

Clinical Trial Protocol HS-11-421

A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel Group, Multi-center Trial Assessing the Efficacy and Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Treatment of 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)

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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 50 mg/mL q1w (buprenorphine FluidCrystal [®] once-weekly subcutaneous injection depot) CAM2038 356 mg/mL q4w (buprenorphine FluidCrystal [®] once-monthly subcutaneous injection depot)
Name of Active Ingredient: Buprenorphine
Trial Title: A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel Group, Multi-center Trial Assessing the Efficacy and Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injection Depot of Buprenorphine (CAM2038) in Treatment of Adult Outpatients with Opioid Use Disorder
Objectives: The primary objective is to demonstrate non-inferiority of the CAM2038 buprenorphine (BPN) treatment arm as compared to the sublingual (SL) BPN treatment arm in treating adult outpatients with opioid use disorder, as measured by the primary efficacy measure of response rate (RR). The secondary objectives are: <ul style="list-style-type: none">▪ To demonstrate non-inferiority of CAM2038 compared to SL BPN in adult outpatients with opioid use disorder, as measured by the secondary efficacy measure of percentage negative urines.▪ To evaluate the efficacy of CAM2038 compared to SL BPN in adult outpatients with opioid use disorder, as measured by the secondary efficacy measure of time to sustained abstinence from illicit opioid use.▪ To evaluate the efficacy of CAM2038 compared to SL BPN in adult outpatients with opioid use disorder, as measured by the secondary efficacy measure retention rate.▪ To evaluate the efficacy of CAM2038 compared to SL BPN in adult outpatients with opioid use disorder, as measured by the exploratory efficacy measures.▪ To evaluate the safety of CAM2038 in adult outpatients with opioid use disorder.
Methodology: This is a randomized, double-blind, double-dummy, active-controlled, parallel group multi-center trial, designed to evaluate the non-inferiority of CAM2038 compared to an existing standard of care (SL BPN) in initiation and maintenance treatment with BPN. The trial will involve 4 phases: Screening, Phase 1 (weekly visits), Phase 2 (monthly visits), and Follow-up. Following Screening and confirmation of eligibility, subjects will be randomized to one of two treatment groups in a 1:1 ratio: <ul style="list-style-type: none">▪ Group 1: SL BPN tablets + placebo subcutaneous (SC) injections▪ Group 2: CAM2038 SC injections + SL placebo tablets Following randomization, subjects will undergo initiation of BPN treatment with either SL BPN or SC CAM2038 q1w, and participate in weekly visits for 12 weeks (Phase 1). After Week 12, subjects will be transitioned to Phase 2 with monthly visits. During Phase 2, subjects in Group 1 will continue treatment

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Name of Active Ingredient: Buprenorphine
<p>with monthly dispensing of daily SL BPN treatment and monthly placebo SC injections, and subjects in Group 2 (receiving CAM2038 q1w) will be transferred to monthly injections of CAM2038 q4w and monthly dispensing of daily SL placebo. Subjects will participate in up to 6 visits during the 12 weeks of Phase 2; 3 scheduled monthly visits and 3 random urine toxicology visits. At each visit, efficacy and safety outcome measures will be assessed. After Phase 2, subjects will be followed-up for 4 weeks.</p> <p>A total of 18 opioid urine toxicology samples will be collected during Phase 1 and Phase 2 of the trial, whereof 12 samples will be collected at the scheduled weekly visits during Phase 1. A total of 6 opioid urine toxicology samples will be collected during the 12 weeks of Phase 2 (3 at the scheduled monthly visits and 3 at random urine toxicology visits). A self-report of drug use will accompany every urine toxicology test.</p> <p>Subjects who complete the 24 weeks of treatment (i.e., Phase 1 and Phase 2) will be transitioned to standard of care (e.g., SL BPN) and be followed up for 4 weeks.</p> <p>All subjects will be blinded to their treatment group assignment, as will all trial staff with the exception of the clinician(s)/staff performing the SC injections and designated personnel who will be responsible for drug accountability (i.e., counting the active and placebo SL BPN returned tablets).</p> <p>To ensure adequate enrollment and address potential inconvenience to subjects, all subjects (regardless of randomized group) will receive appropriate compensation for time and travel expenses related to attendance at trial visits. All costs of medications and counseling will also be covered.</p> <p>Investigators will be instructed to use manual-guided psychosocial counseling for trial subjects throughout the trial period.</p>
Number of Subjects (Planned): Approximately 380 subjects (190 subjects per arm) will be randomized.
Diagnosis and Main Criteria for Inclusion: This trial will enroll adult outpatients with opioid use disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V) who are not currently being treated and have not been treated with opioid maintenance therapy for the past 60 days before randomization.
Investigational Product, Dosage and Mode of Administration: CAM2038 q1w: BPN FluidCrystal [®] SC injection depot for once weekly administration (50 mg/mL) at doses of 8, 16, 24 and 32 mg (BPN base) (0.16, 0.32, 0.48 or 0.64 mL SC injection). CAM2038 q4w: BPN FluidCrystal [®] SC injection depot for once monthly administration (356 mg/mL) at doses of 64, 96, 128 or 160 mg (BPN base) (0.18, 0.27, 0.36 or 0.45 mL SC injection).
Reference Therapy, Dosage and Mode of Administration: <i>Active Comparator</i> SL BPN: 2 mg/0.5 mg or 8 mg/2 mg BPN/naloxone tablets administered daily, at doses of 8 mg/2 mg to 32 mg/8 mg per day.

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Name of Active Ingredient: Buprenorphine
Placebos CAM2038 placebo: 0.16, 0.32, 0.48 and 0.64 mL SC injection administered once weekly or once monthly (matching volumes for CAM2038 q1w and near-matching volumes for CAM2038 q4w). SL placebo: tablets matching 2 mg/0.5 mg and 8 mg/2 mg SL BPN doses, administered daily.
Duration of Trial: Each subject will participate in the trial for up to 31 weeks, including up to 24 weeks of treatment with SL BPN or SC CAM2038.
Criteria for Evaluation: <u>Primary Efficacy Variable</u> The primary efficacy variable will be the responder rate. The responder rate will be derived based on urine samples obtained from Weeks 10, 11, 12 and 13 in Phase 1 and samples obtained at Weeks 17 (Month 1), 21 (Month 2) and 25 (Month 3) and at the 3 random samples in Phase 2. To be a responder for Phase 1, the subject must have no evidence of illicit opioids use at Week 13 and have no evidence of illicit opioids use for at least 2 out of the three weeks from Week 10 to Week 12. To be a responder for Phase 2, the subject must have no evidence of illicit opioids use at Month 6 (last illicit opioids use assessment in Month 6 or Week 25) and have no evidence of illicit opioids use in 5 out of the 6 illicit opioids use assessments in Phase 2. To be a responder for the study, the subject must be a responder for both Phases 1 and 2. <u>Secondary Efficacy Variables:</u> <ul style="list-style-type: none">▪ Percentage of urine samples negative for illicit opioids (This variable will be defined in the manner per EMA's request. This variable will serve as the primary efficacy variable for EMA NDA and will not be applicable for US NDA submission)▪ Cumulative Distribution Function (CDF) of percent samples that are negative for illicit opioids (Weeks 5-25)▪ Time to sustained abstinence of opioid use▪ Percent of subjects remainin in the trial (retention rate) <u>Exploratory Efficacy Variables:</u> <ul style="list-style-type: none">▪ RR for Phase 1▪ RR for Phase 2▪ Percent negative urine samples in Phase 1▪ Percent negative urine samples in Phase 2

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Name of Active Ingredient: Buprenorphine
<ul style="list-style-type: none">▪ Percent of subjects with evidence of no illicit opioid use by time point▪ Cumulative percentage of subjects with evidence of no illicit opioid use by time point▪ Percent of subjects with no self-reported illicit opioid use by time point▪ Percentage of subjects meeting criteria of stability at Week 13▪ Measures of opioid craving:<ul style="list-style-type: none">o Desire to Use visual analogue scale (VAS)o Need to Use VAS▪ Measures of opioid withdrawal:<ul style="list-style-type: none">o Clinical Opioid Withdrawal Scale (COWS)o Subjective Opioid Withdrawal Scale (SOWS)▪ Percentage of subjects without evidence of using other drugs of abuse by time point▪ Supplemental BPN use▪ Additional supplemental counseling▪ Measures of morning need to use/desire to use▪ Quantity of illicit opioid use
<u>Safety Variables</u> Safety data including adverse events, clinical laboratory parameters, electrocardiogram, physical and injection site examinations, concomitant medications, vital signs and C-SSRS. <ul style="list-style-type: none">▪

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Name of Active Ingredient: Buprenorphine
Statistical Methods (Data Analysis): Primary Efficacy Analysis The primary efficacy variable will be the responder rate. The responder rate will be derived based on urine samples obtained from Weeks 10, 11, 12 and 13 in Phase 1 and samples obtained at Weeks 17 (Month 1), 21 (Month 2) and 25 (Month 3) and at the 3 random samples in Phase 2. To be a responder for Phase 1, the subject must have no evidence of illicit opioids use at Week 13 and have no evidence of illicit opioids use for at least 2 out of the three weeks from Week 10 to Week 12. To be a responder for Phase 2, the subject must have no evidence of illicit opioids use at Month 6 (last illicit opioids use assessment in Month 6 or Week 25) and have no evidence of illicit opioids use in 5 out of the 6 illicit opioids use assessments in Phase 2. To be a responder for the study, the subject must be a responder for both Phases 1 and 2. An analysis of non-inferiority in the primary efficacy variable between the two treatment arms will be performed using a margin of 13.5% point. Non-inferiority will be concluded if the two-sided 95% confidence interval for the difference between the probabilities of response (Active- Control) is above -0.135. The 95% confidence interval, (LB, UB), will be derived using normal approximation: $LB = (P_T - P_C) - 1.96 * (1/N_T * P_T * (1 - P_T) + 1/N_C * P_C * (1 - P_C))^{0.5}, \text{ and}$ $UB = (P_T - P_C) + 1.96 * (1/N_T * P_T * (1 - P_T) + 1/N_C * P_C * (1 - P_C))^{0.5}, \text{ where}$ P_T and P_C are observed proportions of the responders for the treatment and the control, respectively, and N_T and N_C are the sample sizes for the treatment and the control, respectively. Sample Size Calculation The primary efficacy variable is based on data from Week 2 to Week 25. Approximately 380 subjects (190 subjects per arm) will be randomized. The sample size of 190 subjects per treatment arm (380 total) was selected to achieve approximately 82% power to establish non-inferiority based on the primary efficacy variable, RR (Week 2-25). In the sample size calculation, it is assumed that both arms have a 70% RR, and that the non-inferiority margin is 13.5%.

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC _{inf}	Area under the plasma concentration-time curve from time zero to infinity
BMI	Body mass index
BPN	Buprenorphine
CDF	Cumulative Distribution Function
CFR	Code of Federal Regulations
C _{max}	Maximum plasma concentration
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
CRF	Case report form (may include electronic data capture systems or paper forms)
CS	Clinically significant
CSA	Clinical Study Agreement
C _{ss,av}	Average plasma concentration during a dosing interval at steady state
C _{ss,max}	Maximum plasma concentration during a dosing interval at steady state
C-SSRS	Columbia Suicide Severity Rating Scale
C _{ss,trough}	Trough plasma concentration during a dosing interval at steady state
C _t	Plasma concentration at time t post administration
C _{trough}	Trough plasma concentration
CV	Coefficient of variation
CYP3A4	Cytochrome P450 3A4
DSM-V	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
ECG	Electrocardiogram
EDC	Electronic data capture
EMA	European Medicines Agency
EOT	End Of Treatment
FC	FluidCrystal®
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus

ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
MedDRA	Medical Dictionary of Regulatory Activities
mITT	Modified Intent-to-Treat
MOP	Manual of procedures
NCS	Not clinically significant
PT	Prothrombin time
QTc	Fridericia's corrected QT interval
RBC	Red blood cell
RR	Response rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SL	Sublingual
SOC	System Organ Class
SOWS	Subjective Opiate Withdrawal Scale
SUSAR	Suspected Unexpected Serious Adverse Reaction
VAS	Visual analogue scale

5. INTRODUCTION

5.1. Background

Buprenorphine (BPN) is an opioid with mixed agonist-antagonist properties that, together with appropriate counselling 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 (1-4).

CAM2038 (BPN FluidCrystal[®] [FC] subcutaneous [SC] injection depot) once-weekly (hereafter referred to as CAM2038 q1w) and once-monthly (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 in the SC tissue. The phase transition proceeds from the outside towards the center of the injected FC by absorption of minute quantities of water. Thus, injection of CAM2038 q1w or q4w into SC tissue results in an immediate and spontaneous formation of controlled BPN release matrix providing long-acting release *in vivo* with a minimum initial burst release. The dual nature of the FC system, i.e., a true liquid drug product *in vitro* before injection and stable gel *in vivo* after injection, enables a ready-to-use drug product in a prefilled syringe. CAM2038 q1w and q4w are designed for convenient and safe SC injection using a prefilled syringe including a needle safety device and with no need for mixing or temperature adjustment prior to administration. In addition, the injection volumes for CAM2038 q1w and q4w are relatively low (from 0.15 to 0.6 mL volume, depending on dose and product) and can be administered using a fine gauge needle (23 G). CAM2038 depots have been designed with a focus on enabling easy administration, dosing flexibility, and importantly, minimizing risks of misuse, diversion and poor patient adherence.

