HS-15-549 **Phase II**

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

Statistical Analysis Plan (SAP)

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SPONSOR APPROVAL

The undersigned have reviewed the format and content of this prospective statistical analysis plan (SAP) and have approved it for use to analyze the HS-15-549 data.

BRAEBURN PHARMACEUTICALS

Sonnie Kim, Pharm.D.		Dec. 29, 2016
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STATISTICIAN

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1.0 DOCUMENT HISTORY

Version	Date	Changes made since previous version
0.01	4 August, 2016	First draft
1.00	16 December, 2016	Incorporate comments

2.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AUC_{ss}	Area under the plasma concentration-time curve (AUC) during a dosing interval at steady state
BMI	Body Mass Index
BPN	Buprenorphine
COWS	Clinical Opioid Withdrawal Scale
CRF	Case Report Form (may include electronic data capture systems or paper forms)
CSR	Clinical Study Report
$C_{ss,av}$	Average plasma concentration during a dosing interval at steady state
$C_{ss,max}$	Maximum observed plasma concentration during a dosing interval at steady state
C_{trough}	Observed plasma concentration prior to next actual or scheduled hypothetical dose
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
norBPN	Norbuprenorphine
PK	Pharmacokinetics
PT	MedDRA Preferred Term
SAE	Serious Adverse Event
SL BPN	Sublingual Buprenorphine or Buprenorphine/Naloxone
SOC	MedDRA System Organ Class
SOWS	Subjective Opioid Withdrawal Scale
TEAE	Treatment-Emergent Adverse Event
$t_{ss,max}$	Time to $C_{ss,max}$
VAS	Visual Analog Scale
%Fluctuation	Percent fluctuation during a dosage interval at steady state

3.0 INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol HS-15-549, Amendment 4: 5.0, 05 OCT 2016.

The purpose of this document is to provide details and clarifications on study populations and on how the variables will be derived, how missing data will be handled, as well as details on statistical methodologies to be used to analyze the pharmacokinetics (PK), safety and efficacy data from the study.

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file before database is locked. Deviations from the final approved plan will be noted in the clinical study report.

4.0 STUDY DESCRIPTION

4.1 STUDY OBJECTIVES

Primary objectives of the study are:

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

The secondary objective of the study is:

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

The exploratory objectives of the study are:

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

4.2 STUDY TREATMENTS

Within 21 days of a medical Screening visit and confirmation of eligibility, subjects will be randomized to 1 of 2 treatment groups (refer to Section 10.2 of the clinical study protocol, Eligibility Review and Randomization, for more detail. Please also note that Group 3 was not randomized.):

- Group 1: 3 single weekly SC injections of 32 mg CAM2038 q1w (50 mg/mL) administered in the buttock to reach steady state, rotating between right and left buttock sites, followed by 4 single

weekly SC injections of 32 mg CAM2038 q1w administered in the buttock (reference), abdomen, thigh, and back of upper arm in a randomized, crossover manner, with injection site sequence allocated using a randomized crossover design.

- Group 2: 4 monthly SC injections of 128 mg CAM2038 q4w (356 mg/mL) administered in the buttock, rotating between right and left buttock injection sites.
- Group 3: 7 daily doses of 24 mg of SL BPN followed by 4 monthly SC injections of 160 mg CAM2038 q4w (356 mg/mL) administered in the buttock, rotating between right and left buttock injection sites.

4.3 STUDY DESIGN

This is a Phase II, open-label, partially randomized, 3-treatment group, multi-site study designed to evaluate the steady state PK of BPN and norBPN following repeated SC administration of CAM2038 q1w (Group 1) at different injection sites and to evaluate the steady state PK of BPN and norBPN after repeated SC administration of CAM2038 q4w (Groups 2 and 3) in opioid-dependent subjects with a history of chronic non-cancer pain. The study will involve 4 phases: Screening, Treatment, open label safety extension and Follow-up.

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

- Group 1: 3 single weekly SC injections of 32 mg CAM2038 q1w (50 mg/mL) administered in the buttock to reach steady state, rotating between right and left buttock sites, followed by 4 single weekly SC injections of 32 mg CAM2038 q1w administered in the buttock (reference), abdomen, thigh, and back of upper arm in a randomized, crossover manner, with injection site sequence allocated using a randomized crossover design.
- Group 2: 4 monthly SC injections of 128 mg CAM2038 q4w (356 mg/mL) administered in the buttock, rotating between right and left buttock injection sites.
- Group 3: 7 daily doses of 24 mg of SL BPN followed by 4 monthly SC injections of 160 mg CAM2038 q4w (356 mg/mL) administered in the buttock, rotating between right and left buttock injection sites.

