HS-11-421 **Phase III**

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

Statistical Analysis Plan (SAP)

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

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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-11-421 data.

BRAEBURN PHARMACEUTICALS

Sonnie Kim, Pharm.D.		Nov 4, 2016
Print Name	Signature	Date

STATISTICIAN

Michael Chen		Nov 4, 2016
Print Name	Signature	Date

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1.0 DOCUMENT HISTORY

Version	Date	Changes made since previous version
0.01	27 Jan, 2016	First draft
1.00	20 October, 2016	Final after receiving FDA's comments dated on 01 Sept 2016
1.01	4 November, 2016	Due to differences in analyses requested by the FDA and EMA and to avoid confusion, as stated in the protocol, two SAPs will be prepared, one for FDA submission and one for the EMA submission. Additionally, this version incorporates FDA's comments dated on 04 Nov 2016. Version 1.00 was revised to reflect statistical analysis plan for the US FDA submission. The EMA specific variables are removed from Version 1.00. No analysis methodologies are changed from Version 1.00.

2.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BMI	Body Mass Index
BPN	Buprenorphine or Buprenorphine/Naloxone
CDF	Cumulative Distribution Function
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form (may include electronic data capture systems or paper forms)
FID	First Injection Date
ICH	International Council for Harmonisation
ITT	Intent-to-Treat
LD	Last Date in the study
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intent-to-Treat
PT	MedDRA Preferred Term
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SL	Sublingual
SOC	MedDRA System Organ Class
SOWS	Subjective Opiate Withdrawal Scale
TEAE	Treatment-Emergent Adverse Event
VAS	Visual Analog Scale

3.0 INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol HS-11-421 Amendment 5, dated on November 3, 2016.

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.

The primary endpoint response rate will be used to address the regulatory requirements as outlined by the US Food and Drug Administration (FDA). Specifically, the FDA requested an alternative primary efficacy responder definition on September 1, 2016, which have been incorporated in this final SAP. Additionally, the FDA provided comments on November 4, 2016 and recommended a NI margin of 10% points to be reasonable NI margin for the study. This change is reflected in this final SAP.

The European Medical Agency (EMA) has requested percent negative urine samples as the primary endpoint and retention rate as key secondary endpoint. These requests are addressed in a separate SAP for EMA submission. The variables related to the percentage of urine sample negative (EMA specific variables) are removed from Version 1.01 that is for FDA submission.

4.0 STUDY DESCRIPTION

4.1 STUDY OBJECTIVES

The primary objective of the study 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 of the study are:

- To evaluate the efficacy of CAM2038 compared to SL BPN in adult outpatients with opioid use disorder, as measured by cumulative distribution function of percent negative urines (supported by self-reported opioid use results) between Weeks 5 and 24.
- 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.

4.2 STUDY TREATMENTS

In this double-blind and double-dummy study, subjects will be randomized to one of two treatment groups in a 1:1 ratio:

Treatment Group 1: SL BPN tablets + placebo subcutaneous (SC) injections

Treatment Group 2: CAM2038 SC injections + SL placebo tablets

4.3 STUDY DESIGN

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 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 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 6 visits during the 12 weeks of Phase 2; 3 scheduled monthly visits and 3 random urine toxicology visits. At each random urine toxicology visit, subject's self-reported illicit use will be collected. After Phase 2, subjects will be followed-up for 4 weeks.

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.

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.

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 study related medications and counseling will also be covered.
Investigators will be instructed to use manual-guided psychosocial counseling for trial subjects throughout the trial period.

4.4 RANDOMIZATION AND BLINDING

Randomization will be used to avoid bias in the assignment of subjects to treatment sequences, 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 study.

Subjects who have met the eligibility criteria (outlined in Section 8 of the clinical trial protocol) will be randomized to one of the 2 treatment groups in a 1:1 ratio (Treatment Group 1: SL BPN tablets + placebo SC injections or Treatment Group 2: CAM2038 SC injections + SL placebo tablets). Due to the size of the study, 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 study will use central randomization, as described in Section 10.2 of the protocol.

