 (24 mg SL BPN followed by 160 mg CAM2038 q4w), approximately 16 subjects will be enrolled into each Group.

Diagnosis and Main Criteria for Inclusion:

This study will enroll opioid-dependent adult subjects (19 to 65 years of age) with a history of moderate to severe chronic non-cancer pain. Subjects must have been taking a daily dose of 24 mg SL BPN (Subutex® equivalent) for at least 30 days prior to Screening. Subjects must meet each of the following inclusion criteria in order to be eligible for participation in the study:

1. Subject must provide written informed consent prior to the conduct of any study-related procedures.
2. Male or non-pregnant, non-lactating female subject, aged 19 to 65 years, inclusive.
3. Body mass index between 19 and 35 kg/m^2, inclusive.
4. Current diagnosis of moderate to severe opioid use disorder (according to the DSM-V) or past medical history of opioid use disorder currently being treated with SL BPN.

5. Subject must be taking SL BPN (Subutex® equivalent) 24 mg daily (Group 1 and Group 2) or ≥24 mg (Group 3) for at least 30 days prior to Screening.
6. Subject has a history of moderate to severe chronic non-cancer pain.
7. Male and female subjects of childbearing potential must be willing to use a reliable method of contraception during the entire study (Screening visit to Follow-up phone call).
8. Subject must be willing and able to comply with all study procedures and requirements.

Subjects will not be eligible to participate in this study if any of the following exclusion criteria are met:

1. Individuals meeting DSM-V substance use disorder criteria for alcohol, benzodiazepines, central nervous system (CNS) stimulants, or other drugs of abuse (excluding caffeine, tobacco or THC/marijuana).
2. Any clinically significant abnormality on the basis of medical history, vital signs, physical examination, 12-lead electrocardiogram (ECG; Fridericia's corrected QT interval [QTcF] ≥450 msec. for males or ≥470 msec. for females), and laboratory evaluations (including hematology, clinical chemistry, urinalysis at Screening), in the opinion of the Investigator.
3. 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 study, including subjects who are at a risk for gastrointestinal obstruction or paralytic ileus or who have severe respiratory insufficiency, respiratory depression, airway obstruction, gastrointestinal motility disorders, biliary tract disease, severe hepatic insufficiency, planned surgery and prior treatment with monoamine oxidase inhibitors.
4. Use (therapeutic or non-therapeutic) of opioids other than SL BPN.
5. Aspartate aminotransferase (AST) levels > 3 X the upper limit of normal, alanine aminotransferase (ALT), levels > 3 X the upper limit of normal, total bilirubin > 1.5 X the upper limit of normal, or creatinine > 1.5 X upper limit of normal on the Screening laboratory assessments, or other clinically significant laboratory abnormalities, which in the opinion of the Investigator may prevent the subject from safely participating in study.
6. Pregnant or lactating or planning to become pregnant during the study.
7. Diagnosis of, or currently under investigation for, fibromyalgia, complex regional pain syndrome, neurogenic claudication due to spinal stenosis, spinal cord compression, acute nerve root compression, severe or progressive lower extremity weakness or numbness.
8. History of chemotherapy or confirmed malignancy (except basal cell or squamous carcinoma of the skin) within the past 2 years.
9. Clinically significant history of, or current evidence for, suicidal ideation or those who are actively suicidal, as based on the Columbia-Suicide Severity Rating Scale (C-SSRS; grade 4 or 5).
10. Clinically significant history of major depressive disorder that is poorly controlled with medication.
11. Hypersensitivity or allergy to BPN or other opioids, or excipients of CAM2038.
12. Exposure to any investigational drug within the 4 weeks prior to Screening.
13. Participants with a clinically significant history of risk factors of Torsades de Pointes and any existing ventricular tachyarrhythmias such as bigeminy, trigeminy, heart failure, hypokalemia, family history of Long QT Syndrome.

14. On medications that have the potential for prolonging the QT interval or who may require such medications during the course of the study along with clinically significant abnormalities on screening electrocardiogram (ECG) readings as deemed by the investigator (Appendix 17.1).
15. Requires current use of agents that are 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).
16. Intolerance to venipuncture and/or difficulty with venous access, as per the judgment of the Investigator/research staff.
17. Is an employee of the Investigator or the study site, with direct involvement in the proposed study or other studies under the direction of the Investigator or study site, or is a family member of an employee or of the Investigator.
18. Any pending legal action that could prohibit participation or compliance in the study.

Investigational Product, Dosage, and Mode of Administration

CAM2038 q1w (Group 1): BPN FluidCrystal® SC injection depot for once weekly administration (50 mg/mL) at a dose of 32 mg (BPN base), 0.64 mL SC injection.

CAM2038 q4w (Group 2): BPN FluidCrystal® SC injection depot for once monthly administration (356 mg/mL) at a dose of 128 mg (BPN base), 0.36 mL SC injection.

CAM2038 q4w (Group 3): BPN FluidCrystal® SC injection depot for once monthly administration (356 mg/mL) at a dose of 160 mg (BPN base), 0.45 mL SC injection.

Reference Product, Dosage, and Mode of Administration

Group 3: SL BPN (Subutex® equivalent) 24 mg (3 tablets of 8 mg BPN) for once daily administration

Duration of Study:

Group 1: Each subject will participate in the study for up to approximately 17 weeks.
Group 2: Each subject will participate in the study for up to approximately 26 weeks.
Group 3: Each subject will participate in the study for up to approximately 21 weeks.

Criteria for Evaluation:

Pharmacokinetic Endpoints:

The following PK parameters will be derived based on the plasma concentrations of BPN and norBPN, if applicable:

- Group 1:
  - AUC_{ss} (area under the plasma concentration-time curve during a 7-day dosing interval at steady state) for each injection site, i.e., buttock (reference), abdomen, thigh and back of upper arm.
  - $C_{ss,av}$ (average plasma concentration during a dosing interval at steady state) for each injection site.
  - $C_{ss,max}$ (maximum observed plasma concentration during a dosing interval at steady state) for each injection site.
  - $t_{ss,max}$ (time to $C_{ss,max}$) for each injection site.

- norBPN/BPN ratios for AUC_{ss} and $C_{ss,max}$ for each injection site.

- Group 2 and Group 3:
  - AUC_{ss} (AUC during a 24-hour dosing interval at steady state for SL BPN [Group 3 only] and a 28-day dosing interval at steady state for CAM2038 q4w)
  - $C_{ss,av}$
  - $C_{ss,max}$
  - $t_{ss,max}$
  - $C_{ss,28days}$ (observed plasma concentration 28 days after administration of CAM2038 q4w at steady state)
  - $C_{ss,24h}$ (observed plasma concentration 24 hours after administration of SL BPN at steady state) (Group 3 only)

In Group 3, relative bioavailability of BPN will be assessed at steady state following repeated SC administration of 160 mg CAM2038 q4w as compared with repeated SL administration of 24 mg BPN.

Efficacy Variables:

The following exploratory efficacy variables will be assessed during the study:

- Urine toxicology: Frequency and incidence of positive results for opioids (excluding BPN) and other non-opioid drugs.
- NRS scale for pain: change from baseline in weekly average of daily Worst Pain score.

Safety Variables:

The following safety variables will be assessed during the study:

- Adverse events
- Concomitant medications/procedures
- Clinical laboratory assessments (hematology, biochemistry and urinalysis)
- Vital signs (body temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate)
- 12-lead ECG
- Physical examination
- Injection site examination
- C-SSRS
- Subjective Opioid Withdrawal Scale
- Clinical Opioid Withdrawal Scale

Statistical Methods (Data Analysis):

Three study populations are defined:

- **Safety population:** All subjects who receive at least part of an injection of the study medications. All safety analysis will be based on the Safety population.
- **Pharmacokinetic population:** The PK population will consist of all subjects in the Safety population who have provided sufficient PK data for all 4 randomized injection sites to derive PK parameters of interested (Group 1), or have provided PK data after the last injections of CAM2038 q4w (Group 2 and Group 3). All PK summaries will be based on the PK population.
- **Efficacy population**: The efficacy population will be the intent-to-treat population consisting of all subjects that have received at least 1 injection of CAM2038 and provided some efficacy measures.

PK parameters of BPN and norBPN will be summarized by descriptive statistics, if appropriate. For Group 1 (CAM2038 q1w), the following considerations will apply in the PK analysis. The primary PK parameters will be AUC_{ss} and $C_{ss, max}$ after steady state injections of CAM2038 q1w at different injection sites. The injection site buttock will be the reference. The analyses will be based on log-transformed data. The natural log-transformed AUC_{ss} and $C_{ss, max}$ data will be analyzed using an ANOVA model, sequence, subject within sequence (1, 2, 3, 4 corresponding to A/B/D/C, B/C/A/C, C/D/B/A, D/A/C/B, where A=buttock, B=abdomen, C=thigh, or D=back of upper arm), period, and treatment (treatment sites: A=buttock, B=abdomen, C=thigh, or D=back of upper arm). The estimated treatment effects, treatment differences versus the reference (B-A, C-A, and D-A), and the 90% confidence intervals of the estimated difference will be presented. The above estimates will be expressed on the raw scale (expressed after performing the anti-log). All other PK parameters will be summarized by descriptive statistics.

For Group 2 (128 mg CAM2038 q4w) and Group 3 (24 mg SL BPN and 160 mg CAM2038 q4w), the PK parameters will be summarized by descriptive statistics. The primary PK parameters will be AUC_{ss} and $C_{ss, max}$. Relative bioavailability of BPN will be assessed at steady state for 160 mg CAM2038 q4w for comparison with 24 mg SL BPN (Group 3).

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{ss}	AUC during a dosing interval at steady state
BMI	Body mass index
BPN	Buprenorphine
CFR	Code of Federal Regulations
CNS	Central nervous system
COWS	Clinical Opioid Withdrawal Scale
CRF	Case Report Form (may include electronic data capture systems or paper forms)
CRU	Clinical research unit
CSA	Clinical Study Agreement
C-SSRS	Columbia-Suicide Severity Rating Scale
$C_{ss,24h}$	Observed plasma concentration 24 hours after administration at steady state
$C_{ss,28days}$	Observed plasma concentration 28 days after administration at steady state
$C_{ss,av}$	Average plasma concentration during a dosing interval at steady state
$C_{ss,max}$	Maximum observed plasma concentration during a dosing interval at steady state
$C_{ss,trough}$	Trough plasma concentration during a dosing interval at steady state
CV%	Coefficient of variation percentage
CYP	Cytochrome P450
DSM-V	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
ECG	Electrocardiogram
EDC	Electronic data capture
EOT	End of Treatment
FC	FluidCrystal®
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board

IV	Intravenous
LLOQ	Lower limit of quantification
msec	Millisecond
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary of Regulatory Activities
norBPN	Norbuprenorphine
NRS	Numerical rating scale
PCP	Phencyclidine
PI	Pain Intensity
PID	Pain Intensity Difference
PK	Pharmacokinetics
QTcF	Fridericia's corrected QT interval
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SL	Sublingual
SOC	System Organ Class
SOWS	Subjective Opioid Withdrawal Scale
SUSAR	Suspected unexpected serious adverse reaction
THC	Tetrahydrocannabinol
$t_{ss,max}$	Time to $C_{ss,max}$
US	United States
UDS	Urine drug screen

5 INTRODUCTION

5.1 Background

Buprenorphine (BPN) is an opioid with mixed agonist-antagonist properties that, together with appropriate counseling and psychotherapy, has been shown to be effective in the treatment of opioid dependence. Treatment with BPN has been demonstrated to significantly reduce opioid-positive urines, i.e., to reduce illicit drug use, and increase retention of subjects in outpatient treatment programs (Johnson et al., 1992; Strain et al., 1994; Schottenfeld et al.,1997; Ling et al., 1998). Buprenorphine is available in several sublingual (SL) formulations for the treatment of opioid use disorders, alone (e.g., Subutex®) or as a combination product with naloxone (e.g., Suboxone®), as well as in buccal combination formulations (e.g., Bunavail®).

In addition to treatment of opioid use disorders, BPN is currently available in injectable formulations to treat moderate to severe (acute) pain (e.g., Buprenex®), transdermal formulations to treat chronic pain (e.g., BuTrans®), and buccal formulations to treat chronic severe pain (e.g., Belbuca®).

CAM2038 (50 mg/mL BPN FluidCrystal® [FC] subcutaneous [SC] injection depot) once-weekly (hereafter referred to as CAM2038 q1w) and once-monthly (356 mg/mL; hereafter referred to as CAM2038 q4w) are ready-to-use, extended-release BPN products with a target of once-weekly or once-monthly SC dosing posology, respectively.

CAM2038 q1w and 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 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 prior to administration at ambient temperature. In addition, the injection volumes for CAM2038 q1w and q4w are relatively low (from 0.15 to 0.6 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 subject adherence.