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

For subjects in Group 2, SC injections of CAM2038 q4w will be administered in the buttock, rotating between right and left buttock, on Day 1, Day 29, Day 57 and Day 85, for a total of 4 doses. Following the first administration, subjects will attend an interim visit on Day 2 to evaluate safety and tolerability of the transition from 24 to CAM2038 q4w. Following administration of the first 3 doses, PK samples will be collected pre-dose and at scheduled times post-dose on an outpatient basis to determine achievement of steady state. To characterize steady state PK of BPN and norBPN, subjects will be confined to the CRU and serial PK samples will be collected for up to 24 hours following the fourth dose, administered on Day 85; subsequent PK samples will be collected up to 28 days' post-dose on an outpatient basis. At each study visit, safety and efficacy assessments will be conducted at pre-specified times. At the Day 113 (EOT) visit, CAM2038 q4w 128 mg subjects may continue on with open-label extension phase for up to 6 weeks and will be switched to CAM2038 q1w 32 mg. Subjects will also be required to record their worst daily pain and average daily pain using an11-point NRS on an electronic device.

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

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

4.4 RANDOMIZATION AND BLINDING

Up to a total of 40 subjects will be randomized at a 3:2 ratio to Group 1 (CAM2038 q1w) or Group 2 (CAM2038 q4w). Per Protocol Amendment 05, up to additional 16 subjects will be enrolled to Group 3 to receive 160 mg CAM2038 q4w. The study is not blinded.

At least 20 subjects, and up to 24 subjects, will be randomized to Group 1 and assigned to 1 of the following 4 injection site sequences at a 1:1:1:1 ratio: ABDC, BCAD, CDBA, and DACB, where A=buttock (reference), B=abdomen, C=thigh, and D=back of upper arm. For Group 2 (CAM2038 q4w), approximately 16 subjects will be enrolled.

5.0 ANALYSIS POPULATIONS

5.1 SAFETY POPULATION

The safety population will include all subjects who have received study medication. Analyses based on this population will group subjects according to the treatment they actually received regardless of the treatment they are randomized to receive. All safety analyses will use the safety population.

5.2 PHARMACOKINETIC POPULATION

Pharmacokinetic (PK) population will consist of all subjects in the Safety population who have provided PK data.

5.3 EVALUABLE PHARMACOKINETIC POPULATION

Evaluable pharmacokinetic (PKEVAL) population will consist of all subjects in the PK population who have provided sufficient PK data for all 4 randomized injection sites to derive PK parameters of interested (Group 1), or have provided PK data after the last injections of CAM2038 q4w (Groups 2 and 3). All primary PK summaries will be based on the PKEVAL population.

5.4 INTENT-TO-TREAT POPULATION

The efficacy population will be the intent-to-treat population consisting of all subjects that have received at least 1 injection of CAM2038 and provided some efficacy measures. All efficacy summaries will be based on the ITT population.

6.0 GENERAL CONVENTIONS

Unless otherwise stated, all statistical analyses will be performed using SAS Version 9.2 and all hypothesis tests will be conducted at a two-sided significance level of 0.05. P-values will be presented with 3 decimals and p-values that are less than 0.001 will be presented as <0.001.

Continuous (non survival related) data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be used to summarize categorical (discrete) data. Presentations of categorical data will generally suppress percentages for items where the count is zero in order to draw attention to the nonzero counts. In general, mean, standard deviation, median, minimum, maximum, and percentages will be presented with one decimal.

Unless otherwise stated, confidence intervals, when presented, will be constructed at the two-sided 95% level. For binomial variables, the 95% confidence intervals will be constructed using the exact method.

Data listings will present all data collected on CRFs by study drug, center, and subject number. Unless otherwise stated data will be presented by treatment and overall.

6.1 DEFINITION OF BASELINE

Unless otherwise stated, the last observed measurement on the date of randomization will be considered the baseline measurement. If multiple observations are made during baseline, the baseline will be defined as average of the observations obtained during the baseline phase.

6.2 SOFTWARE

Analyses will be conducted using SAS Version 9.2 or higher.