In order to reduce the potential for bias in the study, 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 study will not be aware of the treatment group assignments. Sublingual BPN tablets used during the study will have a nearly-matching placebo.

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 study.

5.0 ANALYSIS POPULATIONS

5.1 SAFETY POPULATION

The safety population will include all subjects who have any dose of SL BPN/placebo or SC CAM2038/placebo injection. 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.

5.2 INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) population will consist of all randomized subjects. The primary efficacy analyses will be based on the ITT population.

5.3 MODIFIED INTENT-TO-TREAT POPULATION

The modified Intent-to-Treat (mITT) population will consist of all randomized subjects who received any SL BPN/placebo or SC CAM2038/placebo injection. It is expected that the ITT and mITT population will be nearly identical. The results for the mITT population will not be presented if the two populations are differed by less than five (5) subjects as in this case the conclusions based on the two populations should be identical.

5.4 PER PROTOCOL POPULATION

The Per Protocol population will include all subjects in the ITT population with no major protocol violations. Major protocol violation criteria will be established prior to the data base lock. Protocol deviations will be presented in the clinical study report. Efficacy analyses may also be performed based on the per protocol population.

6.0 GENERAL CONVENTIONS

Unless otherwise stated, all analyses will be performed using SAS Version 9.2 or higher 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 normal approximation without continuity correction.

Data listings will present all data collected on case report forms (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 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 unblinding.

7.0 DESCRIPTION OF THE STUDY POPULATIONS

All tables, figures, and listings must include a population descriptor (e.g., ITT population, mITT population, safety population, or per protocol population) in the title.

7.1 DISPOSITION

Subject disposition summaries will be presented by treatment arm and will include the number of subjects randomized, the number and percentage of randomized subjects in the safety, ITT, mITT and per protocol (if applicable) 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 safety, ITT, mITT, and per protocol populations (if applicable) separately.

7.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

A summary of demographics and baseline characteristics will be presented by treatment arm and overall for the ITT 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 (including height, weight and body mass index [BMI]), psychosocial history, and substance abuse treatment history will be summarized by treatment group and overall.

7.3 MEDICAL HISTORY

Medical history will be coded using MedDRA dictionary Version 18. Medical history will be presented.

8.0 PRIOR AND CONCOMITANT MEDICATIONS

All medications recorded on the CRFs will be coded using the WHO DRUG Dictionary Enhanced March 2015. Prior and concomitant medications will be summarized by treatment arm in the safety population by anatomical therapeutic chemical 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

9.1 PRIMARY EFFICACY VARIABLE – RESPONDER RATE

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 (end of Month 1 of Phase 2), 21 (end of Month 2 of Phase 2) and 25 (end of Month 3 of Phase 2) 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 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.

Please note that EMA requested percent negative urine samples as the primary endpoint for their evaluation. Percent negative urine samples is the first secondary endpoint (see Section 9.2.1) for this study.

9.1.1 DERIVATION OF RESPONSE RATE

For the purpose of deriving the RR, the following rules will be used:

Time Windows for Illicit Opioid Use Assessment

For easy discussion, unless otherwise stated a window denoted as Week (x+, y) for efficacy assessment is a window that covers a period between Week x +1 day to Week y day (exclusive of Week x day but inclusive of Week y day). A window denoted as Weeks x-y for efficacy assessment is a window that covers a period between Week x day to Week y day (inclusive of Week x day and Week y day).

Subjects will receive 12 weekly injections from Week 1 (Day 1 Week 1) through Week 12. Subjects will then receive three monthly injections at Week 13, Week 17, and Week 21. Since the last weekly dosing will occur at Week 12, the efficacy assessments collected at Week 13 reflected effects of weekly dosing in Phase 1. The Phase 1 window is Week (1+, 13). Since the last monthly dosing will occur at Week 21 Phase 2 efficacy window will be Week (13+, 25).

Due to visit date deviation, the actual days in Phase 1 and Phase 2 may not be exactly equal to 91 days (13 weeks) and 84 days (12 weeks), respectively. Similarly, for analysis purpose, weekly and monthly windows will be based on the visit windows, instead of exact 7-day and exact 30-day windows.

