Clinical Trial Protocol
HS-14-499

An Open-Label Multicenter Study Assessing the Long-Term Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injection Depot of Buprenorphine (CAM2038) in Adult Outpatients with Opioid Use Disorder

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

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

EUDRACT 2015-003035-35

IND 114082

Original Protocol: v1.0, 29-Jul-2015

Global Protocol Amendment 1: v2.0, 21-Dec-2015

Global Protocol Amendment 2: v3.0, 12-Jul-2016

Global Protocol Amendment 3: v4.0, 18-Nov-2016

Global Protocol Amendment 4: v5.0, 09-Dec-2016

BRAEBURN PHARMACEUTICALS:

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1. SPONSOR AND KEY PERSONNEL CONTACT INFORMATION

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2. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Braeburn Pharmaceuticals

Name of Investigational Products:
CAM2038 q1w (buprenorphine FluidCrystal® once-weekly injection depot)
CAM2038 q4w (buprenorphine FluidCrystal® once-monthly injection depot)

Name of Active Ingredient: Buprenorphine

Study Title:

An Open-Label, Multicenter Study Assessing the Long-Term Safety of a Once-Weekly and Once-Monthly Long-Acting Subcutaneous Injection Depot of Buprenorphine (CAM2038) in Adult Outpatients with Opioid Use Disorder

Objectives:

Primary Objective:

To demonstrate the safety and tolerability of CAM2038 products in 12-month (48-week) buprenorphine (BPN) treatment in adult outpatients with opioid use disorder.

Secondary Objectives:

To evaluate efficacy of CAM2038 through several efficacy parameters, including urine toxicology, signs and symptoms of withdrawal and cravings in adult outpatients with opioid use disorder.

Methodology:

This is an open-label multi-center, 12-month safety study, consistent with standard practice for long-term safety studies. This one year safety study will utilize CAM2038 q1w (once weekly) and q4w (once monthly) and will have 3 phases: Screening, Treatment, and Follow-up.

Patients who are currently taking sublingual (SL) BPN (weekly or monthly prescription visits) or individuals who are actively seeking BPN treatment but who have not yet begun a treatment regimen, may be eligible for the study.

Following Screening, qualified subjects meeting inclusion criteria and not meeting exclusion criteria will be initiated on either CAM2038 q1w or q4w, based on their current treatment status (qualified subjects currently on SL BPN or seeking BPN treatment).

Qualified subjects will be initiated or transitioned to CAM2038 q1w or q4w as follows:

- Initiation of BPN treatment – initiate with CAM2038 q1w
- Currently receiving SL BPN treatments – transfer to corresponding CAM2038 q1w or q4w dose

Subjects will be allowed to receive supplemental BPN during the study with booster SC injections of CAM2038 q1w 8 mg at the discretion of the Investigator. Dose adjustments (up or down titrations) will also be allowed at scheduled visits.

The study will end when at least 100 subjects have been exposed to CAM2038 for 12 months (48 weeks). All subjects will be transitioned back to usual care and followed for an additional 4 weeks (up to Week 52).

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 and counseling will also be covered.

Name of Sponsor/Company: Braeburn Pharmaceuticals
Name of Investigational Products: CAM2038 q1w (buprenorphine FluidCrystal® once-weekly injection depot) CAM2038 q4w (buprenorphine FluidCrystal® once-monthly injection depot)
Name of Active Ingredient: Buprenorphine
Number of Subjects (Planned): The study will enroll approximately 228 subjects (new entrants to CAM2038 treatment) with estimated dropout rate of approximately 50% to ensure at least 100 subjects are exposed to CAM2038 for up to 48 weeks. The study will end after at least 100 subjects have been exposed to CAM2038 for 48 weeks.
Diagnosis and Main Criteria for Inclusion: This study will enroll adult outpatients with opioid use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V). Subjects must meet one of the following criteria for BPN treatment history: a. Voluntarily seeking treatment for opioid use disorder (not currently on BPN treatment for at least last 60 days but seeking BPN treatment), **or**; b. Currently on SL BPN treatment
Investigational Product, Dosage and Mode of Administration: CAM2038 q1w: buprenorphine FluidCrystal® subcutaneous (SC) injection depot for once weekly administration) (50 mg/mL) at doses of 8, 16, 24 and 32 mg (buprenorphine base) (0.16, 0.32, 0.48 or 0.64 mL SC injection). CAM2038 q4w: buprenorphine FluidCrystal® SC injection depot for once monthly administration (356 mg/mL) at doses of 64, 96, 128 or 160 mg (buprenorphine base) (0.18, 0.27, 0.36 or 0.45 mL SC injection).
Reference Therapy, Dosage and Mode of Administration: This is an open-label study, no reference therapy (placebo or active comparator) will be administered.
Duration of Study: This is a 12-month (48-week) treatment study. Subject with no previous exposure to CAM2038 will receive treatment for up 48 weeks.

Name of Sponsor/Company: Braeburn Pharmaceuticals

Name of Investigational Products:
CAM2038 q1w (buprenorphine FluidCrystal® once-weekly injection depot)
CAM2038 q4w (buprenorphine FluidCrystal® once-monthly injection depot)

Name of Active Ingredient: Buprenorphine

Criteria for Evaluation:

Safety Endpoints:

- Adverse events (AEs) and serious adverse events (SAEs)
- Clinical laboratory tests
- Electrocardiogram (ECG)
- Vital signs
- Physical and injection site examinations
- Concomitant medications

Efficacy Measures:

- Urine toxicology results for illicit opioids
- Self-reported illicit opioid use
- Retention (%) in treatment
- Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH)
- EQ-5D-5L Health Questionnaire
- Patient Satisfaction Scale
- Measures of opioid withdrawal:
    - Clinical Opiate Withdrawal Scale (COWS)
    - Subjective Opiate Withdrawal Scale (SOWS)
- Measures of opioid craving:
    - Desire to Use visual analogue scale (VAS)
    - Need to Use VAS
- Urine toxicology results for other drugs of abuse

Statistical Methods (Data Analysis):

Two safety populations will be considered: the Full Exposure Safety population and the Overall Safety Population. The Full Exposure Safety Population will include all subjects who have been exposed to CAM2038 for 48 weeks. The Overall Safety Population will include all subjects who received at least one CAM2038 treatment. Exposure and safety summaries will be presented for both populations.

Adverse events 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. Summaries of these AE subsets will be presented for relationship to study drug, intensity, seriousness, AEs or SAEs leading to discontinuation and AEs occurring in 5% or greater of any treatment group (by preferred term). Frequencies for deaths and

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Name of Active Ingredient: Buprenorphine
hospitalizations will also be summarized. Data for clinical laboratory tests, ECG, vital signs, and physical and injection site examinations will be summarized using standard descriptive and change from baseline statistics. Shift tables and tabular summaries of abnormalities will be provided, where appropriate. Medications will be coded using the World Health Organization Drug dictionary and summarized using descriptive statistics. By-subject listings will be provided for all safety data. Exploratory efficacy measures will be summarized by visit using standardized descriptive statistics and listed by subject.

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BPN	Buprenorphine
BPX	Buprenorphine/naloxone
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CNS	Central nervous system
COWS	Clinical Opioid Withdrawal Scale
CRF	Case Report Form (may include electronic data capture systems or paper forms)
CS	Clinically significant
CSA	Clinical Study Agreement
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{trough}	Concentration levels prior to next injection
DSM-V	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
ECG	Electrocardiogram
EDC	Electronic data capture
FC	FluidCrystal®
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary of Regulatory Activities
MOP	Manual of Procedures
NCS	Not clinically significant
PAC-SYM	Patient Assessment of Constipation Symptoms
PT	Prothrombin time
RBC	Red blood cell

SAE	Serious adverse event
SC	Subcutaneous
SL	Sublingual
SOC	System Organ Class
SOWS	Subjective Opioid Withdrawal Scale
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States

5. INTRODUCTION

5.1. Background

Buprenorphine (BPN) is an opioid with mixed agonist-antagonist properties, and 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 patients in outpatient treatment programs (Johnson et al, 1992; Strain et al, 1994; Schottenfeld et al, 1997; Ling et al, 1998).

CAM2038 (buprenorphine FluidCrystal® [FC] subcutaneous [SC] injection depot) once weekly (hereafter referred to as CAM2038 q1w) and once monthly (q4w) (hereafter referred to as CAM2038 q4w) are ready-to-use, extended release BPN products developed for opioid dependence treatment 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 and 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 (from 0.15 to 0.6 mL volume depending on dose and product) including a needle safety device and with no need for mixing or temperature adjustment prior to administration. In addition, the injection volumes for CAM2038 q1w and q4w are relatively low and can be administered using a fine gauge needle (23 G). Overall, these ready-to-use, long-acting CAM2038 depots have been designed with a focus of enabling easy administration, dosing flexibility, and importantly, minimizing risks of misuse, diversion and poor patient compliance.

5.1.1. CAM2038 q1w (Once Weekly)

Subcutaneous CAM2038 q1w has so far been investigated after single and repeated doses in 3 clinical trials, in both patients and healthy volunteers. An initial study assessed pharmacokinetics, pharmacodynamics and safety in opioid dependent patients (Study HS-07-307). Study HS-07-307 results also 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 patients (9.5%). Three patients experienced mild injection site pain and 1 patient exhibited transient injection site inflammation (mild) and injection site pruritus (moderate). Two additional clinical studies were subsequently performed in healthy volunteers (under naltrexone blockade) to assess the

pharmacokinetics and bioavailability of single and repeat doses of CAM2038 q1w versus repeated doses of sublingual (SL) BPN (i.e., at steady state) and single dose of intravenous (IV) BPN (Studies HS-11-426 and HS-13-487). These two studies demonstrated that after administration of the studied doses of CAM2038 q1w, the plasma concentrations corresponded to those obtained after administration of SL BPN at approved doses. The BPN levels after administration of CAM2038 q1w were furthermore similar in healthy volunteers and patients 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 in Study HS-11-426 (N_{safety}=60) was very good with no adverse events (AEs) attributed to injection site tolerability. Similarly, local tolerability of CAM2038 q1w was very good in Study HS-13-487, featuring 4 repeated SC injections of CAM2038 q1w into the buttock site (1 subject reported 1 AE of injection site pain).

