Clinical Trial Protocol
HS-13-478

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

CAM2038 q1w (buprenorphine FluidCrystal® once-weekly subcutaneous injection depot), 50 mg/mL

IND 114082

Amendment 1: 2.0, 17-NOV-2015

BRAEBURN PHARMACEUTICALS, INC.:

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Princeton, NJ 08542

Summary of Changes and Justification

Change and Location Within the Protocol	**Rationale**
Updated version and date of the protocol ▪ pp. 1, 71, 72 and footers throughout	To reflect amendment date and version of protocol
Updated Principal Investigator title and address ▪ pp. 2 ▪ Changed "Principal" to "Primary"	To reflect title and to include additional contact information
General stylistic changes and clarifications were made to the overall study design and plan and subsequently to the methodology section of the synopsis to remove redundancies and ensure consistent with the rest of the document: ▪ Synopsis, pp. 3-4 ▪ Section 7, pp. 23-26	Repetitive text was resulting in confusion at CRUs; therefore document was updated to remove redundancies and simplify descriptions.
Date subjects will remain in house was updated to 25 days ▪ Synopsis pp. 4, Inclusion/Exclusion pp. 5 ▪ Section 7.1, pp. 23 ▪ Section 8.1, pp. 35	Number of days was miscounted in original draft
Benzodiazepines excluded from list of exclusionary list of drugs at Screening. ▪ Synopsis Inclusion/Exclusion pp. 5 ▪ Section 8.2, pp. 36	Because opioid-dependent individuals often use benzodiazepines, it was decided to remove the requirement to test negative for benzodiazepines at screening to improve enrollment rates/reduce rescreens etc.
Urine alcohol testing removed from protocol only breath alcohol testing will be conducted ▪ Synopsis Inclusion/Exclusion pp. 5 ▪ Section 8.5, pp. 39 ▪ Table 7, pp. 53 ▪ Section 10.4.4, pp. 54	Urine alcohol tests will not be conducted based on feedback from the CRUs.
Details on reference therapy updated to include how the product will be supplied ▪ Synopsis, pp. 7 ▪ Section 9.2, pp. 40	Additional details added with respect to the hydromorphone product that will be used in Hydromorphone Challenge Sessions, including the amount and make-up of the sterile solution that will be added to ensure that the total injection volume across doses is 1.8 mL.
Change to the primary endpoint and secondary endpoints from "Change from Baseline" to E_{max} ▪ Synopsis, pp 7 ▪ Section 10.7, pp. 58 ▪ Section 12.3.3.1, pp. 63-64	The primary and secondary endpoints were updated to reflect a change to the analysis which will compare results within each hydromorphone challenge session, rather than comparison to baseline/qualification.

Change and Location Within the Protocol	Rationale
Change to the definition of completer and safety analysis populations. Completer population was updated to include all subjects who complete the study (i.e., complete Day 14). Safety population was updated to include all subjects who receive any SC dose of CAM2038. ▪ Synopsis, pp. 8 ▪ Section 12.2, pp. 62	Changes made to include greater detail on the subjects that will be included in each analysis population.
Addition of language to permit one additional dose IR morphine 30 mg, as needed, for the first 3 days of the stabilization portion of the qualification phase, for a total daily dose of 150 mg. ▪ Section 7.1, pp 23 ▪ Section 7.1.2.1, pp. 24 ▪ Table 4, "Footnote z", pp. 30 ▪ Section 7.2, pp. 32 ▪ Section 9.1, pp. 40 ▪ Section 17.2, pp. 75	CRU determined that some subjects may require additional dose during the stabilization phase to avoid withdrawal effects. Therefore, flexibility to administer an additional dose, as needed, was added.
Added subsection to describe in detail the Hydromorphone Challenge Sessions in Section 7.1.4. Subsection is referenced in the following sections: ▪ Section 7.1, pp. 23 ▪ Section 7.1.2.1, pp. 24 ▪ Section 7.1.3.1, pp. 25	Original protocol repeated details of the Hydromorphone Challenge Sessions in multiple locations, subsection was added to avoid redundancies and errors and cross-referenced throughout document.
Language to permit rescreening at the investigator's discretion was added. ▪ Section 7.1.1, pp. 24	Language to allow rescreening of subjects added at request of clinical sites to improve enrollment.
Option to administer additional treatment, as needed, to subjects who do not meet qualification criteria has been added based on the standard practices of the investigational site. ▪ Section 7.1.2.1, pp. 24	Language added based on request from CRUs.
Updates to ancillary medications: 1) Addition of language to indicate that ancillary medications will be made available for symptomatic relief of all episodes of withdrawal (precipitated by CAM2038 q1w and other) with addition of Table 5 which outlines all allowed ancillary meds ; 2) language added to allow administration of ancillary medication at check-in for symptomatic treatment of withdrawal; 3) language to allow ancillary medications (PRNs) as needed, with the exception of Hydromorphone Challenge Session days starting from midnight (i.e., approximately 9 hours prior to dosing) through to the end of the Hydromorphone Challenge Session (i.e., approximately 5 hours after	Update was made to allow for administration of additional ancillary medications.

