HS-13-478 **Phase II**

A Multiple Dose Opioid Challenge Study to Assess Blockade of Subjective Opioid Effects of CAM2038 q1w (Buprenorphine FluidCrystal® Subcutaneous Injection Depots) In Adults with Opioid Use Disorder

Statistical Analysis Plan (SAP)

Sponsor
BRAEBURN PHARMACEUTICALS
47 Hulfish Street, Suite 441
Princeton, NJ 08542
Tel: (609) 751-5375
Fax: (609) 921-2156

Version Final 1.01 June 13, 2016

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-13-478 data.

BRAEBURN PHARMACEUTICALS

Sonnie Kim, Pharm.D.		June 13, 2016
Print Name	Signature	Date
Print Name	Signature	Date
Print Name	Signature	Date

STATISTICIAN

Michael Chen, PhD	M chen	June 13, 2016
Print Name	Signature	Date

TABLE OF CONTENTS

1.0 DOCUMENT HISTORY

Version	Date	Changes made since previous version
0.01	10 November, 2015	First draft
Final 1.00	17 February, 2016	Final after incorporated all comments
Final 1.01	13 June, 2016	To clarify languages and remove certain summaries that cannot be performed because data were not collected.

2.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}168h}$	AUC beween time 0 and 168 hours after latest injection
BMI	Body Mass Index
BW	Body Weight
C_{av}	Average plasma concentration during a dosing interval
C_{max}	Maximum plasma concentration
COWS	Clinical Opioid Withdrawal Scale
CRF	Case Report Form (may include electronic data capture systems or paper forms)
CSR	Clinical Study Report
C_{trough}	Plasma concentration 7 days after the latest injection
CV%	Coefficient of variation percentage
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
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
PK	Pharmacokinetics
PT	MedDRA Preferred Term
SAE	Serious Adverse Event
SD	Standard Deviation
SL BPN	Sublingual Buprenorphine or Buprenorphine/Naloxone
SOC	MedDRA System Organ Class
SOWS	Subjective Opioid Withdrawal Scale
TEAE	Treatment-Emergent Adverse Event
Tau (τ)	Dosing interval
VAS	Visual Analog Scale

3.0 INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol HS-13-478, Amendment 1, dated Nov 10, 2015.

The purpose of this document is to provide details 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 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 and treatment codes are unblinded. Deviations from the approved plan will be noted in the clinical study report.

4.0 STUDY DESCRIPTION

4.1 STUDY OBJECTIVES

The primary objective of this study is:

- To evaluate the degree of opioid blocking effects of CAM2038 q1w following administration of intramuscular (IM) hydromorphone (6 mg and 18 mg) compared to administration of 0 mg IM hydromorphone (placebo) on subjective opioid effects in subjects with opioid use disorder, as measured by the Drug Liking visual analog scale (VAS).

The secondary objectives of this study are:

- To evaluate the degree of opioid blocking effects of CAM2038 q1w following administration of IM hydromorphone (6 mg and 18 mg) compared to administration of 0 mg IM hydromorphone (placebo) on subjective opioid effects in subjects with opioid use disorder, as determined by the secondary outcome measures.
- To explore the relationship between plasma buprenorphine (BPN) concentration and blockade of the subjective opioid effects of hydromorphone.
- To examine the safety and tolerability of CAM2038 q1w when co-administered with hydromorphone.

4.2 STUDY TREATMENTS

In this study, subjects will be randomized to one of two treatment groups in a 1:1 ratio to receive either CAM2038 1qw 24 mg or CAM2038 1qw 32 mg. Subjects within both CAM2038 1qw dosing groups will be randomized to one of 6 sequences of ordered hydomorphone challenge sessions: A/B/C, A/C/B, B/A/C, B/C/A, C/A/B, and C/B/A, where A, B, and C denote hydromorphone 0 mg, 6 mg, and 18 mg.

4.3 STUDY DESIGN

This is a multi-site, randomized, double-blind, repeat-dose Phase 2 study to evaluate the degree and duration of action of multiple doses of CAM2038 q1w in blocking the effects of a mu-opioid agonist (hydromorphone) in patients with moderate or severe opioid use disorder. The study will involve 4 phases: Screening, Qualification, Treatment, and Follow-up.