6.3 CHANGES TO PLANNED ANALYSES

Draft versions of the SAP will be numbered sequentially as Version 0.0i. The final approved version will be numbered as Version 1.00. Revisions after the "Final" version will be numbered as Version 1.0x. The Clinical Study Report will document any changes made after the final version approved before the data base lock.

7.0 DESCRIPTION OF THE STUDY POPULATIONS

All tables, figures, and listings must include a population descriptor (e.g., ITT population, Safety Population, PKEVAL Population, or PK Population) in the title.

7.1 DISPOSITION

Subject disposition summaries will be presented by treatment arm and treatment sequence and will include the number of subjects randomized, the number and percentage of randomized subjects in the Safety, ITT, PKEVAL, and PK populations, as well as the number and percentage of subjects who complete the study. The summaries will also include the reasons for early discontinuation from the study.

7.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

A summary of demographics and baseline characteristics will be presented by treatment arm and treatment sequence for the ITT, Safety, Evaluable PK and PK populations. The demographic characteristics will consist of age, sex, ethnicity, and race using descriptive statistics.

Age will be calculated based on the following conditional algorithm:

- Has the subject had his/her birthday this year?
    - Yes, then AGE = (year of informed consent) – (year of birth).
    - No, then AGE = (year of informed consent) – (year of birth) – 1.

Clinical baseline characteristics summaries will include BMI, Psychosocial History. Clinical baseline characteristics will summarized by treatment group, sequence, and overall.

7.3 MEDICAL HISTORY

Medical history will be coded using MedDRA dictionary. A medical history listing will be presented.

8.0 PRIOR AND CONCOMITANT MEDICATIONS

All medications recorded on the CRFs will be coded using the WHO DRUG Dictionary. Prior and concomitant medications will be summarized by treatment arm in the safety population by anatomical therapeutic chemical (ATC) Class Level 4 and WHO Drug base substance preferred name.

Prior medications are defined as medications with stop dates occurring before the date of first administration of any study treatment component. Concomitant medications are defined as medications with start dates occurring on or after the date of first administration of any study treatment and no more than 30 days after the last administration of study treatment. Medications with start and stop dates that bracket the date of first administration of any study treatment component will be summarized as both prior and concomitant medications.

Medications that clearly stopped prior to date of first administration study treatment will be included in the prior medications table, and medications that clearly started on or after date of first administration of

study treatment will be included in the concomitant medications table. All other medications will be included in both the prior and concomitant medications tables.

Prior and Concomitant medication will be summarized for the safety population.

9.0 EFFICACY ANALYSES

The primary objective of the study is to assess PK profile. The efficacy evaluation is for exploratory purpose only.

9.1 NUMERICAL RATING SCALE (NRS) FOR PAIN

Numerical Rating Scale (NRS) for pain will be used to assess the worst daily and average daily pain. The NRS is an 11-point scale with anchors 0 (no pain) and 10 (worst pain imaginable). Subjects will record their Worst and Average Pain Score over the past 24 hours in an electronic diary on a daily basis.

The average of the worst daily pain (AWDP) at a visit will be defined as the average of the non-missing worst daily pain score since previous visit; the average of the average daily pain (AADP) at a visit will be defined as the average of the non-missing average daily pain score since previous visit.

Changes from baseline in AWDP will be defined as Baseline AWDP – Post-baseline AWDP. A positive change is indicative of improvement. Similarly, changes from baseline in AADP will be defined as Baseline AADP – Post-baseline AADP. A positive change is indicative of improvement.

Changes from baseline in AADP and in AADP will be summarized over post-baseline visits by treatment group based on the subjects who have provided baseline assessments.

AADP and in AADP will be summarized over post-baseline visits by treatment group.

9.2 URINE TOXICOLOGY

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

9.3 INTERIM ANALYSES

No interim analysis will be performed. Data for all subjects from Groups 1 and 2 who either completed or discontinued prematurely from this open label study will be cleaned and locked. The data will then be analyzed according to the SAP and the results may be presented in a preliminary report. Regardless of the analysis results, no additional subjects will be enrolled into Groups 1 and 2.

Data from subjects in Group 3 will continue to be cumulated after data from subjects in Groups 1 and 2 are locked. After all subjects in Group 3 are either completed or discontinued prematurely from this open label study, these data will be cleaned and locked. The final analyses from all data from Groups 1, 2, and 3 will be performed according to the SAP after Group 3 data are locked. The formal results of the study will be presented in the CSR.