5.1.1. CAM2038 q1w (Once Weekly)

SC CAM2038 q1w has so far been investigated after single and repeated doses in three clinical trials, where a total of 176 human subjects (patients and healthy volunteers) have been exposed to the CAM2038 drug products. An initial trial assessed pharmacokinetics, pharmacodynamics and safety in opioid dependent patients (Trial HS-07-307). The results showed that CAM2038 q1w was well tolerated, both locally and systemically. Importantly, no treatment emergent serious adverse events (SAEs) were observed and drug-related local tolerability findings were limited to 4 of 42 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 trials were subsequently performed in healthy volunteers (under naltrexone blockade) to assess the pharmacokinetics and bioavailability of single and repeated doses of CAM2038 q1w versus repeated doses of sublingual (SL) BPN (i.e., at steady state) and single dose of intravenous (IV) BPN (Trials HS-11-426 and HS-13-487). These two trials demonstrated that after administration of the studied doses of CAM2038 q1w, the plasma concentrations corresponded to those obtained after administration of SL BPN at approved doses (i.e., 8 mg, 16 mg, or 24 mg doses). The BPN levels after administration of CAM2038 q1w were furthermore similar in healthy volunteers and patients with opioid dependence. The systemic tolerability of CAM2038 q1w was good in both trials and similar to the reference products, IV and SL BPN. Local tolerability was very good with no local adverse events (AEs) reported in Trial HS-11-426 ($N_{\text{safety}}=60$) related to injection site tolerability. Similarly, local tolerability of CAM2038 q1w was also very good in Trial HS-13-487, featuring 4 repeat SC injections of CAM2038 q1w into the buttock site (1 subject reported 1 AE of injection site pain).

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

- Extended BPN release over one week in target plasma concentrations ranges
- 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 trial
- Observed and predicted average plasma concentration during a dosing interval at steady state ($C_{\text{ss,av}}$) and trough plasma concentration during a dosing interval at steady state ($C_{\text{ss,trough}}$) values for CAM2038 q1w within known therapeutic plasma levels
- 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 trials is also supported by a large body of data generated in non-clinical pharmacokinetic and toxicology studies in the dog, mini-pig and rat of single and repeat SC doses of CAM2038 q1w, including repeat weekly doses of the FC vehicle formulation for 6 months. SC administration of CAM2038 q1w has been shown to be well tolerated both systemically and locally in the non-clinical studies. The treatment-related findings have been limited to clinical observations in agreement with and considered related to known pharmacological effects of the drug substance BPN, and to reversible, local inflammatory reactions at the SC site of injection. The latter findings were similar to the physiological response to a foreign body. The FC related injection site findings appeared to be reversible and self-limiting, and only apparent at the immediate vicinity of test article deposition. In summary, non-clinical data have indicated no systemic toxicity associated with CAM2038 q1w or the FC injection depot vehicle.

5.1.2. CAM2038 q4w (Once Monthly)

SC CAM2038 q4w has been investigated in one bridging clinical pharmacokinetic trial in healthy volunteers versus repeat dose CAM2038 q1w (i.e., at steady state), repeat dose SL BPN (i.e., at steady state), and single dose of IV BPN (Trial 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
- 6- to 8-fold higher bioavailability versus SL BPN, comparable to CAM2038 q1w
- BPN plasma concentrations over 4 weeks comparable to CAM2038 q1w over one week, and to SL BPN over 24 hours at steady state (i.e., for approved 8 mg, 16 mg, or 24 mg doses), supporting dose selection for this Phase III trial
- Predicted $C_{ss,av}$ and $C_{ss,trough}$ values for 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 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 BPN, and for the components of the vehicle, suggests safe use of CAM2038 q4w for the proposed clinical development. This conclusion is further supported by results from non-clinical studies and clinical trials of the once weekly product, CAM2038 q1w, comprising the same active substance and functional lipid components.

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

5.1.3. Dosing Rationale

In this Phase III trial, several dose levels of the weekly product CAM2038 q1w, the monthly product CAM2038 q4w and the daily product SL BPN (administered as Subutex[®]) will be investigated. [Figure 1](#) A-C presents observed and/or predicted BPN exposure after steady state administration of CAM2038 q1w and CAM2038 q4w SC injections and SL BPN at comparable dose levels in healthy volunteers under naltrexone blockade. [Table 1](#) and [Table 2](#) summarize observed and predicted BPN exposure after single ([Table 1](#)) and repeat administration ([Table 2](#))

of the products. Although there are inherent differences in the pharmacokinetic profiles for daily, weekly and monthly administered products, the results presented in Figure 1 A-C demonstrate that the pharmacokinetic profiles of the CAM2038 q1w and q4w formulations are similar with respect to steady state maximum plasma concentration (C_{max}) and trough plasma concentration (C_{trough}) of BPN and that CAM2038 q1w and q4w products can be dose adjusted to the pharmacokinetic profiles after SL BPN administration. Based on these similarities, the two CAM2038 products are expected to be interchangeable when subjects go from weekly to monthly dosing regimen, and the treatments can be adjusted in accordance with subject needs and maintenance doses of SL BPN.

Figure 1A

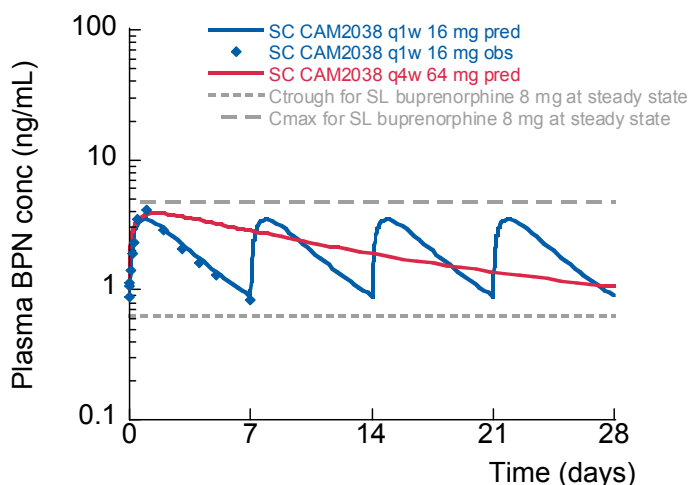


Figure 1B

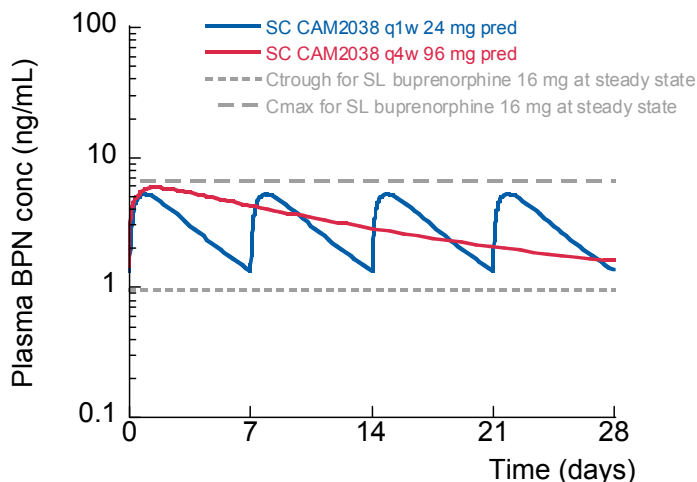


Figure 1C

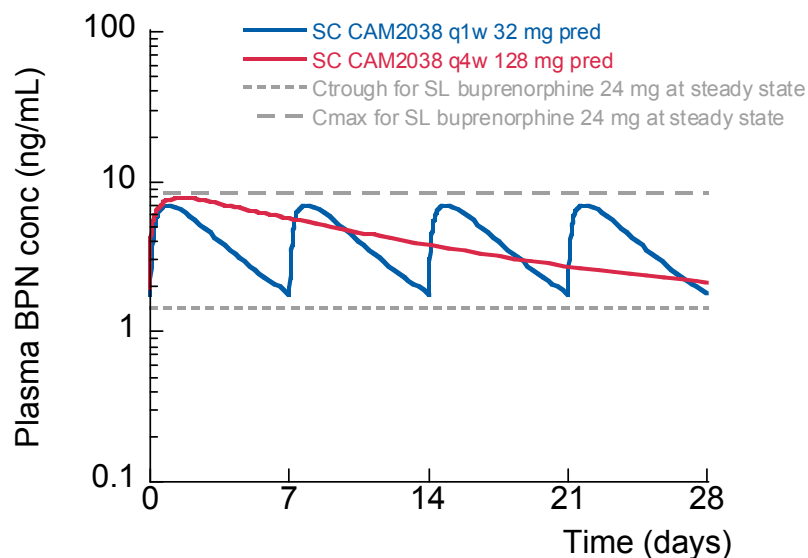


Figure 1 Observed steady state arithmetic mean C_{max} and C_{trough} of buprenorphine after sublingual administration of Subutex[®], and observed (obs) and predicted (pred) steady state plasma concentration profiles after subcutaneous administration of CAM2038 q1w and CAM2038 q4w based on data from Trials HS-11-426 and HS-13-487 (semi-logarithmic scales)

C_{max} = maximum plasma concentration; C_{trough} = trough plasma concentrations; q1w= once-weekly dosing; q4w= once-monthly dosing

Geometric mean observed steady state C_{max} and C_{trough} for Subutex[®] from Trials HS-11-426 and HS-13-487

Predicted plasma concentration versus time profiles for CAM2038 q1w from single and repeat dose data in Trial HS-13-487

Observed steady state plasma concentration versus time profiles for CAM2038 q1w 16 mg from Trial HS-13-487

Predicted steady state plasma concentration versus time profiles for CAM2038 q4w from single-dose data in Trial HS-13-487

Table 1 Observed and predicted buprenorphine exposure after single administration of subcutaneous CAM2038 q1w, subcutaneous CAM2038 q4w, and sublingual Subutex® in healthy subjects

Treatment	Trial	Geometric Mean (geometric CV%)		
		C _{max} (ng/mL)	C _t (ng/mL) ^a	AUC _{inf} (ng*h/mL)
SC CAM2038 q1w				
8 mg	HS-11-426	1.7 (36)	0.30 (26)	166 (20)
16 mg	HS-11-426	3.1 (49)	0.61 (25)	335 (13)
24 mg		4.2 ^b	0.86 ^b	487 ^b
32 mg	HS-11-426	5.3 (45)	1.1 (24)	638 (12)
SC CAM2038 q4w				
64 mg	HS-13-487	3.8 (60)	0.45 (57)	1360 (33)
96 mg		5.2 ^b	0.69 ^b	1960 ^b
128 mg	HS-13-487	6.6 (68)	0.93 (33)	2550 (26)
160 mg		7.9 ^b	1.2 ^b	3120 ^b
SL Subutex				
8 mg	HS-11-426	4.3 (32)	0.25 (38)	NC
16 mg	HS-11-426	6.7 (62)	0.38 (36)	NC
24 mg	HS-11-426	7.1 (19)	0.49 (39)	NC

AUC_{inf} = area under the plasma concentration-time curve from time zero to infinity; C_{max} = maximum plasma concentration; C_t = plasma concentration at time t post administration; CV = coefficient of variation; NC = Not calculated; SL = sublingual
a. C_t at 7 days for SC CAM2038 q1w, C_t at 28 days for SC CAM2038 q4w and C_t at 1 day (24 hours) for SL Subutex®
b. Predicted from linear regression analysis of logarithmic pharmacokinetic variable vs. logarithmic dose

Table 2 Observed and predicted buprenorphine exposure after steady state administration of subcutaneous CAM2038 q1w, subcutaneous CAM2038 q4w, and sublingual Subutex® in healthy subjects

Treatment	Trial	Geometric Mean (geometric CV%)		
		C _{ss,max} (ng/mL)	C _{ss,av} (ng/mL)	C _{ss,trough} (ng/mL)
SC CAM2038 q1w				
8 mg		1.7 ^a	1.0 ^b	0.45 ^a
16 mg	HS-13-487	4.3 (44)	2.1 (24)	0.84 (22)
24 mg		5.2 ^a	2.9 ^{b,c}	1.4 ^a
32 mg		6.9 ^a	3.8 ^b	1.8 ^a
SC CAM2038 q4w				
64 mg		3.9 ^a	2.0 ^b	1.1 ^a
96 mg		5.8 ^a	2.9 ^{b,c}	1.6 ^a
128 mg		7.8 ^a	3.8 ^b	2.1 ^a
160 mg		9.8 ^a	4.6 ^{b,c}	2.7 ^a
SL Subutex				
8 mg	HS-11-426	4.7 (29)	1.1 (34)	0.61 (46)
16 mg	HS-11-426	6.3 (49)	1.6 (37)	0.79 (58)
24 mg	HS-11-426	7.8 (37)	2.3 (29)	1.2 (44)

C_{ss,max} = maximum plasma concentration at steady state; C_{ss,av} = average plasma concentration during a dosing interval at steady state; C_{ss,trough} = trough plasma concentration during a dosing interval at steady state; CV = coefficient of variation
a. Predicted by simulation from a nonlinear mixed effects pharmacokinetic model describing observed pharmacokinetic data
b. Predicted and calculated from AUC_{inf} after single dosing and assuming time-independent pharmacokinetics
c. Predicted from linear regression analysis of logarithmic pharmacokinetic variable vs. logarithmic dose

On the first trial day, all subjects will receive a test dose of 4 mg SL BPN prior to randomization to confirm tolerability by assessing signs and symptoms of withdrawal as measured by the Clinical Opiate Withdrawal Scale (COWS). Additionally, the 4 mg SL BPN test dose will provide adequate BPN exposure until clinically relevant levels of BPN are achieved with CAM2038 q1w, which is expected within approximately 2-4 hours post injection. Figure 2 shows plasma concentration-time curves of BPN after a single dose of 8 mg SL BPN (i.e., double test dose) and a single dose of 16 mg SC CAM2038 q1w. Dose proportional pharmacokinetic parameters were assumed between 4 and 8 mg of SL BPN, as indicated by Ciraulo D et al. (5).