Within approximately 3 weeks of initiating outpatient screening, subjects will be admitted to a clinical research unit (CRU) for the Qualification Phase. Following check in to the CRU, subjects will be transitioned to an oral immediate-release (IR) opioid, morphine 30 mg, 4 times daily (QID) for a minimum of 3 days and a maximum of 7 days prior to the Qualification/Baseline Hydromorphone Challenge Session, which consists of 3 consecutive days of testing. During the Qualification/Baseline Hydromorphone Challenge Session, subjects will not receive their late evening or early subjects will not receive their late evening or early the following morning Morphine -IR; therefore, the last active dose of morphine therefore, the last active dose of morphine -IR will be administered a minimum of 12 hours before administration of the hydromorphone challenge doses.

Following the 3-day Qualification/Baseline Hydromorphone Challenge Session (Days -3 to -1), eligible subjects will be randomized in a 1:1 ratio to one of 2 groups to receive CAM2038 q1w at doses of 24 mg or 32 mg, stratified by gender. Subjects will receive two, once weekly injections of CAM2038 q1w, 7 days apart, (injections on Day 0 and Day 7) and will remain inpatient in the CRU for a total of approximately 3 weeks, during which time, 1 qualification/baseline Hydromorphone Challenge session will occur prior to CAM2038 administration then 4 Hydromorphone Challenge Sessions (3 consecutive days each with dose randomized) will be conducted on Days 1 to 3, Day 4 to 6, Days 8 to 10, and Days 11 to 13 after the first CAM2038 administration. Each Hydromorphone Challenge Session will consist of 3 doses of hydromorphone 10 mg/mL IM injections (doses of 0 mg [placebo], 6 mg and 18 mg) administered on 3 consecutive days in randomized order. Eligible subjects will be randomized in a 1:1:1:1:1:1 ratio to 1 of 6 treatment sequences according to two 3 × 3 William squares. The following treatment sequences will be used: ABC, ACB, BAC, BCA, CAB, and CBA, where A, B, and C are IM hydromorphone doses, 0 mg (placebo), 6 mg, and 18 mg, respectively. The doses, 0 mg (placebo), 6 mg or 18 mg, will be administered once daily during the hydromorphone challenge sessions. Safety assessments will be conducted immediately following each dose of hydromorphone administered in each Challenge Session and scheduled pharmacodynamic evaluations will occur over approximately 5 hours post dose. Plasma BPN and norbuprenorphine (NorBPN) levels will also be obtained approximately 60 minutes prior to hydromorphone dosing (predose) on each day of the Hydromorphone Challenge Sessions.

Subjects will be discharged on Day 14 and a follow-up phone interview will be conducted on Day 21.
The degree of hydromorphone dose tolerability will be determined based on the site-specific study Investigator's review of the subject's oximetry data, vital signs, behavior, and physical demeanor.

5.0 ANALYSIS POPULATIONS

Three populations are defined for the study. Intent-to-treat (ITT) population will consist of all subjects who receive study drug and provide some post baseline efficacy values. Completer population will include all subjects who complete the study. The primary efficacy analyses will be based on the Completer population. Safety population will include all subjects who receive study drug. All safety analyses will be based on the Safety population.

6.0 GENERAL CONVENTIONS

Unless otherwise stated, all analyses will be performed using SAS Version 9 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.

Summaries of plasma concentrations of BPN and norbuprenorphine will be presented for the Completer population by treatment group. The following descriptive statistics will be presented at each nominal time point: n, arithmetic mean, SD, coefficient of variation percentage (CV%), median, geometric mean, geometric CV%, minimum and maximum values. Individual plasma concentrations of BPN and norbuprenorphine will be listed for the Safety population by treatment group. Mean plasma concentration-time data will be displayed for the Completer population in linear and semi-logarithmic scales.

The pharmacokinetic parameter data will be listed and summarized by treatment for the Completer population. Summary statistics will include n, arithmetic mean, SD, CV%, median, geometric mean, geometric CV%, minimum and maximum values.

Data listings will present all data collected on CRFs by study drug, center, and subject number.

6.1 DEFINITION OF BASELINE

Unless otherwise stated, the last observed measurement prior to or 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 data base lock and treatment unblinding.

7.0 DESCRIPTION OF THE STUDY POPULATIONS

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

7.1 DISPOSITION

Subject disposition summaries will be presented by treatment arm (CAM2038 q1w 24 mg and CAM2038 q1w 32 mg) and sequence (ABC, ACB, BAC, BCA, CAB, and CBA) and will include the number of subjects randomized, the number and percentage of randomized subjects in each of the predefined 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.