9.4 ADJUSTMENTS FOR MULTIPLICITY

As the efficacy evaluation is for exploratory purpose only, no adjustment for multiple testings will be made.

9.5 POWER AND SAMPLE SIZE JUSTIFICATION

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

10.0 SUMMARIES OF PHARMACOKINETIC ANALYSIS

10.1 PHARMACOKINETIC PARAMETERS

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

Group 1:

- AUC_{ss} (area under the plasma concentration-time curve during a 7-day dosing interval at steady state) for each injection site, i.e., buttock (reference), abdomen, thigh and back of upper arm
- Average plasma concentration during a dosing interval at steady state ($C_{ss,av}$) for each injection site, i.e., buttock (reference), abdomen, thigh and back of upper arm
- Maximum observed plasma concentration during a dosing interval at steady state ($C_{ss,max}$) for each injection site, i.e., buttock (reference), abdomen, thigh and back of upper arm
- Time to $C_{ss,max}$ ($t_{ss,max}$) for each injection site, i.e., buttock (reference), abdomen, thigh and back of upper arm.
- Trough concentration $C_{ss,trough}$ measured prior to the next actual dose or next scheduled hypothetical dose at steady state.
- norBPN/BPN ratios for AUC_{ss} and $C_{ss,max}$ for each injection site, i.e., buttock (reference), abdomen, thigh and back of upper arm.

Group 2:

- AUC_{ss} (AUC during a 28-day dosing interval at steady state)
- $C_{ss,av}$
- $C_{ss,max}$
- $t_{ss,max}$
- $C_{ss,trough}$
- %Fluctuation
- norBPN/BPN ratios for AUC_{ss} and $C_{ss,max}$

Group 3:

- AUC_{ss} (AUC during a 24-hour (SL BPN) and 28-day (CAM2038 q4w) dosing interval at steady state)
- $C_{ss,av}$
- $C_{ss,max}$
- $t_{ss,max}$
- $C_{ss,trough}$
- %Fluctuation
- norBPN/BPN ratios for AUC_{ss} and $C_{ss,max}$

AUC_{ss} will be calculated using the linear trapezoidal method up to $C_{ss,\ max}$ and the logarithmic trapezoidal method for the remainder of the curve up to 168 hours after dose for CAM2038 q1w, 672 hours after dose for CAM2038 q4w and 24 hours after dose for SL BPN.

$C_{ss,av}$ will be calculated as AUC_{ss}/τ, where τ is the dosing interval (168 hours for CAM2038 q1w, 672 hours for CAM2038 q4w and 24 hours for SL BPN.

%Fluctuation will be calculated as $(C_{ss,max} - C_{ss,min})*100/C_{ss,av}$ for CAM2038 q4w and SL BPN, where $C_{ss,min}$ is the minimum plasma concentration during a dosage interval at steady state (4^{th} dose for CAM2038 q4w and 7^{th} dose for SL BPN).

The norBPN/BPN ratios for AUC_{ss} and $C_{ss,max}$ will be adjusted for differences in molecular weight between buprenorphine (molecular weight 467.64 g/mol) and norbuprenorphine (molecular weight 413.55 g/mol).

Plasma concentration levels of BPN and norBPN assessed prior to next actual or hypothetical dose (C_{trough}) will be assessed after Dose 1 to 7 in Group 1 and after Dose 1 to 4 for CAM2038 q4w in Groups 2 and 3.

Unless otherwise stated, PK data will be analyzed by a third party Clinical Research Organization (CRO), Worldwide Clinical Trials. PK results will be produced by the CRO in a separated report. The PK results will also be discussed in the Clinical Study Report (CSR) by reference to the PK report.

10.2 HANDLING OF VALUES BELOW THE LLOQ

Plasma concentration values below the limit of quantification (LLOQ) will be assigned a value of zero when they ~~preceed~~precede the first quantifiable sample. Values below LLOQ embedded between two quantifiable data points or occuring after the last quantifiable concentration will be treated as missing data.

10.3 ANALYSIS OF PHARMACOKINETICS

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

The PK parameters (Section 10.1) will be listed for the PK population and summarized for the PKEVAL population and PK population by group and injection site, if applicable. Summary statistics will include n, arithmetic mean, standard deviation, CV%, median, geometric mean, geometric CV%, minimum and maximum values.

