HS-14-499 **Phase III**

An Open-Label Multicenter Study Assessing the Long-Term Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injection Depot of Buprenorphine (CAM2038) in 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

Version 1.01 20 April 2017

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-14-499 data.

BRAEBURN PHARMACEUTICALS

Sonnie Kim, Pharm. D.		20 Apr 2017
Print Name	Signature	Date

STATISTICIAN

Michael Chen, Ph.D.		20 Apr 2017
Print Name	Signature	Date

TABLE OF CONTENTS

1.0 DOCUMENT HISTORY

Version	Date	Changes made since previous version
1.00	25 January 2017	Final
1.01	20 April 2017	Updates on the sample size and inclusion of separate analysis of subjects new to treatment.

2.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
BPN	Buprenorphine or Buprenorphine/Naloxone
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form (may include electronic data capture systems or paper forms)
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
PT	MedDRA Preferred Term
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 Analogue Scale
WPAI-GH	Work Productivity and Activity Impairment Questionnaire General Health

3.0 INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol HS-14-499, Version 3.0, dated 18-Nov-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 the 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

Primary Objective: To demonstrate the safety and tolerability of CAM2038 products in 12-month (48-week) buprenorphine (BPN) treatment in adult outpatients with opioid use disorder.

Secondary Objectives: To evaluate efficacy of CAM2038 through several efficacy parameters, including urine toxicology, signs and symptoms of withdrawal and cravings in adult outpatients with opioid use disorder.

4.2 STUDY TREATMENTS

Following Screening, qualified patients will be initiated on either CAM2038 q1w or q4w, based on their current treatment status (qualified patients currently on sublingual (SL) BPN or seeking BPN treatment). Qualified patients will be initiated or transitioned to CAM2038 q1w or q4w as follows:

- Initiation of BPN treatment – initiate with CAM2038 q1w
- Currently receiving SL BPN treatments – transfer to corresponding CAM2038 q1w or q4w dose

Patients will be allowed to receive supplemental BPN during the study with booster SC injections of CAM2038 q1w 8 mg up to a maximum dose of 40 mg CAM2038q1w per week. For patients on CAM2038 q4w, a maximum of two booster doses of CAM2038 q1w 8 mg SC injections may be given per week. Dose adjustments (up or down titrations) will also be allowed at scheduled visits.

4.3 STUDY DESIGN

This is an open-label multi-center, 12-month safety study, consistent with standard practice for long-term safety studies. This one-year safety study will utilize CAM2038 q1w (once weekly) and CAM2038 q4w (once monthly) and will have 3 phases: Screening, Treatment, and Follow-up.

Patients who are currently taking SL BPN (weekly or monthly prescription visits) or individuals who are actively seeking BPN treatment but who have not yet begun a treatment regimen, may be eligible for the study.

Following Screening, qualified patients will be initiated on either CAM2038 q1w or CAM2038 q4w and receive study treatment as described in Section 4.3.

The study will end when at least 100 patients have been exposed to CAM2038 for 12 months (48 weeks). All patients will be transitioned back to usual care and followed for an additional 4 weeks (up to Week 53).

4.4 RANDOMIZATION AND BLINDING

This is an open-label study.

5.0 ANALYSIS POPULATIONS

5.1 OVERALL SAFETY POPULATION

All patients who received at least one dose of CAM2038.

5.2 FULL EXPOSURE SAFETY POPULATION

All patients who have been exposed to CAM2038 for 48 weeks.

5.3 EFFICACY POPULATION

In addition to the protocol-specified populations, the efficacy population will include all patients who have received at least one dose of CAM2038 and have provided some post-baseline efficacy measurements.

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. 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 patient number.

6.1 DEFINITION OF BASELINE

Unless otherwise stated, the last observed measurement before the first dose of CAM2038 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

Most 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 database lock.