5.1.1 CAM2038 q1w (Once Weekly)

CAM2038 q1w has so far been investigated after single and repeated doses in 3 clinical trials, where a total of 176 human subjects (subjects and healthy volunteers) have been exposed to the CAM2038 drug products. An initial study assessed pharmacokinetics (PK), pharmacodynamics and safety in opioid-dependent subjects (Study HS-07-307). Study HS-07-307 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%), 3 subjects experienced mild injection site pain and 1 subject exhibited transient injection site inflammation (mild) and injection site pruritus (moderate).

Two clinical 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 SL BPN (i.e., at steady state) and single dose of intravenous (IV) BPN (Studies HS-11-426 and HS-13-487). These 2 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., approved 8 mg, 16 mg or 24 mg doses) with less fluctuation between maximum and minimum plasma concentrations compared to SL BPN. 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 IV and SL BPN products. Local tolerability was very good with no adverse events (AEs) related to injection site tolerability reported in HS-11-426 (N safety=60). Similarly, local tolerability of CAM2038 q1w was also very good in HS-13-487 (1 subject reported 1 AE of injection site pain), during which 4 repeat SC injections of CAM2038 q1w were administered into the buttock site.

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

- Extended BPN release over 1 week at target plasma concentrations
- Dose proportionality and flexible/multiple dosing options
- 6- to 8-fold higher bioavailability as compared to SL BPN
- BPN plasma concentrations over 7 days within the ranges of those produced by corresponding SL BPN doses at steady state (i.e., approved 8 mg, 16 mg, or 24 mg doses)
- Observed and predicted average plasma concentration during a dosing interval at steady state ($C_{ss,av}$) and trough plasma concentration during a dosing interval at steady state ($C_{ss,trough)}$ values for CAM2038 q1w within known therapeutic plasma levels
- Good safety and systemic tolerability in subjects
- Safety in healthy volunteers comparable to reference 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. Subcutaneous administration of CAM2038 q1w has been shown to be well tolerated both systemically and locally in single and repeat dose non-clinical studies in the rat and in the dog. 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, nonclinical studies have not identified systemic toxicity associated with CAM2038 q1w or the FC injection depot vehicle.

5.1.2 CAM2038 q4w (Once Monthly)

The PK and safety of CAM2038 q4w has been investigated after single administration in a bridging clinical 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 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 at target plasma concentrations
- Dose proportionality was shown within the dosage interval 64 to 192 mg CAM2038 q4w
- 6- to 8-fold higher bioavailability than SL BPN, comparable to CAM2038 q1w
- Observed BPN plasma concentrations over 4 weeks comparable to CAM2038 q1w over 1 week, and to SL BPN over 24 hours at steady state (i.e., for approved 8 mg, 16 mg, or 24 mg doses)
- Predicted $C_{ss,av}$ and $C_{ss,trough}$ values for 64, 96 and 128 mg CAM2038 q4w similar to CAM2038 q1w and SL BPN (i.e., for approved 8 mg, 16 mg, or 24 mg doses); and predicted exposure for 160 mg CAM2038 q4w similar to SL BPN 26 mg to 32 mg
- Safety profile comparable to reference IV and SL BPN treatments
- Good local tolerability

The most commonly reported drug-related AEs after CAM2038 q1w and CAM2038 q4w administration were nausea, dizziness and vomiting. The local tolerability was good with 6 subjects experiencing 7 AEs that were assessed as related to CAM2038 q4w (injections 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 (SUSAR). 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 publically 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 the once weekly product, 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.

5.1.3 Study Rationale

This is a Phase II, open-label, partially randomized, 3 treatment groups study assessing the steady state PK of BPN and norbuprenorphine (norBPN) after SC injections of CAM2038 q1w at different injection sites (Group 1), SC injections of 128 mg CAM2038 q4w (Group 2), and 160 mg CAM2038 q4w (Group 3). After the PK portion of the study, subjects in Group 1 and Group 2 have the option of continuing into an extension portion of the study where subjects will receive 6 injections of CAM2038 q1w.

In clinical practice, CAM2038 may be administered at different injection sites depending on local preferences or other reasons. While repeat dose PK has previously been evaluated with multiple injections of CAM2038 q1w in healthy volunteers (Study HS-13-487), the injections have only been administered in the buttock. The current study will evaluate the impact of using different injection sites (arm, abdomen, buttock and thigh) on the exposure of BPN and norBPN (as assessed by area under the plasma concentration-time curve during a dosing interval at steady state [AUCss] and the maximum observed plasma concentration during a dosing interval at steady [Css,max]) after administration of CAM2038 q1w at steady state. The injection sites to be evaluated in this study are the buttock (reference), abdomen, thigh and back of upper arm.

This study will also evaluate the PK of BPN and norBPN at steady state following repeated dose administration of 128 mg CAM2038 q4w (Group 2) and 160 mg CAM2038 q4w (Group 3) by SC injection in the buttock. Additionally, relative bioavailability of BPN will be assessed at steady state for 160 mg CAM2038 q4w as compared with 24 mg SL BPN (Group 3).

5.2 Overall Risk-Benefit

BPN is a substance with well-established use for treatment of opioid drug dependence. The CAM2038 products contain BPN in a new FC formulation for SC injection. Clinical trials have demonstrated effectiveness of BPN in reducing illicit opioid use and improving retention rates of patients in outpatient maintenance treatment of opioid dependence, as well as substantial reduction in criminal activity, deaths, and human immunodeficiency virus (HIV) transmission. The need for daily administration of SL BPN may negatively influence patients' compliance and BPN tablets or film can be easily diverted for illicit use, injected for greater effect, or accidentally ingested, especially by children. There is only one approved long-acting (6 months) BPN formulation, Probuphine™. Probuphine™ is indicated for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal BPN containing product (i.e., doses of no more than 8 mg per day of Subutex® or Suboxone® SL tablet or generic equivalent). Additional long-acting injection depot formulations of BPN such as CAM 2038 would likely complement Probuphine™ and offer dosage forms with different indications to treat opioid-dependent subjects and improve retention in treatment. For example, subjects with chronic cancer and non-cancer pain, long-acting formulations (e.g., transdermal) of BPN have proven effective, with a reduction in the need for additional oral analgesics and improved quality of life (Liker et al, 2003; Sittl et al., 2005).

While the rate of BPN delivery can be controlled and stable plasma concentrations achieved by using a transdermal BPN formulation (BuTrans US Prescribing Information, 2014). However, transdermal BPN formulations 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. Transdermal systems may also be accidently ingested, particularly by children. Traditional oral opioid therapies are even more subject to diversion and abuse, resulting in significant public health concerns (Salinas et al., 2012; Joint Commission and Food and Drug Administration [FDA], 2012). Therefore, CAM2038 SC injection depots have been designed with a focus on enabling easy administration, dosing flexibility, and importantly, minimizing risks of misuse, diversion and poor subject compliance. CAM2038 q1w and CAM2038 q4w are intended for convenient and safe SC injection of BPN depot with a prefilled syringe including a needle safety device and with no need for mixing or temperature adjustment prior to administration. The route of administration (i.e. SC injection) of CAM2038 by health care providers is expected to reduce the risks of diversion and abuse even when compared to transdermal and oral opioid formulations, indicating that CAM2038 SC injection depot may be particularly well suited for opioid-dependent subjects. In addition, like transdermal formulations, CAM2038 SC injection depot may also be suitable for subjects who have difficulty swallowing. The sustained and stable plasma concentrations demonstrated for CAM2038 q1w and CAM2038 q4w are likely to provide an optimal treatment modality for many opioid-dependent subjects. The PK profile of CAM2038 q1w indicates that a rapid and long-acting release of BPN will lead to rapid 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.

In summary, CAM2038 SC injection depot is anticipated to provide a convenient and advantageous alternative to existing opioid medications, with the potential added benefits of obtaining consistent and stable plasma levels of BPN. CAM2038 SC injection depot, which is stable at room temperature and introduced through a small gauge needle (e.g. 23G), should thus eliminate the need to take daily medications. Moreover, it should help to markedly reduce diversion and accidental pediatric exposures, which continue to be important public health goals of the FDA and other regulators.

6 STUDY OBJECTIVES

6.1 Primary Objectives

The primary objectives of the study are:

- To evaluate the steady state PK of BPN and norBPN following repeated SC administration of CAM2038 q1w (50 mg/mL) at 4 different injection sites in adult opioid-dependent subjects with chronic pain.
- To evaluate steady state PK of BPN and norBPN following repeated SC administration of CAM2038 q4w (356 mg/mL) with the buttock as the injection site in adult opioid-dependent subjects with chronic pain.

6.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of CAM2038 q1w and CAM2038 q4w in adult opioid-dependent subjects with chronic pain.
- To assess relative bioavailability of BPN at steady state following repeated SC administration of 160 mg CAM2038 q4w compared with repeated SL administration of 24 mg BPN in adult opioid-dependent subjects with chronic pain.

6.3 Exploratory Objectives

The exploratory objectives of the study are:

- To evaluate maintenance of treatment efficacy when transferring adult opioid-dependent subjects from SL BPN to CAM2038 q1w and q4w, as determined by urine toxicology.
- To evaluate subject-rated worst daily pain and average daily pain, using an 11-point numerical rating scale (NRS), following repeated SC administration of CAM2038 q1w and CAM2038 q4w in adult opioid-dependent subjects.

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

This is a Phase II, open-label, partially randomized, 3-treatment group study designed to evaluate the steady state PK of BPN and norBPN following multiple weekly SC administrations of CAM2038 q1w at different injection sites (Group 1), and following multiple monthly SC administrations of CAM2038 q4w (Group 2 and Group 3), and to evaluate relative bioavailability of BPN following SC administration of 160 mg CAM2038 q4w as compared with 24 mg SL BPN (Group 3) in opioid-dependent subjects with a history of chronic non-cancer pain. The study will involve 4 phases: Screening, Treatment, open label safety extension and Follow-up.

Medical and eligibility screening will occur within approximately 21 days of the Treatment Phase. At Screening, subjects will provide written informed consent to participate in the study before any protocol-specified procedures or assessments are completed. The Screening visit will include standard medical screening procedures, complete medical/psychosocial history, brief substance abuse history and treatment history, clinical laboratory assessments, urine toxicology, as outlined in Table 1 (Group 1), Table 2 (Group 2), and Table 3 (Group 3). Subjects will be eligible for further participation if they meet all of the inclusion criteria and do not meet any of the exclusion criteria (as outlined in Section 8.1 and Section 8.2).

Subjects will remain on their daily SL BPN dose (24 mg/day) throughout the Screening phase. The last SL BPN dose will be taken on Day -1 (i.e., the day before the first CAM2038 dose). On Day 1, eligibility will be confirmed and up to approximately 40 eligible subjects will be randomized to either CAM2038 q1w (Group 1) or 128 mg CAM2038 q4w (Group 2). An additional group of 16 subjects was added following completion of randomization to Groups 1 and 2, in order to evaluate a higher dose of CAM2038 q4w (160 mg) after initial daily treatment with SL BPN (Group 3); therefore, these subjects will be enrolled, but not randomized. After enrollment/randomization, subjects will be administered CAM2038 SC injection depot formulation (all Groups) and SL BPN (Group 3) and monitored for at least 3 hours to ensure that the CAM2038 and SL BPN products are tolerated.

Subjects will be treated as follows:

- Group 1: 3 single weekly SC injections of 32 mg CAM2038 q1w (50 mg/mL) administered in the buttock to reach steady state, rotating between right and left buttock and injection site per Appendix 17.2, followed by 4 single weekly SC injections of 32 mg CAM2038 q1w administered in the buttock (reference), abdomen, thigh, and back of upper arm in a randomized, crossover manner, with injection site sequence allocated using a randomized crossover design. At the Day 50 (end-of-treatment [EOT]) visit, subjects may continue on with open-label extension phase for up to 6 weeks.
- Group 2: 4 monthly SC injections of 128 mg CAM2038 q4w (356 mg/mL) administered in the buttock, rotating between right and left buttock and injection site per Appendix 17.2. At the Day 113 (EOT) visit, CAM2038 q4w 128 mg subjects

may be transferred to 32 mg of CAM2038 q1w and continue in an open-label extension phase for up to 6 weeks.

- Group 3: 7 consecutive single daily doses of 24 mg SL BPN, followed by 4 monthly SC injections of 160 mg CAM2038 q4w (356 mg/mL) administered in the buttock, rotating between right and left buttock per Appendix 17.2. Note: 160 mg CAM2038 q4w (356 mg/mL) is estimated to be equivalent to 26 mg to 32 mg SL BPN.