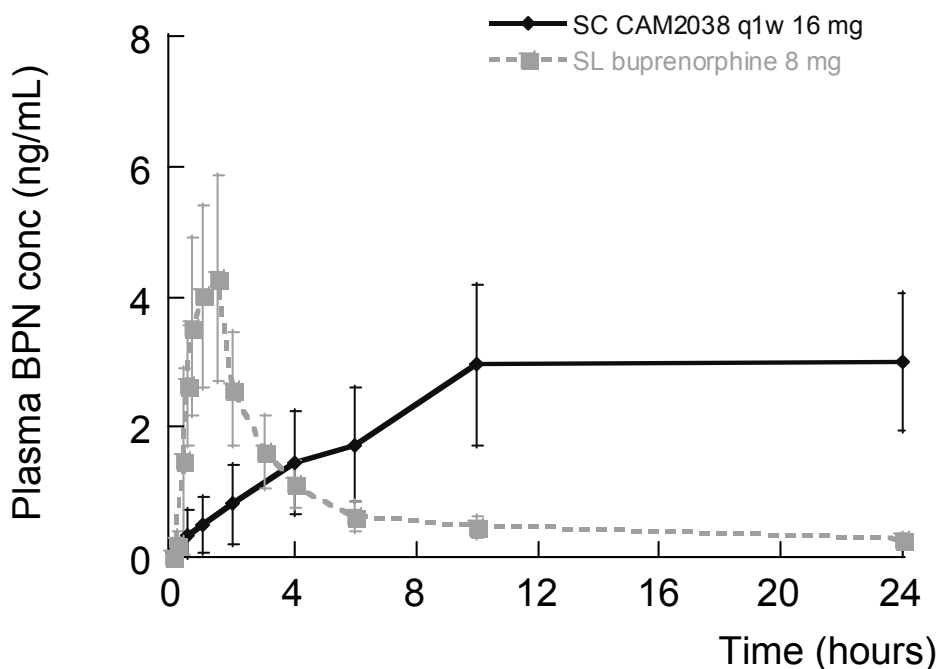


Figure 2 Plasma concentration-time curves of buprenorphine after a single dose of 8 mg sublingual buprenorphine and a single dose of 16 mg subcutaneous CAM2038 q1w (arithmetic mean \pm SD), Trial HS-11-426

5.2. Trial Rationale

Opioid drug use disorder is a major health and social issue and is a chronic medical condition that often requires long-term maintenance treatment. An important aim of the treatment programs for opioid drug dependence is to assist in helping the patients stop abusing illicit drugs. 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 will also reduce the burden on the society and relatives. Moreover, opioid addicts often inject with used syringes and

needles, and thus expose themselves to high risk of transmission of infectious diseases, including human immune deficiency virus (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 illicit opioid use, criminal activity, deaths, and HIV transmission (6). Patients often discontinue treatment prematurely, an outcome associated with higher rates of relapse to drug use, which means that treatment strategies that aim to keep patients in treatment longer and/or improve patient adherence may have additional advantages (7). While daily dosing with SL BPN has proven effective, the need for daily administration of treatment may negatively influence patients' adherence and duration of therapy. Moreover, SL tablets or film can be easily abused and diverted for illicit use, injected for greater effect, or accidentally ingested, especially by children (7, 8). 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.

During initiation of treatment with BPN, some patients do not actually take the SL tablets dispensed to them, and they may also request doses that are higher than necessary in order to potentially abuse or divert the extra doses (9). In this regard, CAM2038 q1w is ideal for initiation as it can't be abused or diverted by patients and may help prevent patients from requesting medically unnecessary doses, giving clinicians greater control over what the patient actually needs and receives. CAM2038 q1w is available in multiple doses, thereby permitting flexibility in dosing options and allowing for weekly visits during the initial stages of treatment to provide clinicians with the opportunity to optimize and individualize treatment for each patient.

In addition to the above mentioned potential advantages, CAM2038 q1w demonstrated more stable concentrations with less peak-trough fluctuation over 7 days as compared with daily doses of SL BPN. Moreover, the bioavailability of BPN administered as CAM2038 q1w is approximately 7-fold that of SL BPN products. The pharmacokinetic profile of CAM2038 q1w indicates that a rapid and long-acting release of BPN should lead to rapid and smooth onset of action, in combination with a prolonged and stable treatment effect in opioid dependent patients with control of withdrawal symptoms for at least 7 days following a single dose. Notably, the pharmacokinetic profile of CAM2038, with a smooth and stable release of BPN and time to peak plasma concentrations within the first 24 hours after dosing, mimics a typical SL BPN titration schedule with low but increasing starting doses of SL BPN or BPN/naloxone tablets during the first 24 to 48 hours, followed by more constant dosing. Patients who have recently used opioids and are not in withdrawal at the time of BPN ingestion or who have taken a long-acting opioid too recently, may experience precipitated withdrawal with onset of BPN treatment. The primary motivation behind the initial 4 mg incremental titration schedule in the present trial is to follow current guidelines that recommend gradually introducing patients to an appropriate maintenance dose of BPN while minimizing the risk of precipitated withdrawal. CAM2038 q1w provides this slow increase in plasma levels without the potential compliance and diversion issues associated with taking multiple SL tablets during the day. Thus, the pharmacokinetic profile of CAM2038 q1w may help to improve tolerability during treatment induction (including potentially reducing the probability of withdrawal symptoms in individuals with residual full opioid agonist). This

possibility has been supported in a previous clinical trial (Trial HS-07-307) in opioid dependent patients where the pharmacokinetic profile of CAM2038 q1w was associated with decreased subjective and clinical opiate withdrawal scores (Subjective Opiate Withdrawal Scale [SOWS] and COWS), over at least 1 week. Both SOWS and COWS scores were sustained below the limit of “mild” symptoms for the majority of patients up to and beyond 7 days after a single SC dose. Similarly, the mean time to first intake of rescue BPN medication was 10 days after a single dose of CAM2038 q1w.

Patients in greater stages of withdrawal or those who have a lesser degree of physical dependence at onset of initiation may experience agonist effects of BPN during initiation. Although less than full agonist opioids, BPN may nonetheless be associated with euphoria and other opioid-like effects, even in opioid-dependent individuals (10-12). Thus, for some patients, use of CAM2038 q1w, with its more gradual onset, may result in lower peak euphoria and other desirable effects that can be associated with the relatively rapid and defined peak in plasma concentrations associated with SL BPN. The potential for reducing these lingering desirable effects of BPN may help patients start the recovery process in a more optimal way than with current SL BPN treatments.

Generally, stabilization of opioid maintenance treatment with BPN begins after initiation with BPN and is usually completed within 1 to 2 months, when the patient is not experiencing withdrawal symptoms, is experiencing minimal or no side effects, and no longer has uncontrollable cravings for opioid agonist. During the stabilization phase, dose adjustments and frequent contact with patients increase the likelihood of compliance and successful treatment outcomes. Therefore, weekly assessment is usually indicated to make necessary dose adjustments. The profile of CAM2038 q1w provides an alternative to SL BPN products during this phase with potential added benefits of obtaining consistent and stable plasma levels of BPN, taking away the need to take daily medications, and helping to prevent diversion and accidental pediatric exposures during initial phases of opioid maintenance treatment.

Similarly, pharmacokinetic results indicate that CAM2038 q4w produces consistent and stable plasma levels over 4 weeks with flexible and multiple dosing options. These results suggest that CAM2038 q4w may be an effective and safe BPN formulation for delivery of relatively constant levels of BPN over one month. Monthly visits and injection are regarded as a suitable frequency for stabilized patients on BPN maintenance treatment. Therefore, CAM2038 q4w is considered as a promising alternative to current daily medications for BPN maintenance treatment of patients with opioid use disorder who have been stabilized and qualify for monthly visits for BPN therapy.

Overall, features of 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.

Therefore, the purpose of this trial is to demonstrate the efficacy and safety of CAM2038 (q1w and q4w) as an office-based therapy for initiation and continuation of opioid maintenance treatment with BPN in patients with opioid use disorder.

5.3. Benefit – Risk Assessment

BPN is a substance with well-established use for treatment of opioid drug dependence. The CAM2038 products contain BPN in a new FC formulation for SC injection. Clinical trials have demonstrated effectiveness of BPN in reducing illicit opioid use and improving retention rates of patients in outpatient maintenance treatment of opioid dependence, as well as substantial reduction in criminal activity, deaths, and 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 substitution treatment of opioid drug dependence, and provide 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 help preventing patients from requesting unnecessarily high BPN doses, and it will provide clinicians greater control over what the patient actually needs and receives. Compared with the SL BPN 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 BPN 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 trials (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 SC administration and include dermal ulcers or necrotic wounds at the injection site. Additional potential AEs include over-dose of BPN and allergy to BPN. 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 and once-every-4-week administration of CAM2038 q4w in dogs showed absence of systemic toxicity by assessment of complete clinical pathology, histopathology and toxicokinetics. 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 feces, as well as reduction in body weight and food consumption) and to local, transient injection site findings, characterized 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 evaluate the efficacy of CAM2038 q1w and q4w by demonstrating non-inferiority of CAM2038 in BPN treatment compared to SL BPN in adult outpatients with opioid use disorder. The safety monitoring practices employed by this protocol are adequate to protect the patients' safety and should detect all treatment-emergent AEs.

The approximate volume of blood is 94 mL for each subject over the course of the entire trial (Screening to End of Treatment (EOT) visit), but not including repeat or additional tests ordered by the Investigator) and 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.

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

6. TRIAL OBJECTIVES

6.1. Primary Objective

The primary objective of the trial is:

- To demonstrate non-inferiority of the CAM2038 BPN treatment arm as compared to the SL BPN treatment arm in treating adult outpatients with opioid use disorder, as measured by the primary efficacy measure of response rate (RR).

6.2. Secondary Objectives

The secondary objectives of the trial are:

- To demonstrate non-inferiority of CAM2038 compared to SL BPN in adult outpatients with opioid use disorder, as measured by the secondary efficacy measure of percentage negative urines.
- To evaluate the efficacy of CAM2038 compared to SL BPN in adult outpatients with opioid use disorder, as measured by the secondary efficacy measure of time to sustained abstinence from illicit opioid use.
- To evaluate the efficacy of CAM2038 compared to SL BPN in adult outpatients with opioid use disorder, as measured by the secondary efficacy measure retention rate.
- To evaluate the efficacy of CAM2038 compared to SL BPN in adult outpatients with opioid use disorder, as measured by the exploratory efficacy measures.
- To evaluate the safety of CAM2038 in adult outpatients with opioid use disorder.

7. INVESTIGATIONAL PLAN

7.1. Overall Trial Design and Plan

This is a randomized, double-blind, double-dummy, active-controlled, parallel group multi-center trial, designed to evaluate the non-inferiority of CAM2038 compared to an existing standard of care (SL BPN) in initiation and maintenance treatment with BPN. The trial will involve 4 phases: Screening, Phase 1 (weekly visits), Phase 2 (monthly visits), and Follow-up.

Following Screening and confirmation of eligibility, subjects will be randomized to one of two treatment groups in a 1:1 ratio:

- Group 1: SL BPN tablets + placebo SC injections
- Group 2: CAM2038 SC injections + SL placebo tablets

Following randomization, subjects will undergo initiation of BPN with either SL BPN or SC CAM2038 q1w and participate in weekly visits for 12 weeks (Phase 1). After Week 12, subjects will be transitioned to Phase 2 with monthly visits. During Phase 2, subjects in Group 1 will continue treatment with monthly dispensing of daily SL BPN treatment and monthly placebo SC injections, and subjects in Group 2 (receiving CAM2038 q1w) will be transferred to monthly injections of CAM2038 q4w and monthly dispensing of daily SL placebo. Subjects will participate in up to 6 visits during the 12 weeks of Phase 2; 3 scheduled monthly visits and 3 random urine toxicology visits. At each visit, efficacy and safety outcome measures will be assessed. After Phase 2, the subjects will be followed-up for 1 month.

A total of 20 opioid urine toxicology samples will be collected during the study:

- 1 sample at Screening
- 1 sample at baseline (Day 1/Week 1) before first dose of CAM2038 q1w
- 12 samples will be collected at the scheduled 12 weekly visits of Phase 1 (Week 2 to Week 13 [i.e. 1 week after the last CAM2038 q1w treatment])
- 6 samples will be collected during the 12 weeks of Phase 2
 - 3 at the scheduled monthly visits (Weeks 17, 21 and 25)
 - 3 at random urine toxicology visits (taken during the period from Week 13 to Week 25).

A self-report of drug use will accompany every urine toxicology test as outlined in Table 3 and Table 4. Each subject will participate in the trial for up to 31 weeks, including up to 24 weeks of treatment with SL BPN or CAM2038. Subjects who complete the 24 weeks of treatment will be transitioned to standard of care (e.g., SL BPN) and be followed up for 4 weeks.

All subjects will be blinded to their treatment group assignment, as will all trial staff with the exception of the clinician(s)/staff performing the SC injections and designated personnel who will be responsible for drug accountability (i.e., counting the active and placebo SL BPN returned tablets).

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

Investigators will be instructed to use manual-guided psychosocial counseling for trial subjects throughout the trial period.

An overview of the trial design is provided in Figure 3.

Section 10 provides additional information on the baseline, efficacy and safety assessments included in the trial. Efficacy and safety variables are described in Section 10.6 and the statistical analyses are described in Section 12.

