HS-16-555 **Phase III**

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Enriched-Enrollment Withdrawal, Multicenter Study to Evaluate the Efficacy and Safety of a Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Subjects with a Recent History of Moderate to Severe Chronic Low Back Pain Currently Treated with Opioids

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 to analyze the HS-16-555 data.

BRAEBURN

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1. DOCUMENT HISTORY

Version	Date	Changes made since previous version
0.01	20 NOV 2017	Draft
0.02	22 NOV 2017	Draft
0.03	27 NOV 2017	Draft
1.00	31 AUG 2018	Final

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
API	Average pain intensity
BPN	Buprenorphine
C-SSRS	Columbia–Suicide Severity Rating Scale
CGI-I	Clinical Global Impression of Improvement
CLBP	Chronic low back pain
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form (may include electronic data capture systems or paper forms)
CRO	Contract research organization
ECG	Electrocardiogram
EERW	Enriched-enrollment randomized withdrawal
ITT	Intent-to-treat
MedDRA	Medical Dictionary of Regulatory Activities
MMRM	Mixed-model repeated measures
NRS	Numerical rating scale
PGI-I	Patient Global Impression of Improvement
q1w	Once-weekly
q4w	Once-monthly
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
SOWS	Subjective Opiate Withdrawal Scale
TEAE	Treatment-emergent adverse event
WAAPI	Weekly average of average pain intensity
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment
WPI	Worst pain intensity

3. INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol HS-16-555, Protocol Amendment 9, v 10.0, 12 April 2018. This SAP defines the analysis plan for the Double-Blind Treatment Phase, including the Open-Label Titration and Double-Blind Treatment Phases. A separate SAP will be prepared for the Open-Label Safety Extension Phase, and therefore, this phase is not discussed any further beyond the objectives in this document.

The purpose of this document is to provide details on study populations and how the variables will be derived, how missing data will be handled, and on statistical methodologies to be used to analyze the safety and efficacy data from the Double-Blind Treatment Phase.

4. STUDY DESCRIPTION

4.1 STUDY OBJECTIVES

Primary Objective:

The primary objective of this study is to evaluate the efficacy of long-acting subcutaneous (SC) injectable depots of buprenorphine (BPN) (CAM2038 once-weekly [q1w] and CAM2038 once-monthly [q4w]) compared to placebo on average pain intensity (API) scores, as measured on an 11-point numerical rating scale (NRS-11) in subjects currently taking daily opioids for moderate to severe chronic low back pain (CLBP).

Secondary Objectives:

The secondary objectives of the study are to evaluate:

- The change from baseline in the weekly average of daily worst pain intensity (WPI) scores at Week 12 of the Double-Blind Treatment Phase, based on an NRS-11;
- The proportion of subjects meeting the clinical responder definition of at least 30% and 50% improvement in API from the Open-Label Titration Phase baseline to the end of the Double-Blind Treatment Phase;
- Time to loss of efficacy during the Double-Blind Treatment Phase;
- The change from baseline to Week 12 of the Double-Blind Treatment Phase in the Patient Global Impression of Improvement (PGI-I) scale (as assessed by each subject);
- The change from the Open-Label Titration Phase baseline to the end of the Double-Blind Treatment Phase in quality of life and work productivity measures, using Work Productivity and Activity Impairment (WPAI) subject-reported assessments and EuroQoL Group 5-dimension 5-level self-report questionnaire (EQ-5D-5L) scores; and
- Rescue medication utilization during the Double-Blind Treatment Phase.

4.2 STUDY TREATMENTS

Subjects meeting randomization criteria (Protocol Section 7.4) will be randomized to receive weekly or monthly injections in 1 of 2 treatment groups in the Double-Blind Treatment Phase:

- Group 1: CAM2038 SC injections (4 mg, 8 mg or 12 mg q1w; or 64 mg, 96 mg or 128 mg q4w)
- Group 2: Placebo SC injections

4.3 STUDY DESIGN

This is a Phase III, randomized, double-blind, placebo-controlled, enriched-enrollment randomized withdrawal (EERW), multicenter study to evaluate the efficacy and safety of CAM2038 q1w and CAM2038 q4w in subjects currently taking opioids with a recent history of moderate to severe chronic low back pain for an extended period.