GROUP 1:

Each subject in Group 1 will participate in the study for up to approximately 17 weeks, including up to 3 weeks for screening, 13 weeks for treatment, and approximately 1 week for follow-up. In order to achieve steady state PK of BPN and norBPN, the first 3 SC injections of 32 mg CAM2038 q1w will be administered in the buttock, rotating between right and left buttock and injection site per Appendix 17.2 on Day 1, Day 8 and Day 15. Subjects will be administered each CAM2038 q1w injection at the clinical research unit (CRU) on an outpatient basis. Following the first administration, subjects will attend an interim visit on Day 2 to evaluate safety and tolerability of the transition from SL BPN 24 mg to CAM2038 q1w.

To evaluate steady state PK of BPN and norBPN following CAM2038 q1w administration at various sites, CAM2038 q1w will be administered at 4 different injection sites, i.e., buttock (reference), abdomen, thigh and back of upper arm, on Day 22, Day 29, Day 36 and Day 43. The sequence of injection site administration will be randomized using a crossover design. Subjects will be confined to the CRU for 24 hours while serial PK samples will be collected. Subsequent PK samples will be collected for up to 168 hours post-dose.

On Day 50 (EOT), all subjects will be allowed to continue their CAM2038 q1w dose for up to 6 weeks for an open-label safety extension phase or transition back to standard care. The CAM2038 q1w injections may be rotated in previously not used SC sites in the abdomen, arm, buttock and the thigh. For those subjects enrolling into the open-label extension, transition back to standard care will begin on Day 92 (EOT - OLE).

At each study visit, safety and efficacy assessments will be conducted at pre-specified times. Subjects will also be required to record their worst daily pain and average daily pain using an 11-point NRS on an electronic device.

GROUP 2:

Each subject in Group 2 will participate in the study for up to 26 weeks, including up to approximately 3 weeks for screening, 22 weeks for treatment, and approximately 1 week for follow-up. SC injections of 128 mg CAM2038 q4w will be administered in the buttock, rotating between right and left buttock and injection site per Appendix 17.2, on Day 1, Day 29, Day 57 and Day 85, for a total of 4 doses. Following the first administration, subjects will attend an interim visit on Day 2 to evaluate safety and tolerability of the transition from SL BPN 24 mg to CAM2038 q4w.

Following administration of the first 3 doses, PK samples will be collected pre-dose and at scheduled times post-dose on an outpatient basis to determine achievement of steady state. To

characterize steady state PK of BPN and norBPN, subjects will be confined to the CRU and serial PK samples will be collected for up to 24 hours following the fourth dose, administered on Day 85; subsequent PK samples will be collected up to 28 days post-dose on an outpatient basis. At the Day 113 (EOT) visit, CAM2038 q4w 128 mg subjects may continue on with open-label extension phase for up to 6 weeks and will be switched to CAM2038 q1w 32 mg, or transition back to standard care. For those subjects enrolling into the open-label extension, transition back to standard care will begin on Day 155 (EOT - OLE).

At each study visit, safety and efficacy assessments will be conducted at pre-specified times. Subjects will also be required to record their worst daily pain and average daily pain using an 11-point NRS on an electronic device.

GROUP 3:

Each subject in Group 3 will participate in the study for up to 21 weeks, including up to approximately 3 weeks for screening, 17 weeks for treatment, and approximately 1 week for follow-up. Single daily doses of 24 mg SL BPN will be administered in the mornings on Day 1 through Day 7 for a total of 7 doses. This will be followed by SC injections of 160 mg CAM2038 q4w in the buttock, rotating between right and left buttock and injection site per Appendix 17.2, on Day 8, Day 36, Day 64 and Day 92, for a total of 4 doses. Following the first CAM2038 q4w administration, subjects will attend an interim visit on Day 9 to evaluate safety and tolerability of the transition from SL BPN to CAM2038 q4w.

Following administration of the first 3 doses of CAM2038 q4w, PK samples will be collected pre-dose and at scheduled times post-dose on an outpatient basis to determine achievement of steady state. To characterize steady state PK of BPN and norBPN and evaluate relative bioavailability CAM2038 q4w as compared with SL BPN, subjects will be confined to the CRU and serial PK samples will be collected for up to 24 hours following the seventh dose of SL BPN administered on Day 7, and following the fourth dose of CAM2038 q4w administered on Day 92. Subsequent PK samples will be collected up to 28 days post-dose on an outpatient basis.

At each study visit, safety and efficacy assessments will be conducted at pre-specified times. Subjects will also be required to record their worst daily pain and average daily pain using an 11-point NRS on an electronic device.

For all Groups, subjects will be transitioned to standard care as needed at the EOT or EOT-OLE visit, as applicable, and a follow-up call will be conducted approximately 7 days after the last study visit. Subjects who discontinue early will undergo EOT visit assessments, including PK sampling and urine toxicology.

GENERAL CONSIDERATIONS:

To ensure adequate enrollment and address potential inconvenience to subjects, all subjects will receive appropriate compensation for time and travel expenses related to attendance at study visits. All costs of medications will also be covered.

Section 10 provides additional information on the PK, efficacy and safety assessments included in the study. Statistical analyses are described in Section 12.

7.2 Discussion of Study Design

Subjects with current diagnosis of opioid use disorder (based on criteria defined in the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition [DSM-V]) or past medical history of opioid use disorder and currently being treated with SL BPN with concomitant chronic non-cancer pain will be enrolled in this study. Because this is the intended patient population, results from this study will be directly applicable to the therapeutic use of CAM2038 q1w and CAM2038 q4w in clinical practice. In addition to the requirement of opioid dependence, eligible subjects will be required to be on maintenance treatment of 24 mg SL BPN to ensure that the subjects will be able to safely tolerate the treatment dose levels planned for evaluation (32 mg CAM2038 q1w, 128 mg CAM2038 q4w, and 160 mg CAM2038 q4w).

As 1 of the 2 primary objectives, the study will evaluate the comparability of steady state exposure to BPN and norBPN after SC administration of CAM2038 q1w at different injection sites (Group 1) planned for treatment in a clinical setting, which will require rotation. Subjects allocated to Group 1 will first be administered CAM2038 q1w in the buttock, rotating between right and left buttock and injection site per Appendix 17.2, once weekly for the first 3 weeks to reach steady state. Once at steady state, CAM2038 q1w will be injected in the buttock (reference), abdomen, thigh and back of upper arm, using a randomized crossover design. A randomized crossover design will be used to minimize the variability in the study and avoid bias in the assignment of injection site sequence, as well as to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across injection site sequence. Exposure to BPN and norBPN after administration of CAM2038 q1w will be evaluated by means of AUC_{ss}, $C_{ss,max}$, $C_{ss,av}$, time to $C_{ss,max}$ ($t_{ss,max}$), norBPN/BPN ratios for $C_{ss,max}$ and AUC_{ss}, and other derived PK parameters, as applicable.

The present study will also evaluate steady state PK of BPN and norBPN after 4 monthly injections of 2 dose levels of CAM2038 q4w in the buttock (128 mg [Group 2] and 160 mg [Group 3]). Steady state conditions will be confirmed by collecting pre-dose plasma samples prior to each SC administration for analysis of BPN and norBPN concentrations. Steady state exposure to BPN and norBPN will be characterized following administration of the last dose of CAM2038 q4w, with AUC_{ss}, $C_{ss,max}$, $C_{ss,av}$, $t_{ss,max}$, norBPN/BPN ratios for $C_{ss,max}$ and AUC_{ss} and other PK parameters, as appropriate. Relative bioavailability of BPN will be assessed at steady state conditions after the fourth dose of 160 mg CAM2038 q4w and the seventh dose of 24 mg SL BPN (Group 3). Once the PK of 32 mg CAM2038 q1w and 128 mg CAM2038 q4w PK evaluation phases are over, subjects in Group 1 and Group 2 will have the option of receiving 6 more CAM2038 q1w 32 mg injections in an extension phase of the study.

In addition to evaluating the PK and safety of multiple doses of CAM2038 q1w and q4w, urine toxicology will be included as an exploratory efficacy measure of CAM2038 in maintaining opioid abstinence. Individuals who are in treatment for opioid dependence also commonly have a history of chronic pain (Rosenblum et al., 2003; Brands et al., 2004; Wiest et al., 2014). Long-acting transdermal BPN has proven effective in individuals with chronic cancer and non-cancer pain, with a reduction in the need for additional oral analgesics and improved quality of life (Likar et al. 2003; Sittl et al., 2005). Therefore, an additional exploratory objective of the current study is to assess daily pain intensity, as measured using an 11-point NRS, following SC administration of CAM2038 q1w and q4w.

8 SELECTION OF STUDY POPULATION

At least 20 subjects, but no more than 24 subjects, will be enrolled to Group 1 (CAM2038 q1w). Approximately 16 subjects will be enrolled into each of Group 2 (128 mg CAM2038 q4w) and Group 3 (160 mg CAM2038 q4w), for a total of approximately 32 subjects administered CAM2038 q4w. These sample sizes are consistent with typical PK studies. Replacement subjects may be added at the discretion of the Sponsor with the agreement of the Principal Investigator.

8.1 Inclusion Criteria

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

1. Subject must provide written informed consent prior to the conduct of any study-related procedures.
2. Male or non-pregnant, non-lactating female subject, aged 19 to 65 years, inclusive.
3. Body mass index between 19 and 35 kg/m^2, inclusive.
4. Current diagnosis of moderate to severe opioid use disorder (according to the DSM-V) or past medical history of opioid use disorder currently being treated with SL BPN.
5. Subject must be taking SL BPN (Subutex® equivalent) 24 mg (Group 1 and Group 2) or ≥24 mg (Group 3) daily for at least 30 days prior to Screening.
6. Subject has a history of moderate to severe chronic non-cancer pain.
7. Male and female subjects of childbearing potential must be willing to use a reliable method of contraception during the entire study (Screening visit to Follow-up phone call) (Section 8.4.1).
8. Subject must be willing and able to comply with all study procedures and requirements.

8.2 Exclusion Criteria

Subjects will not be eligible to participate in this study if any of the following exclusion criteria are met:

1. Individuals meeting DSM-V substance use disorder criteria for alcohol, benzodiazepines, central nervous system (CNS) stimulants, or other drugs of abuse (excluding caffeine, tobacco or tetrahydrocannabinol [THC]/marijuana).
2. Any clinically significant abnormality on the basis of medical history, vital signs, physical examination, 12-lead electrocardiogram (ECG; Fridericia's corrected QT interval [QTcF] ≥450 msec. for males or ≥470 msec. for females), and laboratory evaluations (including hematology, clinical chemistry, urinalysis at Screening), in the opinion of the Investigator.
3. 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 study, including subjects who are at a risk for gastrointestinal obstruction or paralytic ileus or who have severe respiratory insufficiency, respiratory depression, airway obstruction,

gastrointestinal motility disorders, biliary tract disease, severe hepatic insufficiency, planned surgery and prior treatment with monoamine oxidase inhibitors.

4. Use (therapeutic or non-therapeutic) of opioids other than SL BPN.
5. Aspartate aminotransferase (AST) levels > 3 X the upper limit of normal, alanine aminotransferase (ALT), levels > 3 X the upper limit of normal, total bilirubin > 1.5 X the upper limit of normal, or creatinine > 1.5 X upper limit of normal on the Screening laboratory assessments, or other clinically significant laboratory abnormalities, which in the opinion of the Investigator may prevent the subject from safely participating in study.
6. Pregnant or lactating or planning to become pregnant during the study.
7. Diagnosis of, or currently under investigation for, fibromyalgia, complex regional pain syndrome, neurogenic claudication due to spinal stenosis, spinal cord compression, acute nerve root compression, severe or progressive lower extremity weakness or numbness.
8. History of chemotherapy or confirmed malignancy (except basal cell or squamous carcinoma of the skin) within the past 2 years.
9. Clinically significant history of, or current evidence for, suicidal ideation or those who are actively suicidal, as based on the Columbia-Suicide Severity Rating Scale (C-SSRS; grade 4 or 5).
10. Clinically significant history of major depressive disorder that is poorly controlled with medication.
11. Hypersensitivity or allergy to BPN or other opioids, or excipients of CAM2038.
12. Exposure to any investigational drug within the 4 weeks prior to Screening.
13. Participants with a clinically significant history of risk factors of Torsades de Pointes and any existing ventricular tachyarrhythmias such as bigeminy, trigeminy, heart failure, hypokalemia, family history of Long QT Syndrome.
14. On medications that have the potential for prolonging the QT interval or who may require such medications during the course of the study along with clinically significant abnormalities on screening electrocardiogram (ECG) readings as deemed by the investigator (Appendix 17.1).
15. Requires current use of agents that are 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).
16. Intolerance to venipuncture and/or difficulty with venous access, as per the judgment of the Investigator/research staff.
17. Is an employee of the Investigator or the study site, with direct involvement in the proposed study or other studies under the direction of the Investigator or study site, or is a family member of an employee or of the Investigator.
18. Any pending legal action that could prohibit participation or compliance in the study.