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

- Extended BPN release over one week at target plasma concentrations
- Dose proportionality and flexible/multiple dosing options
- 6- to 8-fold higher bioavailability versus SL BPN
- BPN plasma concentrations over 7 days within ranges of those produced by corresponding SL BPN doses at steady-state (i.e., approved 8 mg, 16 mg, or 24 mg doses), supporting dose selection for this Phase III study
- Observed and predicted (repeated dose), $C_{average}$ and C_{trough} values for CAM2038 q1w within therapeutic plasma levels
- Repeated-dose administration demonstrated time-independent pharmacokinetics
- Good safety and systemic tolerability in patients
- Safety in healthy volunteers comparable to reference IV and SL BPN treatments
- Good local tolerability in patients and healthy volunteers

The clinical pharmacokinetic 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 pharmacokinetic and toxicology studies in the dog, minipig and rat of single and repeat SC doses of CAM2038 q1w, including repeat weekly doses of the FC vehicle formulation for 6-months. In summary, nonclinical data have indicated no systemic toxicity associated with CAM2038 q1w or the FC injection depot vehicle. 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.

5.1.2. CAM2038 q4w (Once Monthly)

Subcutaneous CAM2038 q4w has been investigated after single administration in the bridging clinical pharmacokinetic study in healthy volunteers versus repeated dose CAM2038 q1w (i.e., at steady state), repeated dose SL BPN (i.e., at steady state), and single dose of intravenous (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 of 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 one week, and to SL BPN over 24 hours at steady-state (i.e., for approved 8 mg, 16 mg, or 24 mg doses), supporting dose selection for this Phase III study
- 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)
- 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 to the healthy volunteers under naltrexone blockade in the study were nausea (63% of subjects), dizziness (54% of subjects) and vomiting (39% of subjects). The local tolerability was good with 6 subjects experiencing 7 AEs that were assessed as related to CAM2038 q4w (injection site reactions, injection site pain, injection site induration and application site bruise). Two SAEs were reported by 2 subjects after treatment with 192 mg CAM2038 q4w. The first SAE was an event of withdrawal reaction and the second SAE was an event of dehydration due to nausea and vomiting. Both SAEs were assessed as related to CAM2038 q4w (withdrawal reaction was also assessed as related to the concomitant treatment with naltrexone) and the event of withdrawal reaction qualified for reporting as a suspected unexpected serious adverse reaction (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 buprenorphine 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.

5.2. Study Rationale

Opioid drug dependence is a major health and social issue and is often a chronic medical condition that requires long-term maintenance treatment. An important aim of the treatment programs for opioid drug dependence is to enable the patients to become abstinent. Further important aims are to improve their mental and physical health, as well as their social conditions. This can be achieved by increasing patients' quality of life and reducing the burden on the society and relatives. Moreover, opioid people often inject with used syringes and needles, and

thus expose themselves to high risk of transmission of infectious diseases, including HIV and hepatitis C.

Opioid maintenance treatment, such as SL BPN, is one of the most effective treatment options available for opioid dependent drug users and is associated with substantial reductions in deaths, and HIV transmission (WHO, 2004). However, because patients often discontinue treatment prematurely, an outcome associated with higher rates of relapse to drug use, treatment strategies that aim to keep patients in treatment longer and/or improve patient adherence may have additional advantages (Chandler et al, 2009). While daily dosing with SL BPN has proven effective, the need for daily administration of treatment may negatively influence patients' compliance. Moreover, SL tablets or film can be easily diverted for illicit use, injected for greater effect, or accidentally ingested, especially by children (Chandler et al, 2009; Winstock et al, 2008). The limitations associated with SL BPN are of particular relevance to patients who have children at home, to those who have difficulty making frequent visits to the physician's office (e.g., patients in remote locations, those with limited mobility, or those who travel frequently) or to those who have difficulty managing the responsibility of daily dosing.

CAM2038 q1w and q4w may increase patient compliance relative to daily SL BPN dosage forms, and may help prevent treatment noncompliance in higher-risk patients (i.e., those patients who take "drug holidays" from their BPN when they wish to abuse illicit opioids). In addition, CAM2038 q1w and q4w may provide significant potential for reducing risks of diversion, abuse, and accidental pediatric exposure, which continue to be important public health consequences of SL BPN therapy.

In animal repeat-dose toxicity studies, CAM2038 q1w or FC vehicle formulation have been administered weekly for up to 6-months with no systemic toxicity associated with CAM2038 q1w or the FC injection depot vehicle observed. However, the long-term safety profiles of CAM2038 q1w and q4w in humans have not been described. In Study HS-13-487, pharmacokinetic profiles were evaluated for 4 repeat doses of CAM2038 q1w (one SC injection per week for 4 weeks) and one dose of CAM2038 q4w. In an upcoming parallel Phase III safety and efficacy study (HS-11-421), CAM2038 q1w and CAM2038 q4w will each be administered for up to 12 weeks (3 months). Therefore, the purpose of this study is to demonstrate the long-term safety of CAM2038 (q1w and q4w) as an office-based therapy for opioid maintenance treatment with BPN in patients with opioid use disorder.

5.3. Dosing Rationale

The weekly subcutaneous CAM2038 q1w product has so far been investigated after single and repeated doses in three separate clinical trials, in both patients and healthy volunteers. An initial study assessed pharmacokinetics, pharmacodynamics and safety in opioid dependent patients (Study HS-07-307). Following FDA's advice at the pre-IND meeting (PIND 114,082), two additional clinical studies were subsequently performed in healthy volunteers to assess the pharmacokinetics and bioavailability of CAM2038 q1w versus repeated doses of sublingual (SL) BPN (i.e., at steady state) and single dose of intravenous (IV) BPN (Studies HS-11-426 and HS-13-487). The total number of subjects exposed to CAM2038 q1w in these studies was 114.

Subcutaneous CAM2038 q4w has been investigated in one bridging clinical pharmacokinetic study in healthy volunteers versus repeat dose CAM2038 q1w, repeat dose SL BPN (i.e., at steady state), and single dose of intravenous (IV) BPN (Study HS-13-487). The total number of exposed subjects in this study was 79, with 62 subjects receiving CAM2038 q4w.

During the induction, stabilization, and as needed for maintenance treatments, subcutaneous doses of 8 to 32 mg CAM2038 q1w will be provided based on the clinical needs of the patients. This dose range is expected to cover the needs of patients that are currently eligible to SL BPN treatment. This assumption is based on the head-to-head comparison of BPN exposures of CAM2038 q1w versus SL BPN (Subutex®), which were assessed in the HS-11-426 and HS-13-487 Phase 1 trials. Occasionally, an SC booster injection of 8 mg CAM2038 q1w may be needed on top of the weekly dose of 32 mg. For maintenance treatment with CAM2038 q4w, the corresponding planned dose range is 64 mg to 160 mg.

Figures below demonstrate observed and predicted BPN plasma concentrations for different dose combinations of CAM2038 q1w, CAM2038 q4w and Subutex® over 28 days. These data demonstrate that observed and predicted plasma concentrations of CAM2038 q1w over one week and CAM2038 q4w over one month are comparable to SL BPN over 24 hours at steady-state (i.e., for approved 8 mg, 16 mg, or 24 mg doses), thus supporting doses selected for the Phase III studies.

Figures below are geometric mean observed steady state C_{max} and C_{trough} for Subutex from HS-11-426 and HS-13-487; Predicted plasma concentration versus time profiles for CAM2038 q1w from single and repeat dose data in HS-13-487; Observed steady state plasma concentration versus time profiles for CAM2038 q1w 16 mg from HS-13-487; and Predicted steady state plasma concentration versus time profiles for CAM2038 q4w from single-dose data in HS-13-487.

Figure 1: Observed and Predicted Plasma Concentration Versus Time Profiles for CAM2038