Change and Location Within the Protocol	Rationale
dosing). Once the session has ended, PRNs will be permitted. Ancillary medications will also not be permitted from midnight on Day -1 (i.e., approximately 9 hours prior to dosing) until after administration of the first dose of CAM2038 on Day 0; 4). ▪ Section 7.1.2.1, pp. 24 ▪ Section 9.7, pp. 44 ▪ Table 5, pp. 45 ▪ Section 10.6.2, pp. 58	
Changes to Table 4 included the following (additions bolded): ▪ ET (early termination) added to Day 14 heading (i.e., 14/**ET**) ▪ Serology panel- no testing Day-10 to Day -6. Also serology panel was updated to **optional**. Also updated in the following sections: o Section 8.2, pp.36 o Table 7, pp.53 ▪ Vital signs will be collected on Day 14/ET ▪ Footnote E: Abbreviated (symptom-directed) physical examination performed at the investigator's discretion (**height will not be measured)** ▪ ECG added on Day 7 with Footnote F. Footnote F has been updated to the following: **ECGs performed prior to dosing with CAM2038 q1w.** ▪ Footnote G**:** Urine drug screen will be administered at **Screening** and **inpatient** check-in. **Additional urine drug screens may be performed at the investigator's discretion.** ▪ Footnote H: A serum pregnancy test will be performed for all females of childbearing potential during **Screening** and **at** inpatient check-in. **Following inpatient** check-in and **throughout the duration of confinement, urine pregnancy tests may be administered at the Investigator's discretion.** ▪ Footnote I: **A urine pregnancy test will be performed for all females of child-bearing potential only prior to IM hydromorphone injection on Day -3 and prior to dosing with CAM2038 q1w on Day 0 and Day 7.** ▪ Addition of row with "FSH Test" with administration at Screening. o Footnote J added: **If post-menopausal females do not have a record of a FSH**	Numerous changes made to footnotes and table to ensure consistency and implement additions requested by investigators. (additions bolded):

Change and Location Within the Protocol	Rationale
test, post-menopausal females will have a FSH test at Screening. ▪ Pulse Oximetry/Cardiac monitoring/Respiratory Rate Monitoring added on all study days except screening. ▪ Footnote M: **Pulse oximetry/Cardiac monitoring/Respiratory rate monitoring will be included on each Hydromorphone Challenge Session day (i.e., Days -3, -2, -1, 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, and 13). Monitoring will be continuous from pre-dose up to 5 hours post-dose or longer, if clinically indicated. After each dose of hydromorphone, subject's oxygen saturation, respiratory rate, and overall safety profile will be reviewed by the research/nursing staff to determine whether it is safe to proceed with administration of the next dose of hydromorphone.** ▪ Vital signs added on Day 0 and Day 7 with the following Footnote P: **On CAM2038 q1w dosing days (i.e., Days 0 and 7), vital signs will be collected at pre-dose and at 15, 30, and 60 minutes post-dose, then hourly up to 6 hours post-dose.** ▪ MADRS added on Days -9,-8, -7, -6, OR -5 to -4 ▪ COWS added on Day 1 to3 & 4 to 6 AND Day 7 and Days 8 to 10 &11 to 13. Footnote T added: ▪ COWS will be administered on each CAM2038 q1w dosing day, prior to dosing. In order to be dosed on Day 0, subjects must have a COWS score ≥ 8. If opioid withdrawal occurs after dosing with CAM2038 q1w (precipitated withdrawal), COWS and OOWS will be collected every 4 hours while the subject is awake for at least 24 hours after dosing. COWS and OOWS will be administered prior to dosing on each Hydromorphone Challenge Session day. ▪ OOWS administered on Day 0 and Day 7. Footnote U updated: COWS **and OOWS** will be administered prior to dosing **on each Hydromorphone Challenge Session and as needed, if a subject experiences precipitated withdrawal following administration of CAM203 q1w.** ▪ Footnote V: Subjects will be given a short-acting oral opioid, **IR** morphine 30 mg, QID, for a minimum of 3 days and a maximum of 7 days	