For Group 1 (CAM2038 50 mg/mL q1w), the following considerations will apply in the PK analyses. The primary PK parameters will be AUC_{ss} and $C_{ss,max}$ after steady state injections of CAM2038 q1w at different injection sites. The injection site buttock will be the reference. The analyses will be based on log-transformed data. The natural log-transformed AUC_{ss} and $C_{ss,max}$ data will be analyzed using an ANOVA model, sequence, subject within sequence (1, 2, 3, 4 corresponding to A/B/D/C, B/C/A/D, C/D/B/A, D/A/C/B, where A=buttock, B=abdomen C=thigh, or D=back of upper arm), period, and

treatment sites (treatment sites: A=buttock, B=abdomen C=thigh, or D=back of upper arm). The estimated injection site effects, injection site differences versus the reference (B-A, C-A, and D-A), and the 90% confidence intervals of the estimated differences will be presented. The above estimates will be expressed on the raw scale (expressed after performing the anti-log).

No interim analysis will be performed. However, after all Groups 1 and 2 subjects either completed the study or discontinued from the study prematurely, the above analysis may be performed before subjects from Group 3 complete the study or discontinued from the study prematurely. Before the analysis is conducted all data records related to the PK parameters will be locked. Any changes to the records after the analysis will be discussed in the CSR. No additional subjects will be permitted to enter Groups 1 or 2 after the analysis is conducted.

For Groups 2 and 3 (CAM2038 q4w), the PK parameters will be summarized by descriptive statistics. The primary PK parameters will be AUC_{ss} and $C_{ss,max}$. Relative bioavailability of BPN will be assessed at steady state for 160 mg CAM2038 q4w vs 24 mg SL BPN by ANOVA with 90% confidence intervals tabulated for treatment differences (back transformed and expressed as a percentage).

11.0 SUMMARIES OF MEASURES OF SAFETY

Safety analyses will be performed for the safety population. Safety evaluations will be based on the incidence, intensity, and type of adverse events, as well as on clinically significant changes in the subject's physical examination, vital signs, and clinical laboratory results, Injection site examination and wound care. Safety variables will be tabulated and presented by study drug actually received.

Because there is no pre-specified safety outcome defined in terms of AEs, clinically relevant laboratory parameters, or vital signs, any formal comparisons between the treatment arms with respect to specific safety parameters will be post-hoc.

11.1 EXTENT OF EXPOSURE

Summary statistics (number and percentage) of weeks of exposure to study drug (i.e. from date of initial injection to the end of the study) will be tabulated by treatment group.,

11.2 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Columbia-Suicide Severity Rating Scale (C-SSRS) will be summarized for the Safety Population.

11.3 COWS AND SOWS

Clinical Opioid Withdrawal (COWS) Scale, and Subjective Opioid Withdrawal (SOWS) Scale will be summarized over time by treatment group.

11.4 ADVERSE EVENTS

Each AE and SAE term recorded on the case report forms (CRFs) by primary system organ class (SOC) and will be mapped to a preferred term using the MedDRA dictionary. The investigator will assess AE severity and relationship to the study treatment.

A treatment emergent adverse event (TEAE) is defined as any AE with an onset date on or after date of randomization (Groups 1 and 2) or first SL BPN dose (Group 3), or any ongoing event on the date of first dose that worsens in severity after date of randomization. Only TEAEs with an onset date prior to date of last dose + 30 days will be tabulated in summary tables. For the purpose calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix A.

TEAEs will be summarized by the number and percent of subjects in each primary SOC and preferred term. Subjects will be counted only once for each primary SOC and each preferred term. Summary tables of TEAEs by primary SOC, preferred term and intensity will be provided. If a subject has more than one TEAE coded to the same preferred term, the subject will be counted only once for that preferred term by using the event with the highest intensity. Similarly, if a subject has more than one TEAE within a primary SOC category, the subject will be counted only once in that SOC category by using the event with the highest intensity. TEAEs by primary SOC, preferred term and relationship to study drug will be provided as well. If a subject has more than one TEAE coded to the same preferred term, the subject will be counted only once for that preferred term by using the most related event. Similarly, if a subject has more than one TEAE within a primary SOC category, the subject will be counted only once in that primary SOC category by using the most related event. In addition, serious adverse events (SAE) by primary SOC and preferred term will be provided. Deaths and SAEs will be summarized similarly to AEs. All adverse event tables will also include the total number of events, counting multiple events per subject.