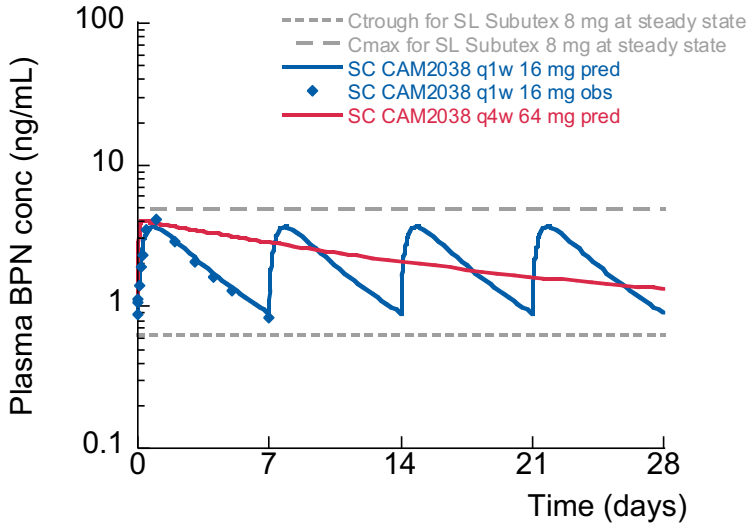


Figure 2: Predicted Plasma Concentration Versus Time Profiles For CAM2038

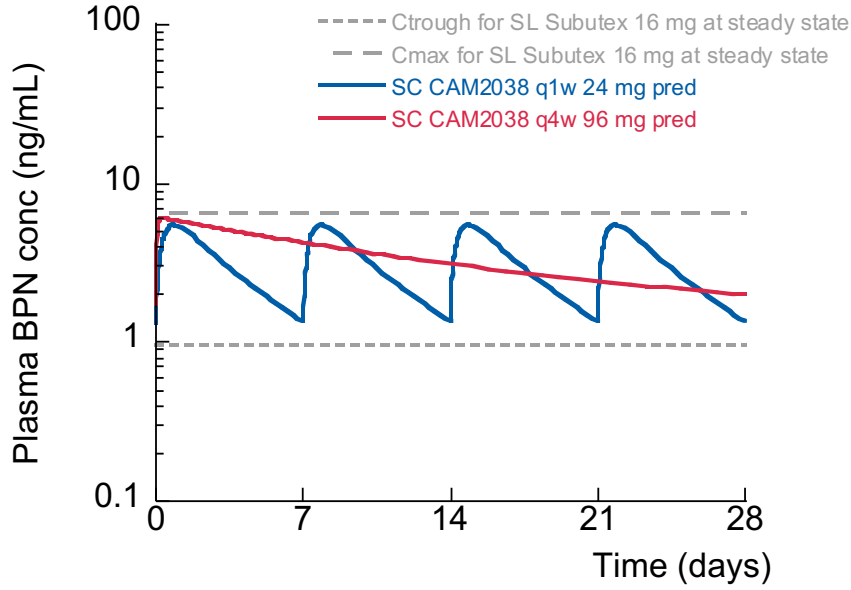
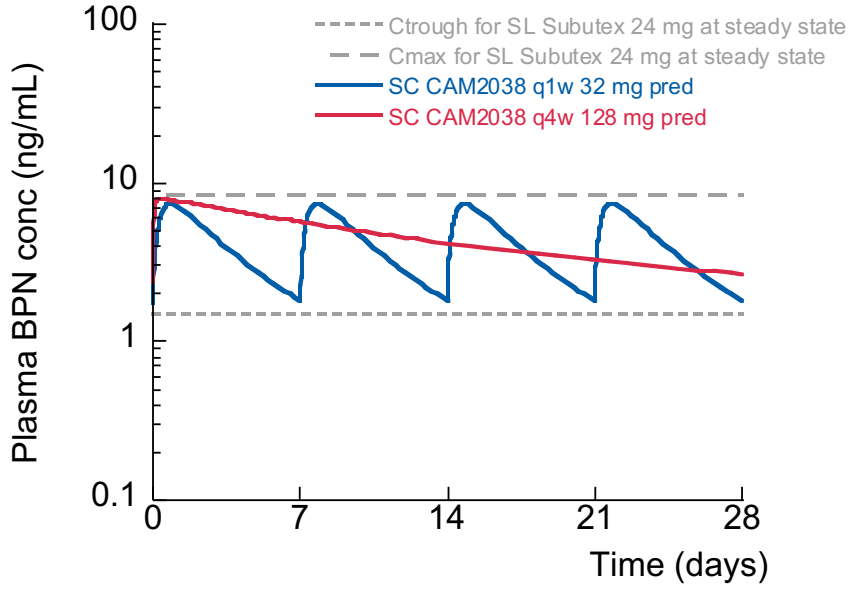


Figure 3: Predicted Plasma Concentration Versus Time Profiles For CAM2038



The following table demonstrates the estimation of plasma buprenorphine levels during the induction treatment with CAM2038 q1w. These plasma levels provide a rationale that induction treatment with CAM2038 q1w may mimic the gradual increase in the plasma buprenorphine levels provided with titration methods with SL BPN.

Table 1: Plasma Concentrations of Buprenorphine (Geometric Mean) After Single Subcutaneous Administration of CAM2038 q1w to Healthy Subjects Under Naltrexone Blockage

Time after dose (h)	Plasma concentrations of buprenorphine (ng/mL)		
	CAM2038 q1w 8 mg	CAM2038 q1w 16 mg	CAM2038 q1w 32 mg
Pre-dose	<0.025	<0.025	<0.025
0.5	0.0759	0.253	0.220
1	0.119	0.396	0.391
2	0.257	0.722	0.748
4	0.568	1.39	1.83
6	0.767	1.63	2.61
10	1.40	2.84	4.42

24	1.65	2.84	5.00
36	1.11	2.02	3.76

5.4. Overall Risk Benefit Assessment

BPN is a substance with well-established use in the treatment dependence on opioid drugs. The CAM2038 products contain BPN in a new FluidCrystal (FC) formulation for subcutaneous (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 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.

CAM2038 q1w and CAM2038 q4w are ready-to-use, SC BPN FC Injection depots that are being developed as alternative dosage form for treatment of opioid drug dependence by providing extended BPN release at target plasma concentrations over the weekly and monthly dosing intervals, respectively. Due to the fact that CAM2038 products need to be administered by a clinician, CAM2038 products cannot be abused or diverted by patients. In addition, it may decrease the tendency for patients to request unnecessarily high BPN doses. It will also ensure that the dose required is the dose received. Compared with the sublingual buprenorphine products on the market, CAM2038 q1w and CAM2038 q4w have several potential advantages: 1) rapid therapeutic onset (with maximum plasma concentrations established within 24 hours after injection) followed by steady long-acting release; 2) reduced variation in buprenorphine plasma levels over time (stable plasma levels attained for at least 28 days (CAM2038 q4w) and 7 days (CAM2038 q1w) resulting in more consistent therapeutic plasma levels and a possible reduction in morning "cravings"; 3) less frequent dosing resulting in reduced frequency of clinic visits and need for medical support; 4) significantly higher bioavailability, meaning less drug substance in circulation and on the street; 5) decreased risk of drug diversion; and 6) easier dose adjustment.

To date, three Phase I/II clinical studies (HS-07-307, HS-11-426 and HS-13-487) have been conducted in both opioid dependent and healthy volunteers under naltrexone block. The safety profile of CAM2038 q1w and CAM2038 q4w is comparable to reference SL BPN approved treatment and good local tolerability was demonstrated with findings limited to only a few cases of transient, mild, local inflammation, pruritus and/or injection site pain.

A number of potential AEs can be associated with the administration of long-acting depots. The most severe side-effects specific for the investigational product that may occur are related to local reactions at the site of injection after subcutaneous administration and include dermal ulcers or necrotic wounds at the injection site. Additional potential AEs include over-dose of buprenorphine and allergy to buprenorphine. There is also a potential risk of local obstruction and blockage at the injection site with accidental intravascular injection

Systemic repeated toxicity for up to 4 months of once-weekly SC administration of CAM2038 q1w, once weekly and CAM2038 q4w, once-every-4-week administration in dogs showed absence of systemic toxicity by assessment of complete clinical pathology, histopathology and toxicokinetics (TK). The treatment related findings were limited to reversible clinical effects compatible with known pharmacological effects of BPN (reduced activity, ataxia, sporadic salivation, and intermittent soft faeces, as well as reduction in body weight and food consumption) and to local, transient injection site findings, characterised as foreign body response. No novel toxicological aspects arose for BPN in the CAM2038 drug product formulations in comparison with available information on the drug substance alone. Absence of systemic toxicity has also been shown for up to chronic SC exposure of the FC system in rodents and non-rodents. The local toxicity findings at the injection site following SC administration of the CAM2038 drug products in a large number of non-clinical studies were described by necropsies and histopathology as a reversible local continuum of an inflammatory response consistent with the physiological inflammatory reactions occurring in response to the injection of an insoluble material.

The current protocol is intended to demonstrate the long-term 12-month safety of CAM2038 q1w and q4w for the treatment of opioid dependence. The safety monitoring practices employed by this protocol are adequate to protect the patients' safety and should detect all expected treatment-emergent AEs (TEAEs).

The volume of blood removed from the subject is approximately 30 mL over the course of the entire study (Screening to Follow-up, but does not include repeat or additional tests ordered by the Investigator). This volume presents no undue risk to the subjects.

Therefore, CAM2038 q1w and q4w may provide alternative treatment options that potentially can increase patient compliance relative to daily SL BPN dosage forms, and may help prevent treatment noncompliance in higher-risk patients (i.e., those patients who take "drug holidays" from their BPN when they wish to abuse illicit opioids). In addition, CAM2038 q1w and q4w may provide significant potential for reducing risks of diversion, abuse, and accidental pediatric exposure, which continue to be important public health consequences of SL BPN therapy.

In addition an indirect health benefit to the patients enrolled in this trial is the free medical tests received during the study.

The available information suggests that the present clinical study has a favorable risk-benefit ratio.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of the study is:

- To demonstrate the safety and tolerability of CAM2038 products in 12-month (48-week) BPN treatment in adult outpatients with opioid use disorder.

6.2. Secondary Objective

The secondary objective of the study is:

- To evaluate efficacy of CAM2038 through several efficacy parameters, including urine toxicology, signs and symptoms of withdrawal and cravings in adult outpatients with opioid use disorder.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is an open-label multi-center, 12-month (48-week) safety study, consistent with standard practice for long-term safety studies. This one year safety study will utilize CAM2038 q1w (once weekly) and q4w (once monthly) and will have 3 phases: Screening, Treatment, and Follow-up.

Patients who are currently taking SL BPN (weekly or monthly prescription visits) or those individuals who are actively seeking BPN treatment but who have not yet begun a treatment regimen may be eligible for the study.

Following Screening, qualified subjects meeting inclusion criteria and not meeting exclusion criteria will be initiated on either CAM2038 q1w or q4w, based on their current treatment status (qualified subjects currently on SL BPN or seeking BPN treatment).

Qualified subjects will be initiated or transitioned to CAM2038 q1w or q4w as follows:

- Initiation of BPN treatment – initiate with CAM2038 q1w
- Currently on SL BPN treatments – transfer to corresponding CAM2038 q1w or q4w dose

Subjects will be allowed to receive temporary dose adjustments during the study with rescue booster SC injections of CAM2038 q1w 8 mg, at the discretion of the Investigator. Dose adjustments will also be allowed at scheduled visits.

During the Treatment Phase, subjects will receive CAM2038 treatment for up to 48 weeks. The study will end when at least 100 subjects have been exposed to CAM2038 for 12 months (48 weeks). All subjects will be transitioned back to usual care and followed for an additional 4 weeks (up to Week 53).