Evidence of Illicit Opioid Use within a Window

Subject response for Phase 1 will be based on the 12 scheduled weekly post-baseline urine samples collected from Weeks 2-13. Subject response for Phase 2 will be based on the 3 scheduled monthly urine samples collected at Weeks 17, 21, and Week 25 and the 3 random samples. Evidence of illicit opioid use within a window is defined as a positive opioid urine toxicology result or self-reported illicit opioid use within that window, including the results from random urine toxicology samples (in Phase 2) obtained within that window. Therefore, there is evidence of illicit opioid use, if self-reported illicit opioid use is present, regardless of the opioid urine toxicology result is positive or negative.

If urine toxicology samples are missing, for example, due to missing scheduled visit, early discontinuation of the study, or subject's refusal to provide the samples (scheduled or random samples), the results will be imputed as positive according to the Missing Value Imputation rules discussed in Section 9.1.3 of the SAP.

9.1.2 PRIMARY ANALYSIS

The primary analysis of RR will be performed based on the ITT population.

An analysis of non-inferiority in the primary efficacy variable between the two treatments arms will be performed using a margin of 10% 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 –0.10. 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.

9.1.3 MISSING VALUE IMPUTATION

Unless otherwise stated the following procedures will be used to handle missing values for urine toxicology.

All missing urine toxicology samples (scheduled or random samples), regardless of reasons, will be imputed as positive.

Unless otherwise stated all other missing values will not be imputed.

9.2 SECONDARY EFFICACY VARIABLES

Secondary efficacy variables will include:

- Cumulative Distribution Function (CDF) of percent urine samples negative for illicit opioids (supported by self-reported illicit opioids use results) based on Weeks 5-25;

- Time to sustained abstinence of opioid use (supported by self-reported illicit opioids use results);
- Percent of subjects remaining in the study (retention rate);

9.2.1 CUMULATIVE DISTRIBUTION FUNCTION (CDF) OF PERCENT SAMPLES THAT ARE NEGATIVE FOR ILLICIT OPIOIDS (WEEKS 5-25)

Percent negative samples from 15 samples (9 weekly assessments obtained from Weeks 5 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 5-25 will be tested at the 5% significance level using Wilcoxon Rank-Sum test. The empirical CDF plot will be presented.

9.2.2 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 two months), the time will be defined 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).

The same definition for evidence of illicit opioid use (see Section 9.1.1) and the same rules for missing value imputation (see Section 9.1.3) will be used in the calculation.

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.

9.2.3 PERCENT OF SUBJECTS REMAINING IN THE STUDY (RETENTION RATE)

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. In addition, the retention rate will be analyzed using a chi square test.

An analysis of non-inferiority in this variable between the two treatments arms will be performed using a margin of 15% point. Non-inferiority will be concluded if the two-sided 95% confidence interval for the difference in retention rate (Active- Control) is above 15%.

9.3 EXPLORATORY EFFICACY VARIABLES

Exploratory efficacy variables will include:

- Primary endpoint RR for Phase 1;
- Primary endpoint RR for Phase 2;
- Percentage negative urine samples in Phase 1;
- Percentage 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 after two months of treatment by time point (from Week 9 to Week 25);
- Percent of subjects with no self-reported illicit opioid use by time point;
- Percent of subjects meeting criteria of stability at Week 13;
- Measures of craving: Desire to Use visual analog scale (VAS) and Need to Use VAS;
- Measures of withdrawal: Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS);
- 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

9.3.1 RESPONSE RATE (RR) FOR PHASE 1

The treatment differences in RR based on the primary responder definition and based on responder for Phase 1 will be analyzed using chi square test. The percentages for each treatment and between treatment percentage differences will be estimated. The 95% confidence intervals of the estimates will be presented using normal approximation.

9.3.2 RESPONSE RATE (RR) FOR PHASE 2

The treatment differences in RR based on the primary responder definition for Phase 2 will be analyzed using chi square test. The percentages for each treatment and between treatment percentage differences will be estimated. The 95% confidence intervals of the estimates will be presented using normal approximation.