7.0 SAMPLE SIZE

A total of 100 patients with at least 48 weeks of CAM2038 exposure will be needed for the safety assessments. Approximately 228 patients will be enrolled initially into this study with an estimated drop-out rate of 50% to ensure a total of 100 patients are exposed to CAM2038. Originally, the study was to end when at least 100 subjects had been exposed to CAM2038 for 12 months (48 weeks). However, a decision was made to allow all enrolled subjects to complete the entire treatment period and to not end the study after at least 100 subjects had completed 48 weeks of treatment.

8.0 DESCRIPTION OF THE STUDY POPULATIONS

All tables, figures, and listings must include a population descriptor (e.g., pre-defined populations: overall safety population, full exposure safety population and efficacy population) in the title.

8.1 DISPOSITION

Patient disposition summaries will be presented and will include the number of patients enrolled, the number and percentage of enrolled patients in each of the pre-defined populations, as well as the number and percentage of patients 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 pre-defined populations separately.

8.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

A summary of demographics and baseline characteristics will be presented for each of the pre-defined 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, weight, body mass index, region (Europe, the US and Australia), type of primary opioid use, years of drug use, when first diagnosed with opioid dependence, proportion of patients previously treated for opioid dependence and duration of buprenorphine treatment.

8.3 MEDICAL HISTORY

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized and listings will be presented.

9.0 PRIOR AND CONCOMITANT MEDICATIONS

All medications recorded on the CRFs will be coded using the WHO DRUG Dictionary. Prior and concomitant medications will be summarized by 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 the first administration of any study treatment component. Concomitant medications are defined as medications with start dates occurring on or after the date of the 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 the first administration of any study treatment component will be summarized as both prior and concomitant medications.

Medications that clearly stopped prior to date of the 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 the 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 populations.

10.0 EFFICACY ANALYSES

10.1.1 EFFICACY VARIABLES

This is a long-term safety study and efficacy evaluation is not the primary objective of the study. All efficacy variables will be summarized using the efficacy population. The efficacy variables will include the following:

- Urine toxicology results for illicit opioids
- Self-reported illicit opioid use
- Retention (%) in treatment (identical to exposure)
- Retention (%) in study
- Measures of opioid withdrawal:
  - Clinical Opiate Withdrawal Scale (COWS)
  - Subjective Opiate Withdrawal Scale (SOWS)

- Measures of opioid craving:
    - Desire to Use Visual Analogue Scale (VAS)
    - Need to Use VAS
- Urine toxicology results for other drugs of abuse
- Work Productivity and Activity Impairment Questionnaire General Health (WPAI-GH)
- EQ-5D-5L Health Questionnaire
- Patient Satisfaction Scale

10.1.2 URINE TOXICOLOGY RESULTS FOR ILLICIT OPIOIDS

Percentage of patients with urine samples negative for illicit opioids (with and without self-reports of illicit opioid use) will be presented by week and month. Mean percentage of urine samples negative for illicit opioids (with and without self-reports of illicit opioid use) will also be presented. Additionally, mean urine samples negative for illicit opioids (with and without self-reports) will be presented by week and month separately for those subjects who were new to treatment upon entry into the study. Due to the flexible visit schedule, no imputation of missing data will be applied.

10.1.3 SELF-REPORTED ILLICIT OPIOID USE

Percentage of patients reporting no illicit opioid use will be presented by week and month. Mean percentage of reports of no illicit opioid use will also be presented. Due to the flexible visit schedule, no imputation of missing data will be applied.

10.1.4 RETENTION IN TREATMENT

Duration of treatment is defined as the time from the first dose of CAM2038 to the last dose plus 28 days if the last treatment was CAM2038 q4w or plus 7 days if the last treatment was CAM2038 q1w.

Duration of treatment will be summarized by the percentage of patients retained in treatment by week. Data will also be presented using Kaplan-Meier plots.

10.1.5 RETENTION IN STUDY

Duration in study is defined as the time from first dose of CAM2038 to the date of study discontinuation.