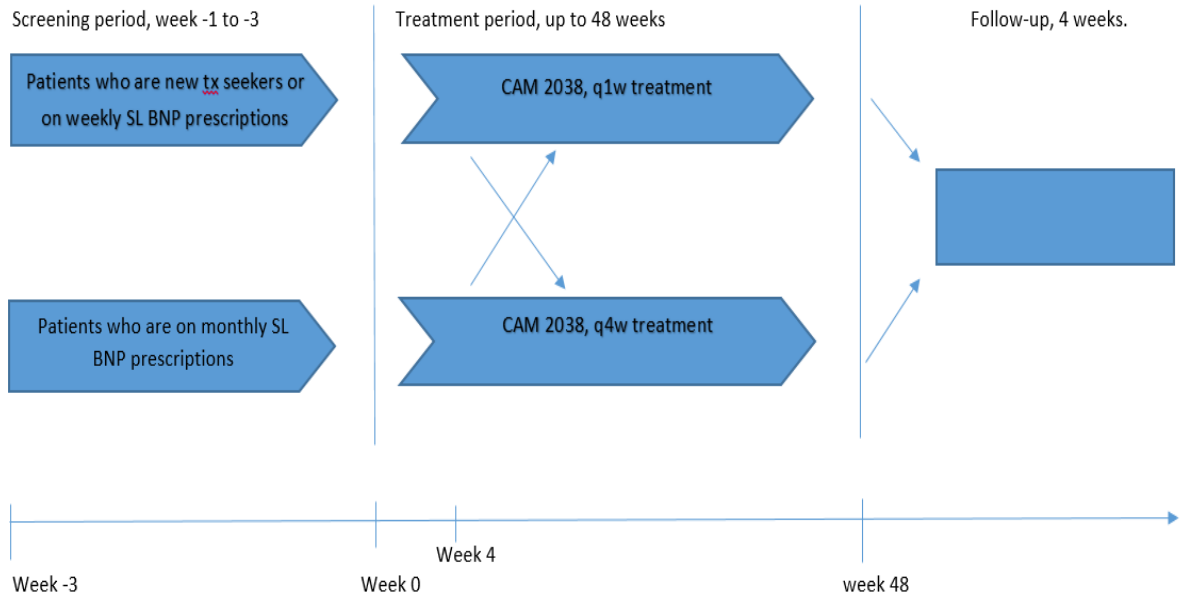
To ensure adequate enrollment and address potential inconvenience to subjects, all subjects will receive appropriate compensation for time and travel expenses related to attendance at study visits. All costs of medications and counseling will also be covered.

Germany only: The subject management procedures in the study comply with the statutory requirements in the German Verordnung über das Verschreiben, die Abgabe und den Nachweis des Verbleibs von Betäubungsmitteln (Betäubungsmittel-Verschreibungsverordnung – BtMVV, last amended 15 July 2009) and the drug substitution processes comply with German Richtlinien der Bundesärztekammer zur Durchführung der substitutionsgestützten Behandlung Opiatabhängiger (19 February 2010).

The overall study design is illustrated in Figure 4.

Section 9 provides additional information on the baseline, safety, and efficacy assessments included in the study. Study endpoints are described in Section 9.6 and Section 9.7. Statistical analysis is described in Section 11.

Figure 4: Overview of Study Design



BPN=buprenorphine; SL=sublingual.
Note: Subjects in the CAM2038 q1w once weekly group may be transferred to CAM2038 q4w once monthly at any time during the study at the Investigator's discretion, using the guidance provided in Section 7.1.2.3.

7.1.1. Screening Visit (Week -3 to Week -1):

Medical and eligibility screening will occur within 1-3 weeks of the Treatment Phase (Day 1). 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, urine toxicology and detailed substance use and treatment history, as outlined in Table 3.

7.1.2. Treatment Phase (Week 1 to Week 48)

7.1.2.1. Day 1 (Week 1) (CAM2038 q1w)

New entrants to BPN Treatment: On Day 1, for subjects who are **not currently receiving SL BPN or buprenorphine/naloxone (SL BPN/BPX)**, treatment will be initiated with CAM2038 q1w in the following manner:

Day 1: On Day 1, subjects will receive the following, while on site:

- A 4 mg SL BPN tablet test dose and observed for at least 1 hour prior to study drug administration.
- Once tolerability is confirmed (i.e., no precipitated withdrawal symptoms), a single CAM2028 q1w (once-weekly) 16 mg injection (0.32 mL of active) will be administered.

Day 2: All subjects will return to the clinic on Day 2 to ensure tolerability.

Day 4: All subjects will return to the clinic. Subjects who return on Day 4 still experiencing withdrawal symptoms should receive a single CAM2038 q1w 8 mg SC injection (0.16 mL of active). A visit window of

±1 day is allowed for the Day 4 visit.

Days 5 to 7: Subjects requiring additional dosage adjustments may return to the clinic on Days 5 to 7 if needed, based on withdrawal symptoms or tolerability. Subjects who require additional increases in dose will receive up to two additional CAM2038 q1w 8 mg SC injections (0.16 mL of active) (i.e., up to a maximum of 40 mg SC injection dose per week).

Subjects Currently on Weekly BPN Treatment: Subjects who are **currently receiving SL BPN/BPX** and are considered a candidate for CAM2038 q1w treatment by the Investigator will be transitioned to CAM2038 q1w in the following manner:

- Subjects will receive a single CAM2038 q1w SC injection that corresponds to their current SL BPN/BPX dose prior to Day 1:
  - ≤ 6 mg SL BPN/BPX: 8 mg (0.16 mL) CAM2038 q1w SC injection
  - 8-10 mg SL BPN/BPX: 16 mg (0.32 mL) CAM2038 q1w SC injection
  - 12-16 mg SL BPN/BPX: 24 mg (0.48 mL) CAM2038 q1w SC injection
  - 18-24 mg SL BPN/BPX: 32 mg (0.64 mL) CAM2038 q1w SC injection

- Subjects may return to the clinic for additional titration with CAM2038 q1w (8 mg SC booster injections), as needed, up to a maximum weekly dose of 40 mg per week.

Subjects should not take their ordinary SL BPN tablet(s) on Day 1 (i.e., the last dose of SL BPN should be taken on the day before dosing with CAM2038 q1w).

Subjects will return to the clinic for weekly visits during which they will receive their CAM2038 q1w SC injection treatments.

7.1.2.2. Day 1 (Week 1) (CAM2038 q4w)

Subjects Currently on Monthly BPN Treatment: Subjects who are **currently receiving SL BPN/BPX** and are considered a candidate for CAM2038 q4w treatment by the Investigator may be transitioned to CAM2038 q4w in the following manner:

- Subjects will receive a single CAM2038 q4w SC injection that corresponds to their current SL BPN/BPX dose prior to Day 1:
    - 8-10 mg SL BPN/BPX: 64 mg (0.18 mL) CAM2038 q4w SC injection
    - 12-16 mg SL BPN/BPX: 96 mg (0.27 mL) CAM2038 q4w SC injection
    - 18-24 mg SL BPN/BPX: 128 mg (0.36 mL) CAM2038 q4w SC injection
    - 26-32 mg SL BPN/BPX: 160 mg (0.45 mL) CAM2038 q4w SC injection

Subjects should not take their ordinary SL BPN tablet(s) on Day 1 (i.e., the last dose of SL BPN should be taken on the day before dosing with CAM2038 q4w).

7.1.2.3. Treatment Visits (Weeks 2 to 48)

Subjects will return to clinic for visits based on each subject's dose of CAM2038 (q1w – once weekly or q4w – once monthly).

Subjects receiving **CAM2038 q1w** will return to the clinic weekly to receive their next dose and for safety and other assessments as outlined in Table 3. At the discretion of the Investigator, subjects may receive dose adjustments during the scheduled CAM2038 q1w weekly dose visits (up to a maximum weekly dose of 40 mg per week).

Subjects may return to the clinic for additional titration with CAM2038 q1w (8 mg SC booster injections) as needed (i.e., at unscheduled visits), up to a maximum weekly dose of 40 mg per week.

At any weekly visit, the Investigator may transition subjects from weekly (CAM2038 q1w) to monthly (CAM2038 q4w) clinic visits after, at the minimum, taking the following criteria into consideration on the day of the visit where the transition of dose will occur (ie. Prior to new dose administration):

- Subject is on a stable dose of CAM2038 q1w without any additional fluctuations in dose for 4 weeks
- Subject has minimal subjective and no objective withdrawal symptoms, based on the SOWS and COWS scores (SOWS $\leq$7 and COWS $\leq$5).
- Subject exhibits diminished desire/need to use, based on VAS scores.

- Subject has diminished use of illicit opioids, according to the Investigator's discretion

Subjects who are eligible for **transitioning from CAM2038 q1w to CAM2038 q4w** will be transitioned in the following manner:

- Subjects will receive a single CAM2038 q4w SC injection, using the following conversion guidelines:
  - 16 mg (0.32 mL) CAM2038 q1w: 64 mg (0.18 mL) CAM2038 q4w
  - 24 mg (0.48 mL) CAM2038 q1w: 96 mg (0.27 mL) CAM2038 q4w
  - 32 mg (0.64 mL) CAM2038 q1w: 128 mg (0.36 mL) CAM2038 q4w

In addition, per Investigator's discretion, subjects may be switched back from monthly CAM2038 q4w visits to CAM2038 q1w weekly visits at any time during the Treatment Phase, if weekly dose visits are deemed to be appropriate based on the Investigator's clinical judgment on subject's level of stability.

Subjects receiving **CAM2038 q4w** will return to the clinic monthly to receive their next dose, and for safety and other assessments outlined in Table 3.

Subjects may receive temporary dose adjustment while receiving CAM2038 q4w, at the Investigator's discretion, using booster CAM2038 q1w 8 mg SC injections at any time during the study (through unscheduled visits, as needed). At the discretion of the Investigator, subjects may also receive dose adjustments during the scheduled CAM2038 q4w monthly dose visits. The temporary dose adjustments, or booster CAM2038 q1w 8 mg SC injection may be given at a maximum of two boosters per week.