4.4 RANDOMIZATION AND BLINDING

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

During the Open-Label Titration Phase, subjects will be dosed with CAM2038 q1w until a stabilized dose and adequate analgesic effect has been achieved for at least 2 consecutive weeks prior to randomization to the Double-Blind Treatment Phase, in accordance with pre-defined randomization criteria. Subjects whose pain is controlled on 4 mg, 8 mg or 12 mg CAM2038 q1w during the Open-Label Titration Phase will be maintained on 4 mg, 8 mg or 12 mg CAM2038 q1w, or corresponding placebo, during the Double-Blind Treatment Phase. Subjects whose pain is controlled on 16 mg, 24 mg or 32 mg CAM2038 q1w during the Open-Label Titration Phase will be transitioned to CAM2038 64 mg, 96 mg or 128 mg q4w, or corresponding placebo, during the Double-Blind Treatment Phase. Subjects will be randomized to either active CAM2038 or placebo control in a 1:1 ratio within each of the q1w or q4w regimens.

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. ANALYSIS POPULATIONS

5.1 RANDOMIZED POPULATION

The Randomized Population will consist of all subjects who have been assigned random treatment.

5.2 MODIFIED INTENT-TO-TREAT POPULATION

The modified Intent-to-Treat (mITT) Population will consist of all randomized subjects with the exception of all subjects from Sites 068 and 077 due to persistent non-compliance.

Site 068:

A for-cause audit was performed on 02 Oct 2017 for Site 068 in response to a quality event. There were several Critical and Major observations noted during the audit; the deficiencies noted during the audit were based on a random sampling of data. Below are some of the observations noted:

The Critical observations were:

- Subject signatures on revised informed consent forms could not be confirmed as authentic.
- The data on subject diaries could not be attributed to the subjects themselves.
- Subject eligibility could not be confirmed with provided source documents.

The Major observations were:

- Source documentation provided was found to be inadequate and/or unreliable.
- There was inadequate accountability and review by site staff of subject diaries.
- There was inadequate reporting and assessment of adverse events.
- The site did not have appropriate research staff based on qualification, training and experience.

The above observations have led to uncertainty in the integrity and reliability of the data collected at this site. Therefore, the data will not be included in the efficacy analysis.

Site 077:

Multiple audits, including a for-cause audit and several quality visits, were conducted by the Sponsor, Medpace (the contract research organization [CRO]) and third-party auditors, due to the Site 077 enrolling a large number of subjects into the study. These audits and quality visits led to several Critical and Major observations noted below:

The Critical observations were:

- Not all subjects spoke, read or comprehended English, and as a result, the Informed Consent (IC) process and every study visit was conducted in Spanish or through an interpreter/impartial witness. This was not permitted in the protocol and was not documented in the source documentation.
- The study staff were unblinded throughout the entire study. The study staff who administered the investigational product also performed the protocol-required assessments at each visit.
- Source documentation was manually changed, allowing several subjects to meet inclusion and exclusion criteria for the study.
- The medical records at the site were incomplete or missing.As a result, it could not be determined whether the subjects met inclusion criteria to qualify for the study.

The Major observations were:

- The questionnaires, scales and diaries required to be completed by subjects at each visit could not be attributed to the appropriate subjects.
- There was inadequate accountability for and review of subject diaries by site staff.
- The electronic medical records were not validated and contained numerous inconsistencies.

The above observations have led to uncertainty in the integrity and reliability of the data collected at this site. Therefore, the data will not be included in the efficacy analysis.

The primary efficacy analyses will be based on the mITT Population.