Duration in study will be summarized by the percentage of patients retained in the study by week. Data will also be presented using Kaplan-Meier plots.

10.1.6 MEASURES OF OPIOID WITHDRAWAL

Measures of withdrawal include COWS and SOWS. The COWS is comprised of 11 items, each with a score of 0 through 4 or 5. Higher scores are associated with greater withdrawal symptoms. The items are meant to be objective measures of a patient's withdrawal symptoms (e.g., resting pulse rate). 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 that are evaluated by the patient and are therefore subjective (e.g., I feel anxious, 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely).

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.

COWS and SOWS data will be presented by visit. Data will also be presented as change from baseline by subtracting the baseline values from the post-baseline values. Negative changes are thus indicative of improvement.

10.1.7 MEASURES OF OPIOID CRAVING

Measures of craving include Desire to Use VAS and Need to Use VAS and will be assessed using unipolar 100 mm VAS; "Since your last scheduled assessment visit, indicate your worst or strongest desire/need to use opioids between 0 = No desire/need to use and 100 = Maximum desire/need to use on this scale".

VAS data for Desire to Use and Need to Use will be presented by visit. Data will also be presented as change from baseline by subtracting the baseline values from the post-baseline values. Negative changes are thus indicative of improvement.

10.1.8 URINE TOXICOLOGY RESULTS FOR OTHER DRUGS OF ABUSE

Percentage of patients with urine samples positive for other drugs of abuse will be presented by week and month. Mean percentage of urine samples positive for other drugs of abuse will also be presented. Due to the flexible visit schedule, no imputation of missing data will be applied.

10.1.9 WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE GENERAL HEALTH (WPAI-GH)

Data for WPAI-GH will be presented by item over time.

10.1.10 EQ-5D-5L HEALTH QUESTIONNAIRE

Data for EQ-5D-5L will be presented over time.

10.1.11 PATIENT SATISFACTION SCALE

Patient satisfaction scale scores will be presented by item over time.

11.0 SUMMARIES OF MEASURES OF SAFETY

Safety analyses will be performed for the overall safety population and full exposure 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 patient's vital signs, electrocardiogram (ECG), clinical laboratory results and injection site examinations.

11.1.1 EXTENT OF EXPOSURE

Summary statistics (number and percentage) of weeks of exposure to study drug (i.e. from the date of the first injection to the date of the last injection plus 28 days if the last treatment was CAM2038 q4w or plus 7 days if the last treatment was CAM2038 q1w) will be presented. Number of patients, number of

injections and exposure years will be presented by dose, treatment (CAM2038 q1w and CAM2038 q4w) and in total.

11.1.2 ADVERSE EVENTS

Each AE and serious adverse event (SAE) term recorded on the CRFs by primary system organ class (SOC) and will be mapped to a preferred term (PT) 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 the date of the first study treatment, or any ongoing event started on the date of the first dose that worsens in severity. Only AEs with an onset date prior to the date of the last dose + 30 days will be tabulated in summary tables. For the purpose of 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 patients in each primary SOC and PT. Patients will be counted only once for each primary SOC and each PT. Summary tables of AEs by primary SOC, PT and intensity will be provided. If a patient has more than one AE coded to the same PT, the patient will be counted only once for that PT by using the event with the highest intensity. Similarly, if a patient has more than one AE within a primary SOC category, the patient will be counted only once in that SOC category by using the event with the highest intensity. AEs by primary SOC, PT and relationship to study drug will be provided as well. If a patient has more than one AE coded to the same PT, the patient will be counted only once for that PT by using the most related event. Similarly, if a patient has more than one AE within a primary SOC category, the patient will be counted only once in that primary SOC category by using the most related event. In addition, SAEs by primary SOC and PT will be provided. Deaths and SAEs will be summarized similarly to AEs. All AE 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. Summaries of these AE subsets will be presented for the following categories:

- Study drug-related
- Intensity
- Serious
- AEs which led to treatment/study discontinuation
- SAEs which led to treatment/study discontinuation
- AEs occurring in 5% or greater of patients (by preferred term)

In the AE summary, the SOCs and the PTs within each SOC will appear in descending order of frequency.