Disposition summaries will be presented for each of the predefined populations separately.

7.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

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

Demographic data including age, race, ethnicity, and gender, as well as baseline clinical characteristics will be summarized. Age will be calculated based on the following conditional algorithm:

- Has the patient 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 summarized will include, if available, BW, BMI, type of primary opioid use (heroin, prescription opioid pain relievers, other), years of drug use, when first diagnosed with opioid dependence, proportion of patients previously treated for opioid dependence, duration of buprenorphine treatment, duration of 8 mg or less buprenorphine treatment, and dose of buprenorphine treatment prior to randomization. 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 Enhanced. 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 component and no more than 30 days after the last administration of any study treatment component. 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 of any study treatment component will be included in the prior medications table, and medications that clearly started on or after date of first administration of any study treatment component 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

Many of the efficacy variables are visual analog scale (VAS) based. Each VAS will be scored as an integer from 0 to 100. When appropriate, VASs will be administered as bipolar measures, meaning

that the neutral point equals 50 (i.e., Drug Liking and Alertness/Drowsiness VAS). The neutral point will also be labeled with an anchor, such as "neither like nor dislike." Unipolar VASs (i.e., High, Good, Bad, and Any Effects VAS) are presented with anchors such as "not at all" (score = 0) to "extremely" (score = 100), where the neutral point equals 0. The use of unipolar scale is determined by the nature of the subjective effect being measured. If precipitated withdrawal occurs after administration of CAM2038, patients will have a unipolar VAS assessment of opioid withdrawal severity.

The table lists the subjective effects VAS question text and response anchors.

Interpretation	Include Pre-dose	Description	Question Text	Response Anchors
Balance	No	Drug Liking	At this moment, my liking for this drug is	0: Strong disliking 50: Neither like nor dislike 100: Strong liking
Other effects	No	Any Drug Effects	At this moment, I feel any drug effects	0: Not at all 100: Extremely
Positive	Yes	High	At this moment, I feel high	
Positive	No	Good Drug Effects	At this moment, I feel good drug effects	
Negative	No	Bad Drug Effects	At this moment, I feel bad drug effects	
Other Effects	Yes	Desire to use opioids	At this moment, I desire opioids	0: Definitely not 100: Definitely so
Other Effects	Yes	Alertness/Drowsiness	At this moment, my mental state is	0: Very drowsy 50: Neither drowsy nor alert 100: Very alert

9.1 PRIMARY EFFICACY OUTCOME – E_{MAX} DRUG LIKING VAS

The primary efficacy variable will be E_{max} of Drug Liking VAS.

9.1.1 DERIVATION OF E_{MAX} DRUG LIKING VAS

Four hydromorphone challenge sessions (3 consecutive days each with dose randomized) will be conducted on Days 1 to 3, Day 4 to 6, Days 8 to 10, and Days 11 to 13 after the first CAM2038 administration. Each Hydromorphone Challenge Session will consist of 3 doses of hydromorphone 10 mg/mL IM injections (doses of 0 mg [placebo], 6 mg and 18 mg) administered on 3 consecutive days in randomized order. The drug liking VAS will be rated by the subjects at predose and at 5, 10, 15, 30, 45,

60, 75, 90, 120, 150, 180, 210, 240, 270 and 300 minutes post-dose. The primary efficacy variable E_{max} of drug liking VAS will be the maximum of the above post-dosing drug liking VAS scores.

9.1.2 PRIMARY ANALYSIS

The primary analysis of the primary efficacy variable, E_{max} of drug liking VAS, will be performed using the completer population. This variable will be analyzed via a mixed model including sequence (ABC, ACB, BAC, BCA, CAB, CBA), dosing (challenge dosing A=0 mg, B=6 mg, or C=18 mg), period (1, 2, or 3 to indicate first, second, or third day of each challenge session), session (challenge session 1, 2, 3, or 4), and dosing-by-session interaction as fixed effects, and subject as random effects. The maximum likelihood estimation will be used to estimate the parameters. Specifically, the following pseudo SAS codes will be used for the analysis:

```
proc mixed data=Efficacy_Data method=ml;
class SubjectID ChallengeDose Sequence Period Session;
model Emax=Sequence ChallengeDose Period Session  ChallengeDose*Session;
random SubjectID / Subject= SubjectID;
LSMEANS ChallengeDose*Session/diff cl alpha=0.05;
Run;
```

The estimated treatment effects, differences in treatment effects (test dose – the reference dose of 0 mg), 95% confidence intervals of the differences will be presented. Blockade effects will be claimed if the upper bound of the treatment difference is <=11.