Change and Location Within the Protocol	Rationale
prior to the Qualification/Baseline Hydromorphone Challenge Session. **One additional dose of IR morphine 30 mg may be administered for the first 3 days of stabilization, as needed, at the investigator's discretion. Subjects will not receive their dose of oral IR morphine 30 mg for approximately 12 hours prior to dosing with CAM2038 q1w on Day 0.** ▪ Footnote W: Subjects will be dosed with either CAM2038 q1w 24 mg or 32 mg SC injection **depending on the subject's treatment group assignment.** A second dose of CAM2038 q1w will be administered on Day 7. ▪ Pharmacokinetic sampling added on Day 7 and Days 8 to 10 & 11 to 13. ▪ Footnote BB: **Pharmacodynamic training may be administered as frequently as required, but all subjects must complete at least one training session prior to the Qualification/Baseline Hydromorphone Challenge Session. Training can only occur prior to or after, but not during the Hydromorphone Challenge Sessions.** ▪ Row added with Severity of Opioid Withdrawal VAS on Days 0 and 7. Footnote DD added: **Severity of Opioid Withdrawal VAS will be administered, as needed, if a subject experiences precipitated withdrawal following administration of CAM203 q1w.** *Tracked version numbering is not accurate, please refer to clean version.	
Addition of "clinically significant" language to exclusion criteria. ▪ Section 7.2, pp.32 ▪ Section 8.2, Exclusion Criteria 7 and 12	Clarification of exclusion criteria at request of the investigators.
Changes made to language within Section 7.2 to be in-line with updates to protocol, improve readability and remove redundancies. Details on how to asses withdrawal and allowable ancillary meds, deleted and moved to different sections. ▪ Section 7.2, pp.32 and 33	Language in Section 7.2 updated to reflect changes in amendment.
Smoking restrictions updated to restrict smoking for at least 30 minutes prior to hydromorphone dosing and allow smoking at short breaks (approximately 5-10 minutes in duration) at the discretion of the CRU staff. Language also added to ensure that if a smoking break is permitted, it must not interfere with study procedures. Language	Based on differences between CRUs, language was added to allow greater flexibility to allow subjects to smoke at the discretion of the investigator. In addition, to avoid nicotine withdrawal,