Frequencies of deaths and hospitalizations will also be summarized.
Other safety analyses will be performed as appropriate

11.1.3 LABORATORY ASSESSMENTS

Chemistry, hematology, urinalysis and coagulation profile will be assessed at baseline and over time. 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 patient 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 first dose of CAM2038.

11.1.4 VITAL SIGNS

Vital signs will be assessed over time. Vital sign values and change from baseline in the vital signs will be summarized.

11.1.5 PHYSICAL EXAMINATION

Physical examination data at Screening will be summarized.

11.1.6 12-LEAD ELECTROCARDIOGRAM

12-Lead ECGs will be assessed over time. The ECG variables will include ventricular heart rate and the PR, QRS, QT, QTcB and QTcF intervals. The ECGs will be signed and dated by a medically-qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant.

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

The number and percent of patients 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 patients with increases in these parameters of <30 msec, 30 to <60 msec and greater than/equal to 60 msec will be summarized at each visit.

11.1.7 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.

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

11.1.8 C-SSRS

Data on Columbia-Suicide Severity Rating Scale (C-SSRS) will be summarized over time.

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

Not applicable.

15.0 APPENDICES

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

List of Tables

Number	Title
TABLE 14.1.1.1	Disposition of Enrolled Patients (Overall Safety Population)
TABLE 14.1.1.2	Disposition of Enrolled Patients (Full Exposure Safety Population)
TABLE 14.1.1.3	Disposition of Enrolled Patients (Efficacy Population)
TABLE 14.1.2.1	Demographics (Overall Safety Population)
TABLE 14.1.2.2	Demographics (Full Exposure Safety Population)
TABLE 14.1.2.3	Demographics (Efficacy Population)
TABLE 14.1.3.1	Baseline Clinical Characteristics (Overall Safety Population)
TABLE 14.1.3.2	Baseline Clinical Characteristics (Full Exposure Safety Population)
TABLE 14.1.3.3	Baseline Clinical Characteristics (Efficacy Population)
TABLE 14.1.4.1	Summary of Psychiatric History (Overall Safety Population)
TABLE 14.1.4.2	Summary of Psychiatric History (Full Exposure Safety Population)
TABLE 14.1.4.3	Summary of Psychiatric History (Efficacy Population)
TABLE 14.1.5.1.1	Prior Medications (Overall Safety Population)
TABLE 14.1.5.1.2	Prior Medications (Full Exposure Safety Population)
TABLE 14.1.5.1.3	Prior Medications (Efficacy Population)
TABLE 14.1.5.2.1	Concomitant Medications (Overall Safety Population)
TABLE 14.1.5.2.2	Concomitant Medications (Full Exposure Safety Population)
TABLE 14.1.5.2.3	Concomitant Medications (Efficacy Population)
TABLE 14.1.6.1	Substance Abuse Treatment History (Overall Safety Population)
TABLE 14.1.6.2	Substance Abuse Treatment History (Full Exposure Safety Population)
TABLE 14.1.6.3	Substance Abuse Treatment History (Efficacy Population)
TABLE 14.2.1.1	Summary of Urine Toxicology Results for Illicit Opioid Use Supported by Self-Reported Illicit Opioid Use over Time (Efficacy Population)
TABLE 14.2.1.2	Summary of Urine Toxicology Results for Illicit Opioid Use Without Self-Reported Illicit Opioid Use over Time (Efficacy Population)
TABLE 14.2.2.1	Summary of Mean Percentage of Urine Toxicology Results for Illicit Opioid Use Supported by Self-Reported Illicit Opioid Use (Efficacy Population)
TABLE 14.2.2.2	Summary of Mean Percentage of Urine Toxicology Results for Illicit Opioid Use