9.3.3 PERCENTAGE NEGATIVE URINE SAMPLES IN PHASE 1 (WEEKS 3-13)

The percentages for each treatment and between treatment percentage differences will be estimated for Phase 1. The 95% confidence intervals of the estimated treatment differences, based on a normal approximation, will be presented. In addition, the percentage negative urine samples will be analyzed using a chi square test.

9.3.4 PERCENTAGE NEGATIVE URINE SAMPLES IN PHASE 2 (WEEKS 14-25)

The percentages for each treatment and between treatment percentage differences will be estimated for Phase 2. The 95% confidence intervals of the estimated treatment differences, based on a normal approximation, will be presented. In addition, the percentage negative urine samples will be analyzed using a chi square test.

9.3.5 PERCENT OF SUBJECTS WITH NO ILLICIT OPIOID USE BY TIME POINT

For the purpose of deriving percent of subjects with no illicit opioid use by month, the same definitions for monthly window and evidence of illicit opioid use (see Section 9.1.1) and the same rules for missing value imputation (see Section 9.1.3) will be used in the calculation.

The treatment differences in these by month variables will be analyzes using chi square tests. The percentages for each treatment and between treatment percentage differences will be estimated. The 95% confidence intervals of the estimates will be presented using normal approximation.

The overall treatment difference will be tested via Wei and Lachin procedure. In this analysis, missing values were not imputed.

9.3.6 CUMULATIVE PERCENTAGE OF SUBJECTS WITH EVIDENCE OF NO ILLICIT OPIOID USE BY TIME POINT AFTER 2 MONTHS OF TREATMENT

The cumulative percentage of evidence of no illicit opioid use will be calculated for all post baseline scheduled visits after two months of treatment (from Week 9 to Week 25). The same definition for evidence of illicit opioid use (see Section 9.1.1) and the same rules for missing value imputation (see Section 9.1.3) will be used in the calculation. As the percentage is derived on a cumulative basis, subject will be included in the numerator (i.e., users) at a given scheduled visit, if the subjects have evidence of use at any prior visits or at the current visit.

The cumulative percentages by month will be analyzed using chi square tests. The percentages for each treatment and between treatment percentage differences will be estimated. The 95% confidence intervals of the estimated treatment differences will be presented.

The overall treatment difference will be also tested via Wei and Lachin procedure. In this analysis, missing values were not imputed.

9.3.7 PERCENT OF SUBJECTS WITH NO SELF-REPORTED ILLICIT OPIOID USE BY TIME POINT

Percent of subjects with No Self-Reported Illicit Drug Use by time points (by scheduled post baseline visit) will be analyzed using chi square tests. The percentages for each treatment and between treatment percentage differences will be estimated. The 95% confidence intervals of the estimated treatment differences will be presented.

9.3.8 PERCENT OF SUBJECTS MEETING CRITERIA OF STABILITY BY TIME POINT

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 (defined as at least 50% reduction from baseline in the VAS score)?
- Does the subject exhibit diminished use of illicit opioids, according to the Investigator's discretion?

Percent of subjects meeting criteria of stability by time point (by scheduled post baseline visit) will be analyzed using chi square tests. The Week 13 will be the primary time point. The percentages for each

treatment and between treatment percentage differences will be estimated. The 95% confidence intervals of the estimated treatment differences will be presented. Additionally, for the primary time point (Week 13), sensitivity analysis will be performed quantifying the number of subjects with at least 25% reduction in positive urine test performed at Weeks 10-13 compared to Weeks 2-5.

The overall treatment difference will be also tested via Wei and Lachin procedure.

9.3.9 MEASURES OF CRAVING (VAS)

Measures of craving include Desire to Use VAS and Need to Use VAS, will be administered using unipolar 100 mm VAS ("In the past week/month, how intense has been your average desire/need to use "drug name?", 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). They will be measured at baseline and some selected post baseline visits (For more detail, please refer to Table 3, Schedule of Assessments, in Section 10 of the protocol, TRIAL PROCEDURES AND ASSESSMENTS).

Changes from baseline in the above VASs will be derived by subtracting the baseline values from the post-baseline values, thus, negative changes are indicative of improvement. Changes from baseline in measurements of craving 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 the treatment differences will be presented. In this primary analysis, missing values will be imputed using Last Observation Carried Forward (LOCF) method.