5.3 PER PROTOCOL POPULATION

The Per Protocol Population will include all subjects in the mITT Population with no major protocol violations. Major protocol violation criteria (defined as CSR reportable violations) have been be established (prior to database lock) and included in the Protocol Deviation Plan. These protocol violations will be presented in the Clinical Study Report. Efficacy analyses may also be performed based on the Per Protocol Population.

5.4 SAFETY POPULATION

The Safety Population will include all subjects who have received any dose of study medication. Analyses based on this population will group subjects according to the treatment they received rather than the treatment they were randomized to receive. All safety analyses will use the Safety Population.

In the primary safety summaries, data for Sites 068 and 077 mentioned in Section 5.2 will be excluded, due to an inability to verify compliance with adverse event reporting requirements, leading to possible under-reporting of adverse events. However, supportive safety summaries will include the data from Sites 068 and 077.

6. GENERAL CONVENTIONS

Unless otherwise stated, all 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 decimal places, 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, SD, median, minimum, maximum and percentages will be presented with one decimal place.

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 randomization baseline will be defined as the last assessment recorded on the day of randomization (e.g., weekly average in pain intensity).

Open-label titration pain score baseline is defined as a single assessment prior to entering the Open-Label Titration Phase.

Analyses will be conducted using SAS Version 9.2 or higher.

6.2 CHANGES TO PLANNED ANALYSES

Draft versions of the SAP will be numbered sequentially as Version 0.0x. 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 approved version before unblinding.

7. DESCRIPTION OF THE STUDY POPULATIONS

All tables, figures and listings must include population descriptors in the titles (e.g., mITT Population, Safety Population, Per Protocol Population).

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 primary Safety, 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 the primary Safety, 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 mITT and the primary Safety Population. The demographic characteristics will consist of age, sex, ethnicity, and race, and will use descriptive statistics.

Demographic data including age, sex, ethnicity, and race, as well as baseline clinical characteristics, will be summarized. 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

Since the birth dates capture the months and years only, the days will be imputed as the first day of the month before applying the above rules to derive the ages.

Clinical baseline characteristics summarized will include, at minimum, body mass index, current employment status, duration of low back pain, and pain score at the beginning of the open-label titration phase. Clinical baseline characteristics will be summarized by treatment group and overall.

7.3 MEDICAL HISTORY

Medical history will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). A medical history listing will be presented.

8. 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 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 medication. 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.

Prior and concomitant medication will be summarized for both Primary and Supportive Safety Populations.

9. EFFICACY ANALYSES

Twenty-four hour API, WPI and rescue medication use will be collected daily by electronic diary. Paper diary entries will be collected in situations where electronic diary transmission issues occur and where electronic diaries are unavailable. For cases where both electronic and paper diaries are available, only the data from the electronic source will be used. Pain-related efficacy evaluation will be based on electronic diary data only. Additional sensitivity analyses will be conducted with both electronic and paper diary data as supportive efficacy.

9.1 PRIMARY EFFICACY OUTCOME

The primary efficacy variable will be the change from baseline in weekly average API (WAAPI), and the primary timepoint will be Week 12.

9.2 DERIVATION OF THE PRIMARY EFFICACY VARIABLE

WAAPI scores will be calculated for each weekly interval (i.e., 7-day intervals) relative to randomization date (first randomized treatment date) for all subjects (both subjects on q1w and q4w). For example, WAAPI at Week 0 will be the average of available (non-missing) APIs captured during the 7 days prior to Treatment Day 1 (the first randomized treatment day). WAAPI at Week 1 will be the average for the next 7 days including the score captured on Day 1. WAAPI at Week 12 (the primary timepoint) will be the average for the APIs captured from Day 78 to Day 84. The baseline WAAPI score will be the WAAPI at Week 0. The changes from baseline at any post-baseline timepoint will be calculated as baseline minus post-baseline, so that a positive change is indicative of improvement.

9.3 PRIMARY ANALYSIS

The primary analysis will be performed based on the mITT Population.