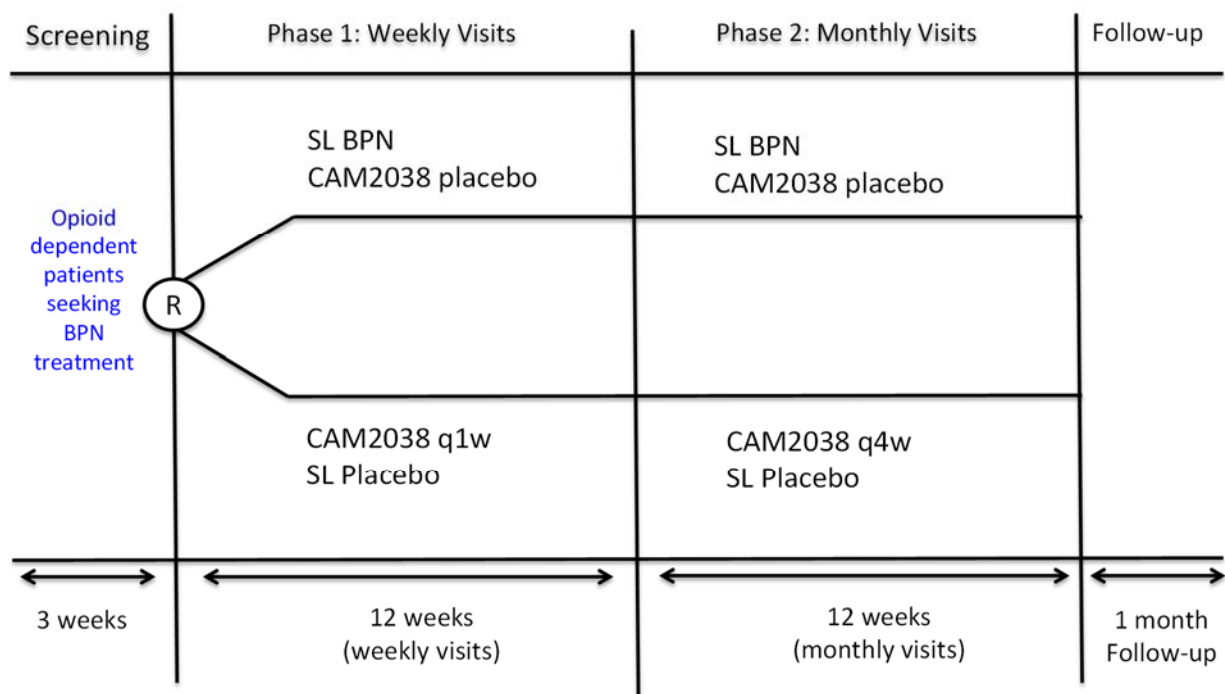


Figure 3 Overview of Trial Design

BPN = buprenorphine; R= randomization; SL = sublingual

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

Medical and eligibility screening will occur within 3 weeks of the first day of Phase 1 (Day 1). At Screening, subjects will provide written informed consent to participate in the trial 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.

Following Screening, subjects will be eligible for further participation if they meet all of the inclusion criteria and do not meet any of the exclusion criteria.

7.1.2. Phase 1 (Weekly Visits)

Week 1 (Initiation of Treatment):

Eligible subjects will be initiated on BPN treatment, during which time they will attend trial visits at the site as needed based on their withdrawal symptoms. Prior to Day 1, subjects will be instructed to arrive at their Day 1 visit in a state of mild withdrawal, to avoid precipitated withdrawal with BPN.

A flow chart summarizing induction procedures is provided in Figure 4.

Day 1: On Day 1, after confirmation that subjects are in at least mild state of withdrawal, subjects will have an ECG performed as well as have their vitals taken. Subjects will then receive a test dose of unblinded 4 mg SL BPN film under observation prior to randomization to confirm tolerability by assessing signs and symptoms of precipitated withdrawal as measured by COWS.

One (1) hour, after tolerability has been confirmed and eligibility criteria have been re-checked, subjects will be randomized to one of two groups in a 1:1 ratio:

- Group 1 (SL BPN): Daily SL BPN + placebo SC injections
- Group 2 (CAM2038): CAM2038 SC BPN injections + daily SL placebo

After randomization, subjects will receive the following, while on site:

- A blinded dose of 4 mg SL tablets (active or placebo) will be administered under observation. Thus, the total Day 1 SL BPN dose is 8 mg (4 mg unblinded BPN film + 4 mg blinded BPN tablets) for Group 1 and 4 mg (4 mg unblinded BPN film) for Group 2.
- A single CAM2038 q1w (once-weekly) 16 mg SC injection (0.32 mL of active or placebo) will be administered.
- After receiving the first dose of study medications, the ECG and vitals will be repeated.
- If withdrawal symptoms are still not relieved after the second SL dose on Day 1, symptomatic relief with non-opioid medications should be provided.
- Subjects will be instructed to return to the clinic on Day 2 for observation and Day 2 dosing.

Day 2 and Day 3: All subjects will return to the clinic only on Day 2 for an additional observed dosing of SL BPN/Placebo to ensure continued tolerability. All subjects will receive 16 mg SL BPN/Placebo (two 8mg SL BPN or placebo tablets).

Administration of Day 2 SL BPN/Placebo dose will be observed in the clinic.

Subjects will also be provided with Day 3 take-home dose (two 8 mg SL BPN/Placebo tablets per day).

Day 4: All subjects will return to the clinic on Day 4 and will receive a single CAM2038 q1w 8 mg or Placebo SC injection (0.16 mL of active or placebo). In situations where the visit cannot occur on Day 4 due to logistical constraints, the visit may occur one day early or one day late (+/- 1 day). However, it is strongly encouraged to have the subject return on Day 4.

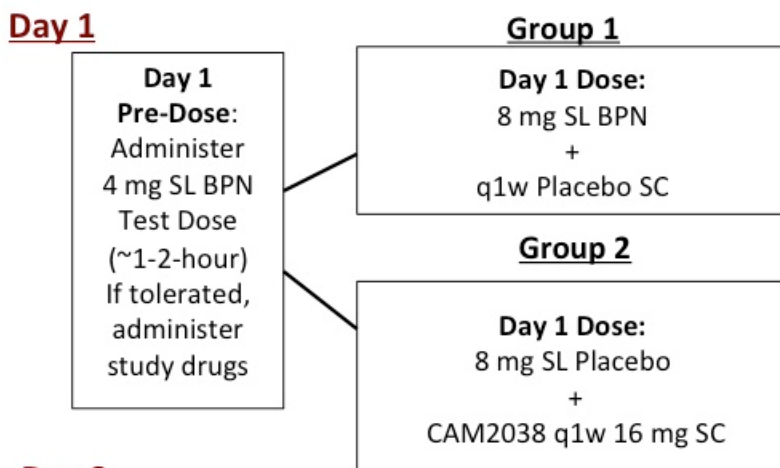
All subjects will continue with the 16 mg SL BPN/Placebo (two 8mg SL BPN or placebo tablets per day). This may be observed in the clinic or be taken at home.

Subjects will be provided with adequate amount of SL BPN/Placebo tablets for take-home to last through Day 7.

Days 5 to 7: All subjects will be allowed to return to the clinic through an Unscheduled Visit, if continued withdrawal symptoms are present. During Days 5 to 7, one additional SC injection (CAM2038 q1w 8 mg or Placebo – not to exceed total weekly dose of CAM2038 q1w 32mg or placebo) and increase in SL BPN/Placebo dose may be provided (not to exceed 24 mg SL BPN/Placebo per day).

Additional outcomes measures and procedures to be performed at each visit are outlined in Table 3.

Week 1 CLINIC VISIT FLOW CHART



Day 2

- All subjects will return on Day 2 for observations on tolerability/safety and observed dosing for SL BPN/Placebo (16 mg SL BPN/Placebo).
- Subjects will be provided take home dose of 16 mg SL BPN/Placebo for Day 3.

Day 4

- All subjects return to the clinic on Day 4 for an additional CAM2038 q1w 8 mg SC or Placebo SC injection.
- All subjects will receive 16 mg SL BPN/Placebo daily to take home for Days 4-7 (Day 4 can be taken in the clinic or be taken at home).

Day 5-7

- All subjects will be instructed to return to the clinic if their withdrawal symptoms are not adequately controlled. Subjects that are not adequately controlled should receive additional SL BPN/Placebo (not to exceed 24 mg or 3 tabs/day) and one additional CAM2038 q1w 8 mg or placebo SC injection.

Figure 4 Overview of Induction Procedures

BPN=buprenorphine; SC=subcutaneous; SL=sublingual

On Day 2, subjects will be provided with SL tablets and instructions for dosing. The daily SL BPN/Placebo dose for Days 2-4 will be 16 mg and the maximum daily SL BPN/Placebo dose for Days 5-7 will be 24 mg.

Weeks 2 to 12:

Day 8 (Week 2): All subjects will return to the clinic on Day 8.

Subjects will receive a CAM2038 q1w SC injection (24 mg or 32 mg or Placebo, based on total dose given by end of Week 1/Day 7). Subjects will also be provided with one-week take-home SL BPN/Placebo (16 mg, or 24 mg SL BPN/Placebo, based on total daily dose established at end of Week 1/Day 7 (the take home medication will be provided in 7 count bottles of 8 mg tablets)). If subject is still experiencing withdrawal symptoms on Day 8, the Investigator can increase the dose to a maximum of 24 mg per day SL BPN/Placebo and a 32 mg injection of CAM2038/Placebo.

Week 3 to Week 12: From Week 3 to Week 12, at minimum subjects will attend weekly scheduled visits. At each scheduled visit, a SC injection of CAM2038 q1w (or placebo) will be administered. The scheduled visit should be at the beginning of each week (± 2 days), preferably Mondays (see Section 10.3.1). During these visits, additional dose adjustments will be allowed (increases and decreases). At each weekly visit, sufficient SL tablets (BPN or placebo) will be dispensed to last until the next visit. Dosage adjustments are given in 8 mg increments for both SL BPN and SC CAM2038 and can only be done at scheduled clinic visits. Total daily dose of SL BPN/Placebo cannot exceed 24 mg/day. Total weekly dose of CAM2038/placebo q1w cannot exceed 32 mg injection per week.

Weekly visit assessments will include:

- Urine samples for opioid toxicology, evaluated using both qualitative and quantitative methods. Urine will also be tested for other drugs of abuse using qualitative methods.
- Self-reported use of all drugs, including illicit or prescription opioids and other prescribed or illicit drugs.
- Measures of withdrawal using COWS and SOWS
- Measures of craving using Desire to Use and Need to Use visual analogue scales (VAS)
- Psychosocial counseling
- Additional outcomes measures and safety assessments for each visit, as outlined in [Table 3](#).

At each weekly visit, starting at Week 5, the subjects will be evaluated with regard to the following stability criteria:

- Has the subject been on a stable dose of CAM2038 q1w/Placebo SC injections without any fluctuations in doses for the last 4 weeks?
- Does the subject exhibit minimal subjective and no objective withdrawal symptoms, based on SOWS ≤ 7 and COWS < 5 ?
- Does the subject exhibit diminished desire/need to use, based on VAS scores?
- Does the subject exhibit diminished use of illicit opioids, according to the Investigator's discretion?

The results of the evaluations will be recorded for data collection purposes, but no subject will be transitioned to monthly dosing before Week 13.

7.1.3. Phase 2 (Monthly Visits)

Weeks 13 to 24:

At Week 13 visit, all subjects will be transitioned to monthly treatment (dispensing for SL BPN/Placebo or SC injections). Before transitioning to CAM2038 q4w, subjects will be evaluated for the stability criteria described above.

Treatment: Subjects will receive the following treatments for a duration of 12 weeks:

- Group 1 (SL BPN): daily SL BPN + injections of once monthly SC placebo
- Group 2 (CAM2038): injections of once monthly CAM2038 q4w SC + daily SL placebo

Subjects will therefore receive their first dose of CAM2038 q4w (or placebo) at the beginning of Week 13 (± 2 days), preferably Monday. Subjects will receive their monthly SL tablets (SL BPN or placebo) and an SC injection (CAM2038 q4w or placebo) while on site.

Subjects will continue to receive the daily dose of SL BPN or SL placebo that they received at the end of Phase 1. Based on their CAM2038 q1w (or SC placebo) dose at the end of Phase 1, subjects will be transitioned to the following doses of CAM2038 q4w or placebo SC injection in Phase 2:

- 16 mg CAM2038 q1w/placebo = 64 mg CAM2038 q4w/placebo
- 24 mg CAM2038 q1w/placebo = 96 mg CAM2038 q4w/placebo
- 32 mg CAM2038 q1w/placebo = 128 mg CAM2038 q4w/placebo

Dosage adjustment will be allowed during Phase 2 at the monthly scheduled visits only, up to a maximum of 32 mg SL BPN (or placebo) and up to 160 mg CAM2038 q4w (or placebo), as outlined in Section 9.1.2.

Subjects will return to the clinic for monthly trial visits during Phase 2. In addition to the monthly visits, subjects will return to the clinic to provide 3 random urine toxicology samples during Phase 2 of the trial. At each scheduled monthly visit, SL tablets (BPN or placebo) sufficient to last until the next visit will be dispensed. Subjects will also receive SC injections on site at the Week 13 (± 2 days), 17 and 21 visits (± 7 days). Urine toxicology samples will be taken at each scheduled or random visit for illicit testing of opiates/opioids and self-reports of illicit drug use will be collected in connection to the urine samplings. Other drugs of abuse will also be assessed. During Phase 2, a total of 6 urine toxicology samples will be collected; 3 at scheduled visits (1 per month) and 3 at random urine toxicology visits. COWS/SOWS and VAS will be performed at each scheduled trial visit. Other outcome measures and safety assessments are outlined in Table 4.

Supplemental BPN: The trial provides dosing of BPN in both Group 1 and 2 that is expected to be adequate for suppression of withdrawal symptoms and progression in reductions on cravings and evidence of illicit opioid use. However, supplemental BPN may be needed during the trial.

Supplemental BPN will be provided utilizing CAM2038 q1w 8 mg SC injection only in Phase 2. Supplemental BPN will be allowed at maximum of one SC injection per month (in between two scheduled clinic visits). SOWs, COWS and Desire/Need to Use VAS will be performed at this

visit. The reason for administering supplemental BPN will be recorded, in addition to SOWS, COWS, and Desire/Need to Use VAS.

7.1.4. Follow-up Phase (Week 25 to Week 29)

At Week 25, subjects will be transitioned to standard care (e.g., SL BPN). Assessment to be performed at this visit and additional assessments to be performed during Weeks 26 to 28 via telephone contact and at final in-clinic Follow-up visit at Week 29 are outlined in [Table 4](#).