9.3.10 MEASURES OF WITHDRAWAL SYMPTOMS

Measures of withdrawal include COWS and SOWS. The COWS is comprised of 11 items each with a score of 0 through 4. Higher scores are associated with greater withdrawal symptoms. The items are meant to be objective (e.g., resting pulse rate) measures of patient's withdrawal symptoms. The SOWS is comprised of 16 items each with a score of 0 through 4. Higher scores are associated with greater withdrawal symptoms. The items are statements which are evaluated by the patient and are there for subjective (e.g., I feel anxious, 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely). Both COWS and SOWS will be measured at baseline and some selected post baseline visits (For more detail, please refer to Table 3, Schedule of Assessments, in Section 10 of the protocol, TRIAL PROCEDURES AND ASSESSMENTS).

If there are >=3 (i.e., >=20%) missing items in the COWS scale at a given visit or >=4 (i.e., >20%) missing items in the SOWS scale at a given visit, the COWS/SOWS score for that visit will be missing. If there are 1 or 2 missing items for the COWS assessment then the total of the non-missing items will be calculated and the product of the calculated total and 11/(11- # missing) will be used for the COWS score for that visit. If 3 or fewer items are missing for the SOWS score then the total of the non-missing items will be calculated and the product of the calculated total and 16/(16 - # missing) will be used for the SOWS score. Missing total scores or scores with more than two missing components in COWS, or more than 3 missing components in SOWS, will be imputed using LOCF method.

Changes from baseline in COWS and SOWS will be derived by subtracting the baseline values from the post-baseline values, thus, negative changes are indicative of improvement. Changes from baseline in measurements of withdrawal will be analyzed via ANCOVA model with treatment and baseline effects. Treatment effects and treatment differences will be estimated. The two-sided 95% confidence intervals

of the treatment differences will be presented. In this primary analysis, missing values will be imputed using LOCF method.

9.3.11 PERCENT OF SUBJECTS WITHOUT EVIDENCE OF USING OTHER DRUGS OF ABUSE BY TIME POINT

The list of drugs of abuse will include cocaine, benzodiazepines, barbiturates, amphetamines, phenycyclidine, and THC. Percent of subjects without using each of the above drugs by time point (by scheduled post baseline visit) will be analyzed using chi square tests. The percentages for each treatment and between treatment percentage differences will be estimated. The 95% confidence intervals of the estimated treatment differences will be presented.

9.3.12 SUPPLEMENTAL BPN USE

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).

Percentages of subjects who require supplemental uses and total number of supplemental use episodes will be summarized.

9.3.13 ADDITIONAL SUPPLEMENTAL COUNSELING

Percentages of subjects who required additional unscheduled visits to obtain counseling to manage withdrawal symptoms or desire to use illicit opioids during each of the two phases as well as during the study will be summarized. In addition, number of unscheduled visit to obtain such counseling during each of the two phases as well as during the study will also be summarized.

9.3.14 MEASURES OF MORNING NEED TO USE/DESIRE TO USE (VAS)

Measures of VAS scores include Morning Desire to Use VAS and Morning Need to Use VAS, will be administered using unipolar 100 mm VAS ("In the past week/month, how intense has been your average desire/need to use "drug name?", 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). They will be measured at baseline and some selected post baseline visits (For more detail, please refer to Table 3, Schedule of Assessments, in Section 10 of the protocol, TRIAL PROCEDURES AND ASSESSMENTS).

Changes from baseline in the above VASs will be derived by subtracting the baseline values from the post-baseline values, thus, negative changes are indicative of improvement. Changes from baseline in measurements of craving 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 the treatment differences will be presented. In this primary analysis, missing values will be imputed using Last Observation Carried Forward (LOCF) method.

9.4 INTERIM ANALYSES

No interim analyses will be performed.