At each visit (weekly or monthly), the following will be assessed:

- Urine samples for opioid toxicology, evaluated using immunoassay (qualitative) with reflex quantitative confirmation methods. Urine will also be tested for other drugs of abuse (e. g., cocaine, benzodiazepines, barbiturates, amphetamines, phencyclidine, and THC) and for alcohol using qualitative methods.
- Self-reported use of all drugs, including illicit or prescription opioids and other prescribed or illicit drugs.
- Measures of withdrawal using the Clinical Opioid Withdrawal Scale (COWS) and the Subjective Opioid Withdrawal Scale (SOWS)
- Measures of craving using Desire to Use and Need to Use visual analog scales (VAS)
- Other safety assessments and measures as outlined in Table 3.

7.1.3. Follow-up Phase (Week 49 to 53):

Following the last Treatment Visit, subjects will be transitioned to standard care (e.g., SL BPN/BPX) at Week 49. Additional assessments will be performed during Week 53 outlined in Table 3.

7.2. Discussion of Study Design

The evaluation of safety will be performed in an open-label manner, consistent with standard practice for long-term safety follow-up studies. The use of a placebo-controlled study was considered unethical due to the high risk of failure of these patients on placebo treatment, and the potential harms associated with treatment failure (FDA CDER and CBER, 2010). A broad group of potential subjects will be eligible for participation as well as subjects not currently receiving BPN treatment.

7.3. Selection of Study Population

The study will enroll approximately 228 subjects (new entrants to CAM2038 treatment) with an approximate dropout rate of approximately 50% to ensure at least 100 subjects have exposure to CAM2038 for up to 48 weeks. The study will end after at least 100 subjects have been exposed to CAM2038 for 48 weeks.

This study will enroll adult outpatients with opioid use disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V).

7.4. Inclusion Criteria

Subjects must meet each one 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 female, 18-65 years of age, inclusive.
3. Female subjects of childbearing potential must be willing to use a highly effective method of contraception during the entire study (Screening Visit to Follow-Up Visit) (Section 9.1.6).
4. Current diagnosis of moderate or severe opioid use disorder (DSM-V) or past medical history of opioid use disorder currently being treated with SL BPN.
5. Considered by the Investigator to be a good candidate for BPN treatment, based on medical and psychosocial history.
6. Subjects must meet one of the following criteria for BPN treatment history:
    a. Voluntarily seeking treatment for opioid use disorder (not currently on BPN treatment for at least last 60 days but seeking BPN treatment), **or**;
    b. Currently on SL BPN treatment.

7.5. Exclusion Criteria

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

1. Current diagnosis of Acquired Immune Deficiency Syndrome (AIDS).
2. Current diagnosis of chronic pain requiring opioids for treatment.
3. Current DSM-V diagnosis for moderate to severe substance use disorder (including alcohol) other than opioids, caffeine or nicotine and currently being treated as the primary substance use disorder.
4. Recent history of or current evidence of suicidal ideation or active suicidal behavior as based on the Columbia Suicide Severity Rating Scale (C-SSRS) ("Yes" responses to questions 4 or 5).
5. Pregnant or lactating or planning to become pregnant during the study.
6. Hypersensitivity or allergy to naloxone (only for subjects receiving the SL BPX test dose), BPN or excipients of CAM2038.
7. Requires chronic use of agents that are strong inhibitors or inducers of cytochrome P450 3A4 (CYP 3A4) such as some azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., clarithromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir).
8. Hepatitis, unless under stable treatment, at the discretion of the Investigator.
9. Any pending legal action that could prohibit participation or compliance in the study.
10. Exposure to any investigational drug within the 4 weeks prior to Screening.
11. 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.
12. Participants with a history of risk factors of Torsades de Pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome) or an ECG demonstrating a Fridericia's corrected QT interval (QTcF) >450 msec in males and QTcF > 470 in females at screening.
13. 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. This includes, but is not limited to, subjects with attention deficit hyperactivity disorder receiving central stimulants (e.g. methylphenidate or other central stimulants), as well as subjects with severe respiratory insufficiency, respiratory depression, airway obstruction, gastrointestinal motility disorders, severe hepatic insufficiency, planned surgery and prior treatment with monoamine oxidase inhibitors.
14. Is an employee of the Investigator or the trial site, with direct involvement in the proposed trial or other studies under the direction of the Investigator or trial site, or is a family member of an employee or of the Investigator.

7.6. 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, increased concomitant use of recreational drugs, alcohol, psychotropic agents or methadone, 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
- At the request of the Sponsor, regulatory agency, or Institutional Review Board (IRB)
- Subject is lost to follow-up
- Pregnancy (UK only)
- 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:

- Subject refuses or is unable to adhere to the study protocol
- Protocol violation
- Pregnancy (in the UK, pregnant subjects must be discontinued, see above)
- Requirement for continual use of opioid analgesics >7 days or requirement for general anesthesia for surgery

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.

All efforts should be made by the Investigator to continue collection of safety assessments at the protocol-defined study visit intervals, including concomitant medications, and AEs in subjects that discontinue study drugs, unless the subject withdraws his/her consent at the time of early discontinuation. The Investigator should also ask the subject to return for the Follow-up assessments, provided that the subject has not withdrawn consent for those assessments. If a subject refuses to complete early termination procedures and/or Follow-up, this information will be recorded.

8. TREATMENTS

8.1. Treatment Administration

Subjects will receive CAM2038 treatment for up to 12 months (48 weeks) during the study:

- For subjects who are not currently receiving SL BPN or SL BPN/BPX, treatment will be initiated with a single CAM2038 q1w 16 mg SC injection (following a 4 mg SL BPX test dose); additional dose adjustments will be allowed up to maximum weekly dose of 40 mg.
- Subjects who are currently receiving SL BPN/BPX will be transitioned to CAM2038 q1w or q4w SC injections according to their current dose of SL BPN/BPX (Table 2).
- SC injection administration sites: Rotate from left and right side of buttock. Injection with CAM2038 q1w will be rotated in a manner to not re-inject in the same location for at least 8 weeks, (i.e., injection into the same site will only occur after 8 weeks). Injection with CAM2038 q4w will be rotated and the same site will not be utilized for the duration of the study.
- Additionally, a q4w injection dose can be injected into a previously used q1w injection site following the q1w rule: Injection with CAM2038 q1w will be rotated in a manner to not re-inject in the same location for at least 8 weeks, (i.e., injection into the same site will only occur after 8 weeks

  A diagram of potential injection sites will be provided in the Study Manual of Procedures (MOP).

Table 2: Doses of CAM2038 q1w and q4w for Subjects Transitioning from SL BPN/BPX

Weekly SL BPN/BPX Category	**Once Weekly CAM2038 q1w SC Injection[a]**
≤ 6 mg	8 mg (0.16 mL)
8-10 mg	16 mg (0.32 mL)
12-16 mg	24 mg (0.48 mL)
18-24 mg	32 mg (0.64 mL)
Monthly SL BPN Category	**Once Monthly CAM2038 q4w SC Injection[b]**
8-10 mg	64 mg (0.18 mL)
12-16 mg	96 mg (0.27 mL)
18-24 mg	128 mg (0.36 mL)

26-32 mg	160 mg (0.45 mL)

BPN = buprenorphine; BPX = buprenorphine/naloxone; SC = subcutaneous; SL = sublingual
[a] Subjects may return to the clinic for additional dose adjustments with CAM2038 q1w at scheduled visits or 8 mg SC booster injections at unscheduled visits, as needed, up to a maximum weekly dose of 40 mg per week.
[b] Subjects needing additional temporary BPN while receiving CAM2038 q4w may receive a maximum of two boosters of CAM2038 q1w 8 mg SC injection per week (i.e., unscheduled visits). Dose adjustments may also be implemented at the discretion of the Investigator at scheduled visits.

8.2. Identity of Investigational Product(s)

The following treatments will be used during the study:

- CAM2038 q1w (buprenorphine FluidCrystal® Injection depot for once weekly administration), 50 mg/mL: 8, 16, 24 and 32 mg (buprenorphine base), 0.16, 0.32, 0.48 and 0.64 mL SC injection.
- CAM2038 q4w (buprenorphine FluidCrystal® Injection depot for once monthly administration), 356 mg/mL: 64, 96, 128 and 160 mg (buprenorphine base), 0.18, 0.27, 0.36 and 0.45 mL SC injection.

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

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

More information regarding the CAM2038 q1w and q4w can be found in the Study MOP.

All containers/packages /boxes of study drug will be clearly labeled with study-specific information meeting all the applicable regulatory/institutional requirements.

8.2.1. 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.

CAM2038 products must be stored according to the requirements outlined in the Study MOP.

Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed, the running inventory, and the unused quantities returned to the Sponsor's drug supply vendor at the end of the trial. All unused supplies and empty IP kits from used injection depots will be checked against the drug accountability records during the study and/or at the end of the study. Additional details are provided in the Study MOP.

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.

8.2.2. Dispensing and Administration

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

CAM2038 q1w and q4w SC injections will be administered by designated healthcare professional(s) at the investigational site. Detailed instructions for use will be provided in the Study MOP.

Investigator will be instructed to treat additional symptoms as they would usually, including additional counseling sessions, CAM2038 q1w booster injections, or other pharmacological interventions. Any CAM2038 q1w booster injections, additional counseling, and other pharmacological interventions provided by the Investigator will be recorded, along with the reasons for determining the need for these interventions.

8.2.3. Sublingual Buprenorphine/Naloxone

Subjects who are not currently receiving SL BPN or SL BPN/BPX at the time of study entry will receive a 4 mg test dose of BPX on Day 1. The BPX test dose consists of 2 SL tablets of Suboxone®, each containing 2 mg BPN and 0.5 mg naloxone (Indivior UK Limited). Suboxone will be sourced locally, handling and storage of the product will be in accordance with the Suboxone Summary of Product Characteristics.

8.3. 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.

Subjects will not be randomized to a treatment group; subjects who have met the eligibility criteria (Section 7.4) will receive CAM2038 q1w or CAM2038 q4w treatment based on their prior history of BPN treatment (Section 7.1.2 and 8.1).