WAAPI over time will be performed by longitudinal data analysis using mixed-model repeated measures (MMRM) methods. All post-randomization baseline observations will be utilized; missing values will remain as missing (i.e. no attempt will be made to impute missing values, and only observed values will be used in the data analysis). The model will include treatment, post-baseline weeks, treatment by week interaction as fixed effects, and baseline WAAPI as the covariate. The covariance will assume to be unstructured. If the estimates do not converge, SAS default covariance structure (variance components) will be assumed. The MMRM with maximum likelihood estimation will utilize the following pseudo-SAS code for analysis:

```
proc mixed data = WAAPI Data method = ml;
class treatment week subject;
model Change in WAAPI = treatment week treatment*week baseline;
repeated week / subject = subject type = un;
lsmeans treatment / pdiff cl e;
lsmeans treatment*week /slice = week cl diff;
ods output diffs = alldiff;
```

If the estimation under type=un cannot converge, the SAS default (variance components) will be used. The estimated treatment effects, treatment differences, and the two-sided 95% confidence intervals of the treatment differences at all post-baseline timepoints will be presented. The primary comparison will be the treatment difference at Week 12.

A clear advantage of using MMRM is that this method does not require artificial missing imputations that would often create biases. The MMRM method is valid if the "missing at random" assumption holds. The trial is designed to minimize missing values: (a) Subjects who discontinue taking study medication are permitted to remain in the study, and safety and efficacy data will continue to be collected from these subjects; (b) Liberal use of rescue medication is allowed during the study, and data collection will continue even after subjects take these medications, and (c) Robust efficacy data collection procedures will be used in the trial.

Using the procedures above, it is expected that missing values will be minimal and that "missing at random" is a reasonable assumption. Therefore, the "MMRM without missing" imputation is reasonable. Sensitivity analyses of missing value imputations will be performed to support the robustness of the conclusion (see Section 9.4).

Additional analyses outlined in the sensitivity analyses section (9.4) will be performed to assess the robustness of the analysis results.

9.4 SENSITIVITY ANALYSES

Missing values sensitivity analyses:

As the MMRM analysis does not impute missing values, sensitivity analyses with various missing value imputation methods will be performed. Sensitivity analyses based on the random replace and tipping point methods will be performed to assess the robustness of the primary efficacy data.

If all daily ratings are missing for a given week, the missing change from baseline values at a given week will be imputed using the following methods.

Random replacement method
Missing change from baseline in WAAPI at Week J will be imputed with randomly generated values from a normal distribution using a seed of 153928221. The normal distribution will be assumed to have a mean x and a standard deviation of y, where x and y are the mean and standard deviation of the changes at Week J based on all subjects (i.e., subjects from both treatment groups) with non-missing values. It should be noted that, if treatment is effective, the results of this missing value imputation method will be more conservative (i.e., biased in favor of the control).

Tipping point method
Missing change values at Week J from placebo subjects will be imputed with the value that is equal to the mean changes among placebo subjects at that week. Missing change values from active treatment subjects will be imputed with the value that is k% worse than the mean WAAPI from the placebo group at that week, where k=0, 5, 10, 20, 30, 40…100, until tipping (i.e., the treatment difference at Week 12 is no longer significant at a two-sided significance level of 0.05).

Additional Sensitivity Analyses:

Inclusion of paper diary data from the primary analysis
The primary efficacy variable will be analyzed including available paper diary data collected.

Exclusion of weekly average diary entries that do not have at least 5 daily entries during randomization baseline week (Week -1) and at the end of treatment (Week 12)
The primary efficacy variable will be analyzed after treating WAAPI for any giving week as missing if average pain scores are available for less than 5 days in that week.)

Exclusion of subjects who do not complete at least 4 weeks of treatment
The primary efficacy variable will be analyzed in subjects who participate in the study for at least 4 weeks of the double-blind period.