8.3 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 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
- Clinically significant QTc interval prolongation following administration of CAM2038 q1w or q4w, as judged by the Investigator and agreed upon by the Medical Monitor
- At the request of the Sponsor, regulatory agency, or Institutional Review Board (IRB)
- Subject is lost to follow-up
- 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
- Major protocol violation
- Pregnancy
- Use of unacceptable concomitant medication(s) (Section 9.5)

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, if possible, although the subject is not obligated to provide such a reason. In the event a subject is lost to follow-up, a third party could be hired to locate the subject.

All efforts should be made by the Investigator to continue collection of concomitant medications, and AEs in subjects that discontinue study drugs, unless the subject withdraws his/her consent at the time of early discontinuation. Subjects discontinued due to clinically significant QTc interval prolongation should be monitored closely by undergoing daily ECGs, until ECG readings return to baseline, or QTc interval values are no longer judged to be clinically significant. The Investigator should also ask the subject to complete the Follow-up phone-call, provided that the subject has not withdrawn consent. If a subject refuses to complete EOT procedures and/or Follow-up, this information will be recorded.

8.4 Study restrictions

In addition to the criteria described in Sections 8.1 and 8.2, the subject must agree to abide by the following study restrictions.

8.4.1 Contraception Requirements

Male and female subjects of childbearing potential must be using and willing to continue using medically acceptable contraception during the study. Examples of medically acceptable forms of contraception include:

- True abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Hormonal contraceptives (combined oral pill, patch or vaginal ring, intrauterine device or system, progestin implant or injection)
- Surgical sterilization (e.g. vasectomy or bilateral tubal ligation)
- Condom plus spermicidal agent (foam/gel/film/cream/suppository) during sexual intercourse with a female partner. In addition, the female partner should also be on another form of contraception (e.g., occlusive cap/diaphragm/intrauterine device/hormonal contraception, etc.) if she is of childbearing potential.
- To prevent exposure of any partner to the semen from a male subject who has been exposed to the investigational product, male subjects must use a condom during non-vaginal intercourse with any partner - male or female.

The chosen contraception method(s) must be followed from the first administration of CAM2038 until at least 3 months after receiving the last dose of the investigational product.

Female subjects of non-childbearing potential are not required to use contraception or undergo pregnancy tests; however, they must be 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 amenorrheic for at least 2 years without another cause or amenorrheic for at least 1 year without another cause and a documented follicle stimulating hormone (FSH) level ≥50 mIU/mL. If females are not amenorrheic for 2 years or amenorrheic for 1 year with a documented FSH level ≥50 mIU/mL or surgically sterile, then females will have to undergo the pregnancy procedures as stated in Table 1 (Group 1), Table 2 (Group 2), and Table 3 (Group 3).

Female subjects must not donate ova starting at Screening and throughout the clinical study period and for 3 months after final investigational product administration.

Male subjects must not have unprotected sexual intercourse with a female who is pregnant or breastfeeding during the study and for 3 months after final investigational product administration.

Subjects must not donate sperm throughout the study and for at least 3 months after receiving the last dose of the investigational product.

8.4.2 Dietary and Fluid Restrictions

Subjects will be required to fast from all food or drink (except water) for at least 4 hours before the Screening visit and the EOT visit. During the in-house stay in the CRU, standardized meals and fluids will be provided.

No food and drink containing grapefruit, Chinese grapefruit (pomelo), or Seville orange (including marmalade) will be allowed from 48 hours before each visit to the CRU and while subjects are confined to the CRU.

Quinine-containing products (e.g., tonic water) will not be allowed from 7 days before each confinement to the CRU and while subjects are confined to the CRU.

To avoid falsifying urine drug screen (UDS) results, no food or drink containing poppy seeds (e.g., specialty breads and muffins) will be allowed from 72 hours before Screening and 7 days before the first administration of CAM2038 through the end of the study.

8.4.3 Alcohol, Caffeine and Other Drug Use

Alcohol consumption must be avoided from 48 hours before any study visit and while subjects are confined to the CRU. Alcohol abstinence will be confirmed with a breath alcohol test.

Subjects should not regularly consume > 21 units per week for males and > 14 units of alcohol per week for females during the off-site days during the study (1 unit is equal to approximately ½ pint [200 mL] of beer, 1 small glass [100 mL] of wine, or 1 measure [25 mL] of spirits).

No food or drink containing caffeine (e.g., chocolate, coffee, tea, cola, Red Bull, etc.) will be allowed from 24 hours before each study visit and while subjects are confined to the CRU. At other times during the study, caffeine intake will be restricted to no more than 6 cups/day (1 cup = 120 mg caffeine).

Subjects will be asked to abstain from illicit drug use or non-medical use of therapeutic drugs throughout the study.

8.4.4 Activity and Exercise

Subjects should refrain from carrying out heavy physical training (e.g., long distance running, weight lifting, or any physical activity to which the subject is not accustomed) from 7 days before the first administration of CAM2038, while subjects are confined to the CRU, and through the EOT visit. Subjects should neither start any new physical training nor increase the intensity of their usual training during study participation. Subjects may participate in light recreational activities during confinement to the CRU (e.g., watch television, play computer games, read).

Subjects should refrain from driving a car or other vehicles, operating machines or engaging in potentially dangerous activities that require focused attention and intact physical balance until the subjects understand how CAM2038 affects their focus.

8.4.5 Other Restrictions

Subjects will be required to avoid using any prohibited medications, as described in Section 9.5. Subjects must not donate blood or plasma from 3 months before the first administration of CAM2038 and for at least 3 months after completion of the study.

Subjects will be required to follow the informed consent form (ICF) and any clinic rules and requirements.

9 TREATMENTS

9.1 Treatment Administration

Subjects will remain on their daily SL BPN treatment from Screening until Day -1 (the day before the first CAM2038 dose).

On Day 1, subjects will be randomized to Group 1 (32 mg CAM2038 q1w) or Group 2 (128 mg CAM2038 q4w), or be enrolled into the additional Group 3 (24 mg SL BPN and 160 mg CAM2038 q4w). All study drugs will be administered in an open-label manner throughout the study. Subjects will receive the following treatments in the study:

- Group 1: 3 single weekly SC injections of 32 mg CAM2038 q1w (0.64 mL) administered in the buttock to reach steady state, rotating between right and left buttock and injection site per Appendix 17.2, followed by 4 single weekly SC injections of 32 mg CAM2038 q1w administered in the buttock (reference), abdomen, thigh, and back of upper arm in a randomized, crossover manner, with injection site sequence allocated using a randomized crossover design. After the four weeks of rotating injections, subjects may continue to receive up to 6 open-label injections rotated in the abdomen, arm, buttocks and thigh. A pictorial of potential injection sites is provided in Appendix 17.2. The Investigator will keep a record of the specific injection site location at each treatment visit based on the pictorial of injection site location provided. Each injection should be rotated such that no injections are administered into the same site.
- Group 2: 4 monthly SC injections of 128 mg CAM2038 q4w (0.36 mL) administered in the buttock, to reach steady state. The sites of all of the CAM2038 q4w injections will be rotated between right and left buttock such that no injections are administered into the same site (Appendix 17.2). At the Day 113 (EOT) visit, CAM2038 q4w 128 mg subjects may continue on with open-label extension phase for up to 6 weeks and will be switched to CAM2038 q1w 32 mg for up to 6 injections of CAM2038 q1w 32 mg. Buttock injection sites will be rotated in accordance to Appendix 17.2.
- Group 3: 7 consecutive daily doses of 24 mg of SL BPN to reach steady state followed by 4 monthly SC injections of 160 mg CAM2038 q4w (0.45 mL) administered in the buttock, to reach steady state. The sites of all of the CAM2038 q4w injections will be rotated between right and left buttock such that no injections are administered into the same site (Appendix 17.2).

Subjects in Group 1 will receive treatment for up to 13 weeks, subjects in Group 2 will receive treatment for up to 22 weeks, and subjects in Group 3 will receive treatment for up to 17 weeks during the study.

9.2 Identity of Investigational Products

The following treatments will be used during the treatment phase:

- Group 1: CAM2038 q1w (BPN FluidCrystal® Injection depot for once weekly administration), 50 mg/mL: 32 mg (BPN base), 0.64 mL SC injection.

- Group 2: CAM2038 q4w (BPN FluidCrystal® Injection depot for once monthly administration), 356 mg/mL: 128 mg (BPN base), 0.36 mL SC injection.
- Group 3: SL BPN (Subutex® equivalent) 24 mg (3 tablets of 8 mg BPN) for once daily administration, followed by CAM2038 q4w (BPN FluidCrystal® Injection depot for once monthly administration), 356 mg/mL: 160 mg (BPN base), 0.45 mL SC injection.

The following treatment will be used during the open-label extension phase:

- Group 1 and Group 2: CAM2038 q1w (BPN FluidCrystal® Injection depot for once weekly administration), 50 mg/mL: 32 mg (BPN base), 0.64 mL SC injection.

9.2.1 Description of CAM2038 q1w and CAM2038 q4w SC Injection Products

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

CAM2038 q4w will be supplied as pre-filled syringe with safety device and plunger containing the following: BPN, soybean phosphatidylcholine, glycerol dioleate, and N-Methyl-2-pyrrolidone. All containers/packages/boxes of study drug will be clearly labeled with study-specific information meeting all the applicable regulatory/institutional requirements.

9.2.2 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. A description of storage conditions for CAM2038 and SL BPN will be provided to the CRU.

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 study. All unused supplies will be checked against the drug accountability records during the study and/or at the end of the study.

Buprenorphine is a Schedule III controlled substance and study drugs 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.

9.2.3 Dispensing and Administration

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

CAM2038 q1w and CAM2038 q4w SC injections will be administered by designated healthcare professional(s) at the CRU. Detailed instructions for use will be provided to the study staff.

Subjects in Group 3 will be instructed to place SL BPN tablets (3 x 8 mg tablets) under the tongue until dissolved. Tablets should be placed in different areas under the tongue at the same time. Administration of SL BPN will be conducted at the CRU.

Study drug administration, including SL BPN administration in Group 3, will be clearly documented.

9.3 Method of Assigning Subjects to Treatment Groups

Subjects who have provided 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. Once any subject number or randomization number is assigned, it cannot be reassigned to any other subject.

On Day 1, before the first dose of CAM2038, subjects will be randomized into Group 1 (CAM2038 q1w) or Group 2 (128 mg CAM2038 q4w) in a 3:2 ratio, or enrolled into the additional Group 3 (160 mg CAM2038 q4w).

For subjects in Group 1, injection site rotation will be randomized (on Day 1) to avoid bias in the assignment of injection site sequence. The sequences will be as follows, ABDC, BCAD, CDBA, and DACB, where A=buttock, B=abdomen, C=thigh, and D=back of upper arm. The injection site sequence assignment will be made at the time of Group randomization.

9.4 Selection of Doses

The study will include 3 dose levels of CAM2038, a once weekly CAM2038 q1w 32 mg SC injection, a once monthly CAM2038 q4w 128 mg SC injection, and a once monthly CAM2038 q4w 160 mg SC injection. For CAM2038 q1w, this study is expected to provide data on the plasma BPN and norBPN levels across 4 injections sites (buttock [reference], abdomen, thigh and back of upper arm). The 32 mg dose is the highest single dose strength available for CAM2038 q1w and predicted steady state plasma concentrations of BPN are expected to be within known therapeutic plasma levels based on previous studies (HS-11-426 and HS-13-487).

A previous study (HS-13-487) has demonstrated PK parameters for CAM2038 q4w after single dose administration; this study is expected to provide PK of CAM2038 q4w at steady state. The 128 mg CAM2038 q4w dose is 33% lower and the 160 mg CAM2038 q4w dose is 17% lower than the maximum dose given as a single dose (192 mg) to healthy subjects under naltrexone blockade, and which was shown to be safe and well tolerated.

9.5 Prior and Concomitant 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 several days following discontinuation of SL BPN treatment, or up to 2 weeks (Group 1) or up to a month (Group 2 [for subjects not entering the open-label extension] and Group 3) 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. Particular care should be taken in subjects with chronic respiratory disease, bowel disease and liver disease during anesthesia and the post-operative period.
- BPN is metabolized via CYP3A4. Because CYP3A4 inhibitors may increase plasma concentrations of BPN, if 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 required, the Medical Monitor must be consulted. Interactions with CYP3A4 inducers have not been investigated; therefore it is recommended that the use of agents such as phenobarbital, carbamazepine, phenytoin and rifampicin be avoided in subjects receiving study treatment. The Medical Monitor must be consulted prior to starting subjects on any of these agents.
- Concomitant use of other narcotic anesthetics, benzodiazepines, phenothiazines, other tranquilizers, or other CNS depressants (including alcohol and sedative/hypnotics) may cause respiratory and CNS depression. Use of these substances should be minimized during treatment with CAM2038 (see also Section 8.4.3). If these sedatives are required during the study, the Medical Monitor must be consulted prior to providing narcotic anesthetics, benzodiazepines, phenothiazines, other tranquilizers, or other CNS depressants (including alcohol and sedative/hypnotics). Subjects should be advised of the danger of concomitant use of sedatives while participating in 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.