8.4. Selection of Doses

The study will include the proposed range of CAM2038 q1w and q4w doses to be used in clinical practice, based on each subject's individual needs. As in clinical practice, dose adjustments (increases in case of withdrawal effects or cravings or decreases for tolerability reasons) will be allowed during the study. In addition, booster injections of CAM2038 q1w 8 mg will be allowed during the study for those receiving either CAM2038 q1w or CAM2038 q4w (up to a maximum weekly dose of 40 mg per week for subjects receiving CAM2038 q1w, or a maximum of two boosters per week for subjects receiving CAM2038 q4w).

8.5. Selection and Timing of Dose

Subjects will receive either CAM2038 q1w or CAM2038 q4w at individualized doses. The dose levels will be sufficient to prevent withdrawal symptoms and cravings, as in clinical practice. The SC injections may be given at any time during the day.

No fasting or special dietary requirements are required for the study.

8.6. Blinding

This is an open-label study and no blinding will be used.

8.7. 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 (q1w) or month following the last CAM2038 (q4w) 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.
- Buprenorphine 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, analgesics, benzodiazepines, phenothiazines, other tranquilizers, or other central nervous system (CNS) depressants (including alcohol and sedative/hypnotics) may cause respiratory and CNS depression. Use of these substances should be minimized during treatment with CAM2038 or SL BPX. If patients are taking these sedatives during Screening, the Medical Monitor must be consulted to evaluate eligibility into the study, taking into consideration the stability of the patient on the sedatives. If these sedatives are required during the study, the Medical Monitor must be consulted. Subjects must 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 alcohol while under treatment with CAM2038.

9. STUDY PROCEDURES AND ASSESSMENTS

All study assessments will be performed at the visits and time points outlined in the Schedule of Assessments (Table 3); the following sections outline the details and procedures associated with the assessments. Additional details on the assessments, including copies of questionnaires, logs, manuals, and information sheets are provided in the Study MOP.

Table 3: Schedule of Assessments

Study Phase:	Screening	Treatment Phase						EOT	Follow-up
Treatment:	-	CAM2038 q1w or q4w	CAM2038 q1w			CAM2038 q4w			All Subjects
Study Population:	All Subjects[a]	All Subjects	New to BPN Treatment[b]		Transition from SL BPN/BPX[c]	Transition from CAM2038 q1w[d]	Transition from SL BPN/BPX (Monthly)[e]		
Month[f]:	M-1	M1	M1	M1 to Mx	M1 to Mx	Mx to M12[g]	M1 to M12[h]		M13
Week[h]:	-3	W1	W1	W2 to Wx[i]	W1 to Wx[i]	Wx to W48	W1 to W48	W49	W53
Day:	-	Day 1	Day 2-7[j]	-	-	-	-		-
Informed Consent[k]	X								
Eligibility Criteria Review[l]	X	X							
Medical and Medication Hx	X								
Substance Abuse/Treatment Hx (questionnaires)	X								
DSM-V	X								
Physical Examination[m]	X								

[a] All subjects will undergo screening procedures.
[b] Subjects seeking treatment with BPN, but treatment with BPN has not yet begun.
[c] Subjects receiving SL BPN/BPX at the time of study entry and considered by the Investigator to be a candidate for CAM2038 q1w once weekly treatment.
[d] Subjects who started treatment with CAM2038 q1w and are transitioned to CAM2038 q4w after meeting criteria.
[e] Subjects receiving SL BPN/BPX at the time of study entry and considered by the Investigator to be a candidate for CAM2038 q4w once monthly treatment.
[f] A window of ±7 days will be allowed for monthly visits.
[g] The last monthly injection will be administered at the end of Month 11 (Week 45); additional assessments will be performed at the Week 49 visit, including transition back to usual care.
[h] A window of ±3 days will be allowed for weekly visits.
[i] Subjects may transition to CAM2038 q4w and monthly visits at any time during the 12 months, once they meet criteria for transitioning (Section 7.1.2).
[j] A window of ±1 day will be allowed for the visit performed on Day 4.
[k] Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.
[l] Prior to enrollment in the Treatment Phase of this study, all Inclusion and Exclusion criteria must be met.
[m] A complete physical exam of all major body systems will be performed at the Screening Visit.

Study Phase:	**Screening**	**Treatment Phase**						**EOT**	**Follow-up**
Treatment:	**-**	**CAM2038 q1w or q4w**	**CAM2038 q1w**			**CAM2038 q4w**			**All Subjects**
Study Population:	**All Subjects[a]**	**All Subjects**	**New to BPN Treatment[b]**		**Transition from SL BPN/BPX[c]**	**Transition from CAM2038 q1w[d]**	**Transition from SL BPN/BPX (Monthly)[e]**		
Month[f]:	**M-1**	**M1**	**M1**	**M1 to Mx**	**M1 to Mx**	**Mx to M12[g]**	**M1 to M12[h]**		**M13**
Week[h]:	**-3**	**W1**	**W1**	**W2 to Wx[i]**	**W1 to Wx[i]**	**Wx to W48**	**W1 to W48**	**W49**	**W53**
Day:	**-**	**Day 1**	**Day 2-7[j]**	**-**	**-**	**-**	**-**		**-**
Weight, BMI	X	X		Monthly	Monthly	Monthly	Monthly		
Height	X								
Abbreviated Review of Systems		X						X	
Vital Signs[n]	X	X		Weekly	Weekly	Monthly	Monthly	X	X
ECG	X			X[o]	X[o]	X[o]	X[o]	X	
Laboratory tests[p]	X							X	
Pregnancy Test[q]	X	X		Weekly	Weekly	Monthly	Monthly	X	
Hepatitis B/C, HIV[r]	X								
Injection Site Examination		X		Weekly	Weekly	Monthly	Monthly	X	X
Dispense Treatment ID Card		X							
Urine Toxicology	X	X		Weekly	Weekly	Monthly	Monthly	X	
Illicit Drug Use Self-Report	X	X		Weekly	Weekly	Monthly	Monthly	X	
SOWS, COWS VAS	X	X	(X)	Monthly	Monthly	Monthly	Monthly	X	
EQ-5D-5L	X	X		Monthly	Monthly	Monthly	Monthly	X	

[n] Includes temperature, blood pressure, pulse rate, respiration rate.
[o] ECG will be performed after the first administration of CAM2038 q1w or CAM2038 q4w (i.e., prior to dosing at Week 2 for CAM2038 q1w or Week 5 for CAM2038 q4w). During the study, ECGs will be performed after dose increases (excluding the initial dose titration and booster injections) and after intake of QT-extending drugs or CYP3A4 inhibitors.
[p] Includes chemistry, hematology, urinalysis and coagulation profile.
[q] A serum pregnancy test will be performed at Screening and EOT (Week 49). An "in-office" urine pregnancy test will be required at Day 1 PRIOR to the first injection of CAM2038 and then at each visit thereafter (for women of childbearing potential).
[r] It is the Investigator's responsibility to understand and comply with all laws and regulations that apply to HIV, Hepatitis B, and Hepatitis C and testing of blood. Hepatitis B/C and HIV testing is required unless a site's IRB prohibits such testing.

Study Phase:	Screening	Treatment Phase						EOT	Follow-up
Treatment:	-	CAM2038 q1w or q4w	CAM2038 q1w			CAM2038 q4w			All Subjects
Study Population:	All Subjects[a]	All Subjects	New to BPN Treatment[b]		Transition from SL BPN/BPX[c]	Transition from CAM2038 q1w[d]	Transition from SL BPN/BPX (Monthly)[e]		
Month[f]:	M-1	M1	M1	M1 to Mx	M1 to Mx	Mx to M12[g]	M1 to M12[h]		M13
Week[h]:	-3	W1	W1	W2 to Wx[i]	W1 to Wx[i]	Wx to W48	W1 to W48	W49	W53
Day:	-	Day 1	Day 2-7[j]	-	-	-	-		-
WPAI-GH	X	X		Monthly	Monthly	Monthly	Monthly	X	
Patient Satisfaction				Month 6	Month 6	Month 6	Month 6	X	
C-SSRS[s]	X	X		Weekly	Weekly	Monthly	Monthly	X	X
CAM2038 SC injection[t]		X	(X)	Weekly	Weekly	Monthly	Monthly		
Psychosocial Counseling		X		Monthly	Monthly	Monthly	Monthly		
Adverse Events[u]	X	X	(X)	Weekly	Weekly	Monthly	Monthly	X	X
Concomitant Meds/Procedures	X	X		Weekly	Weekly	Monthly	Monthly	X	X
On-site Visits	X	X	(X)	Weekly	Weekly	Monthly	Monthly	X	X

Abbreviations: BMI=Body Mass Index; COWS=Clinical Opiate Withdrawal Scale; C-SSRS=Columbia Suicide Severity Rating Scale; DSM-V=Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition; ECG=electrocardiogram; HIV=Human Immunodeficiency Virus; Hx=history; ID= identification; M= month; SC=subcutaneous; SOWS=Subjective Opioid Withdrawal Scale; VAS=visual analogue scale; W= week; WPAI-GH=Work Productivity and Activity Impairment Questionnaire-General Health; (X)=optional visit based on individual subject titration needs.

[s] Screening version at Visit 1 (Screening), Since Last Visit version at all subsequent visits.
[t] CAM2038 q1w for weekly visits and CAM2038 q4w for monthly visits.
[u] Any spontaneously reported adverse events will be recorded after the subject signs the informed consent form. In addition, adverse events will be elicited using a non-leading question each time the subject visits the clinic.

9.1. Demographics and Other Baseline Characteristics

9.1.1. Informed Consent

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

9.1.2. Demographics

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

9.1.3. Medical History

The complete medical history based on patient interview of 5 years prior to the screening visit and any clinically significant medical history greater than 5 years prior to the screening visit will be collected, these will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems. All findings on medical history will be evaluated by the Investigator for clinical significance.

9.1.4. Medication History

All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) taken by the subjects during the 30 days prior to Screening will be recorded in the source documentation as medication history. Substance Abuse History and Treatments will be collected separately.

9.1.5. Substance Use and Treatment History

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. This will include drugs used, type, frequency and patterns of abuse, routes, doses, drug preferences and concomitant medications, using questionnaires. Detailed information on substance use and treatment history is provided in the Study MOP.