Exclusion of subjects who do not complete at least 8 weeks of treatment
The primary efficacy variable will be analyzed in subjects who participate in the study for at least 8 weeks of the double-blind period.

9.5 SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints are as follows:

- Change from baseline in the weekly average of daily WPI scores at Week 12 of the Double-Blind Treatment Phase, based on an NRS-11;
- Percentage of subjects with a 30% and 50% or greater decrease in API from the Open-Label Titration Phase baseline to Week 12 of the Double-Blind Treatment Phase;
- Time to loss of efficacy, defined as discontinuations from the study or study drug for lack of efficacy;
- Change from baseline to Week 12 of the Double-Blind Treatment Phase in the PGI-I scale (as assessed by each subject)
- Change from baseline to Week 12 of the Double-Blind Treatment Phase in WPAI scores;
- Change from baseline to Week 12 of the Double-Blind Treatment Phase in EuroQoL Group EQ-5D-5L scores; and
- Rescue medication days during the Double-Blind Treatment Phase.

9.5.1 CHANGE FROM BASELINE IN THE WEEKLY AVERAGE OF DAILY WPI SCORES AT WEEK 12 OF THE DOUBLE-BLIND TREATMENT PHASE

This variable, based on an NRS-11, will be analyzed via similar methods to those for the primary efficacy variable.

9.5.2 PROPORTION OF RESPONDERS WITH A ≥30% AND ≥50% REDUCTION FROM THE OPEN-LABEL TITRATION PHASE BASELINE IN API SCORE OVER TIME

Percent reduction from the Open-Label Titration Phase baseline in NRS score to a given post-baseline week will be derived as 100*(Titration Baseline pain score – Post-Baseline WAAPI) / (Titration Baseline pain score). A subject is a responder if the percent reduction is at least 30% and 50%.

This variable will be analyzed using the chi-square test. The percentages, the difference of the percentages, and the two-sided 95% confidence interval of the treatment difference will be presented. The 95% confidence intervals of the treatment difference will be calculated using normal approximation.

9.5.3 TIME TO LOSS OF EFFICACY

Lack of efficacy is defined as discontinuation from the study or study drug for lack of efficacy. The time will be defined as the following:

Discontinuation Date – Randomization Date + 1

Time to loss of efficacy will be analyzed via a log-rank model with treatment effects. The time-to-event "survival" curve will be presented using the Kaplan-Meier method. Median time-to-event and the 95% confidence interval of the median times will be presented, if estimable. In these time-to-event analyses, subjects who do not have the event during the entire study will be censored at Day 84 (end of Week 12 day).

9.5.4 CHANGE FROM BASELINE TO LAST WEEK OF TREATMENT IN PGI-I SCALE

Change from baseline in PGI-I will be analyzed via similar methods to those for the primary efficacy variable.

9.5.5 CHANGE FROM THE OPEN-LABEL TITRATION PHASE BASELINE TO THE LAST WEEK OF TREATMENT OF THE DOUBLE-BLIND TREATMENT PHASE IN WPAI SCORE

This variable will be analyzed via similar methods to those for the primary efficacy variable.

9.5.6 CHANGE FROM THE OPEN-LABEL TITRATION PHASE BASELINE TO THE LAST WEEK OF TREATMENT OF THE DOUBLE-BLIND TREATMENT PHASE IN EUROQOL GROUP EQ-5D-5L SCORE

This variable will be analyzed via similar methods to those for the primary efficacy variable.

9.5.7 RESCUE MEDICATION USAGE (NUMBER OF DAYS) DURING THE DOUBLE-BLIND TREATMENT PHASE.

Rescue medication usage will be collected from the electronic diaries.

There were technical issues with the electronic diaries for rescue medication usage. For example, subjects entered data multiple times (more than 30 times per day in some cases), possibly due to poor internet connectivity. As a result of these issues, the total rescue dosage was not reliable. Therefore, the electronic diary source of rescue medication usage will be used only to derive the number of days that rescue medication was used.