The same methodology will be used to analyze CAM2038 q1w 24 mg and 32 mg separately.

9.1.3 MISSING VALUE IMPUTATION

Missing scores will not be imputed, unless otherwise stated.

9.1.4 SUPPORTIVE ANALYSES

As a supportive analysis, the primary efficacy variable will be analyzed based on ITT subjects using the same methodology.

9.2 SECONDARY EFFICACY OUTCOMES

In addition to the primary endpoint of change from baseline in Emax of Drug Liking VAS, the following secondary endpoints will be calculated:

- High VAS E_{max}
- Good Effects VAS E_{max}
- Bad Effects VAS E_{max}
- Sedated VAS E_{max}
- Any Effects VAS E_{max}
- Desire to use VAS E_{max}

All these variables will be analyzed via the same methodology used to analyze the primary efficacy variable.

The follow secondary efficacy variables will be summarized by CAM2038 treatment group on the scheduled days that they are measured:

- Clinician-Rated Opioid Withdrawal Scale (COWS);
- Subjective Opioid Withdrawal Scale (SOWS);

9.3 INTERIM ANALYSES

No interim analyses will be performed.

9.4 ADJUSTMENTS FOR MULTIPLICITY

The study involves multiple comparisons. Procedures will be used to control for the overall Type I error rate at the significance level of 0.05. The following ordered comparisons of blocking effect will be tested at the 0.05 level of significance:

1. Hydromorphone 6 mg vs Hydromorphone 0 mg for CAM2038 q1w 32 mg;
2. Hydromorphone 6 mg vs Hydromorphone 0 mg for CAM2038 q1w 24 mg;
3. Hydromorphone 18 mg vs Hydromorphone 0 mg for CAM2038 q1w 32 mg;
4. Hydromorphone 18 mg vs Hydromorphone 0 mg for CAM2038 q1w 24 mg;

Blockade effect cannot be claimed unless all preceding blocking effects, if any, are established.

9.5 PK/PD RELATIONSHIPS

The relationship between plasma BPN concentration and blockade of the subjective opioid effects of hydromorphone will be explored as appropriate.

9.6 POWER AND SAMPLE SIZE JUSTIFICATION

A sample size of 24 subjects will provide 90% power for the CAM2038 32 mg to demonstrate no significant difference in the mean E_{max} score of the Drug Liking VAS comparing to 0 mg hydromorphone at a two-sided 0.05 significance level with a non-significant difference cutoff at ≤ 11 points. In the sample size calculation it was assumed that the true difference was less than or equal to 1.5 and the standard deviation was 9.8.

Additional 24 subjects will be enrolled to CAM2038 24 mg group. This sample size will provide approximately 83% power for the CAM2038 24 mg to demonstrate no significant difference in the mean Emax score of the Drug Liking VAS comparing to 0 mg hydromorphone at a two-sided 0.05 significance level with a non-significant difference cutoff at ≤ 11 points. In the sample size calculation it was assumed that the true difference was less than or equal to 2.5 and the standard deviation was 9.8.

The plan will be to enroll a sufficient number of subjects to ensure that approximately 48 subjects complete the study (24 subjects per treatment group) by over-enrollment as needed.

10.0 SUMMARIES OF PHARMACOKINETIC ANALYSIS

Pharmacokinetic endpoints include:

The following pharmacokinetic parameters will be estimated for BPN and norbuprenorphine:

- C_{max} (maximum plasma concentration)
- C_{trough} (plasma concentration level 7 days after the latest injection)
- C_{av} (average plasma concentration during a dosing interval)

C_{av} will be calculated as ($AUC_{0\text{-}168h}/\tau$), where $AUC_{0\text{-}168h}$ is the area under the plasma concentration-time curve (AUC) between time 0 and 168 hours after latest injection and τ the dosing interval (168 hours). $AUC_{0\text{-}168h}$ will be calculated using the linear trapezoidal method up to C_{max} and the logarithmic trapezoidal method for the remainder of the curve up to 168 hours after latest injection.