9.6 Treatment Compliance

Study drugs will be administered by study personnel; thus no subject compliance procedures are necessary.

10 STUDY PROCEDURES AND ASSESSMENTS

All study assessments will be performed at the visits and the time points outlined in the Schedule of Assessments for Group 1 (Table 1), Group 2 (Table 2), and Group 3 (Table 3). The following sections outline the details and procedures associated with the assessments.

Table 1: Schedule of Assessments – Group 1 (CAM2038 q1w)

Study	Screening	Treatment Phase						Open-label Safety Extension Phase							FU
Treatment:		**CAM2038 q1w**						**CAM2038 q1w**							
CAM2038 q1w Dose:		**Doses 1 to 3**				**Doses 4 to 7**		**Doses 8 to 13**							
Day:	**-21 to -1**	**D1**	**D2**	**D8**	**D15**	**D22, D29 D36, D43**	**D23-27, D30-34, D37-41, D44-48**	**D50/ EOT**	**D57**	**D64**	**D71**	**D78**	**D85**	**D92/ EOT**	**D99/FU**
Informed Consent[a]	X														
Eligibility Criteria Review[b]	X	X													
Medical, Psychosocial and Medication History	X														
Substance Use and Treatment History	X														
Complete Physical Examination	X							X						X	
Weight, BMI	X							X						X	
Height	X														
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[d]	X	X	X			X	X	X	X	X	X	X	X	X	
Biochemistry, Hematology, Urinalysis, and Coagulation Profile	X	X		X[e]	X[e]	X[e]		X	X	X	X	X	X	X	
Pregnancy Test[f]	X	X		X	X	X		X			X			X	
Adverse Events[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.
[b] Prior to treatment on Day 1, all Inclusion and none of the Exclusion criteria must be met.
[c] Vital signs (temperature, blood pressure, pulse rate, respiratory rate) will be measured pre-dose and 15 minutes' post-dose after each CAM2038 q1w administration and will be measured once at each non-dosing visit.
[d] ECG will be measured at the Screening and EOT visits, and pre-dose and 23 (±2) hours after the first CAM2038 q1w administration. ECGs will be measured at 1, 4, 6, 10, 24, 48, 72, 96 and 168 hours post-dose on doses 4 through 7.
[e] Assessment of serum sodium, bicarbonate, potassium, magnesium, calcium levels only.
[f] A serum pregnancy test will be performed at Screening and EOT visits. An "in-office" urine pregnancy test will be required prior to all doses of CAM2038 q1w (for women of childbearing potential) during days 1 through 50. An "in-office" urine pregnancy test will be required prior to all doses of CAM2038 q1w (for women of childbearing potential) for those women who continue in the extension phase will also be required.
[g] 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 and once daily during inpatient stays.

Study Period/Phase:	Screening	Treatment Phase						Open-label Safety Extension Phase							FU
Treatment:		CAM2038 q1w						CAM2038 q1w							
CAM2038 q1w Dose:		Doses 1 to 3				Doses 4 to 7		Doses 8 - 13							
Day:	-21 to -1	D1	D2	D8	D15	D22, D29 D36,	D23-27, D30-34, D37-41, D44-48	D50/ EOT	D57	D64	D71	D78	D85	D92/ EOT	D99/ FU
C-SSRS[h]	X	X	X	X	X	X		X			X			X	
Injection Site Examination[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	
PK samples		X[j]		X[j]	X[j]	X	X[k]	X[k]						X	
COWS[l]		X	X	X	X	X		X						X	
SOWS[l]		X	X	X	X	X		X						X	
UDS and Breath Alcohol Test	X	X	X	X	X	X	X	X			X			X	
NRS for Pain[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization[n]		X													
CAM2038 q1w SC injection[o]		X		X	X	X		X	X	X	X	X	X		
Admission to CRU						X									
Discharge from CRU							X								
Outpatient visits		X	X	X	X			X	X	X	X	X	X	X	
Telephone call															X
Transfer to previous BPN therapy								X[p]						X	

[h] C-SSRS-Screening will be performed at Screening and then C-SSRS-since last visit will be performed at other subsequent visits.
[i] Injection site examinations will occur at each visit and once daily during inpatient stays.
[j] Pharmacokinetic samples will be collected at pre-dose CAM2038 q1w doses 1, 2 and 3.
[k] Pharmacokinetic samples will be collected at pre-dose and at 0.5, 1, 2, 4, 6, 10, 24, 30, 48, 72, 96, 120 and 168 hours post CAM2038 q1w doses 4, 5, 6 and 7. When a pre-dose and 168 hour post-dose time point coincide, only 1 PK sample will be collected. If a subject terminates early from the study, then a PK blood sample is to be drawn.
[l] COWS and SOWS will be performed pre-dose on all dosing days and at each other visit.
[m] Average daily NRS pain score will be recorded each day using an electronic device.
[n] Randomization to Group 1 or Group 2. Randomization to Group 1 will also include injection site sequence.
[o] The first 3 SC injections (Day 1, Day 8, Day 15) will be administered in the buttock (rotating between right and left buttock and injection site per Appendix 17.2) then the injection site sequence (buttock [reference], abdomen, thigh, back of upper arm) for the last 4 SC injections (Day 22, Day 29, Day 36, Day 43) will be randomly allocated to each subject utilizing 1 of 4 pre-determined sequences. On Days 50, 57, 64, 71,78 and 85 injections will be rotated in abdomen, arm, buttocks, thigh in the opposite arm of doses 4-7.
[p] If not participating in the open-label safety extension or terminated early from the study, subjects will transition back to standard care at the Day 50/EOT study visit.

BMI=body mass index; BPN=buprenorphine; COWS=Clinical Opioid Withdrawal Scale; CRU= clinical research unit; C-SSRS=Columbia-Suicide Severity Rating Scale; D=day; ECG=electrocardiogram; EOT=End of Treatment; NRS=numerical rating scale; PK=pharmacokinetic; SC=subcutaneous; SOWS=Subjective Opioid Withdrawal Scale; UDS=urine drug screen.

Table 2: Schedule of Assessments – Group 2 (128 mg CAM2038 q4w)

Study Period/Phase:	**Screening**	**Treatment Phase**										**Open-label Safety Extension Phase CAM2038 q1w**							**FU**
Treatment:		**128 mg CAM2038 q4w**																	
CAM2038 q4w Dose:		**Dose 1**			**Dose 2**		**Dose 3**		**Dose 4**										
Day:	**-21 to -1**	**D1**	**D2**	**D8 D15 D22**	**D29**	**D31 D36 D43 D50**	**D57**	**D59 D64 D71 D78**	**D85**	**D86**	**D87, D88 D89, D90 D92, D95 D99, D106**	**D113/ EOT**	**D120**	**D127**	**D134**	**D141**	**D148**	**D155/ EOT**	**D162**
Informed Consent[a]	X																		
Eligibility Criteria Review[b]	X	X																	
Medical, Psychosocial and Medication History	X																		
Substance Use and Treatment History	X																		
Complete Physical Examination	X											X						X	
Weight, BMI	X											X						X	
Height	X																		
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[d]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Biochemistry, Hematology, Urinalysis, and Coagulation Profile	X	X			X[e]		X[e]		X[e]			X	X	X	X	X	X	X	
Pregnancy Test[f]	X	X			X		X		X			X			X			X	
Adverse Events[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.
[b] Prior to treatment on Day 1, all Inclusion and none of the Exclusion criteria must be met.
[c] Vital signs (temperature, blood pressure, pulse rate, respiratory rate) will be measured pre-dose and 15 minutes post-dose after each CAM2038 q4w administration. Vital signs will also be measured at the Screening, Day 2 and EOT visits, and at each admission.
[d] ECG will be measured at the Screening and EOT visits, and pre-dose and 6 (±1) hours after each CAM2038 q4w administration. After dose 4, ECGs will be measured at 1, 4, 6, 10, 24, 72, 120, 168 (7 days), 336 (14 days) and 672 (28 days) hours post-dose.
[e] Assessment of serum sodium, bicarbonate, potassium, magnesium, calcium levels only.
[f] A serum pregnancy test will be performed at Screening and EOT visits. An "in-office" urine pregnancy test will be required prior to all doses of CAM2038 q4w (for women of childbearing potential) during days 1 through 113. An "in-office" urine pregnancy test will be required prior to all doses of CAM2038 q1w (for women of childbearing potential) for those women that continue to the extension phase.

[g] 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 and once daily during inpatient stays.

Study Period/Phase:	Screening	Treatment Phase										Open-label Safety Extension Phase CAM2038 q1w							FU
Treatment:		128 mg CAM2038 q4w																	
CAM2038 q4w Dose:		Dose 1			Dose 2		Dose 3		Dose 4										
Day:	-21 to -1	D1	D2	D8 D15 D22	D29	D31 D36 D43 D50	D57	D59 D64 D71 D78	D85	D86	D87, D88 D89, D90 D92, D95 D99, D106	D113/ EOT	D120	D127	D134	D141	D148	D155/ EOT	D162
C-SSRS[h]	X	X	X		X		X		X			X			X			X	
Injection Site Examination[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK samples		X[j]		X[j]	X[k]	X[k]	X[k]	X[k]	X[l]	X[m]	X[m]	X						X	
COWS[n]		X	X		X		X		X			X						X	
SOWS[n]		X	X		X		X		X			X						X	
UDS and breath alcohol test	X	X	X	X	X	X	X	X	X	X	X	X			X			X	
NRS for Pain[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization[p]		X																	
CAM2038 q4w SC injection[q]		X			X		X		X										
CAM2038 q1w SC injection[q]												X	X	X	X	X	X		
Admission to CRU									X										
Discharge from CRU										X									
Outpatient visits		X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	
Telephone call																			X
Transfer to previous BPN therapy												X[r]						X	

[h] C-SSRS-Screening will be performed at Screening and then C-SSRS-since last visit will be performed at other subsequent visits.
[i] Injection site examinations will occur at each visit and once daily during inpatient stays.
[j] Pharmacokinetic samples will be collected at pre-dose, 168 hrs (7 days), 336 hrs (14 days) and 504 hrs (21 days) after CAM2038 q4w dose 1. If a subject terminates early from the study, then a PK blood sample is to be drawn.
[k] Pharmacokinetic samples will be collected at pre-dose, one sample any time between 4 and 8 hrs post-dose, approximately 48 hrs, 168 hrs (7 days), 336 hrs (14 days) and 504 hrs (21 days) after CAM2038 q4w doses 2 and 3.
[l] Pharmacokinetic samples will be collected at pre-dose, 0.5, 1, 2, 4, 6, and 10 hours after CAM2038 q4w dose 4.
[m] Pharmacokinetic samples will be collected at approximately 24, 48, 72, 96, 120, 168 (7 days), 240 (10 days), 336 (14 days), 504 (21 days) and 672 (28 days) hours after CAM2038 q4w dose 4.
[n] COWS and SOWS will be performed pre-dose on all dosing days and at each other visit.
[o] Average daily NRS pain score will be recorded using an electronic device each day.

[p] Randomization to Group 1 or Group 2.

[q] The SC injections will be administered in the buttock, rotating between right and left buttock and injection site per Appendix 17.2. On Day 113, subjects will have the option of switching from 128 mg CAM2038 q4w to 32 mg CAM2038 q1w.

[r] If not participating in the open-label safety extension or terminated early from the study, subjects will transition back to standard care at the Day 50/EOT study visit.

BMI=body mass index; BPN=buprenorphine; COWS=Clinical Opioid Withdrawal Scale; CRU=clinical research unit; C-SSRS=Columbia-Suicide Severity Rating Scale; D=day; ECG=electrocardiogram; EOT=End of Treatment; NRS=numerical rating scale; PK=pharmacokinetic; SC=subcutaneous; SOWS=Subjective Opioid Withdrawal Scale; UDS=urine drug screen.