The number of days that rescue medication is used will be normalized on a weekly basis in the analysis (i.e., number of days that rescue medication is used per week) based on the electronic diaries. Specifically, number of days that rescue medication is used per week will be derived as 7*(X/Y), where X=total number of days that rescue medication is taken during the week and Y=total number of days that diaries are available in that week. This variable will be analyzed via similar methods used to analyze the primary efficacy variable.

9.6 EXPLORATORY EFFICACY OUTCOMES

The exploratory efficacy endpoints are as follows:

- Percentage of subjects with a 70% or greater decrease in API from the Open-Label Titration Phase baseline to Week 12 of the Double-Blind Treatment Phase
- Change from baseline to Week 12 of the Double-Blind Treatment Phase in Clinical Global Impression of Improvement (CGI-I) scale (as assessed by the Investigator).

9.6.1 PROPORTION OF RESPONDERS WITH A ≥70% REDUCTION FROM THE OPEN-LABEL TITRATION PHASE BASELINE TO WEEK 12 OF THE DOUBLE-BLIND TREATMENT PHASE IN API SCORE OVER TIME

Percent reduction from the Open-Label Titration Phase baseline in NRS score to a given post-baseline Week will be derived as 100*(Titration baseline pain score – Post-Baseline API) / (Titration baseline pain score). A subject is a responder if the percent reduction is at least 70%. A subject with missing API for a given post-baseline week will be considered as a non-responder.

This variable will be analyzed using the chi-square test. The percentages, the difference of the percentages, and the two-sided 95% confidence interval of the treatment difference will be presented. The 95% confidence intervals of the treatment difference will be calculated using normal approximation.

9.6.2 CHANGE FROM BASELINE TO WEEK 12 IN CGI-I SCALE

Change from baseline in CGI-I will be analyzed via the similar methods to those for the primary efficacy variable.

9.7 INTERIM ANALYSES

No interim analyses will be performed.

9.8 ADJUSTMENTS FOR MULTIPLICITY

There is only one primary comparison for the study. The clinical efficacy endpoints listed below are listed in order of hierarchical importance:

1. The primary efficacy endpoint, which is change from baseline in WAAPI at last week of treatment;
2. Change from baseline in the weekly average of daily WPI scores at last week of treatment of the Double-Blind Treatment Phase, based on an NRS-11;
3. Percentage of subjects with a 50% or greater decrease in API from the Open-Label Titration Phase baseline to the last week of treatment of the Double-Blind Treatment Phase;
4. Percentage of subjects with a 30% or greater decrease in API from the Open-Label Titration Phase baseline to the last week of treatment of the Double-Blind Treatment Phase;
5. Time to loss of efficacy, defined as discontinuation from the study or study drug for lack of efficacy;
6. Change from baseline to last week of treatment of the Double-Blind Treatment Phase in PGI-I scale (as assessed by the subject);
7. Change from baseline to last week of treatment of the Double-Blind Treatment Phase in WPAI score;
8. Change from baseline to last week of treatment of the Double-Blind Treatment Phase in EuroQoL Group EQ-5D-5L score; and
9. Rescue medication usage during the Double-Blind Treatment Phase.

The null hypotheses of no treatment difference for the above endpoints will be tested at a two-sided significance level of 0.05 in the order specified. To protect the family-wise two-sided p-value at the 0.05 significance level, the treatment superiority for an endpoint cannot be claimed, unless the superiority claims for all prior endpoints in the list, if any, have been established.

9.9 POWER AND SAMPLE SIZE JUSTIFICATION

A sample size of 170 subjects per treatment group will provide over 90% power to detect a treatment difference at a two-sided 5% significance level. In the sample size calculation, a treatment difference of 0.7 units and an SD of 2 (or a standardized effect of 0.35) for the primary efficacy variable were assumed.

10. SUMMARIES OF MEASURES OF SAFETY

Safety analyses will be performed for both the Primary and Supportive Safety Populations. 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, electrocardiogram (ECG), clinical laboratory results, and injection site examination. Safety variables will be tabulated and presented by study drug received.