7.2. Discussion of Trial Design

The evaluation of the efficacy and safety of CAM2038 q1w and CAM2038 q4w will be performed using a randomized, double-blind, double-dummy, active-controlled parallel group trial, designed to evaluate the non-inferiority of CAM2038 compared to an existing standard of care (SL BPN) in treatment with BPN. Non-inferiority designs have been used for past clinical trials of maintenance treatment, including BPN products ([13](#), [14](#)). Given the availability of an effective existing treatment for opioid dependence, the use of a placebo-controlled trial was considered unethical due to the high risk of failure of these patients on placebo treatment, and the potential harms associated with treatment failure. In addition, because CAM2038 is an alternative dosage form of an already approved and widely used active substance, which delivers similar overall exposure to once daily SL BPN, a non-inferiority assessment was considered appropriate to confirm the efficacy of the product. Finally, the availability of appropriate placebos for each active treatment will enable a double-blind, double-dummy design, which will help prevent bias in the outcome variables.

8. SELECTION OF TRIAL POPULATION

Approximately 380 subjects (190 subjects per arm) will be randomized. For sample size calculation, please refer to Section 12.5.

This trial will enroll adult outpatients with opioid use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V) who are not currently being treated using opioid maintenance therapy.

8.1. Inclusion Criteria

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

1. Subject must provide written informed consent prior to the conduct of any trial-related procedures.
2. Male or female, 18-65 years of age, inclusive.
3. Diagnosis of moderate or severe opioid use disorder (DSM-V).
4. Voluntarily seeking treatment for opioid use disorder.
5. Have not received medication-assisted treatment for opioid use disorder within 60 days prior to randomization.
6. Considered by the Investigator to be a good candidate for BPN treatment, based on medical and psychosocial history.
7. Male and female subjects of childbearing potential must be willing to use a reliable method of contraception during the entire trial (Screening visit to Follow-up visit) (Section 10.1.6).

8.2. Exclusion Criteria

Subjects will not be eligible to participate in this trial 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 of moderate to severe substance use disorder on any other psychoactive substances other than opioids, caffeine or nicotine (e.g., alcohol, cocaine, sedatives) and the non-opioid substance use disorder(s) are considered primary or co-primary, causing current (last 30 days) significant impairment and/or in the judgement of the Investigator would interfere with the efficacy and safety assessments.
4. Pregnant or lactating or planning to become pregnant during the trial.
5. Hypersensitivity or allergy to BPN or other opioids, naloxone or other opioid antagonists, or excipients of CAM2038 or SL BPN.

6. Requires current use of agents that are strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) such as some azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., clarithromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir).
7. Subjects with active signs or symptoms of hepatitis and requiring treatment. Subjects with no acute signs of inflammation and no clinical necessity for therapy may be allowed at the discretion of the Investigator.
8. 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).
9. Any pending legal action that could prohibit participation or compliance in the trial.
10. Exposure to any investigational drug within the 4 weeks prior to Screening.
11. Participants with a history of risk factors of Torsades de Pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome) or an electrocardiogram (ECG) demonstrating a Fridericia's corrected QT interval (QTcF) >450 msec in males and QTcF >470 in females at screening.
12. 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 trial.
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 trial or obtaining informed consent, or may prevent the subject from safely participating in trial (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the Investigator’s Brochure for CAM2038).
14. Is an employee of the Investigator or the trial site, with direct involvement in the proposed trial or other trials under the direction of the Investigator or trial site, or is a family member of an employee or of the Investigator.

8.3. Removal of Subjects from Therapy or Assessment

A subject is free to withdraw his/her consent and discontinue participation in the trial 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 trial for any of the following reasons:

- Safety reasons, including AEs or significant concomitant illness, injury, or urgent surgeries/procedures that would, in the judgment of the Investigator, affect assessments of clinical status to a significant extent, require discontinuation of trial drug, or both

- At the request of the Sponsor, regulatory agency, or Institutional Review Board (IRB)
- Subject is lost to follow-up
- Subject treatment allocation is unblinded (i.e., individual code break; Section 9.6)
- Death of subject

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

- Subject refuses or is unable to adhere to the trial protocol
- Major protocol violation (e.g. violation of inclusion or exclusion criteria during the trial, failure to adhere to the treatment schedule)
- Pregnancy
- 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 trial prior to completion; the reason(s) for trial discontinuation will be documented. In the event that a subject chooses to withdraw from the trial, 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 will be made to ensure that all subjects are briefed on the importance of the clinical trial and collection of data they provide. Emphasis should be made to subjects that it is more important to attend all visits and be truthful about their use of illicit opioids than to be “clean”. The subjects will be told that they will not be punished or discontinued from the trial for using illicit opioids and their truthful information on illicit opioid use will be an important component of the trial data collection. All efforts should be made by the Investigator to continue collection of urine samples at the protocol-defined trial visit intervals, concomitant medications, and AEs in subjects that discontinue trial 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 for Week 25 (EOT), 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.

9. TREATMENTS

9.1. Treatment Administration

All trial drugs will be administered in a double-blind, double-dummy manner, such that subjects will receive both SL tablets (active BPN or Placebo) and SC injections (active CAM2038 q1w/CAM2038 q4w or Placebo) throughout the trial. Subjects will receive treatment for up to 24 weeks during the trial; 12 weeks during Phase 1 and 12 weeks during Phase 2.

CAM2038/Placebo will be injected in the buttocks, abdomen, thighs and the upper back of the arms and the injection sites will be rotated such that no injections are administered into the same site. A total of 26 sites have been identified and a pictorial of potential injection sites will be provided in the trial Manual of Procedures (MOP). The following rules apply:

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

The Investigator will keep record of the injection site at each treatment visit.

9.1.1. Phase 1 (Weekly Visits)

Week 1:

On Day 1, all subjects will have an ECG and vital signs recorded, and after confirmation of a mild state of withdrawal, a test dose containing 4 mg/1 mg BPN/naloxone (SL film) will be administered under observation. If tolerability to the test dose is shown, subjects will be randomized to Group 1 or Group 2 and will receive the following treatments in Week 1 during Phase 1:

- Group 1:
 - On Day 1, the subjects will receive a total dose of 8 mg SL BPN (4 mg SL BPN film and 4 mg SL BPN tablets) and a total dose of 0.32 mL placebo CAM2038 (matching 16 mg active CAM2038 q1w).
 - On Days 2 and 3, the subjects will receive a daily dose of 16 mg SL BPN.
 - On Day 4, the subjects will receive 16 mg SL BPN and an SC injection of 0.16 mL placebo CAM2038 (matching 8 mg active CAM2038 q1w).
 - On Days 5 to 7, the daily dose of SL BPN will be 16 to 24 mg and the subjects may receive an additional SC injection of 0.16 mL placebo CAM2038.
 - The total Week 1 dose of placebo CAM2038 must not exceed 0.64 mL (matching 32 mg active CAM2038 q1w).
- Group 2:

- On Day 1, the subjects will receive a total dose of 4 mg SL BPN (4 mg SL BPN film and 4 mg SL placebo tablets) and a total dose of 16 mg active CAM2038 q1w (0.32 mL).
- On Days 2 and 3, the subjects will receive a daily dose of 16 mg SL placebo.
- On Day 4, the subjects will receive 16 mg SL placebo and an SC injection of 8 mg active CAM2038 q1w (0.16 mL).
- On Days 5 to 7, the daily dose of SL placebo will be 16 to 24 mg and the subjects may receive an additional SC injection of 8 mg active CAM2038 q1w (0.16 mL).
- The total Week 1 dose of active CAM2038 q1w must not exceed 32 mg (0.64 mL).

Weeks 2 to 12:

- Group 1: Daily SL BPN tablets (containing BPN and naloxone) up to a daily dose of 8 mg to 24 mg (doses from 8 mg/2 mg to 24 mg/6 mg) and weekly SC injections of placebo CAM2038 of 0.32 mL, 0.48 mL or 0.64 mL (matching 16 mg, 24 mg and 32 mg doses of active CAM2038 q1w) per week.
- Group 2: Daily SL placebo tablets (tablets matching 8 mg/2 mg to 24 mg/6 mg doses) and weekly SC injections of active CAM2038 q1w BPN at doses of 16 mg, 24 mg or 32 mg (0.32 mL, 0.48 mL or 0.64 mL) per week.

9.1.2. Phase 2 (Monthly Visits)

Subjects will receive the following treatments during Phase 2 for 12 weeks:

- Group 1: Daily SL BPN tablets (containing BPN and naloxone) up to a maximum daily dose of 32 mg (doses may range from 8 mg/2 mg to 32 mg/8 mg SL BPN daily) and monthly SC injections of placebo CAM2038 of 0.16 mL, 0.32 mL, 0.32 mL or 0.48 mL (near-matching 64 mg, 96 mg, 128 mg and 160 mg active CAM2038 q4w doses) per month.
- Group 2: Daily SL placebo tablets (tablets matching 8 mg/2 mg to 32 mg/8 mg doses) and monthly SC injections of active CAM2038 q4w BPN at total doses of 64 mg (0.18 mL), 96 mg (0.27 mL), 128 mg (0.36 mL) or 160 mg (0.45 mL) per month.

Dosage adjustment will be allowed during Phase 2 only at the monthly visits, up to a maximum of 32 mg SL BPN (or placebo) and up to 160 mg CAM2038 q4w (or placebo).

Supplemental BPN: During Phase 2, supplemental BPN will be provided with CAM2038 q1w 8 mg SC injection (0.16 mL), at a maximum of one SC injection per month. The reason for administering supplemental BPN will be recorded, in addition to SOWS, COWS, and Desire/Need to Use VAS. Supplemental BPN cannot be given once subject is on 32 mg SL BPN (or placebo) and 160 mg (0.45 mL) CAM2038 q4w.

9.2. Identity of Investigational Products

The following treatments will be used during the trial:

- CAM2038 q1w (BPN FC Injection depot for once weekly administration), 50 mg/mL: 8, 16, 24 and 32 mg (BPN base), 0.16, 0.32, 0.48 and 0.64 mL SC injection.

- CAM2038 q4w (BPN FC Injection depot for once monthly administration), 356 mg/mL: 64, 96, 128 and 160 mg (BPN base), 0.18, 0.27, 0.36 and 0.45 mL SC injection.
- CAM2038 placebo: 0.16, 0.32, 0.48 and 0.64 mL SC injection for once weekly or once monthly administration.
- SL BPN: 2 mg/0.5 mg or 8 mg/2 mg BPN/naloxone tablets.
- SL placebo: tablets matching 2 mg/0.5 mg and 8 mg/2 mg SL BPN doses.
- SL BPN film (test dose on Day 1): 4 mg/1 mg BPN/naloxone film.

Description of CAM2038 q1w, q4w, and placebo SC injection products:

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

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

Placebo SC injections will be supplied as matching for CAM2038 q1w or nearly matching (by volume and color) for CAM2038 q4w pre-filled syringes with safety devices and plungers containing the following: soybean phosphatidylcholine, glycerol dioleate, and ethanol. More information regarding the CAM2038 q1w, CAM2038 q4w and matching/near-matching CAM2038 placebo injections can be found in the Trial MOP.

Description of SL BPN and placebo tablets:

Subjects will be required to take daily SL BPN (BPN/naloxone) during the trial. These products will be supplied by the Sponsor or designee. Matching SL placebo tablets will be provided for each dosage strength. More information regarding the SL BPN and near-matching SL placebo products can be found in the Trial MOP.

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

Description of SL BPN film (test dose):

All subjects will receive a 4 mg test dose of BPN/naloxone on Day 1. The test dose consists of 1 film of Suboxone[®] containing 4 mg BPN and 1 mg naloxone (Indivior UK Limited). Handling and storage of the product will be in accordance with the Suboxone Summary of Product Characteristics.

9.2.1. Handling, Storage, and Accountability

All trial 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.

SL BPN should be stored in a secured area and in accordance with the product labeling (a copy is located in the Trial MOP) and all applicable laws, regulations, and local/institutional requirements. A description of storage conditions for CAM2038 is provided in the Trial MOP.

Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed and the running inventory. The unused quantities will be returned to the Sponsor's drug supply vendor at the end of the trial. All unused supplies will be checked against the drug accountability records during the trial and/or at the end of the trial. Subjects will be instructed to return all unused trial drugs to the clinical site. The Investigator or designee must maintain an inventory record of all SL BPN dispensed to subjects for the purpose of treatment use. The drug accountability records for returned SL BPN and placebo tablets will be handled by the unblinded trial site personnel. Additional details are provided in the Trial MOP.

BPN is a Schedule III controlled substance and trial drugs must be handled and stored strictly in accordance with restrictions related to controlled substances. Trial drugs must be kept securely locked with access limited to appropriate trial personnel, according to applicable regulations.

9.2.2. Dispensing and Administration

Only eligible subjects participating in the trial will receive the trial drug. Only authorized research site staff may supply or administer the trial drugs. Once dispensed, trial drug may not be relabeled or reassigned for use by other subjects. Subjects will be provided with a weekly (Phase 1) or monthly (Phase 2) supply of trial medications.

Subjects will be instructed to place SL BPN or placebo tablets under the tongue until dissolved. For dosages requiring more than one SL tablet, tablets should be placed in different areas under the tongue at the same time. No more than two tablets should be placed under the tongue at one time.

CAM2038 q1w, q4w, and placebo SC injections will be administered by designated healthcare professional at the investigational site. Detailed instructions for use will be provided in the Trial MOP.

9.3. Method of Assigning Subjects to Treatment Groups

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

Subjects who 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 trial.

Subjects who have met the eligibility criteria (Section 8) during the re-check on Day 1 and who have tolerated the 4 mg test dose will be randomized to one of the two treatment groups in a 1:1 ratio (Group 1: Daily SL BPN plus SC placebo injections or Group 2: CAM2038 [q1w and q4w] SC injections plus SL placebo tablets). Due to the size of the trial, it is expected that subjects will be balanced for various other baseline factors, including age.

Once any subject number or randomization number is assigned, it cannot be reassigned to any other subject. This trial will use central randomization, through an Interactive Voice Response System and/or by an Interactive Web Response System managed by the Sponsor.