Table 3: Schedule of Assessments – Group 3 (160 mg CAM2038 q4w)

Study Period/Phase:	**Screening**	**Treatment Phase**													**FU**
Treatment:		**SL BPN**		**160 mg CAM2038 q4w**											
				Dose 1			**Dose 2**		**Dose 3**		**Dose 4**				
Day:	**-21 to -1**	**D1 - D6**	**D7**	**D8**	**D9**	**D15 D22 D29**	**D36**	**D38, D43, D50, D57**	**D64**	**D66, D71, D78, D85**	**D92**	**D93**	**D94, D95, D96, D97, D99, D102, D106, D113**	**D120/ EOT**	**D127**
Informed Consent[a]	X														
Eligibility Criteria Review[b]	X	X													
Medical, Psychosocial and Medication History	X														
Substance Use and Treatment History	X														
Complete Physical Examination	X													X	
Weight, BMI	X													X	
Height	X														
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[d]	X	X	X	X			X		X		X	X	X	X	
Biochemistry, Hematology, Urinalysis, and Coagulation Profile	X	X[e]		X			X[f]		X[f]		X[f]			X	
Pregnancy Test[g]	X	X		X			X		X		X			X	
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.
[b] Prior to treatment on Day 1, all Inclusion and none of the Exclusion criteria must be met.
[c] Vital signs (temperature, blood pressure, pulse rate, respiratory rate) will be measured pre-dose and 15 minutes post-dose after the SL BPN dose on Day 1 and after each CAM2038 q4w administration. Vital signs will also be measured at the Screening, Day 8 discharge, Day 9 and EOT visits, and at each admission.
[d] ECG will be measured at the Screening and EOT visits, at pre-dose and 1 hour after SL BPN administration on Day 1, and pre-dose and 6 (±1) hours after each CAM2038 q4w administration. After CAM2038 dose 4, ECGs will be measured at 1, 4, 6, 10, 24, 72, 120, 168 (7 days), 336 (14 days) and 672 (28 days) hours post-dose.
[e] Day 1 only.
[f] Assessment of serum sodium, bicarbonate, potassium, magnesium, calcium levels only.
[g] A serum pregnancy test will be performed at Screening and EOT visits. An "in-office" urine pregnancy test will be required prior to SL BPN dosing on Day 1 and all doses of CAM2038 q4w (for women of childbearing potential).
[h] 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 and once daily during inpatient stays.

Study Period/Phase:	Screening	Treatment Phase													FU
Treatment:		SL BPN		160 mg CAM2038 q4w											
				Dose 1			Dose 2		Dose 3		Dose 4				
Day:	-21 to -1	D1-D6	D7	D8	D9	D15 D22 D29	D36	D38, D43, D50, D57	D64	D66, D71, D78, D85	D92	D93	D94, D95, D96, D97, D99, D102, D106, D113	D120/ EOT	D127
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[i]	X	X	X	X	X		X		X		X			X	
Injection Site Examination[j]				X	X	X	X	X	X	X	X	X	X	X	
PK samples			X[k]	X[k]		X[k]	X[l]	X[l]	X[l]	X[l]	X[m]	X[m]	X[m]	X[m]	
COWS[n]		X	X	X		X	X	X	X	X	X		X	X	
SOWS[n]		X	X	X		X	X	X	X	X	X		X	X	
UDS and breath alcohol test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
NRS for Pain[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SL BPN administration		X	X												
CAM2038 q4w SC injection[p]				X			X		X		X				
Admission to CRU			X								X				
Discharge from CRU				X[q]								X			
Outpatient visits		X			X	X	X	X	X	X			X	X	
Telephone call															X
Transfer to previous BPN therapy														X	

[i] C-SSRS-Screening will be performed at Screening and then C-SSRS-since last visit will be performed at other subsequent visits.
[j] Injection site examinations will occur at each visit after CAM2038 q4w administration and once daily during inpatient stays.
[k] Pharmacokinetic samples will be collected at pre-dose (within 45 minutes), 10, 20, 30 and 40 minutes, and 1, 1.5, 2, 3, 4, 6, 10 and 24 hours after SL BPN dose 7, and pre-dose, 168 hrs (7 days), 336 hrs (14 days) and 504 hrs (21 days) after CAM2038 q4w dose 1. If a subject terminates early from the study, then a PK blood sample is to be drawn.
[l] Pharmacokinetic samples will be collected at pre-dose, one sample any time between 4 and 8 hrs post-dose, approximately 48 hrs, 168 hrs (7 days), 336 hrs (14 days) and 504 hrs (21 days) after CAM2038 q4w doses 2 and 3.
[m] Pharmacokinetic samples will be collected at pre-dose, 0.5, 1, 2, 4, 6, 10, 24, 48, 72, 96, 120, 168 (7 days), 240 (10 days), 336 (14 days), 504 (21 days) and 672 (28 days) hours after CAM2038 q4w dose 4.
[n] COWS and SOWS will be performed pre-dose on all dosing days and at each other visit.
[o] Average daily NRS pain score will be recorded using an electronic device each day.
[p] The 4 SC injections will be administered in the buttock, rotating between right and left buttock and injection site per Appendix 17.2.
[q] Subjects will be discharged at least 6 hours after CAM2038 q4w dose 1, once the ECG and other safety assessments are completed, and the Investigator deems it safe for the subject to leave the CRU.

BMI=body mass index; BPN=buprenorphine; COWS=Clinical Opioid Withdrawal Scale; CRU=clinical research unit; C-SSRS=Columbia-Suicide Severity Rating Scale; D=day; ECG=electrocardiogram; EOT=End of Treatment; NRS=numerical rating scale; PK=pharmacokinetic; SC=subcutaneous; SL=sublingual; SOWS=Subjective Opioid Withdrawal Scale; UDS=urine drug screen.

10.1 Demographics and Other Baseline Characteristics

10.1.1 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 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.

10.1.2 Demographics

The following demographics will be recorded: age (birthdate), sex, weight, height, body mass index (BMI), race, and ethnicity.

10.1.3 Medical and Psychosocial History

The complete medical history will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems in the past five years or deemed to be clinically significant in the opinion of the Investigator. All findings on medical history will be evaluated by the Investigator for clinical significance.

A complete psychosocial history will be obtained including education, employment status, marital/significant other status, residential status and legal status/arrest history.

10.1.4 Medication History

All medications (prescription and non-prescription or herbal medications/natural health products) taken by the subjects during the 30 days prior to Screening will be recorded in the source documentation as medication history. Substance Use and Treatment History (Section 10.1.5) will be collected separately and stored in the subject's file.

10.1.5 Substance Use and Treatment History

DSM-V modules will be included to evaluate alcohol and substance use disorders.

A complete history of previous and current illicit drug use, substance abuse/dependence, and treatments for any substance use disorders (pharmacologic as well as non-pharmacologic) will be obtained using a timeline follow-back type of interview (Fals-Stewart et al., 2000).

10.2 Eligibility Review and Randomization

The Investigator or designee must document that the subjects meet each individual criterion (as outlined in Section 8.1 and Section 8.2) via a signed note or eligibility and clinical stability checklist during Screening. Signatures on these documents must be dated on or before the date of

study start (Day 1). Prior to the first dose with CAM2038 q1w or CAM2038 q4w on Day 1, a re-check of the eligibility criteria will be performed.

Up to a total of 40 subjects will be randomized at a 3:2 ratio to Group 1 (CAM2038 q1w group with 24 subjects) Group 2 (128 mg CAM2038 q4w group with 16 subjects). Approximately 16 subjects will be enrolled into the additional Group 3 (24 mg SL BPN followed by 160 mg CAM2038 q4w).

Subjects randomized to Group 1 (CAM2038 q1w) will be randomized at a 1:1:1:1 ratio to 1 of the following 4 injection sequences: ABDC, BCAD, CDBA, and DACB, where A=buttock (reference), B=abdomen, C=thigh, and D=back of upper arm.

10.3 Pharmacokinetic Assessments

10.3.1 Drug concentration measurements

10.3.1.1 Sample Collection, Preparation and Handling

PK samples for analysis will be collected at the time points specified in Table 1 (Group 1), Table 2 (Group 2), and Table 3 (Group 3).

The actual date and time of each PK sample collection will be recorded. The approximate total PK blood volume (6 mL per sample) to be taken per subject during the study is:

- Group 1 total PK blood volume = 342 mL
- Group 2 total PK blood volume = 204 mL
- Group 3 total PK blood volume = 276 mL

10.3.1.2 Determination of Drug Concentration

Plasma concentrations of BPN and norBPN will be determined using a validated LC-MS-MS method. The method is validated for a range of 0.0250 to 10.0 ng/mL for BPN and 0.0200 to 8.00 ng/mL for norBPN, based on the analysis of 0.500 mL of K_2 EDTA plasma.

10.3.2 Pharmacokinetic parameters

Pharmacokinetic parameters of BPN and its active metabolite norBPN will be estimated using Phoenix® WinNonlin® (Certara, L.P., 100 Overlook Center, Princeton, NJ 08540 USA), version 6.4 or higher. Standard non-compartmental methods and actual dates and times of dosing and blood sampling will be used in the calculations. The following PK parameters will be determined for BPN and norBPN (if applicable):

- Group 1:
  - AUC_{ss} (area under the plasma concentration-time curve during a 7-day dosing interval at steady state) for each injection site, i.e., buttock (reference), abdomen, thigh and back of upper arm.
  - $C_{ss,av}$ for each injection site, i.e., buttock (reference), abdomen, thigh and back of upper arm.

- $C_{ss,\ max}$ for each injection site, i.e., buttock (reference), abdomen, thigh and back of upper arm.
- $t_{ss,max}$ for each injection site, i.e., buttock (reference), abdomen, thigh and back of upper arm.
- norBPN/BPN ratios for AUC_{ss} and $C_{ss\ max}$ for each injection site, i.e., buttock (reference), abdomen, thigh and back of upper arm.

- Group 2 and Group 3:
  - AUC_{ss} (AUC during a 24-hour dosing interval at steady state for SL BPN [Group 3 only] and a 28-day dosing interval at steady state for CAM2038 q4w)
  - $C_{ss,av}$
  - $C_{ss,max}$
  - $t_{ss,max}$
  - $C_{ss,28days}$ (for CAM2038 q4w treatment) and $C_{ss,24h}$ (for SL BPN treatment)
  - norBPN/BPN ratios for AUC_{ss} and $C_{ss,max}$

In Group 3, relative bioavailability of BPN will be assessed at steady state following repeated SC administration of 160 mg CAM2038 q4w as compared with repeated SL administration of 24 mg BPN.

Details of the PK evaluation will be presented in the statistical analysis plan (SAP). Values that are below the lower limit of quantification will be handled as described in the SAP.

10.4 Efficacy Assessments

The following sections provide an overview of the exploratory efficacy assessments included in the study.

10.4.1 Urine Toxicology

A 12-panel UDS will test for the following drugs of abuse: THC/marijuana, cocaine, phencyclidine (PCP), morphine and its related metabolites derived from opium (opiates), methamphetamines, methadone, amphetamines, barbiturates, benzodiazepines, methylenedioxymethamphetamine (MDMA), oxycodone and propoxyphene.

Urine drug screen samples will be collected at the time points specified in Table 1 (Group 1), Table 2 (Group 2), and Table 3 (Group 3) using a urine collection cup containing a temperature sensor. Specimen authenticity will be verified at the site using this sensor to measure the urine temperature immediately following collection. The temperature of a urine sample within 4 minutes of voiding should fall within the range of 32.2 to 37.7 degrees Celsius (90 to 100 degrees Fahrenheit). If test results are outside these ranges, the subject will be asked to immediately provide another urine sample. If this second sample is outside of the temperature range, the sample will be counted as 'missing', and should not be sent for analysis (any such samples must be documented in the subject's records). Direct observation approach to obtaining urine samples may be used if the Investigator deems necessary.

10.4.2 Numerical Rating Scale (NRS) for Pain

The NRS is an 11-point scale with anchors 0 (no pain) and 10 (worst pain imaginable). Subjects will record their Worst and Average Pain Score over the past 24 hours in an electronic diary on a daily basis. Study personnel and subjects will undergo training on how to complete the NRS assessment.

10.5 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 injections may be discontinued as clinically indicated.

10.5.1 Adverse Events and Serious Adverse Events

10.5.1.1 Adverse Event Reporting

Throughout the study, AEs will be documented on the appropriate page of the CRF whether or not considered treatment-related. This includes any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. CAM2038 injections sites will be examined during each scheduled visits for any signs of adverse site reactions, including erythema, pruritus, edema, pain, etc. The new injection site will also be examined shortly minutes after each injection to determine if any site related AEs have occurred. Subjects will also be queried specifically about local tolerability AEs in connection to the examinations.

Conditions existing prior to dosing will be recorded as part of the subject's medical history. The Investigator is responsible for assessing the relationship of AEs to the study drug; relationship will be classified as not related, unlikely related, possibly related, or probably related (see Section 10.5.1.2 for definitions).

All AEs and SAEs will be collected by the Investigator from the time informed consent is signed until 7 days after the EOT visit. This includes any AEs that are ongoing at the completion/termination of the study, and any AEs that start after the last dose of study drug. SAEs and AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization. Any SAEs considered related to study drug should be reported to the Sponsor without regards to these timelines.

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study or within 14 days of the EOT visit or premature discontinuation from the study whether or not related to the study drug, must be reported via email, facsimile or telephone within 24 hours of first being advised of the SAE. Follow-up information collected for any initial report of an SAE must be reported to the Sponsor or designee within 24 hours of receipt by the Investigator. In the event discussion is necessary call the Medical Monitor.