The PK parameters will be calculated using Phoenix WinNonlin Version 6.3 (or higher). The actual sampling times relative to dosing rather than the nominal times will be used in the calculations.
BPN and norbuprenorphine plasma concentrations over time as well as all above PK parameters will be summarized by dose (32 mg and 24 mg) separately.

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 (frequency of number of injections received) will be tabulated by treatment group.

11.2 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, 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 B.

AEs will be summarized by the number and percent of subjects in each primary SOC and preferred term. Patients will be counted only once for each primary SOC and each preferred term. Summary tables of AEs by primary SOC, preferred term and intensity will be provided. If a subject has more than one AE 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 AE within a primary SOC category, the subject will be counted only once in that SOC category by using the event with the highest intensity. AEs by primary SOC, preferred term and relationship to study drug will be provided as well. If a subject has more than one AE 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 AE 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 patient.

AEs will be presented by treatment group (CAM2038 q1w of 24 mg or 32 mg and by hydromorphone treatment groups i.e., 0 mg 6 mg or 18 mg – during qualification period- and CAMP2038 relevant dose/hydromorphone relevant dose – on the days of hydromorphone challenges) and overall. An AE will

be attributed to a hydromorphone dose, if the AE occurred within one hour of the dosing (if the time of the AE is missing, the AE will be attributed to CAM2038). Summaries of these AE subsets will be presented for the following categories:

- Study drug related
- Intensity
- Relationship to injection (Suspected or Not Suspected)
- Suspected to be study drug related by intensity
- Serious
- AEs which led to discontinuation
- SAEs which led to discontinuation
- AEs 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

11.3 LABORATORY ASSESSMENTS

Chemistry, Hematology, Urinalysis and Coagulation Profile will be assessed at baseline and Week 24 (see Section 10.4.3 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.

If a subject has repeated laboratory values for a given time point, the value from the first evaluation at that time point will be used for summarization purposes. For the purpose of determining baseline, the last nonmissing observation on or prior to randomization will be used. The Week 24 values will be the last post-baseline value on or prior to Week 24.

11.4 COLUMBIA SUICIDE SEVERITY RATING SCALE (CSSR-S)

Summary of Columbia Suicide Severity Ratings will be provided by CAM2038 group and by the scheduled day the measurements are obtained.

11.5 MONTGOMERY-ASBERG DEPRESSION RATING SCALE (MADRS)

Summary of Montgomery-Asberg Depression Rating will be provided by CAM2038 group and by the scheduled day the measurements are obtained.

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), and oxygen saturation (%) collected while sitting, following a rest period of at least 3 minutes. 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 CAM2038 group and 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 at screening and at Week 24 after the subject has been resting in a recumbent/supine position for at least 3 minutes. The ECG variables will include ventricular heart rate and the PR, QRS, QT, QTcB and QTcF intervals. The ECGs will be signed and dated by a medically-qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant.

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 change for each ECG parameter.

The results will be summarized by CAM2038 group.

11.9 INJECTION SITE EXAMINATION

The injection site will be visually inspected for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing and any other abnormalities.