9.4. Selection of Doses

The trial will include a range of doses as used in clinical practice (i.e., 8 mg to 24 mg SL BPN per day in phase I and up to 32 mg SL BPN in Phase II), based on each subject's individual needs. Doses of CAM2038 will deliver similar exposure to SL BPN doses. As in clinical practice, dose adjustments (increases in case of withdrawal effects or cravings or decreases for tolerability reasons) will be allowed during the trial at schedule trial visits during both Phase I and Phase II.

9.5. Selection and Timing of Dose

Subjects will be randomized to receive either CAM2038 or SL BPN at individualized doses. The dose levels will be sufficient to prevent withdrawal symptoms and cravings, as in clinical practice.

No fasting or special dietary requirements are required for the trial; however, when taking the SL BPN or placebo tablets, subjects should be advised to not eat or drink anything for 20 minutes before and 20 minutes after the tablet(s) are completely dissolved. To ensure consistency in bioavailability, subjects should follow the same manner of dosing for the duration of the trial.

9.6. Blinding

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

SL BPN tablets used during the trial will have a nearly-matching placebo. Due to minor potential differences between active and placebo SL tablets, subjects will be told that clinical supplies of SL BPN have been specifically developed for this trial and may look or taste different than commercially available products that they may have been treated with previously. Subjects should not interpret these differences as indicative of whether they are receiving SL active or placebo tablets.

There is a slight difference in color and fill volume between the placebo and active CAM2038 q4w; however, the viscosity is the same. In order to maintain the blind given the differences in color and fill volume, the following will be implemented for both Phase 1 and Phase 2:

- The Injecting Clinician and any other staff involved in the injection process will not participate in subject evaluations, nor discuss any information regarding the injections with the subjects or other trial staff.

- To keep the subjects blinded, appropriate steps will be taken to ensure that the subject is unable to view the syringe at any time.
- The trial staff will not ask the Injecting Clinician or any other staff involved in the injection process for information regarding subject group assignment that might inadvertently unblind the trial staff.

Designated site personnel will remain unblinded to maintain drug accountability records for all dispensed and returned SL BPN or SL placebo tablets. This unblinded site personnel must not participate in subject efficacy evaluations nor discuss with other trial staff any information regarding the SL tablets in reference to the subjects.

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

9.7. Prior and Concomitant Therapy

All non-trial 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 trial. The Investigator will determine if the prior/concomitant medication(s) affect the subject's eligibility to participate or continue to participate in the trial. The following restrictions on concomitant medications will be in place during the trial:

- 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 (for CAM2038 q1w) or at least 2 months (for CAM2038 q4w) following the last CAM2038 injection. Therefore, subjects requiring analgesic emergency treatment or anesthesia for surgery should ideally be treated with a non-opioid analgesic. Opioids may be used with caution, but as higher doses may be required for analgesic effect, there may be a higher potential for toxicity with opioid administration. The clinical course should carefully evaluated and be fully documented for subjects who have a requirement for any opioid analgesic for >7 days continually or general anesthesia for surgery.
- BPN is metabolized via CYP3A4. Because CYP3A4 inhibitors may increase plasma concentrations of BPN, 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 CYP 3A4 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 trial treatment. The Medical Monitor must be consulted prior to starting subjects on any of these agents.

- Concomitant use of other narcotic anesthetics, benzodiazepines, phenothiazines, other tranquilizers, or other 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 BPN. If these sedatives are required during the trial, the Medical Monitor must be consulted. Subjects should be advised of the danger of concomitant use of sedatives while participating in in the trial. Subjects should be explicitly advised of the danger of IV abuse of benzodiazepines and abuse of alcohol while under treatment with CAM2038 or SL BPN.

10. TRIAL PROCEDURES AND ASSESSMENTS

All trial assessments will be performed at the visits and time points outlined in the Schedule of Assessments ([Table 3](#) and [Table 4](#)); 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 Trial MOP.

Table 3 Schedule of Assessments: Screening and Phase 1 (Weekly Visits)

	Trial Period/Phase:	Screening	Phase 1 (Weekly Visits)							
	Month:	-1	M1				M1-3			
	Week:	-3 to -1	W1				W2-W11		W12	
	Day:	-21 to -1	D1 ^a	D2	D3	D4	D5-7	D8	Weekly ^b	-
Informed Consent ^c	X									
Eligibility Criteria Review ^d	X	X								
Demographic Data and Psychosocial History	X									
Medical and Medication History/Substance Abuse and Treatment History (questionnaires)	X									
DSM-V	X									
Physical Examination ^e	X									
Weight, BMI	X	X							X	
Height	X									
Vital Signs ^f	X	X ^g				X		X	Weekly	X
ECG	X	X ^g						X	Weekly	X
Biochemistry, Hematology, Urinalysis and Coagulation Profile	X	X								X
Pregnancy Test ^h	X	X						X	Weekly	X
Hepatitis B/C, HIV ⁱ	X									
Injection Site Examination		X	X			X	(X)	X	Weekly	X

^a Subjects will be randomized to 1 of 2 treatment groups (SL BPN or CAM2038) after confirmation of eligibility ≥ 1 hour following a 4 mg SL BPN test dose.

^b A window of ± 2 days will be allowed for weekly visits during Weeks 2 to 12, in addition to Week 13.

^c Subjects must voluntarily provide written informed consent prior to any trial-related procedures being performed.

^d Prior to randomization on Day 1, a review of the eligibility criteria will be made

^e A complete physical exam of all major body systems will be performed at the Screening visit.

^f Includes temperature, blood pressure, pulse rate, respiration rate.

^g Vital signs and ECG will be measured at approximately 15-30 minutes before the test dose and approximately 15-30 minutes after the CAM2038/SL BPN dose on Day 1 and approximately 15-30 minutes pre-dose at the other visits as indicated in the table (or during the visit if no dose is given).

^h A serum pregnancy test will be performed at Screening. An “in-office” urine pregnancy test will be required on Day 1 PRIOR to randomization and test dose administration as well weekly thereafter (for women of childbearing potential).

ⁱ 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.

Trial Period/Phase:	Screening	Phase 1 (Weekly Visits)							
	Month:	-1	M1				M1-3		
	Week:	-3 to -1	W1				W2-W11		W12
	Day:	-21 to -1	D1 ^a	D2	D3	D4	D5-7	D8	Weekly ^b
Dispense Treatment Identification Card		X							
Urine Toxicology	X	X					X	Weekly	X
Illicit Drug Use Self-Report	X	X					X	Weekly	X
SOWS, COWS, VAS ^j	X	X	X		X	(X)	X	Weekly	X
C-SSRS ^k	X	X	X		X	(X)	X	Weekly	X
Measurement of Morning Desire to Use/Need to Use							X	Weekly	X
SL BPN or SL placebo dispensing		X	X		X	(X)	X	Weekly	X
SL BPN or SL placebo administration ^l		X	X	X	X	Daily	X	Daily	X
CAM2038 q1w or placebo SC injection ^m		X			X	(X)	X	Weekly	X
Psychosocial Counseling		X					X	Weekly	X
Adverse Events ⁿ	X	X	X		X	(X)	X	Weekly	X
Concomitant Medications/Procedures	X	X	X		X	(X)	X	Weekly	X
On-site visits	X	X	X		X	(X)	X	Weekly	X

Abbreviations: BMI=body mass index; BPN=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; C-SSRS=Columbia Suicide Severity Rating Scale; D=day; DSM-V= Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition; ECG=electrocardiogram; HIV=human immunodeficiency virus; M=month; SC=subcutaneous; SL=sublingual; SOWS=Subjective Opiate Withdrawal Scale; VAS=visual analogue scale; W=week (X) indicates as needed based on the individual subject.

^j SOWS/COWS/VAS will be completed each time the subject visits the clinic, as needed based on titration and dosage adjustment. On Day 1, COWS, SOWS and VAS will be completed before the test dose is administered (baseline). COWS will also be completed after the test dose on Day 1 to evaluate tolerability, and on Day 2.

^k Screening version at Visit 1 (Screening), Since Last Visit version at all subsequent visits.

^l Not to exceed 24 mg SL BPN (or placebo) per day, this administration will be done at home.

^m Not to exceed 32 mg CAM2038 q1w (or placebo) per week.

ⁿ Any spontaneously reported adverse event 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.

Table 4 Schedule of Assessments: Phase 2 (Monthly Visits) and Follow-up

Trial Period/Phase:	Phase 2 (Monthly Visits)						Follow-up			
	Month:	M4		M5		M6		M7		
	Week: ^a	W13	W14-16	W17	W18-20	W21	W22-24	(EOT) W25	W26-28	W29
Weight and BMI	X		X		X		X			
Physical Examination							X			
Vital Signs ^{b,c}	X		X		X		X			
ECG ^c	X		X		X		X			
Biochemistry, Hematology, Urinalysis and Coagulation Profile	X		X		X		X			
Pregnancy Test ^d	X		X		X		X			
Injection Site Examination	X		X		X		X		X	
Urine Toxicology	X		X		X		X			
Illicit Drug Use Self-Report	X		X		X		X			
Random Urine Toxicology and Illicit Drug Use Self-Report ^e	3 x random urine toxicology									
SOWS, COWS, VAS	X		X		X		X		X	
C-SSRS ^f	X		X		X		X		X	
Measurement of Morning Desire to Use/Need to Use	X		X		X		X		X	
SL BPN or SL Placebo Dispensing	X		X		X					
SL BPN or SL Placebo Administration ^g	X	Daily	X	Daily	X	Daily				

^a Treatment Visits should be conducted within a window of ± 7 days for monthly visits (other than Week 13, which will have a visit window of ± 2 days). If a subject misses a visit or completes a visit early or late, the original schedule should be resumed at the subsequent visit such that the ensuing visits occur as originally scheduled, relative to Day 1.

^b Includes temperature, blood pressure, pulse rate, respiration rate.

^c Vital signs and ECG will be measured approximately 15-30 minutes pre-dose and approximately 15-30 minutes post-dose at Week 13. At the other visits, ECG will be measured approximately 15-30 minutes pre-dose as indicated in the table (or during the visit if no dose is given).

^d A serum pregnancy test will be performed at the End of Treatment visit (Week 25). An “in-office” urine pregnancy test will be required at Week 13, 17 and 21 prior to injection being administered (for women of childbearing potential).

^e A total of 3 random urine toxicology visits during M4-M6, preferably once a month. Illicit drug use self-reports will also be completed by the subjects at these visits.

^f C-SSRS “Since Last Visit version” is to be used.

^g Not to exceed 32 mg/8 mg SL BPN (or placebo) per day.

Trial Period/Phase:	Phase 2 (Monthly Visits)						Follow-up			
	M4		M5		M6		M7			
	Week: ^a	W13	W14-16	W17	W18-20	W21	W22-24	(EOT) W25	W26-28	W29
CAM2038 q4w or Placebo SC Injection ^h	X		X		X					
Transition to Standard Care								X		
Psychosocial Counseling	X		X		X			X		
Adverse Events ⁱ	X		X		X			X	X	X
Concomitant Medications/Procedures	X		X		X			X	X	X
Scheduled On-site Visit	X		X		X			X		X
Telephone Contact									Weekly	

Abbreviations: BMI=body mass index; BPN=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; M=month; SC=subcutaneous; SL=sublingual; SOWS=Subjective Opiate Withdrawal Scale; VAS=visual analogue scale; W=week.

^h Subjects will receive the first CAM2038 q4w injection (active or placebo) at the beginning of Week 13 (±2 days). Not to exceed 160 mg CAM2038 q4w (or placebo) per month. Subjects will receive their last CAM2038 q4w dose at Week 21.

ⁱ 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 and during the telephone contacts in the Follow-up phase.

10.1. Demographics and Other Baseline Characteristics

10.1.1. Informed Consent

The nature of the trial and its risks and benefits will be explained to the subject by the Investigator or designated trial personnel. The subject must voluntarily provide written informed consent on an ethics-approved informed consent form (ICF), prior to performing any trial-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 trial-specific procedures. Documentation that the subject was given adequate time to ask the Investigator (or designee) questions about their participation in the trial 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.

All subjects will be informed on the importance of visit attendance and truthful data on their self-reported illicit opioid use. Subjects will be told that there will not be a bad consequence if there are evidence of opioid use and they will not be discontinued from the trial. Therefore, subjects should be as truthful as possible to provide accurate self-reported use data for this trial. A role induction form (included in the Trial MOP) will be completed at the time of providing informed consent.

10.1.2. 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.

10.1.3. 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.

10.1.4. 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.

10.1.5. 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. Additional data to be collected include, previous episodes of BPN treatment, duration of BPN treatment for each episode,

previous illicit BPN use, and time since illicit BPN use at Screening. Detailed information on substance use and treatment history is provided in the Trial MOP.

10.1.6. Contraceptive Requirements

Both Male and female subjects of childbearing potential must be using and willing to continue using medically acceptable contraception during the trial. Examples of medically acceptable forms of contraception include true abstinence, hormonal contraceptives (combined oral pill, patch or vaginal ring, intrauterine device or system, progestin implant or injection), bilateral tubal ligation, or double-barrier methods (i.e., male condom in addition to a diaphragm or a contraceptive sponge).

Female subjects of non-childbearing potential are not required to use contraception or undergo pregnancy tests; however, they must be surgically sterile (hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy, as determined by subject medical history) or congenitally sterile, or must be post-menopausal. Post-menopausal is defined as being amenorrheic for at least 2 years without another cause or amenorrheic for at least 1 year without another cause and a documented follicle stimulating hormone level ≥ 50 mIU/mL. Male subjects of non-childbearing potential are not required to use contraception, however they must be surgically sterile (Sterilisation with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

10.2. Eligibility Review and Randomization

At screening, the Investigator or designee must document that the subjects meet each individual criterion (as outlined in Section 8.1 and 8.2) via a signed note or eligibility and clinical stability checklist. Signatures on these documents must be dated on or before the date of randomization in Phase 1 (Day 1). Prior to randomization, a re-check of the eligibility criteria will be performed and tolerability of the 4 mg SL BPN test dose will be confirmed.