The Sponsor or designee will determine whether the SAE must be reported within 7 or 15 days to the FDA. If so, the Sponsor (or the Sponsor's representative) will report the event to the FDA. The Investigator will transmit a written report of the circumstances and outcome to the Sponsor as soon

as he or she is made aware of the circumstances. The Investigator will report SAEs to the IRB per IRB policy.

10.5.1.2 Adverse Event Definitions

An AE is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (e.g., biochemistry, ECG, etc.), or worsening of a pre-existing condition associated temporally with the use of the study drug whether or not considered related to the study drug.

A treatment-emergent AE is any condition that was not present prior to treatment with study drug but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

All AEs, including either observed or volunteered problems, complaints, signs, or symptoms must be recorded on the AE page of the CRF, regardless of whether associated with the use of study drug. This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study). AEs should be recorded in standard medical terminology.

The Investigator will evaluate each AE for duration, intensity, and relationship to study drug, record the action taken, and any treatment given. Recurrent symptoms of a chronic pre-existing condition are not considered AEs unless they occur in a worse or unexpected pattern during study drug administration.

10.5.1.3 Intensity of AEs

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

Mild AEs are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.

Moderate AEs introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

Severe AEs interrupt a subject's usual daily activity and typically require systemic drug therapy or other treatment.

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

10.5.1.4 Relationship to Study Drug

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

Not related indicates that the AE is definitely not related to the study drug.

Unlikely related indicates that there are other, more likely causes and study drug is not suspected as a cause.
Possibly related indicates that a direct cause and effect relationship between study drug and the AE has not been demonstrated but there is a reasonable possibility that the event was caused by the study drug.

Probably related indicates that there probably is a direct cause and effect relationship between the AE and the study drug.

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

Assessments are to be recorded on the CRF and must indicate clearly the relationship being assessed.

10.5.1.5 Serious Adverse Event

An SAE is defined as an AE that:

- Results in death
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)
- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or pre-planned surgery, procedure, or drug therapy does not constitute an SAE unless there is a complication resulting in hospitalization prolongation). An AE that results in a visit to an Emergency Room that does not require an inpatient stay is not always classified as an SAE.
- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a patient using the study drug regardless of time to diagnosis)
- Is considered an important medical event

Life-threatening events are defined as events that place the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.5.2 Pregnancy

Pregnancies among study participants or their partners should be reported to the Sponsor or designee as soon as possible after learning of the event. Subjects who become pregnant will not receive any more CAM2038 doses, will be discontinued from the study and referred back to the care of their usual provider or continue in the study after discussion with and documentation by the Investigator or his/her designee. Follow-up information will be obtained where possible (with the consent of the participant or their partner) regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant.

10.5.3 Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood and urine samples will be performed at a selected laboratory. The lab will generate laboratory reports and forward them to the CRU 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 4. Of note, a targeted assessment of electrolytes will be conducted throughout the study at pre-specified time points, and at additional time points at the discretion of the Investigator.

Table 4: 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 Creatine phosphokinase Total cholesterol (non-fasting)	12 panel illicit drug screen 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 and EOT visits. A urine pregnancy test will be required prior to all doses of CAM2038 q1w and q4w for all women of childbearing potential. Results must be reviewed and confirmed to be negative prior to start of CAM2038 treatment (Day 1).

The approximate total blood volume, including PK sample collections (Section 10.3.1.1) to be taken per subject during the study is the following:

- Group 1 total blood volume: approximately 546 mL
- Group 2 total blood volume: approximately 382.5 mL
- Group 3 total blood volume: approximately 352.5 mL

10.5.4 Vital Signs

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

specified in Table 1 (Group 1), Table 2 (Group 2), and Table 3 (Group 3). Clinically significant values will be recorded as AEs.

10.5.5 12-Lead Electrocardiogram

12-Lead ECGs will be performed after the subject has been resting in a recumbent/supine position for at least 3 minutes at the times specified in Table 1 (Group 1), Table 2 (Group 2), and Table 3 (Group 3). The ECG variables will include ventricular heart rate and the PR, QRS, QT, 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 medical history or with an AE. Subjects who have QTc > 500 msec or post-baseline increase > 60 msec will be discontinued from the study and will not receive any more injections of CAM2038. Subjects will then have daily ECGs until QTc values return to baseline. The Investigator can refer the subject to a Cardiologist, if necessary.

10.5.6 Physical Examination

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

Height, weight and BMI will be determined at the Screening visit. Weight and BMI will also be determined at the EOT visit.

10.5.7 Injection Site Examination

All CAM2038 injection sites (new and old) will be examined during each scheduled visit after the first dose of CAM2038 for any signs of adverse site reactions, including erythema, pruritus, edema, pain, etc. Injection site examination form is included in Appendix 17.3. Subjects will also be queried specifically about local tolerability AEs in connection to the examinations. Non-identifying photographs will be taken to document any injection site reactions.

10.5.8 Columbia-Suicide Severity Rating Scale

The C-SSRS will be used to assess both behavior and ideation. The C-SSRS 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 Baseline/Screening version (6 months and lifetime history; Appendix 17.4) and the Since Last Visit version (Appendix 17.5). 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, as indicated in Table 1 (Group 1), Table 2 (Group 2), and Table 3 (Group 3).

The C-SSRS is to be administered by the Investigator or his/her qualified designee. Qualified designee is defined 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.

10.5.9 Subjective Opioid Withdrawal (SOWS) Scale

In the SOWS, subjects rate the intensity of each of 16 common motoric, autonomic, gastrointestinal, musculoskeletal, and psychic symptoms of opioid withdrawal on a 5-point Likert scale, i.e., from 0 ("not at all") to 4 ("extremely"), based on how they were feeling at the time of testing (Appendix 17.6).

10.5.10 Clinical Opioid Withdrawal (COWS) Scale

Study personnel will assess clinical observations indicative of withdrawal using the COWS (Appendix 17.7). This scale consists of 11 common opioid withdrawal signs or symptoms, rated on a numeric scale and based on a timed period of observation of the subject by the rater.

10.5.11 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.

10.5.12 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 until such time that they are reasonably certain that their ability to engage in such activities is not adversely affected.

10.6 Efficacy Variables

10.6.1 Urine Toxicology

The frequency and incidence of urine toxicology results positive for opioids other than BPN, and positive results for other, non-opioid, drugs of abuse will be measured via qualitative methods.

10.6.2 Numerical Rating Scale for Pain

The weekly average of daily Pain Intensity (PI) will be calculated based on non-missing NRS scores (i.e., the missing daily scores will not be used in the calculation for the average). This weekly average will be called PI for that week. Pain Intensity Difference (PID) for a post-baseline Week i will then be derived as

PID at week 1i = PI at baseline – PI at week i.

Based on this definition, a positive PID is indicative of an improvement. The efficacy endpoint will be the change from Baseline in the weekly average of the daily Worst Pain score.

10.7 Appropriateness of Measures

The primary objective of this study is to evaluate steady state PK of CAM2038 q1w following SC injection at various administration sites and steady state PK of CAM2038 q4w; therefore, PK

blood samples will be collected to assess plasma concentrations of BPN and norBPN and derive the necessary PK parameters to evaluate rate and extent of exposure.

Standard safety outcomes, such as AEs, vital signs and clinical laboratory testing will be assessed during the study. In addition, frequent ECG assessments will be included to monitor potential QTc interval prolongation following repeated administration of CAM2038 q1w and q4w. The COWS and SOWS are included to monitor any potential opioid withdrawal symptoms associated with transitiong from SL BPN to CAM2038 and throughout the study.

Exploratory measures include urine toxicology and pain NRS scores, which are typical of studies evaluating efficacy in managing opioid dependence and chronic pain.

11 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 11.2.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators 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 the 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.

11.1 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, laboratory results, participant diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This study will use electronic data capture (EDC). 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.

11.2 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, and 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 International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

12 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1 Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a SAP. The SAP may include more detail of analysis populations, summary strategies, and any clarifications or changes necessary due to, for example, regulatory requests. The SAP must be finalized before database lock. Any changes to the final SAP will be discussed in the final study report.

12.2 Analysis Populations

Three study populations are defined.

- **Safety population:** All subjects who receive at least part of an injection of the study medications. All safety analyses will be based on the Safety population.
- **Pharmacokinetic population**: The PK population will consist of all subjects in the Safety population who have provided sufficient PK data for all 4 randomized injection sites to derive PK parameters of interest (Group 1), or have provided PK data after the last injection of CAM2038 q4w (Group 2 and Group 3). All PK summaries will be based on the PK population.
- **Efficacy population**: The efficacy population will be the intent to treat population consisting of all subjects that have received at least 1 injection of CAM2038 and provided some efficacy measures.

12.3 Planned Analyses

12.3.1 Demographics and Other Baseline Characteristics

Disposition for all enrolled subjects will be summarized. Reasons for discontinuation will be tabulated. Demographic data and baseline psychosocial characteristics will be summarized by sequence and overall. The summaries will be performed by group, and sequence if appropriate.

Tabular summaries and/or listings will be provided for baseline clinical characteristics, such as illicit drug and treatment use history, medical history, inclusion/exclusion criteria, and medication history.

12.3.2 Analysis of Pharmacokinetics

Summaries of plasma concentrations of BPN and norBPN will be presented for the PK population by Group, treatment, and injection site, if applicable. The following descriptive statistics will be presented at each nominal timepoint: n, arithmetic mean, standard deviation, and coefficient of variation percentage (CV%), median, geometric mean, geometric CV%, minimum and maximum values. Mean plasma concentration-time data will be displayed for the PK population in linear and semi-logarithmic scales by Group, treatment and injection site, if applicable. Individual plasma concentrations of BPN and norBPN will be listed for the Safety population by Group, treatment, and injection site, if applicable.

For Group 1 (CAM2038 50 mg/mL q1w), the following considerations will apply in the PK analyses. The primary PK parameters will be AUC_{ss} and $C_{ss,max}$ after steady state injections of CAM2038 q1w at different injection sites. The injection site buttock will be the reference. The analyses will be based on log-transformed data. The natural log-transformed AUC_{ss} and $C_{ss,max}$ data will be analyzed using an ANOVA model, sequence, subject within sequence (1, 2, 3, 4 corresponding to A/B/D/C, B/C/A/D, C/D/B/A, D/A/C/B, where A=buttock, B=abdomen C=thigh, or D=back of upper arm), period, and treatment (treatment sites: A=buttock, B=abdomen C=thigh, or D=back of upper arm). The estimated treatment effects, treatment differences versus the reference (B-A, C-A, and D-A), and the 90% confidence intervals of the estimated differences will be presented. The above estimates will be expressed on the raw scale (expressed after performing the anti-log). All other PK parameters will be summarized by descriptive statistics.

For Group 2 (CAM2038 q4w) and Group 3 (CAM2038 q4w and SL BPN), the PK parameters will be summarized by descriptive statistics. The primary PK parameters will be AUC_{ss} and $C_{ss,max}$.

The PK parameters (Section 10.3.2) will be listed for the Safety population and summarized by Group, treatment, and injection site, if applicable, for the PK population. Summary statistics will include: n, arithmetic mean, standard deviation, CV%, median, geometric mean, geometric CV%, minimum and maximum values.

12.3.3 Analysis of Safety

Exposure will be summarized by Group, treatment, and injection site, as applicable.

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

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

The average SOWS and COWS scores over the Treatment Phase and average change from baseline (Day 1) SOWS and COWS scores will be presented.

Medications will be coded using the World Health Organization Drug dictionary and may be summarized by Group using descriptive statistics.

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

12.3.4 Analysis of Efficacy

The frequency and incidence of urine toxicology results positive for opioids other than BPN, and positive results for other, non-opioid, drugs of abuse will be listed by subject and summarized by Group.

Change from Baseline in the weekly average of the daily Worst Pain score will be listed by subject and summarized by Group.

12.3.5 Missing data

Missing dates/times in AE and concomitant medication data and other missing safety data will be handled as described in the SAP. There will be no imputation schemes applied to missing PK data.

12.4 Determination of Sample Size

At least 20 subjects but no more than 24 subjects will be enrolled to Group 1 (CAM2038 q1w). Approximately 16 subjects will be enrolled into each of Group 2 (128 mg CAM2038 q4w) and Group 3 (160 mg CAM2038 q4w), for a total of approximately 32 subjects administered CAM2038 q4w. These sample sizes are consistent with typical PK studies.

13 STUDY ADMINISTRATION AND INVESTIGATOR RESPONSIBILITIES

Additional details may be outlined in the Clinical Study Agreement (CSA) between the Sponsor and the investigational site.

13.1 Regulatory and Ethical Considerations

13.1.1 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.

13.1.2 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.

13.1.3 Subject Informed Consent

The Investigator (or authorized designee) will ensure that the participant (or the participant's legal representative) 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 will 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.

13.2 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 United States [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 CSA for details.