Injection related TEAEs, Other (non-injection related) TEAEs as well as all TEAEs will be presented by treatment group and overall. Summaries of these TEAE subsets will be presented for the following categories:

- Study drug related
- Intensity
- Relationship to injection
- Serious
- AEs which led to discontinuation
- SAEs which led to discontinuation
- TEAEs occurring in 5% or greater of any treatment group (by preferred term)

In the AE summary, preferred terms within each SOC will appear in alphabetical order.

Frequencies for deaths and hospitalizations will also be summarized by treatment group and overall.

Other safety analyses will be performed as appropriate.

11.5 LABORATORY ASSESSMENTS

Chemistry, Hematology, Urinalysis and Coagulation Profile will be assessed over time (see Section 10.5.3 of the clinical study protocol for a complete list of parameters to be assessed). Summary statistics for these parameters will be presented by visit for the actual value and change from baseline for each test in each laboratory category (Hematology, Chemistry, Urinalysis, and Coagulation Profile). Shift tables will be presented for shifts from baseline lab categories to end of study laboratory category. The three laboratory categories will be: -L (below lower bound of normal range), N (within normal range), and H (above higher bound of normal range).

If a lab value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

For the purpose of determining baseline, the last nonmissing observation on or prior to randomization will be used.

11.6 VITAL SIGNS

Vital signs will consist of blood pressure (systolic and diastolic blood pressure, mmHg), pulse rate (beats per minute), and respiratory rate (breaths/min). Vital sign values and change from baseline in the vital signs will be summarized for each treatment group.

11.7 PHYSICAL EXAM

Number and percent of subjects with abnormal physical exam findings at Screening will be summarized by body system for each treatment group and overall. Physical Exam data for each subject will also be presented in a listing.

11.8 12-LEAD ELECTROCARDIOGRAM (ECG)

12-Lead ECGs will be performed over time. 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.

Number and percent of subjects in each ECG finding category (normal, abnormal not clinically significant, and abnormal and clinically significant), will be summarized for each visit by each treatment group and overall. Summary statistics will be presented for the actual value and actual change for each ECG parameter.

The number and percent of subjects with QT, QTcB and QTcF intervals < 450 msec, 450 to <480, 480 to <500 and greater than/equal to 500 msec at each visit and overall (at any visit) will be summarized. Additionally, the number and percentage of subjects with changes in these parameters of <30 msec, 30 to <60 msec and greater than/equal to 60 msec will be summarized at each visit and overall at the visits where ECG is scheduled).

Buprenorphine plasma concentration vs QT, QTcB and/or QTcF interval relationships will be ~~graphicsllygraphically~~ explored.

11.9 INJECTION SITE EXAMINATION

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

AEs that believed to be associated with injection procedures will be summarized similarly to the summaries for other AEs (not associated with injections).

12.0 IDENTIFICATION AND SUMMARY OF PROTOCOL DEVIATIONS

Major protocol deviations from entry criteria and treatment compliance will be summarized as far as they can be extracted from numeric or coded study data.

13.0 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and cross check of the CRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator. Collected data will be entered into a computer database and subject to electronic and manual quality assurance procedures.

14.0 REFERENCES

None.

15.0 APPENDICES

15.1 APPENDIX A - IMPUTATION ALGORITHM FOR PARTIAL AND MISSING DATES

This section describes missing date imputation methods.

For Adverse Events

If onset date is completely missing, onset date is set to date of randomization.
If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of randomization, then set month and day to month and day of randomization
- If year < year of randomization, then set month and day to December 31.
- If year > year of randomization, then set month and day to January 1.

If month and year are present and day is missing:

- If year=year of randomization and
    - If month = month of randomization then set day to day of first dose
    - If month < month of first dose then set day to last day of month
    - If month > month of first dose then set day to first day of month
- If year < year of randomization then set day to last day of month
- If year > year of randomization then set day to first day of month

For all other cases, set onset date to date of randomization.

- Concomitant Medications/Medical History
- For start date
- If start date is completely missing, start date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to January 1.
- If year and month are present and day is missing, set day to 1st day of month.

For end date

- If end date is completely missing, end date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to December 31.
- If year and month are present and day is missing, set day to last day of the month.

Note: that if both start and end dates are missing then the medication will be classified as concomitant.