10.3. Efficacy Assessments

Details regarding primary, secondary and exploratory variables are provided in Section 10.6 (Efficacy and Safety Variables); and the statistical analyses are discussed in Section 12 (Statistical Analysis). The following sub-sections provide an overview of the efficacy assessments included in the trial. Additional details, such as the questionnaire items/scale text and additional instructions (where applicable) are provided in the Trial MOP.

10.3.1. Urine Toxicology Samples for Opioids

Urine toxicology samples will be collected at each visit (both scheduled and random, excluding Day 2, Day 4 and Follow-up) 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. 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, codeine, oxycodone, hydrocodone, hydromorphone, fentanyl, and methadone). In addition, it is recommended that the scheduled assessment visits take place preferably on Mondays to potentially improve detection of illicit opioid use that may have occurred over the weekend.

There will be 3 random urine visits in Phase 2. Sites should utilize their standard clinical process for scheduling the 3 random urine visits, however it is recommended that no more than one random urine test be conducted between two scheduled visits. Random urine visits should occur within 48 hours after speaking directly with the subject.

10.3.2. 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 at all visits when urine toxicology samples for opioids are taken (15). A copy of the Illicit Drug Use Self-Report form is provided in the Trial MOP.

10.3.3. 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 (16).

Copies of these VASs are provided in the Trial MOP. ***NOTE: Only VAS copies provided by the Sponsor should be used with trial 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).

10.3.4. Measures of Withdrawal

10.3.4.1. Subjective Opiate 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 Trial MOP.

10.3.4.2. Clinical Opiate Withdrawal Scale (COWS)

Trial 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 Trial MOP.

10.3.5. Urine Samples for Other Drugs of Abuse

Urine will be tested for other drugs of abuse (e.g., cocaine, benzodiazepines, barbiturates, amphetamines, phencyclidine and cannabinoids [THC]) using qualitative methods. Positive results will not be confirmed using quantitative methods. Urine samples for testing other drugs of abuse will be taken at the same time points as the urine samples for toxicology tests for opioids.

10.3.6. Unscheduled Visits, Medication and Counseling

Subject-requested or physician-directed unscheduled visits, phone calls or additional counseling, temporary dosage adjustments, or other pharmacological interventions, along with the reason(s) for unscheduled visits, phone calls or additional counseling or other pharmacological interventions, will be recorded.

10.3.7. Measures of Morning Desire to Use/Need to Use

Starting on Day 8 (Week 2), subjects will be asked if they have felt desire or need to use opioids in the mornings since their last visit, and if so, how many mornings and how severe the desire/need has been (average severity of desire/need on a scale from 0 to 100).

10.4. Safety Assessments

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

10.4.1. Adverse Events and Serious Adverse Events

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

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.

10.4.1.1. Adverse Event Reporting

All AEs 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 considers clinically significant.

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 trial drug
- Action and outcome
- Seriousness of event

All AEs will be documented and followed from the time the subject has signed the ICF until 14 days after the Follow-up Visit at Week 29 or early termination. SAEs and AEs that have been designated as related to trial drug will be followed until resolution or stabilization.

10.4.1.2. 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 more than 14 days after the Follow-up Visit at Week 29 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: trial specified hospitalization, short-term administrative hospitalization for procedures, tests or treatments of conditions that would not otherwise constitute an SAE, elective hospitalizations.

10.4.1.2.1. Serious Adverse Event Reporting

SAEs must be reported to the Sponsor or designee within 24 hours of knowledge of the event. All SAEs that occur during the trial and within 14 days following the Follow-up Visit at Week 29 (or 30 days following early termination) are reportable within 24 hours. During the follow-up

period beyond 14 days from Follow-up (or 30 days following early termination), only those SAEs that are considered to be possibly related to trial 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 using the SAE back-up form, if the database cannot be accessed for any reason) 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
 - Dates and doses of temporary and unscheduled visit dosage adjustments
 - Whether the trial drug was discontinued
 - Whether the assigned treatment SL 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 Trial 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.

10.4.1.2.2. Suspected Unexpected Serious Adverse Reactions (SUSAR)

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.

10.4.2. 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 trial and be referred back to the care of their usual provider or continue in the trial after discussion with and documentation by the Principal Investigator or his/her designee. Follow-up information will be obtained where possible (with the consent of the participant or their partner) regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant.

California participants: Subjects who become pregnant at anypoint during the study will be discontinued from the trial 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.

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

Blood and urine samples will be collected, processed, and shipped according to instructions from the safety laboratory. Additional laboratory samples may be taken at the discretion of the Investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety. Specific hematology, coagulation, biochemistry, and urinalysis assessments are listed in Table 5 and timing of the assessments is shown in Table 3 (Screening and Phase 1) and Table 4 (Phase 2 and Follow-up).

Table 5 Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Hematocrit	Sodium	Color
Hemoglobin	Potassium	pH
Red blood cell (RBC) count	Magnesium	Specific gravity
RBC Morphology	Calcium	Ketones
Mean corpuscular volume	Glucose (random)	Protein
Mean corpuscular hemoglobin	Bicarbonate	Glucose
Mean corpuscular hemoglobin concentration	Chloride	Bilirubin
Total and differential (absolute) white blood cell count	Creatinine	Nitrite
Platelets	Total protein	Urobilinogen
	Blood urea nitrogen	Occult blood
	Albumin	Microscopic examination of sediment, <i>only if urinalysis dipstick results are abnormal</i>
	Total bilirubin	
	Alanine transferase	
	Aspartate transferase	
	Lactic dehydrogenase	
	Amylase	
	Lipase	
	Gamma-glutamyl transferase	
	Alkaline phosphatase	
	Creatine phosphokinase	
	Total cholesterol (non-fasting)	
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 End of Treatment visit (Week 25). An “in-office” urine pregnancy test will be required on Day 1 PRIOR both test dose dispensation/ and confirmation of tolerability AND

randomization, and then at each scheduled visits (weekly for Weeks 1-12, monthly for Weeks 13-24) (for women of childbearing potential). Results must be reviewed and confirmed to be negative prior to start of SL BPN and 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 at Screening, 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 trial, and pre- and post-test counseling.

10.4.4. 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, at the time points indicated in Table 3 and Table 4. On Day 1, vital signs will be measured approximately 15-30 minutes before the subjects receive their SL BPN test dose and approximately 15-30 minutes after they have received their doses of blinded CAM2038 q1w/SL BPN (placebo or active). At Week 13, vital signs will be measured approximately 15-30 minutes pre-dose and approximately 15-30 minutes post-dose. At the other visits, vital signs will be measured approximately 15-30 minutes pre-dose (or during the visit if no dose is given). Clinically significant values will be recorded as AEs.

10.4.5. 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, at the time points indicated in Table 3 and Table 4. On Day 1, an ECG will be performed approximately 15-30 minutes before the subjects receive their SL BPN test dose and approximately 15-30 minutes after they have received their doses of blinded CAM2038 q1w/SL BPN (placebo or active). At Week 13, ECGs will be performed approximately 15-30 minutes pre-dose and approximately 15-30 minutes post-dose. At the other visits, ECGs will be performed approximately 15-30 minutes pre-dose (or during the visit if no dose is given). 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.

10.4.6. C-SSRS

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

Two versions of the C-SSRS will be used in this trial: the Baseline/Screening version (6 months and lifetime history) and the Since Last Visit version. The Baseline/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 and Table 4.

The C-SSRS is to be administered by the Investigator or his/her certified designee. The survey should be administered by the same assessor, where possible, throughout the trial.

10.4.7. Physical Examination

A complete physical examination including all major body systems (skin, head, eyes, ears, nose, respiratory, cardiovascular, gastrointestinal, endocrine metabolic, neurological, blood lymphatic and musculoskeletal) will be performed at Screening and Week 25 (EOT).

Height, weight and body mass index (BMI) will be determined as described in Table 3 and Table 4.

10.4.8. Injection Site Examination

CAM2038 or placebo injections sites will be examined during each scheduled visits for any signs of adverse site reactions, including erythema, pruritus, edema, pain, etc. If needed, a photograph of the adverse site reactions will 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 form will be included in the Trial MOP. Subjects will also be queried specifically about local tolerability AEs in connection to the examinations. Injection site examination can only be performed by the blinded site personnel.

10.4.9. Psychosocial Counseling

All subjects will receive manual-guided drug counseling during the trial on a weekly basis during Phase 1 and on a monthly basis during Phase 2, as described in more detail in the Individual Drug Counseling Manual (provided in the Trial MOP) (17). Additional counseling can be provided as clinically indicated; however, all additional counseling, visits or phone calls must be recorded.

10.4.10. Treatment Identification Card

Subjects will receive a wallet card indicating that they are receiving BPN as part of the trial. 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 9.7). Sample wallet cards will be provided for IRB submission.

10.4.11. Other Safety Considerations

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

10.5. Appropriateness of Measures

The primary endpoint was selected to provide an objective assessment of efficacy of the trial medications (i.e., RR based on urine toxicology results for illicit opioids). The most direct method to ascertain the frequency and amount of illicit opioid use would be through the use of patient self-reports. However, these reports may not always be reliable or accurate (18). Thus, the analysis of urine samples for specific drugs or drug metabolites is typically used as an objective criterion for assessing illicit drug use. Urine toxicology has been used in many efficacy assessments of BPN and will be used together with self-reported illicit drug use as to define the primary RR endpoint in this trial.

Retention in treatment, one secondary outcome measure in this trial, is commonly used for determining the efficacy of opioid maintenance treatment in pivotal clinical trials and provides an overall measure of treatment success (13, 14, 19). Additional secondary outcome measures were selected as a series of measures and scales to provide a complete assessment of the efficacy of CAM2038 compared to SL BPN, including investigator- and subject-reported withdrawal and subject-reported cravings. Standard and widely used measures of withdrawal will be included in this trial (COWS and SOWS) (20, 21) in order to ensure that subject's withdrawal symptoms are adequately controlled by CAM2038 as compared to SL BPN. Desire to Use and Need to Use VASs were 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 (16).

10.6. Efficacy and Safety Variables

10.6.1. Primary Efficacy Variable

The primary outcome measure will be RR, where a responder is defined for Phase 1 as: the subject must have no evidence of illicit opioids use at Week 13 and have no evidence of illicit opioids use for at least 2 out of the three weeks from Week 10 to Week 12. To be a responder for Phase 2, the subject must have no evidence of illicit opioids use at Month 6 (last illicit opioids use assessment in Month 6 or Week 25) and have no evidence of illicit opioids use in 5 out of the 6 illicit opioids use assessments in Phase 2. To be a responder for the study, the subject must be a responder for both Phases 1 and 2.

A total of 18 scheduled urine toxicology samples will be collected during the treatment period, whereof 12 samples will be collected in Phase 1 and 6 will be collected in Phase 2 (3 scheduled and 3 random).

10.6.2. Secondary Efficacy Variables

The secondary efficacy variables are:

- Percentage of urine samples negative for illicit opioids (This variable will be defined in the manner per EMA's request. This variable will serve as the primary efficacy variable for EMA NDA and will not be applicable for US NDA submission)

- Cumulative distribution function (CDF) of percent samples that are negative for illicit opioids (Week 5-24)
- Time to sustained abstinence of opioid use
- Percent of subjects remaining in the trial (retention rate)

10.6.3. Exploratory Efficacy Variables

Exploratory efficacy variables in the trial are:

- RR for Phase 1
- RR for Phase 2
- Percent negative urine samples in Phase 1
- Percent negative urine samples in Phase 2
- Percent of subjects with evidence of no illicit opioid use by time point
- Cumulative percentage of subjects with evidence of no illicit opioid use by time point
- Percent of subjects with no self-reported illicit opioid use by time point
- Percentage of subjects meeting criteria of stability at Week 13
- Measures of opioid craving:
 - Desire to Use VAS
 - Need to Use VAS
- Measures of opioid withdrawal:
 - COWS
 - SOWS
- Percentage of subjects without evidence of using other drugs of abuse by time point
- Supplemental BPN use
- Additional supplemental counseling
- Measures of morning need to use/desire to use
- Quantity of illicit opioid use

10.6.4. Safety Variables

Safety variables include AEs, clinical laboratory parameters, ECG, physical and injection site examinations, concomitant medications, vital signs and C-SSRS.

11. DATA QUALITY ASSURANCE

This trial will be conducted under Good Clinical Practice (GCP) and all applicable regulatory requirements. To ensure compliance, the Sponsor or designee may conduct a quality assurance audit, as outlined in Section 11.2.

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

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

11.1. Data Collection

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, participant diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This trial 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 trial personnel. All data entries will be verified for accuracy and correctness by independent monitors. The EDC system maintains a full audit trail.

11.2. Trial Auditing and Monitoring

Monitoring of the trial 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 trial objectives and/or endpoints, the purpose of the trial, trial 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, trial drug stocks, drug accountability records, participant charts and source documents, and other

records related to trial conduct. The purpose of the Sponsor audit or inspection is to systematically and independently examine all trial-related activities and documents to determine whether the trial-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.

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1. Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan (SAP), which will be completed prior to unblinding of the trial data. 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 trial report. A separate document will describe the testing procedure to address the requirements from the European Medicines Agency (EMA) and will only be used for the purpose of an application in the European Union.

12.2. Analysis Populations

- **Intent-to-Treat (ITT) Population:** All subjects who have been randomized to a treatment group. Analyses based on this population will group subjects according to the treatment they were randomized to receive, regardless of actual treatment received. The primary efficacy analysis will be based on this ITT population.
- **Modified Intent-to-Treat (mITT) Population:** All subjects who have been randomized to a treatment group and have received at least one dose of SL BPN/placebo or SC CAM2038/placebo in the treatment phase.
- **Safety Population:** All subjects who are randomized and treated who received any dose of SL BPN/placebo or CAM2038/placebo injections in the treatment phase. Analyses based on this population will group subjects according to the treatment they actually received regardless of the treatment they were randomized to receive. All safety analyses will use the safety population.
- **Per Protocol Population:** All subjects in the mITT population with no major protocol violations. Major protocol violation criteria will be established prior to the database lock.