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

15.0 APPENDICES

15.1 APPENDIX A - LIST OF TABLES, LISTINGS, AND FIGURES

List of Tables

TABLE 14.2.4.2b	Analysis Results for Primary Efficacy Variable Emax of Bad Effects VAS for CAM2038 24 mg (ITT Population)
TABLE 14.2.5.1a	Analysis Results for Primary Efficacy Variable Emax of Sedated Effects VAS for CAM2038 32 mg (Completer Population)
TABLE 14.2.5.1b	Analysis Results for Primary Efficacy Variable Emax of Sedated Effects VAS for CAM2038 24 mg (Completer Population)
TABLE 14.2.5.2a	Analysis Results for Primary Efficacy Variable Emax of Sedated Effects VAS for CAM2038 32 mg (ITT Population)
TABLE 14.2.5.2b	Analysis Results for Primary Efficacy Variable Emax of Sedated Effects VAS for CAM2038 24 mg (ITT Population)
TABLE 14.2.6.1a	Analysis Results for Primary Efficacy Variable Emax of Any Effects VAS for CAM2038 32 mg (Completer Population)
TABLE 14.2.6.1b	Analysis Results for Primary Efficacy Variable Emax of Any Effects VAS for CAM2038 24 mg (Completer Population)
TABLE 14.2.6.2a	Analysis Results for Primary Efficacy Variable Emax of Any Effects VAS for CAM2038 32 mg (ITT Population)
TABLE 14.2.6.2b	Analysis Results for Primary Efficacy Variable Emax of Any Effects VAS for CAM2038 24 mg (ITT Population)
TABLE 14.2.7.1a	Analysis Results for Primary Efficacy Variable Emax of Desire to Use VAS for CAM2038 32 mg (Completer Population)
TABLE 14.2.7.1b	Analysis Results for Primary Efficacy Variable Emax of Desire to Use VAS for CAM2038 24 mg (Completer Population)
TABLE 14.2.7.2a	Analysis Results for Primary Efficacy Variable Emax of Desire to Use VAS for CAM2038 32 mg (ITT Population)
TABLE 14.2.7.2b	Analysis Results for Primary Efficacy Variable Emax of Desire to Use VAS for CAM2038 24 mg (ITT Population)
TABLE 14.2.10.1a	Summary of Change from Baseline in Clinical Opiate Withdrawal Scale (COWS) for CAM2038 32 mg (Completer Population)
TABLE 14.2.10.1b	Summary of Change from Baseline in Clinical Opiate Withdrawal Scale (COWS) for CAM2038 24 mg (Completer Population)
TABLE 14.2.10.2a	Summary of Change from Baseline in Clinical Opiate Withdrawal Scale (COWS) for CAM2038 32 mg (ITT Population)
TABLE 14.2.10.2b	Summary of Change from Baseline in Clinical Opiate Withdrawal Scale (COWS) for CAM2038 24 mg (ITT Population)
TABLE 14.2.11.1a	Summary of Change from Baseline in Objective Opioid Withdrawal Scale (OOWS) for CAM2038 32 mg (Completer Population)
TABLE 14.2.11.1b	Summary of Change from Baseline in Objective Opioid Withdrawal Scale (OOWS) for CAM2038 24 mg (Completer Population)
TABLE 14.2.11.2a	Summary of Change from Baseline in Objective Opioid Withdrawal Scale (OOWS) for CAM2038 32 mg (ITT Population)
TABLE 14.2.11.2b	Summary of Change from Baseline in Objective Opioid Withdrawal Scale (OOWS) for CAM2038 24 mg (ITT Population)
TABLE 14.2.12.1a	Summary of BPN and norpuprenorphine Concentrations for CAM2038 32 mg (Completer Population)
TABLE 14.2.12.1b	Summary of BPN and norpuprenorphine Concentrations for CAM2038 24 mg (Completer Population)
TABLE 14.2.12.2a	Summary of PK Parameters for CAM2038 32 mg (Completer Population)

TABLE 14.2.12.2b	Summary of PK Parameters for CAM2038 24 mg (Completer Population)
TABLE 14.3.1	Summary of CAM2038 Exposure (Safety Population)
TABLE 14.3.2	Summary of All Adverse Events by System Organ Class, Preferred Term, and Relationship to Hydromorphone During Qualification Period (Safety Population)
TABLE 14.3.3.1	Summary of All Adverse Events by System Organ Class, Preferred Term, and Intensity for CAM2038 Doses and Overall (Safety Population)
TABLE 14.3.3.1.2	Summary of All Adverse Events by System Organ Class, Preferred Term, and Intensity for Hydromorphone and CAM2038 24 mg (Safety Population)
TABLE 14.3.3.1.3	Summary of All Adverse Events by System Organ Class, Preferred Term, and Intensity for Hydromorphone and CAM2038 32 mg (Safety Population)
TABLE 14.3.4.1.1	Summary of All Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug for CAM2038 Doses and Overall (Safety Population)
TABLE 14.3.4.1.2	Summary of All Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug for Hydromorphone and CAM2038 24 mg (Safety Population)
TABLE 14.3.4.1.3	Summary of All Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug for Hydromorphone and CAM2038 32 mg (Safety Population)
TABLE 14.3.5	Summary of All Suspected to Be Drug Related Adverse Events by System Organ Class and Preferred Term for CAM2038 Doses and Overall (Safety Population)
TABLE 14.3.6	Summary of Most Common (at least 5%) Adverse Events by System Organ Class and Preferred Term for CAM2038 Doses and Overall (Safety Population)
TABLE 14.3.7	Summary of All Serious Adverse Events by System Organ Class and Preferred Term for CAM2038 Doses and Overall (Safety Population)
TABLE 14.3.8	Summary of All Adverse Events That Lead to Study Discontinuation by System Organ Class and Preferred Term for CAM2038 Doses and Overall (Safety Population)
TABLE 14.3.9	Summary of All Serious Adverse Events That Lead to Study Discontinuation by System Organ Class and Preferred Term for CAM2038 Doses and Overall (Safety Population)
TABLE 14.3.10	Summary of All Deaths and Hospitalizations for CAM2038 Doses and Overall (Safety Population)
TABLE 14.4	Summary of Columbia Suicide Severity Ratings by CAM2038 Doses and Time