9.1.6. Contraceptive Requirements

Women of childbearing potential must agree to use highly-effective method(s) of birth control as defined in the informed consent form and must agree to be tested for pregnancy.

Highly-effective method(s) of birth control include:

- Established use of progestogen-only oral, injectable or implantable hormonal methods of contraception (for example contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release).
- Established use of combined estrogen and progestogen oral, intravaginal or transdermal hormonal methods of contraception (for example contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release).
- Placement of an intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS).
- Vasectomized male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate and provided this partner is the sole sexual partner of the female study participant of childbearing potential).

Male subjects must agree to use condoms throughout the course of the study (from Screening to Follow-up).

Women of childbearing potential must have a confirmed negative pregnancy test at study entry. They must use an effective contraceptive method throughout the entire duration of the study treatment, and agree to repeat urine pregnancy test at designated visits. The applied methods of contraception have to meet the above criteria for a highly effective method of birth control.

Sterilized or infertile subjects are exempt from the requirement to use contraception. In order to be considered sterilized or infertile, subjects must have undergone surgical sterilization (vasectomy/bilateral tubectomy, hysterectomy and bilateral ovariectomy, as determined by subject medical history) or congenially sterile, or must be post-menopausal. Postmenopausal women must be amenorrheic for at least 12 months.

9.2. Eligibility Review

Prior to receiving CAM2038 on Day 1, subjects must meet all inclusion and not meet any exclusion criteria as outlined in Section 7.4 and 7.5.

The Investigator or Sub-Investigator must document that the subjects meet each individual criterion 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 Day 1.

9.3. Efficacy Assessments

Details regarding exploratory efficacy endpoints are provided in Section 9.6 (Efficacy Variables). The following sections provide an overview of the efficacy assessments included in the study. Additional details, such as the questionnaire items/scale text and additional instructions (where applicable) are provided in the Study MOP.

9.3.1. Urine Toxicology for Opioids

Urine toxicology samples will be collected at each visit 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). A direct observation approach to obtaining urine samples may be used if the Investigator deems it necessary (in Sweden and France, supervision of urine sampling is mandatory). Urine samples will be logged and numbered and then sent to a central laboratory for analysis for the presence of opioids (e.g., morphine and metabolites, oxycodone, hydrocodone, hydromorphone, fentanyl, and methadone). In addition, it is recommended that the scheduled assessment visits take place on Mondays to potentially improve detection of illicit opioid use that may have occurred over the weekend.

9.3.2. Self-Reported Illicit Drug Use

Subjects will be questioned about illicit drug use, including illicit or prescription opioids and other drugs of abuse using a timeline follow-back type of interview (Fals-Stewart et al, 2000). A copy of the Illicit Drug Use Self-Report form is provided in the Study MOP.

9.3.3. Measures of Desire and Need to Use

Desire to Use and Need to Use will be administered using unipolar 100 mm VAS ("Since your last scheduled assessment visit, indicate your worst or strongest desire/need to use opioids, where 0 = No desire to use and 100 mm= Strongest possible desire, and from 0=No need to use and 100 mm=Strongest possible need, respectively) outcome (Kozlowski et al, 1989).

Copies of these VASs are provided in the Study MOP. ***NOTE: Only VAS copies provided by the Sponsor should be used with study subjects; photocopies made locally may result in changes to the length of the scale, leading to inaccurate results.***

A separate VAS will be provided for each Desire to Use and Need to Use and measurements must be taken separately (i.e., separated in time or by other procedures).

9.3.4. Quality of Life Questionnaires and Patient Satisfaction Scale

Two quality of life questionnaires will be provided to subjects for completion:

- Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH) (Reilly Associates).
- EQ-5D-5L Health Questionnaire (EuroQOL Group Association).

These are to be completed on a monthly basis, approximately every four weeks at the subjects scheduled visit.

A patient satisfaction scale will be provided to subjects for completion at month 6 and month 12 (EOT).

Copies of the WPAI-GH, EQ-5D-5L and patient satisfaction scale is provided in the Study MOP.

9.3.5. Measures of Withdrawal

9.3.5.1. Subjective Opioid Withdrawal Scale (SOWS)

Subjects will complete a self-assessment of withdrawal symptoms using the SOWS. This form contains 16 questions that rate the intensity of withdrawal from 0 ("Not at all") to 4 ("Extremely"). A copy of the SOWS is provided in the Study MOP.

9.3.5.2. Clinical Opioid Withdrawal Scale (COWS)

Study personnel will assess clinical observations indicative of withdrawal using the COWS. This scale consists of 11 common opiate withdrawal signs or symptoms, rated on a numeric scale and based on a timed period of observation of the subject by the rater. A copy of the COWS is provided in the Study MOP.

9.3.6. Urine Toxicology for Other Drugs of Abuse

Urine will be tested for other drugs of abuse (e.g., cocaine, benzodiazepines, barbiturates, amphetamines, phencyclidine and cannabinoids [THC]) and for alcohol using qualitative methods. Positive results will not be confirmed using quantitative methods.

9.3.7. Unscheduled Visits, Medication and Counseling

Temporary adjustments in BPN doses will be allowed using CAM2038 q1w SC booster injections (8 mg) at unscheduled visit(s). A maximum of two SC booster injections will be allowed per week. Subject-requested or physician-directed supplemental visits, phone calls or additional counseling, or other pharmacological interventions, along with the reason(s) for unscheduled visits, booster injections, phone calls or additional counseling or other pharmacological interventions, will be recorded.

9.4. 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 CRF. CAM2038 injections may be discontinued as clinically indicated.

9.4.1. Adverse Events and Serious Adverse Events

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

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or increase in severity of a preexisting abnormality, temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

9.4.1.1. Adverse Event Reporting

All AEs (except for withdrawal symptoms, see below) must be entered on the AE CRF, regardless of causality or severity. AEs include new AEs, worsening baseline conditions, clinically significant laboratory findings, disease-related signs and symptoms that were not present at baseline, and any events or findings that the Investigator feels are clinically significant. Withdrawal symptoms will be captured via specified assessments and should not be recorded as AEs.

Disease-related signs and symptoms that are present at baseline should not be recorded as AEs unless they worsen in severity or increase in frequency.

Information collected concerning AEs will include the following:

- Name of the event
- Onset date
- Resolution date
- Severity (i.e., mild, moderate, or severe)
- Relationship to study drug
- Action and outcome
- Seriousness of event

Definition of MILD, MODERATE, SEVERE AE:

- Mild- An AE that requires minimal treatment and does not interfere with daily living.
- Moderate-An AE that requires therapeutic intervention and interferes with daily living.
- Severe-An AE that requires intensive therapeutic intervention, significant, etc.

All AEs will be documented and followed from the time the subject has signed the ICF until 14 days after the Follow-up Visit (or 30 days after early termination). Serious AEs and AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization.

9.4.1.2. Serious Adverse Event (SAE)

An SAE or reaction is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in an offspring)

- An Important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All AEs requiring hospitalization or prolongation of a pre-existing hospitalization should be reported as SAEs unless they occur greater than 14 days after the Follow-up Visit (or 30 days after early termination) AND are not considered to be drug-related by the Investigator.

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

9.4.1.2.1. Serious Adverse Event Reporting

Serious AEs must be reported to the Sponsor or designee within 24 hours of knowledge of the event. All SAEs that occur while a subject is receiving study drug and within 14 days following the Follow-up Visit (or 30 days after early termination) are reportable within 24 hours. During the follow-up period beyond 14 days from Follow-up (or 30 days after early termination), only those SAEs that are considered to be possibly related to study drug should be reported within 24 hours.

The procedure for reporting an SAE is as follows:

- Within 24 hours of knowledge of the event, the site must contact the Sponsor (or designee) by telephone or facsimile to report the event.
- The initial report should include all information known at the time of the report (additional information can be reported as discovered). Do not delay the initial reporting in order to obtain resolution or follow-up information.
- The site will enter into the electronic database (or fax, if the database cannot be accessed for any reason) an SAE report, or similar form, that includes the following information, as available:
    - Subject ID
    - Basic demographic information (age, gender, weight)
    - Outcomes attributed to the event (death, life-threatening hospitalization [new or prolonged], disability, congenital anomaly, required medical intervention to prevent permanent impairment/damage, etc.)
    - Onset date and severity of the event
    - Brief description of the event including frequency and severity of symptoms leading to diagnosis
    - List of relevant test results and laboratory data
    - Any other relevant history
    - Whether the study drug was discontinued

- Whether the assigned treatment oral or injectable therapy was discontinued and/or dose titration discontinued, as applicable
- Investigator's assessment of causality

The Medical Monitor or another representative of the Sponsor may contact the Investigator to request additional information regarding the event or to confirm information. All SAEs will be entered on the AE CRF. The same nomenclature should be used on both the SAE report and the AE CRF.

Specific instructions for SAE reporting and a copy of an SAE report form are provided in the MOP.

The Investigator is responsible for the complete and timely reporting of all SAEs to the Sponsor (or designee), reporting pertinent follow-up information on the SAE, and notifying the appropriate IRB/Independent Ethics Committee (IEC) of the occurrence of and details surrounding the event. In the event there is a question as to whether the AE is serious, the event should be reported.

9.4.1.2.2. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is defined as an SAE and where:

- There is a certain degree of probability that the event is harmful, and an undesirable, reaction to the medicinal product being research, regardless of the administered dosage. In other words, there is an adverse reaction.
- The adverse reaction is unexpected. That is to say, the nature and severity of the adverse reaction are not in agreement with the reference safety information as recorded in the Investigator's Brochure.

A SUSAR has additional reporting requirements, as described below.

- If the SUSAR is fatal or life-threatening, associated with the use of the investigational medicinal product, and unexpected, competent authorities and ethics committees will be notified within 7 calendar days after the Investigator learns of the event. Additional follow-up information (cause of death, autopsy report, hospital report) should be reported within an additional 8 days (15 days in total).
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the use of the investigational medicinal product, and unexpected, competent authorities and ethics committees will be notified within 15 calendar days after the Investigator learns of the event.