12.3. Planned Analyses

12.3.1. Demographics and Other Baseline Characteristics

Disposition for all enrolled subjects will be summarized. Reasons for discontinuation will be tabulated.

Demographic data and baseline psychosocial characteristics will be summarized.

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.

12.3.2. Analysis of Efficacy Measures

12.3.2.1. Analysis of the Primary Efficacy Endpoint

The responder definition will be derived based on urine samples obtained from Weeks 10, 11, 12 and 13 in Phase 1 and samples obtained at Weeks 17 (Month 1), 21 (Month 2) and 25 (Month 3) and at the 3 random samples in Phase 2.

To be a responder for Phase 1, the subject must have no evidence of illicit opioids use at Week 13 and have no evidence of illicit opioids use for at least 2 out of the three weeks from Week 10 to Week 12. To be a responder for Phase 2, the subject must have no evidence of illicit opioids use at Month 6 (last illicit opioids use assessment in Month 6 or Week 25) and have no evidence of illicit opioids use in 5 out of the 6 illicit opioids use assessments in Phase 2. To be a responder for the study, the subject must be a responder for both Phases 1 and 2. Evidence of illicit opioid use is defined as a positive opioid urine toxicology result or a self-reported illicit opioid use.

The primary efficacy variable will be RR. The proportion of responders will be calculated in both treatment arms.

An analysis of non-inferiority in the primary efficacy variable between the two treatments arms will be performed using a margin of 13.5% point.

Non-inferiority will be concluded if the two-sided 95% confidence interval for the difference between the probabilities of response (Active- Control) is above -0.135 . The 95% confidence interval, (LB, UB), will be derived using normal approximation:

$$LB = (P_T - P_C) - 1.96 * (1/N_T * P_T * (1 - P_T) + 1/N_C * P_C * (1 - P_C))^{0.5}, \text{ and}$$
$$UB = (P_T - P_C) + 1.96 * (1/N_T * P_T * (1 - P_T) + 1/N_C * P_C * (1 - P_C))^{0.5}, \text{ where}$$

P_T and P_C are observed proportions of the responders for the treatment and the control, respectively, and N_T and N_C are the sample sizes for the treatment and the control, respectively.

12.3.2.2. Handling of Dropouts or Missing Data

Imputation methods to handle dropouts and/or missing data will be detailed in the trial SAP. Varieties of sensitivity analyses will be considered, including the analysis treating missing as evidence of opioids use.

12.3.2.3. Sensitivity Analyses

Sensitivity analyses based on various missing imputation methods will be performed and described in the trial SAP.

12.3.2.4. Analysis of Secondary Efficacy Endpoints

Percentage of Urine Samples Negative for Illicit Opioids

This variable will be defined in the manner per EMA's request. This variable will serve as the primary efficacy variable for EMA NDA and will not be applicable for US NDA submission.

Percent negative urine samples will be derived after applying missing value imputation. This variable will be analyzed via an analysis of variance (ANOVA) model with treatment effects. The difference between the two treatments in percent negative urine samples will be obtained from this model and the two-sided 95% confidence interval for the treatment difference will be presented.

An analysis of non-inferiority in the primary efficacy variable between the two treatments arms will be performed using a margin of 11% point.

Non-inferiority will be concluded if the two-sided 95% confidence interval for the difference between the percent negative urine samples (Active- Control) is above -0.11 .

Cumulative Distribution Function (CDF) of Percent Samples that are Negative for Illicit Opioid (Week 5-24)

Percent negative samples from 14 samples (8 weekly assessments obtained from Weeks 6 to 13, plus 3 monthly assessments obtained at Weeks 17, 21, and 25 and plus 3 random samples) will be calculated for each subject. Missing samples will be imputed as positive before the percentage is derived.

The null hypothesis of no difference in the CDF of the percent of urine samples that are negative for illicit opioids over Weeks 5-24 will be tested at the 5% significance level using Wilcoxon Rank-Sum test. The empirical CDF plot will be presented.

Time to Sustained Abstinence of Opioid Use

For the purpose of deriving time to sustained abstinence of opioid use (i.e., no opioid use through the rest of treatment period for at least 2 months), the time will be define as:

- If the sustained abstinence is obtained during the scheduled visit, time is the number of days between randomization day to the scheduled visit day. For example, if first sustained abstinence is obtained at the Week 8 visit, the time would be 56.
- If the first sustained abstinence is obtained during a random test, time is the number of days between randomization day to the day that random sample is obtained (Random Sample Date – Randomization Date).

Definition for evidence of illicit opioid use and rules for missing value imputation will be outlined in the SAP.

Time to sustained abstinence of opioid use will be analyzed via a log-rank model with treatment effects. Time to event “Survival” curve will be presented using Kaplan-Meier method. Median time to event and the 95% confidence interval of the median times will be presented, if estimable. In this time to event analyses, subjects who do not have any opioid-positive results during the entire study and who do not have any opioid-positive results before discontinuing from the study will be censored at Day 175 (Week 25 day), the day when the last sample will be obtained.

Retention Rate

The secondary endpoint retention rate will be analyzed using a chi square test. The percentages for each treatment and between treatment percentage differences will be estimated. The 95% confidence intervals of the estimated treatment differences, based on a normal approximation, will be presented.

12.3.2.5. Analysis of Exploratory Efficacy Endpoints

The exploratory efficacy endpoints will include RR during weeks on CAM2038 q1w (Phase 1) and during months on CAM2038 q4w (Phase 2). RR for Phase 1 and Phase 2 will be analyzed using chi square test. The percentages of negative urine samples in Phase 1 and Phase 2 will also be analyzed using chi square test. The 95% confidence intervals of the estimates will be presented using normal approximation.

Additionally, the following exploratory efficacy variables will be analyzed:

- Percent of subjects with evidence of no illicit opioid use by time point;
- Cumulative percentage of subjects with evidence of no illicit opioid use by time point;
- Percent of subjects with no self-reported illicit opioid use by time point
- Percent of subjects meeting criteria of stability at Week 13
- Changes from baseline in Desire to Use VAS, Need to Use VAS, COWS and SOWS over time.
- Percent of subjects without evidence of using other drugs of abuse by time point
- Supplemental BPN use
- Additional supplemental counseling
- Measures of morning need to use/desire to use
- Quantity of illicit opioid use

For the exploratory efficacy variables based on the percentages, the percentages, the differences of percentages (based on normal approximation) and 95% confidence intervals of the differences will be presented. Change from baseline variables will be analyzed via Analysis of Covariance (ANCOVA) model with treatment and baseline effects. Treatment effects and treatment differences will be estimated. The two-sided 95% confidence intervals of the between- and within-treatment differences will be presented.

Details of additional measures of efficacy and their analysis will be described prospectively, prior to final database lock and unblinding, in the SAP for this trial.

12.3.2.6. Handling of Multiplicity

This protocol has defined one primary endpoint and four secondary endpoints. The primary endpoint will be used to address the regulatory requirements as outlined by the US Food and Drug Administration (FDA). The two secondary endpoints percent negative urine samples and retention rate will be used to address the regulatory requirements as recommended by EMA.

The method for protecting the overall significance level, when drawing the conclusions based on the primary endpoint and the secondary endpoints, will be described in the associated SAP.

12.4. Analysis of Safety

Exposure will be summarized by treatment group.

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 trial drug, intensity, seriousness, AEs or SAEs leading to discontinuation and AEs occurring in 5% or greater of any treatment group (by preferred term). Frequencies for deaths and hospitalizations will also be summarized by treatment group and overall.

Data for clinical laboratory tests, ECG, 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.

12.5. Determination of Sample Size

The primary efficacy variable is based on data from Week 2 to Week 25. Approximately 380 subjects (190 subjects per arm) will be randomized.

The sample size of 190 subjects per treatment arm (380 total) was selected to achieve approximately 82% power to establish non-inferiority based on the primary efficacy variable, RR (Week 12-25). In the sample size calculation, it is assumed that both arms have a 70% RR, and that the non-inferiority margin is 13.5%.

Choice of non-inferiority margin for the primary endpoint

The proposed 13.5% margin is appropriate from a scientific validity perspective as well as meeting the FDA guidelines for non-inferiority selection (24). The FDA draft guidance on non-inferiority trials suggest 50% of the benefit of the control arm relative to a placebo or no care would be a reasonable approach. The following information provides additional credence to the rationale:

1. In the study by Rosenthal et al (27), the RR between open-label SL BPN/naloxone and placebo was found to be approximately 33% and 6%, a difference of 27% (lower limit of a two-sided confidence interval for the difference; 17%, using an approximate 95% confidence level) over 24 weeks of treatment (data derived from Fig 2 in Rosenthal et al). The expectation, based on this, is that a hypothetical placebo arm in this trial, HS-11-421, would be worse than the SL BPN control arm by at least a 17% difference in RR. Note that using the suggested 50% of the benefit of the control arm in this trial will imply a non-inferiority margin of 13.5%. Thus, using 13.5% as the non-inferiority margin should be viewed as conservative as the lower limit of the associated confidence interval for the difference is 17%.
2. In addition, the FDA Draft Guidance (24) notes that circumstances might support a conservative choice for the margin, including:
 - a. *Pharmacologic properties of the test drug that are very similar to those of the active control* – CAM2038 is an alternative dosage form of the same active entity with the expectation of similar overall average plasma concentrations to the SL BPN arm;
 - b. *Use of a persuasive biomarker* – responder definition in this trial will include the standard and well-accepted objective urine toxicology results to confirm treatment success with with respect to drug use;
 - c. If the test drug were shown to have some important advantage (e.g., on public health, potential to reduce misuse and abuse) – the misuse, abuse and accidental pediatric exposure are well known; the Drug Abuse Warning Network confirmed an increasing trend in adverse medical outcomes associated with SL BPN abuse (26) CAM2038 has the potential to reduce misuse/abuse associated with SL BPN and to have a significant positive public health impact in addition to potentially increasing adherence

The choice of non-inferiority margin for the secondary variable percent negative urine is based on the outcome of the Rosenthal study where a comparison was evaluated over 24 weeks between SL BPN (n=119) and placebo (n=54) for the outcome variable percent negative urine samples. The reported values from the analysis of variance is 35.1% and 14.4%, respectively (difference = 20.7%, p=0.81). This translates to an approximate 95% confidence interval for the difference of (11.5%, 29.9%). The power calculation is based on the the lower limit of this confidence interval representing a level of effect that can be viewed as clinically relevant, and can represent a hypothetical placebo arm in this trial.

A sample size of 190 subjects per treatment arm will provide over 90% power to establish the non-inferiority with 11% point for the percent of urine samples negative for illicit opioids. In the sample size calculation it was assumed that the percentage of samples negative for illicit opioids is the same for the two treatment groups and the standard deviation was 30%.

In summary, the sample size of approximately 190 subjects per treatment arm (380 total) will provide approximately 82% power to establish non-inferiority for the primary efficacy variable at a two-sided significance level of 0.05.

13. TRIAL ADMINISTRATION AND INVESTIGATOR RESPONSIBILITIES

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

13.1. Regulatory and Ethical Considerations

13.1.1. Ethical Conduct of the Trial

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

13.1.2. Ethics Approval

The investigational site's IRB must meet all relevant regulatory requirements. The trial protocol and ICF will be reviewed by the IRB prior to enrolling participants into the trial; 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 trial at his or her research site and notification of trial 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 trial site to the Sponsor in a timely fashion.

13.1.3. Subject Informed Consent

The Investigator (or authorized designee) will ensure that the participant (or the participant's legal representative) is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the trial. Each prospective subject will receive an IRB-approved ICF that summarizes the pertinent trial information and will be given ample time to read the form and ask questions about the trial. 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 trial. If the participant chooses to participate, he/she must sign the ICF before any trial-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 trial 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 trial participant.

13.2. Privacy and Confidentiality

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

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

The knowledge gained through this trial 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 trial to check the validity and accuracy of the data gathered in this trial. 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 trial 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. Trial 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 trial, 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 CSA for details.

13.3. Trial and Site Closure

Upon completion of the trial, all trial data will be provided to the Sponsor following review of site trial records for completeness, and data clarifications and resolutions. Accounting, reconciliation, and final disposition of used and unused trial 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 trial 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 trial, if the trial is suspended or terminated for safety reasons and will inform the regulatory authorities of the suspension or termination of the trial and the reason(s) for the action. If required by applicable regulations, the Investigator will inform the IRB promptly and provide the trial participants with the reason for the suspension or termination. If the trial is prematurely discontinued, all trial data will be returned to the Sponsor.

13.4. Regulatory Documents and Records Retention

The Investigator is responsible for creating and/or maintaining all trial 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 trial. 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 trial 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 trial 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 trial 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 trial 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. Trial records should not be destroyed without consultation with the Sponsor.

13.5. Delegation of Responsibilities and Adequate Resources

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

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 trial responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the investigational site.

13.6. Protocol Amendments

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

13.7. Financial Disclosure

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 trial.

14. SPONSOR APPROVAL PAGE

A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel Group, Multi-center Trial Assessing the Efficacy and Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Treatment of Adult Outpatients with Opioid Use Disorder

Version: v 6.0

Date: 03-Nov-2016

Braeburn Pharmaceuticals



Sonnie Kim, PharmD

VP, Clinical Development & Medical Affairs

Sponsor Representative
Full Title

03-Nov-2016

Date
(DD-MMM-YYYY)

15. INVESTIGATOR PROTOCOL AGREEMENT PAGE

A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel Group, Multi-center Trial Assessing the Efficacy and Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Treatment of Adult Outpatients with Opioid Use Disorder

Version: v 6.0

Date: 03-Nov-2016

I have read this protocol and I agree to conduct the trial 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)

16. REFERENCES

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