	(Safety Population)
TABLE 14.5	Summary of Montgomery-Asberg Depression Rating by CAM2038 Doses and Time (Safety Population)
TABLE 14.6.1.1	Summary of Clinical Hematology Data by CAM2038 Doses and Time (Safety Population)
TABLE 14.6.1.2	Shift from Baseline in Laboratory Tests: Hematology by CAM2038 Doses (Safety Population)
TABLE 14.6.2.1	Summary of Clinical Chemistry Data by CAM2038 Doses (Safety Population)
TABLE 14.6.2.2	Shift from Baseline in Laboratory Tests: Chemistry by CAM2038 Doses (Safety Population)
TABLE 14.6.3.1	Summary of Clinical Coagulation Profile Data by CAM2038 Doses (Safety Population)
TABLE 14.6.3.2	Shift from Baseline in Laboratory Tests: Coagulation Profile by CAM2038 Doses (Safety Population)
TABLE 14.6.4	Number (%) of Patients with Abnormal Physical Examination Findings by CAM2038 Doses (Safety Population)
TABLE 14.6.5	Summary of Vital Signs by CAM2038 Doses at Each Visit (Safety Population)
TABLE 14.6.6	Summary of 12-Lead ECG Conclusions by CAM2038 Doses (Safety Population)
TABLE 14.6.7	Summary of 12-Lead ECG Individual Parameters by CAM2038 Doses (Safety Population)

List of Listings

Number	**Title**
LISTING 16.2.1	Patient Meets Inclusion Criteria
LISTING 16.2.2	Eligibility for Randomization
LISTING 16.2.3	Patient Randomization
LISTING 16.2.4.1	Demographics
LISTING 16.2.4.2	Medical History
LISTING 16.2.4.3	Psychiatric History
LISTING 16.2.5.1	CAM2038 Injection
LISTING 16.2.5.2	Injection Site Examination/ Treatment Compliance
LISTING16.2.6.1	COWS, C-SSRS, MADRS, and OOWS Scales
LISTING16.2.6.2	VAS Scales
LISTING16.2.7.1	Adverse Events
LISTING16.2.7.2	Serious Adverse Events
LISTING16.2.7.3	Adverse Events That Lead to Study Drug Discontinuation
LISTING16.2.7.4	Adverse Events That Have Death as the Outcome
LISTING16.2.7.1	Death Report
LISTING16.2.7.1	Prior and Concomitant Medications/Procedures
LISTING16.2.8.1	Lab Test Samples
LISTING16.2.8.2	Clinical Hematology
LISTING16.2.8.3	Clinical Chemistry
LISTING16.2.8.4	Clinical Coagulation Profile

LISTING16.2.8.5	Urine Collection/Toxicology
LISTING16.2.8.6	Pregnancy Test
LISTING16.2.8.7	Physical Examination
LISTING16.2.8.8	Vital Signs
LISTING16.2.8.9	12-Lead ECG
LISTING16.2.8.10	Patient Disposition
LISTING16.2.8.11	Protocol Deviations
LISTING16.2.8.12	Plasma concentrations
LISTING16.2.8.13	PK Data

List of Figures

15.2 APPENDIX B - 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.

For Concomitant Medications

Start Date: If start date is completely missing and end date is not prior to randomization, then the medication will be classified as concomitant. If start date is completely missing and end date is prior to randomization, then the medication will be classified as prior.

If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to January 1. If year and month are present and day is missing then set day to first day of month.

End Date: If end date is completely missing then the medication will be classified as concomitant.
If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to December 31. If year and month are present and day is missing then 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.