Because there is no pre-specified safety outcome defined in terms of AEs, clinically relevant laboratory parameters, or vital signs in the Double-Blind Treatment Phase of the study, 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 for q4w, or 1 week for q1w) will be tabulated by treatment group.

10.2 ADVERSE EVENTS

All AE and serious adverse event (SAE) terms recorded on the CRFs will be coded by primary system organ class (SOC) and will be mapped to a preferred term using the MedDRA. 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 the first dose of CAM2038, or any ongoing event on the date of first dose that worsens in severity after the first dose of CAM2038. Only TEAEs with an onset date prior to date of last dose plus 30 days will be tabulated in summary tables. For the purpose of calculating TEAEs and inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix A.

AEs will be summarized by the number and percent of subjects in each primary SOC and preferred term, and subjects 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, SAEs 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.

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

- Study drug related AEs
- AEs by intensity
- AE relationship to injection
- Possibly study drug related AEs, by intensity
- AEs reasonably related to injection, by intensity
- SAEs
- AEs that led to discontinuation
- SAEs that led to discontinuation
- AEs occurring in ≥5% 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.

10.3 LABORATORY ASSESSMENTS

Chemistry, hematology, urinalysis and coagulation profiles will be assessed (see Protocol Section 9.5.9 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 timepoint, the value from the first evaluation at that timepoint will be used for summary purposes. For the purpose of determining baseline, the last non-missing observation on or prior to randomization will be used.

10.4 VITAL SIGNS

For the purposes of this SAP, vital signs will consist of blood pressure (systolic and diastolic blood pressure, mm Hg), pulse rate (beats per minute), respiratory rate (breaths/minute) and oxygen saturation (%), collected while sitting, following a rest period of at least 3 minutes. Vital signs values and change from baseline in the vital signs will be summarized for each treatment group.

10.5 PHYSICAL EXAMINATIONS

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 examinations data for each subject will also be presented in a listing.

10.6 12-LEAD ELECTROCARDIOGRAM (ECG)

Twelve-Lead ECGs will be assessed after the subject has been resting in a recumbent/supine position for at least 3 minutes (see Protocol Section 9.5.11 for a complete list of parameters to be assessed). 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; he or she will 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.

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 itching, erythema/redness (with erythema/redness rating), swelling (with swelling rating) and any other abnormalities.

Results from the injection-site examinations will be summarized and listed.

AEs that are believed to be associated with injection procedures will be summarized similarly to how other AEs are summarized (i.e., AEs not associated with injections).

10.8 URINE DRUG SCREEN

Urine drug screen will be summarized and listed.

10.9 COWS

The Clinical Opiate Withdrawal Scale (COWS) data will be summarized and listed.

10.10 SOWS

The Subjective Opiate Withdrawal Scale (SOWS) data will be summarized and listed.

10.11 C-SSRS

Columbia–Suicide Severity Rating Scale (C-SSRS) data will be summarized and listed.

11. 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. 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 will be subject to electronic and manual quality assurance procedures.

Additionally, due to the observations identified in the two sites that have been excluded from the primary ITT dataset (Sites 068 and 077), additional measures were taken to assure the quality of study conduct and data collection from other top sites; these were sites that enrolled more than 10 subjects in the study. The Sponsor's Quality Department, in parallel with an independent third-party auditor, conducted quality visits to these sites, and the results of revealed no critical or major findings or observations that would impact the quality of the data.

13. REFERENCES

None.

14. APPENDICES

14.1 APPENDIX A — IMPUTATION ALGORITHM FOR PARTIAL AND MISSING DATES

This section describes missing date imputation methods.

For Adverse Events

If the onset date is completely missing, the onset date is set to the date of randomization.
If the year is present, and month and day are missing, or if the year and day are present, and the 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 the onset date to the 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 if 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 first 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 if 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, the medication will be classified as concomitant.