	Without Self-Reported Illicit Opioid Use (Efficacy Population)
TABLE 14.2.2.3	Summary of Mean Percentage of Urine Toxicology Results for Illicit Opiiods Use Supported by Self-Reported Illicit Opioid Use by Treatmentment Status at Baseline (New to Treatment [Yes/No])
TABLE 14.2.2.4	Summary of Mean Percentage of Urine Toxicology Results for Illicit Opioid Use Without Self-Reported Illicit Opioid Use by Treatment Status at Baseline (New to Treatment [Yes/No]) (Efficacy Population)
TABLE 14.2.3.1	Summary of Self-Reported Illicit Opioid Use over Time (Efficacy Population)
TABLE 14.2.3.2	Summary of Mean Percentage of Self-Reported Illicit Opioid Use (Efficacy Population)
TABLE 14.2.4.1	Summary of Retention (%) in Treatment over Time (Efficacy Population)
TABLE 14.2.4.2	Time to End of Retention in Treatment (Efficacy Population)
TABLE 14.2.5.1	Summary of Retention (%) in Study over Time (Efficacy Population)
TABLE 14.2.5.2	Time to End of Retention in Study (Efficacy Population)
TABLE 14.2.4.3	Summary of Retention (%) in Treatment over Time by Treatment Status at Baseline (New to Treatment [Yes/No]) (Efficacy Population)
TABLE 14.2.4.4	Time to End of Retention in Treatment by Treatment Status at Baseline (New to Treatment [Yes/No]) (Efficacy Population)
TABLE 14.2.6	Summary of Clinical Opiate Withdrawal Scale (COWS) over Time (Efficacy Population)
TABLE 14.2.7	Summary of Subjective Opiate Withdrawal Scale (SOWS) over Time (Efficacy Population)
TABLE 14.2.8	Summary of Desire to Use VAS over Time (Efficacy Population)
TABLE 14.2.9	Summary of Need to Use VAS over Time (Efficacy Population)
TABLE 14.2.10.1	Summary of Urine Toxicology Results for Other Drugs of Abuse over Time (Efficacy Population)
TABLE 14.2.10.2	Summary of Mean Percentage of Urine Toxicology Results for Other Drugs of Abuse (Efficacy Population)
TABLE 14.2.11	Summary of Work Productivity and Activity Impairment Questionnaire General Health (WPAI-GH) by Item over Time (Efficacy Population)
TABLE 14.2.12	Summary of EQ-5D-5L Health Questionnaire Data over Time (Efficacy Population)
TABLE 14.2.13	Summary of Patient Satisfaction Scale Scores by Item over Time (Efficacy Population)
TABLE 14.3.1.1	Summary of CAM2038 Exposure over Time (Overall Safety Population)
TABLE 14.3.1.2	Summary of CAM2038 Exposure over Time (Full Exposure Safety Population)
TABLE 14.3.1.3	Summary of CAM2038 Exposure by Dose and Number of Injections (Overall Safety Population)
TABLE 14.3.1.4	Summary of CAM2038 Exposure by Dose and Number of Injections (Full Exposure Safety Population)
TABLE 14.3.2.1	Summary of All Adverse Events by System Organ Class, Preferred Term, and Relationship (Overall Safety Population)
TABLE 14.3.2.2	Summary of All Adverse Events by System Organ Class, Preferred Term, and Relationship (Full Exposure Safety Population)
TABLE 14.3.2.3	Summary of All Injection-Related Adverse Events by System Organ Class, Preferred Term, and Relationship (Overall Safety Population)
TABLE 14.3.2.4	Summary of All Injection-Related Adverse Events by System Organ Class,