13.3 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 and treatment codes 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.

13.4 Regulatory Documents and Records Retention

The Investigator is responsible for creating and/or maintaining all study documentation required by 21 Code of Federal Regulations (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 1 of the above 2 time frames 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 or request for marketing approval (New Drug Application/Marketing Authorisation 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.

13.5 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.

13.6 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.

13.7 Financial Disclosure

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, an 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.

14 SPONSOR APPROVAL PAGE

A Phase II, Open-label, Partially Randomized, Three Treatment Groups, Multi-site Study Assessing Pharmacokinetics after Administration of the Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) at Different Injection Sites in Opioid-Dependent Subjects with Chronic Pain

Version: 5.0

Date: 05 OCT 2016

Braeburn Pharmaceuticals Inc.

Sponsor Representative Full Title	Date (DD-MMM-YYYY)

15 INVESTIGATOR PROTOCOL AGREEMENT PAGE

A Phase II, Open-label, Partially Randomized, Two Treatment Groups, Multi-site Study Assessing Pharmacokinetics after Administration of the Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) at Different Injection Sites in Opioid-Dependent Subjects with Chronic Pain

Version: 5.0

Date: 05 OCT 2016

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

Principal Investigator's Name
(please print or type) _____

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

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17 APPENDICES

17.1 Agents Associated with Potential QTc Interval Prolongation

Generic Name	Brand Names (Partial List)	Drug Class
Alfuzosin	Uroxatral®	Alpha1-blocker
Amantadine	Symmetrel®, Symadine®	Antiviral
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Antiarrhythmic
Amitriptyline	Elavil® (Discontinued 6/13), Tryptomer®, Tryptizol®, Laroxyl®, Saroten®, Sarotex® Lentizol®, Endep®	Antidepressant, Tricyclic
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor
Apomorphine	Apokyn®, Ixense®, Spontane®, Uprima®	Dopamine agonist
Aripiprazole	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®	Antibiotic
Bortezomib	Velcade®, Bortecad®	Proteasome inhibitor
Bosutinib	Bosulif®	Tyrosine kinase inhibitor
Ceritinib	Zykadia®	Kinase inhibitor
Chloral hydrate	Aquachloral®, Novo-Chlorhydrate®, Somnos®, Noctec®, Somnote®	Sedative
Chloroquine	Aralen®	Antimalarial
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Antipsychotic / Antiemetic
Cilostazol	Pletal®	Phosphodiesterase 3 inhibitor
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic
Citalopram	Celexa®, Cipramil®	Antidepressant, SSRI
Clarithromycin	Biaxin®, Prevpac®	Antibiotic
Clomipramine	Anafranil®	Antidepressant, Tricyclic

Generic Name	Brand Names (Partial List)	Drug Class
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
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	Cipralex®, 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)	Antidepressant, SSRI
Famotidine	Pepcid®, Fluxid®, Quamatel®	H2-receptor antagonist
Felbamate	Felbatol®	Anticonvulsant

Generic Name	Brand Names (Partial List)	Drug Class
Fingolimod	Gilenya®	Sphingosine phospate receptor modulator
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Antiarrhythmic
Fluconazole	Diflucan®, Trican®	Antifungal
Fluoxetine	Prozac®, Sarafem®, Fontex®	Antidepressant, SSRI
Foscarnet	Foscavir®	Antiviral
Furosemide	Lasix®, Fusid®, Frumex®	Diuretic
Galantamine	Reminyl®, Nivalin®, Razadyne-ER®,	Cholinesterase inhibitor
Gemifloxacin	Factive®	Antibiotic
Granisetron	Kytril®, Sancuso®, Granisol®	Antiemetic
Halofantrine	Halfan®	Antimalarial
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Antipsychotic
Hydrochlorothiazide	Apo-Hydro®, Aquazide H®, BP Zide®, Dichlotride®, Hydrodiuril®, HydroSaluric®, Hydrochlorot®, Microzide®, Esidrex®, Oretic®	Diuretic
Hydroxychloroquine	Plaquenil®, Quineprox®	Antimalarial, Anti-inflammatory
Hydroxyzine	Atarax®, Vistaril®, Aterax®, Alamon®, Durrax®, Equipose®, Masmoran®, Orgatrax®, Paxistil® Quiess®, Tran-Q®, Tranquizine®	Antihistamine
Ibutilide	Corvert®	Antiarrhythmic
Iloperidone	Fanapt®, Fanapta®, Zomaril®	Antipsychotic, atypical
Imipramine	Tofranil®	Antidepressant, Tricyclic
Indapamide	Lozol®, Natrilix®, Insig®	Diuretic
Isradipine	Dynacirc®	Antihypertensive
Itraconazole	Sporanox®, Onmel®	Antifungal
Ketoconazole	Nizoral®, Sebizole®, Ketomed®, Keton®	Antifungal
Lapatinib	Tykerb®, Tyverb®	Kinase inhibitor

Generic Name	Brand Names (Partial List)	Drug Class
Leuprolide	Lupron®, Eligard®, Viadur®, Carcinil®, Enanton®, Leuplin®, Lucrin®, Procren®, Prostap® and others	Gonadotropin receptor agonist/antogist
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®, Maxolon®, Metozolv®, Plasil®, Pramin®, Primperan®, Perinorm®	Antiemetic
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
Paroxetine	Paxil®, Aropax®, Pexeva®, Seroxat®, Sereupin®	Antidepressant, SSRI
Pasireotide	Signifor®	Somatostatin analog

Generic Name	Brand Names (Partial List)	Drug Class
Pazopanib	Votrient®	Tyrosine kinase inhibitor
Pentamidine	Pentam®	Antifungal
Perflutren lipid microspheres	Definity®	Imaging contrast agent
Pimozide	Orap®	Antipsychotic
Posaconazole	Noxafil®, Posamol®	Antifungal
Procainamide (Oral off US mkt)	Pronestyl®, 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®, Sertralin Bluefish®	Antidepressant, SSRI
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general
Solifenacin	VESIcare®	Muscle relaxant
Sorafenib	Nexavar®	Tyrosine kinase inhibitor
Sotalol	Betapace®, Sotalex®, Sotacor®	Antiarrhythmic
Sunitinib	Sutent®	Kinase inhibitor
Tacrolimus	Prograf®, Prograf®, Advagraf®, Protopic®	Immunosuppressant
Tamoxifen	Nolvadex®(discontinued 6/13), Istubal®, Valodex®	Anticancer
Telaprevir	Incivek®, Incivo®	Antiviral
Telavancin	Vibativ®	Antibiotic
Telithromycin	Ketek®	Antibiotic

Generic Name	Brand Names (Partial List)	Drug Class
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, SARI
Trimipramine	Surmontil®, Rhotrimine®, Stangyl®	Antidepressant, Tricyclic
Vandetanib	Caprelsa®	Anticancer
Vardenafil	Levitra®	Phosphodiesterase 5 inhibitor
Vemurafenib	Zelboraf®	Kinase inhibitor
Venlafaxine	Effexor®, Efexor®	Antidepressant, SNRI
Voriconazole	VFend®	Antifungal
Vorinostat	Zolinza®	Histone deacetylase inhibitor
Ziprasidone	Geodon®, Zeldox®	Antipsychotic, atypical

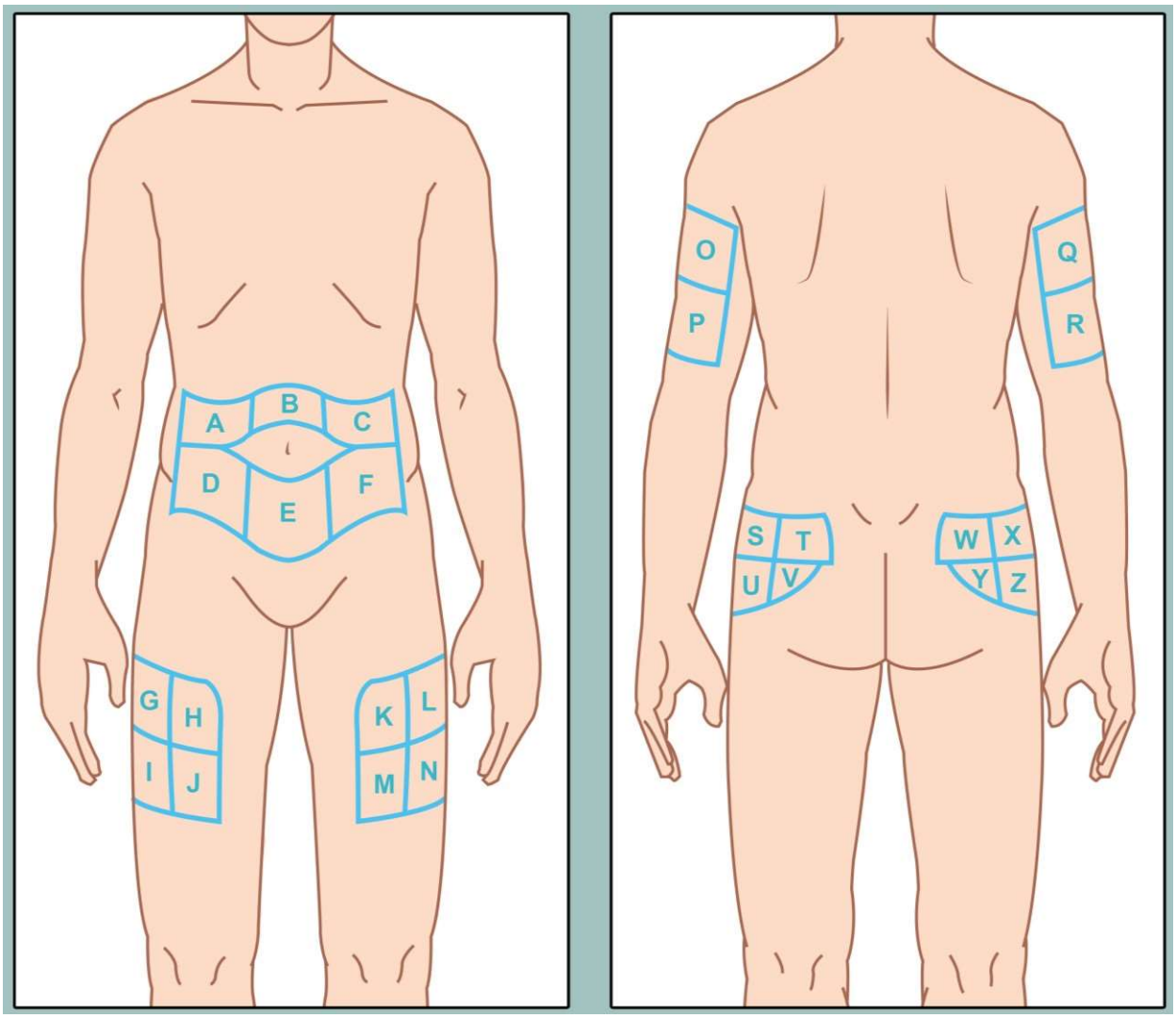
Source: http://www.crediblemeds.org/

17.2 CAM2038 Administration Sites

Twenty-six administration sites have been identified for injection of CAM2038.

- CAM2038 q1w must not be administered into a previously injected site for at least 8 weeks.
- CAM2038 q4w must not be administered in a site previously injected with CAM2038 q4w.

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



17.3 Local Injection Site Tolerability Scale

A 4-point verbal rating scale is employed to assess local tolerability on the following parameters:

1. Erythema
2. Swelling

The investigator will assess the degree of erythema and swelling at the injection site at scheduled time points during the study using the 4-point rating scale:

Erythema

0 = None (no erythema observed)

1 = Mild (erythema barely perceptible)

2 = Moderate (well-defined erythema)

3 = Severe (from beet redness to slight eschar formation)

Swelling (superficial)

0 = None (no swelling observed)

1 = Mild (swelling barely perceptible; longest diameter < 2 cm)

2 = Moderate (well-defined swelling; longest diameter 2-7 cm)

3 = Severe (well-defined swelling; longest diameter >7 cm)

17.4 Columbia-Suicide Severity Rating Scale – Baseline/Screening

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Phase 1 study

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 6 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation*** Past 6 Months - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

Version 1/14/09

17.5 Columbia-Suicide Severity Rating Scale (Since Last Visit)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Completed Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

17.6 The Subjective Opioid Withdrawal Scale (SOWS)

		PLEASE SCORE EACH OF THE 16 ITEMS BELOW ACCORDING TO HOW YOU FEEL NOW				
	SYMPTOM	**NOT AT ALL**	**A LITTLE**	**MODERATELY**	**QUITE A BIT**	**EXTREMELY**
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goosebumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushes	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4

Range 0-64. Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987)
Two New Rating Scales for Opiate Withdrawal, *American Journal of Alcohol Abuse*, 13, 293-308.

17.7 The Clinical Opioid Withdrawal Scale (COWS)

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

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