9.5 ADJUSTMENTS FOR MULTIPLICITY

There are a number of hypothesis testings that will be performed for this study. To control overall Type I error rate at 5%, a closed testing procedure will be employed (Dmitrienko 2004, Dmitrienko, Offen, Westfall 2003). Specifically, the following ordered hypotheses will be tested:

1. Superiority for CDF of percent samples that are negative for illicit opioids (Weeks 5-25);
2. Superiority for the primary efficacy variable, RR (Weeks 2-25);
3. Superiority of active treatment over the control for time to sustained abstinence after 8 weeks of treatment;
4. Non-inferiority with margin of 15% for retention rate;
5. Superiority of active treatment over the control for retention rate.

In this procedure, a comparison will be eligible for non-inferiority or superiority testing only if all previous comparisons, if any, were successfully established at the two-sided 5% significance level.

9.6 POWER AND SAMPLE SIZE JUSTIFICATION

The sample size of approximately 190 per treatment arm (380 total) will provide approximately 82% power to establish the non-inferiority with a 13.5% non-inferiority margin for the primary efficacy variable, RR Weeks 2-25. In the sample size calculation, it was assumed that the proportion of response in both the active treatment arm and control treatment arm is 70%.

10.0 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 (AEs), 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.

10.1 EXTENT OF EXPOSURE

Summary statistics (number and percentage) of weeks of exposure to study drug (i.e. from date of initial injection to 4 weeks after the last injection) will be tabulated by treatment group.

10.2 ADVERSE EVENTS

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

Columbia Suicide Severity Rating Scale (C-SSRS) will be summarized.

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 A.

TEAEs 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 TEAEs 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, SAEs by primary SOC and preferred term will be provided. Deaths and SAEs will be summarized similarly to AEs. All TEAE tables will also include the total number of events, counting multiple events per patient.

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

- Study drug related
- Intensity
- Relationship to injection
- Possibly study drug related by intensity
- Reasonably injection related by intensity
- Serious
- AEs which led to discontinuation of treatment
- SAEs which led to discontinuation of treatment
- 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.

To assess the AE profile during the first week of treatment (first week after the randomization), TEAEs that occur within the first week of treatment will be presented.

Other safety analyses will be performed as appropriate

10.3 LABORATORY ASSESSMENTS

Chemistry, hematology, urinalysis and coagulation profile will be assessed at Screening, Week 1 (baseline), Week 12, Week 13, Week 17, Week 21 and Week 25 (see Section 10.4.3 in the clinical trial 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).

The number and percent of subjects experiencing a value greater than 2x and 3x the upper limit of normal (ULN) for ALT and AST will also be presented for each visit and overall (at any visit).

If applicable, a listing will also be provide for all subjects experiencing a value greater than 3x the upper limit of normal (ULN) for ALT or AST and a doubling of baseline total bilirubin occurring on the same visit.

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 non-missing observation on or prior to randomization will be used. The Week 25 values will be the last post-baseline value on or prior to Week 25.

10.4 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 body temperature 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.

10.5 PHYSICAL EXAMINATION

Number and percent of subjects with abnormal physical examination findings at Screening and Week 25 will be summarized by body system for each treatment group and overall. Physical examination data for each subject will also be presented in a listing.

10.6 12-LEAD ELECTROCARDIOGRAM (ECG)

12-Lead ECGs will be performed at screening, Day 1, Day 8, and all subsequent scheduled visits through Week 25 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 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 any visit).

10.7 INJECTION SITE EXAMINATION

Injection site reactions can occur with injection of CAM2038 or placebo. The injection site will be visually inspected for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing and any other abnormalities. Summaries of all injection site reactions as well as of clinically significant injection site reactions will be presented.

All AEs, AEs that are associated with injection procedures, and other AEs (not associated with injections) will be summarized.

11.0 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.

12.0 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.

13.0 REFERENCES

1. L. J. Wei and J. M. Lachin, Sept 1984, "Two-Samples Asymptotically Distribution-Free Tests for Incomplete Multivariate Observations," Journal of the American Statistical Association, Vol. 79, No. 387 (Sep., 1984), pp. 653-661
2. Dmitrienko, Offen, Westfall 2003, "Gatekeeping strategies for clinical trials that do not require all primary effects to be significant," Statistics in Medicine, 22: 2387-2400

14.0 APPENDICES

14.1 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.

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