All Investigators will receive relevant information about SUSARs in a timely fashion. Follow-up information may be submitted if necessary.

9.4.2. Pregnancy

Pregnancies among trial 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 may withdraw their consent and discontinue the study and be referred back to the care of their usual provider or continue in the study after discussion with and documentation by the Principal

Investigator or his/her designee. (In the UK, participants who become pregnant will be discontinued from the study permanently and be referred back to the care of their usual provider.) 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 during the first year of life.

9.4.3. Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood and urine samples will be performed at a selected central laboratory, with the exception of urine pregnancy tests that are conducted at the study site. The central lab will generate laboratory reports and forward them to the clinical site in a timely manner. It is the responsibility of the Investigator to review and sign all lab reports expeditiously, in order to document appropriate safety monitoring of study subjects. The Investigator should sign and date each lab 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." Per investigator judgment, 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.

Table 4: Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count RBC 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)	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 (PT), International normalized ratio (INR)		

In addition to the clinical laboratory tests, a serum pregnancy test will be performed at the Screening Visit and the End of Treatment Visit. An “in-office” urine pregnancy test will be required at Day 1 PRIOR to first CAM2038 administration, and then at each visit prior to administration of CAM2038 (for women of childbearing potential). Results must be reviewed and confirmed to be negative prior to start of CAM2038 treatment (Day 1).

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

9.4.4. 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.

9.4.5. 12-Lead Electrocardiogram (ECG)

12-Lead ECGs will be performed after the subject has been resting in a recumbent/supine position for at least 3 minutes. The ECG variables will include ventricular heart rate and the PR, QRS, QT, QTcB and QTcF intervals. The ECGs will be signed and dated by a medically-qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant. In general, abnormal, clinically significant ECGs are expected to be associated with an item recorded in medical history or with an AE.

ECGs will be performed at Screening and at the EOT visit. In addition, ECGs will be performed after the first administration of CAM2038 q1w or CAM2038 q4w (i.e., prior to dosing at Week 2 for CAM2038 q1w or Week 5 for CAM2038 q4w). ECGs will also be performed in connection to dose increases (excluding the initial dose titration and booster injections) and after intake of QT-extending drugs or CYP3A4 inhibitors (a list of relevant drugs will be included in the Study MOP).

9.4.6. Physical Examination

A complete physical examination including all major body systems will be performed at Screening. At select subsequent study visits, an abbreviated review of systems will be performed to capture changes since Screening.

Height, weight and BMI will be determined as described in Table 3.

9.4.7. C-SSRS

The Columbia Suicide Severity Rating Scale (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) and the Since Last Visit version. The Screening version of the C-SSRS will be administered at Screening. The Since Last Visit version of the C-SSRS will be administered at all subsequent assessment times, as indicated in Table 3.

The C-SSRS is to be administered by the Investigator or his/her qualified designee. Qualified designee is defined as physician, osteopath, nurse practitioner, clinical psychologist or physician's assistant, who is licensed and has completed the C-SSRS training within the last 2 years. The survey should be administered by the same assessor, where possible, throughout the study.

9.4.8. Injection Site Examination

CAM2038 injection sites will be examined during each scheduled visit for any signs of adverse site reactions, including erythema, pruritus, edema, pain, etc. If needed, a photograph of the adverse site reactions wil be taken and shared with the medical monitor for review. The pain scale will be completed by the subjects within 10 minutes after each injection. The new injection site will also be examined within 15 minutes after each injection to determine if any site related AEs have occurred. Injection site evaluation forms will be included in the Trial MOP. Subjects will also be queried specifically about local tolerability AEs in connection to the examinations.

9.4.9. Psychosocial Counseling

All subjects will receive drug counseling once monthly (at least once every four weeks). Additional counseling can be provided as clinically indicated; however, all additional counseling, visits or phone calls must be recorded.

9.4.10. 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 (see Section 8.7). Sample wallet cards will be provided for IRB submission.

9.4.11. Other Safety Considerations

Buprenorphine may impair the mental and physical abilities required for performance of potentially dangerous tasks. Subjects will be instructed to avoid operating heavy machinery during induction, and to exercise caution in performing activities requiring alertness such as driving a car during the first few days after the beginning of the trial, or until such time that they are reasonably certain that their ability to engage in such activities is not adversely affected.

9.5. Appropriateness of Measures

Standard safety outcomes, such as AEs, ECG, vital signs and clinical laboratory testing will be assessed during the study.

Given the open-label, uncontrolled nature of the study, the efficacy endpoints will be considered exploratory. These additional measures were selected as a series of measures and scales to provide an exploratory assessment of efficacy of CAM2038 q1w and q4w, including monthly urine toxicology with patient self-reported illicit opioid use, retention in treatment, Investigator- and subject-reported withdrawal and subject-reported cravings. Standard and widely used measures of withdrawal will be included in this study (COWS and SOWS) (Handelsman et al, 1987; Wesson and Ling, 2003) in order to ensure that subject's withdrawal symptoms are adequately controlled by CAM2038 q1w and q4w. Desire to Use and Need to Use VASs was selected versus typical Craving VAS because the latter term is ambiguous and may have different meaning to different individuals, while the Desire/Need to Use VAS more directly assesses

the potential behavioral outcome (Kozlowski et al, 1989).

9.6. Safety Variables

Safety variables include:

- AEs and SAEs
- Clinical laboratory tests
- ECG
- Vital signs
- Physical and injection site examinations
- Concomitant medications

9.7. Efficacy Variables

Efficacy variables include:

- Urine toxicology results for illicit opioids
- Self-reported illicit opioid use
- Retention (%) in treatment
- Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH)
- EQ-5D-5L Health Questionnaire
- Patient Satisfaction Scale
- Measures of opioid withdrawal:
    - COWS
    - SOWS
- Measures of opioid craving:
    - Desire to Use VAS
    - Need to Use VAS
- Urine toxicology results for other drugs of abuse

10. DATA QUALITY ASSURANCE

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

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

10.1. Data Collection

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, participant diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, 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 electronic data capture system maintains a full audit trail.

10.2. Study Auditing and Monitoring

Monitoring of the study site (including, but not limited to, reviewing CRFs for accuracy and completeness) will be performed by the Sponsor's designated monitor(s). The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or an IRB may visit the site to perform audits or inspections, including the drug storage area, study

drug stocks, drug accountability records, participant charts and source documents, 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 ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

11. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

11.1. Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in the Study Statistical Analysis Plan (SAP), which will be completed prior to unlocking the database. This document will include more detail of analysis populations, summary strategies, and any amendments to the proposed analyses listed here, if necessary. Any changes to the SAP will be outlined in the final study report.

11.2. Analysis Populations

The study analysis populations will consist of:

- **Full Exposure Safety Population:** All subjects who have been exposed to CAM2038 for 48 weeks
- **Overall Safety Population:** All subjects who received at least one CAM2038 treatment

The safety results will be presented for both Full Exposure Safety Population and Overall Safety Population.

11.3. Planned Analyses

11.3.1. 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 also be summarized.

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

11.3.2. Analysis of Efficacy Measures

Exploratory efficacy measures will be summarized by visit using standardized descriptive statistics and listed by subject.

11.3.3. Analysis of Safety Assessments

Exposure and safety summaries will be presented for both Safety Populations.

All 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. Summaries of these AE subsets will

be presented for relationship to study drug, intensity, seriousness, AEs or SAEs leading to discontinuation and AEs occurring in 5% or greater (by preferred term). Frequencies for deaths and hospitalizations will also be summarized.

Data for clinical laboratory tests, ECG, vital signs, and physical and injection site examinations will be summarized using standard descriptive and change from baseline statistics. Shift tables and tabular summaries of abnormalities will be provided, where appropriate. Medications will be coded using the World Health Organization Drug dictionary and summarized using descriptive statistics.

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

11.4. Determination of Sample Size

A total of 100 subjects with at least 48 weeks of CAM2038 exposure will be needed for the safety assessments. Approximately 228 subjects will be enrolled initially into this study with an estimated dropout rate of approximately 50% to ensure a total of 100 subjects are exposed to CAM2038. Once a total of 100 subjects complete 48 weeks of CAM2038 treatment, the study will be completed.

12. STUDY ADMINISTRATION AND INVESTIGATOR RESPONSIBILITIES

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

12.1. Regulatory and Ethical Considerations

12.1.1. Ethical Conduct of the Study

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

12.1.2. Ethics Approval

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

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

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

12.1.3. Subject Informed Consent

The Investigator (or authorized designee) will ensure that the participant (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 is to be provided in a language understandable to the participant and must not include any language that waives the participant's legal rights. Prospective participants must also be informed of their right to withdraw consent without prejudice at any time during the study. If the participant chooses to participate, he/she must sign the ICF before any study-related procedures are performed.

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

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

12.2. Privacy and Confidentiality

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

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

The knowledge gained through this study is the property of the Sponsor. The Sponsor, representatives and affiliated companies of the Sponsor, the IRB, and regulatory agencies (such as the United States 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 or IEC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of the Sponsor. Please refer to the Clinical Study Agreement (CSA) for details.

12.3. Study and Site Closure

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

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the Sponsor will discuss this with

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

12.4. Regulatory Documents and Records Retention

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

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

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

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

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

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

12.5. Delegation of Responsibilities and Adequate Resources

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

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

12.6. Protocol Amendments

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

12.7. Financial Disclosure

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

13. SPONSOR APPROVAL PAGE

An Open-Label Multicenter Study Assessing the Long-Term Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injection Depot of Buprenorphine (CAM2038) in Adult Outpatients with Opioid Use Disorder

Version: 5.0

Date: 09-Dec-2016

Braeburn Pharmaceuticals

Sonnie Kim, PharmD
VP, Clinical Development & Medical Affairs — 09-Dec-2016

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

14. INVESTIGATOR PROTOCOL AGREEMENT PAGE

An Open-Label Multicenter Study Assessing the Long-Term Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injection Depot of Buprenorphine (CAM2038) in Adult Outpatients with Opioid Use Disorder

Version: 5.0

Date: 09-Dec-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 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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