	Preferred Term, and Relationship (Full Exposure Safety Population)
TABLE 14.3.2.5	Summary of All Injection-Related Adverse Events by Preferred Term, Time to Onset and Duration (Overall Safety Population)
TABLE 14.3.2.6	Summary of All Injection-Related Adverse Events by Preferred Term, Time to Onset and Duration (Full Exposure Safety Population)
TABLE 14.3.2.7	Summary of All Non-Injection Related Adverse Events by System Organ Class, Preferred Term, and Relationship (Overall Safety Population)
TABLE 14.3.2.8	Summary of All Non-Injection Related Adverse Events by System Organ Class, Preferred Term, and Relationship (Full Exposure Safety Population)
TABLE 14.3.3.1	Summary of All Suspected to Be Drug-Related Adverse Events by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.3.2	Summary of All Suspected to Be Drug-Related Adverse Events by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.3.3	Summary of All Injection Related Suspected to Be Drug-Related Adverse Events by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.3.4	Summary of All Injection Suspected to Be Drug-Related Adverse Events by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.3.5	Summary of All Non-Injection Related Suspected to Be Drug-Related Adverse Events by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.3.6	Summary of All Non-Injection Suspected to Be Drug-Related Adverse Events by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.4.1	Summary of All Adverse Events by System Organ Class, Preferred Term, and Severity (Overall Safety Population)
TABLE 14.3.4.2	Summary of All Adverse Events by System Organ Class, Preferred Term, and Severity (Full Exposure Safety Population)
TABLE 14.3.4.3	Summary of All Injection-Related Adverse Events by System Organ Class, Preferred Term, and Severity (Overall Safety Population)
TABLE 14.3.4.4	Summary of All Injection-Related Adverse Events by System Organ Class, Preferred Term, and Severity (Full Exposure Safety Population)
TABLE 14.3.4.5	Summary of All Non-Injection Related Adverse Events by System Organ Class, Preferred Term, and Severity (Overall Safety Population)
TABLE 14.3.4.6	Summary of All Non-Injection Related Adverse Events by System Organ Class, Preferred Term, and Severity (Full Exposure Safety Population)
TABLE 14.3.5.1.1	Summary of Most Common (at least 5%) Adverse Events by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.5.1.2	Summary (number of patients and number of events) of Most Common (at least 5%) Non-Serious Adverse Events by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.5.1.3	Summary (number of patients and number of events) of Serious Adverse Events by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.5.2	Summary of Most Common (at least 5%) Adverse Events by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.5.3	Summary of Most Common (at least 5%) Injection-Related Adverse Events by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.5.4	Summary of Most Common Injection-Related (at least 5%) Adverse Events by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.5.5	Summary of Most Common (at least 5%) Non-Injection Related Adverse Events

	by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.5.6	Summary of Most Common Non-Injection Related (at least 5%) Adverse Events by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.6.1	Summary of All Serious Adverse Events by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.6.2	Summary of All Serious Adverse Events by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.6.3	Summary of All Injection-Related Serious Adverse Events by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.6.4	Summary of All Injection-Related Serious Adverse Events by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.6.5	Summary of All Non-Injection Related Serious Adverse Events by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.6.6	Summary of All Non-Injection Related Serious Adverse Events by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.7.1	Summary of All Adverse Events That Lead to Treatment/Study Discontinuation by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.7.2	Summary of All Adverse Events That Lead to Treatment/Study Discontinuation by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.7.3	Summary of All Injection Related Adverse Events That Lead to Treatment/Study Discontinuation by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.7.4	Summary of All Injection-Related Adverse Events That Lead to Treatment/Study Discontinuation by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.7.5	Summary of All Non-Injection Related Adverse Events That Lead to Treatment/Study Discontinuation by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.7.6	Summary of All Non-Injection Related Adverse Events That Lead to Treatment/Study Discontinuation by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.8.1	Summary of All Serious Adverse Events That Lead to Treatment/Study Discontinuation by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.8.2	Summary of All Serious Adverse Events That Lead to Treatment/Study Discontinuation by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.8.3	Summary of All Injection Related Serious Adverse Events That Lead to Treatment/Study Discontinuation by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.8.4	Summary of All Injection Related Serious Adverse Events That Lead to Treatment/Study Discontinuation by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.8.5	Summary of All Non-Injection Related Serious Adverse Events That Lead to Treatment/Study Discontinuation by System Organ Class and Preferred Term (Overall Safety Population)
TABLE 14.3.8.6	Summary of All Non-Injection Related Serious Adverse Events That Lead to

	Treatment/Study Discontinuation by System Organ Class and Preferred Term (Full Exposure Safety Population)
TABLE 14.3.9.1	Summary of All Deaths and Hospitalizations (Overall Safety Population)
TABLE 14.3.9.2	Summary of All Deaths and Hospitalizations (Full Exposure Safety Population)
TABLE 14.3.9.3	Summary of All Injection-Related Deaths and Hospitalizations (Overall Safety Population)
TABLE 14.3.9.4	Summary of All Injection-Related Deaths and Hospitalizations (Full Exposure Safety Population)
TABLE 14.3.9.5	Summary of All Non-Injection Related Deaths and Hospitalizations (Overall Safety Population)
TABLE 14.3.9.6	Summary of All Non-Injection Related Deaths and Hospitalizations (Full Exposure Safety Population)
TABLE 14.3.10.1	Summary of Columbia-Suicide Severity Ratings over Time (Overall Safety Population)
TABLE 14.3.10.2	Summary of Columbia-Suicide Severity Ratings over Time (Full Exposure Safety Population)
TABLE 14.3.11.1	Summary of Clinical Hematology Data over Time (Overall Safety Population)
TABLE 14.3.11.2	Summary of Clinical Hematology Data over Time (Full Exposure Safety Population)
TABLE 14.3.12.1	Shift from Baseline in Laboratory Tests: Hematology (Overall Safety Population)
TABLE 14.3.12.2	Shift from Baseline in Laboratory Tests: Hematology (Full Exposure Safety Population)
TABLE 14.3.13.1	Summary of Clinical Chemistry Data (Overall Safety Population)
TABLE 14.3.13.2	Summary of Clinical Chemistry Data (Full Exposure Safety Population)
TABLE 14.3.14.1	Shift from Baseline in Laboratory Tests: Chemistry (Overall Safety Population)
TABLE 14.3.14.2	Shift from Baseline in Laboratory Tests: Chemistry (Full Exposure Safety Population)
TABLE 14.3.15.1	Summary of Clinical Coagulation Profile Data (Overall Safety Population)
TABLE 14.3.15.2	Summary of Clinical Coagulation Profile Data (Full Exposure Safety Population)
TABLE 14.3.16.1	Shift from Baseline in Laboratory Tests: Coagulation Profile (Overall Safety Population)
TABLE 14.3.16.2	Shift from Baseline in Laboratory Tests: Coagulation Profile (Full Exposure Safety Population)
TABLE 14.3.17.1	Summary of Vital Signs over Time (Overall Safety Population)
TABLE 14.3.17.2	Summary of Vital Signs over Time (Full Exposure Safety Population)
TABLE 14.3.18.1	Summary of 12-Lead ECG Results (Overall Safety Population)
TABLE 14.3.18.2	Summary of 12-Lead ECG Results (Full Exposure Safety Population)
TABLE 14.3.19.1	Summary of 12-Lead ECG Individual Parameters (Overall Safety Population)
TABLE 14.3.19.2	Summary of 12-Lead ECG Individual Parameters (Full Exposure Safety Population)

List of Listings

Number	Title
LISTING 16.2.1.1	Patient Meeting Inclusion Criteria
LISTING 16.2.1.2	Patients Meeting Exclusion Criteria
LISTING 16.2.2	Protocol Deviations

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 the date of first study dose date.
If (year is present and month and day are missing) or (year and day are present and month is missing):

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

If month and year are present and day is missing:

- If year=year of first dosing and
    - If month = month of first dosing 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 first dosing then set day to last day of month
- If year > year of dosing then set day to first day of month

For all other cases, set onset date to date of first dosing.

For Concomitant Medications

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