Change and Location Within the Protocol	Rationale
updated to allow subjects to use a nicotine-containing transdermal system as needed, at the discretion of the Investigator. ▪ Section 8.5, pp. 39	subjects are permitted to use a nicotine-containing transdermal system as needed.
Morphine IR 30 mg tablet for oral administration added to the list of investigational products and dispensing and administration section. Language updated to remove the bottle count (i.e., Morphine sulphate will be supplied as 30 mg tablets. in XX count bottles.) ▪ Section 9.2, pp. 40 ▪ Section 9.2.2., pp. 41	This was missing or included in error in original protocol. Corrected in amendment.
Detail on replacement subjects added to indicated that replacement subjects will receive the same CAM2038 q1w treatment as the subject they are replacing. ▪ Section 9.3, pp. 42	This clarification was added to ensure that the two treatment groups are balanced and that sufficient subjects are enrolled in each.
Requirements for unblinded staff updated as follows as well as to ensure that treatments are volume matched: In order to maintain the blind, unblinded staff, **not otherwise involved in the study** will prepare the **hydromorphone** doses so that **they are volume-matched (1.8 mL, See Section 9.2)**. ▪ Section 9.6, pp.43	Clarification added to ensure that unblinded staff are not involved in any other study procedures.
Language for subject who require analgesic emergency treatment of anesthesia for surgery updated as follows: Opioid receptors are likely to be occupied by BPN, which may reduce the analgesic effects of an opioid. The dissociation of BPN from the receptors may take up to 2 weeks following the last CAM2038 q1w injection. Therefore, subjects requiring analgesic emergency treatment or anesthesia for surgery should ideally be treated with a non-opioid analgesic. Opioids may be used with caution, but as higher doses may be required for analgesic effect, there may be a higher potential for toxicity with opioid administration. The clinical course should be carefully evaluated and fully documented for subjects who have a requirement for any opioid analgesic for >7 days continually or general anesthesia for surgery **within 2 weeks of the final dose of CAM2038 q1w.** ▪ Section 9.7, pp. 44	Language updated to include time constraints of 2 weeks following last dose of CAM2038 q1w, based on expected time for buprenorphine to dissociate from the opioid receptors.
Medical history language updated to include only those reported conditions affecting major body systems that have occurred within the last five years or that the Investigator deems clinically significant. ▪ Section 10.1.3, pp. 46	This clarification was added at the request of the CRUs to avoid confusion around which medical history events are relevant with respect to inclusion.
Contraceptive requirements updated to include male condom **with spermicide,** and to clarify that female	Updated to avoid confusion and ensure adequate contraceptive practices in place.

Change and Location Within the Protocol	Rationale
subjects of non-childbearing potential are **not** required to use contraception but **must have documentation supporting that** they are surgically sterile. ▪ Section 10.1.6, pp. 47	
The following language was removed and clarified: Retraining of subjects is permitted at the Investigator's Discretion." The following language was added: **Study staff are encouraged to provide additional subject training as needed, to ensure that the subjects comprehend the differences between different types of VASs. Training dates/times will be documented in the subject's files. Subject training can only occur before VAS administration or after the 5 hour Challenge session is completed. The training script will be provided to the sites.** ▪ Section 10.3, pp. 47	Language updated to ensure that subjects are not trained during the Hydromorphone Challenge Sessions
Language added to include the assessment of opioid withdrawal severity if precipitated withdrawal following administration of CAM2038 q1w occurs: **If precipitated withdrawal occurs after administration of CAM2038 q1w, subjects will be requested to complete a unipolar VAS assessment of opioid withdrawal severity.** Opioid Withdrawal Severity VAS added to Table 6 and column "include at pre-dose" removed**.** ▪ Section 103.1, pp. 48 ▪ Table 6, pp. 48	Scale added in order to assess the risk of precipitated withdrawal in subjects following study drug treatment. Because all PD measures will be collected at pre-dose, the column "include at pre-dose" was removed from Table 6.
Updates to serious adverse event reporting included increase of reporting period to 30 days after early termination, the site will be required to also fill out an "other concomitant medication and medical history form" in the event of an SAE, and the AE form will need to be email to the sponsor (or designee) or faxed per instructions in the SAE Reporting and Management Plan. ▪ Section 10.4.1.2.1, pp. 50	This text was updated based on input received from the clinical research organization.
Details on clinical laboratory assessments were updated to ensure that all protocol-specified laboratory tests on blood and urine samples would be performed by each clinical site's local laboratory and that blood volumes would be determined by each site's local laboratory. The following text was also added: **It is up to the investigator to review lab results and determine if the abnormal lab results are clinically significant or not.** ▪ Section 10.4.3, pp. 52 and 53	

Change and Location Within the Protocol	Rationale
The section describing vital signs was separated into 2 subsection, Section 10.4.5.1 Qualification Phase vital signs safety monitoring and Section 10.4.5.2 Treatment Phase Vital Signs Safety Monitoring. The following language was added to Section 10.4.5.2: **After each dose of IM hydromorphone during the Treatment Phase Hydromorphone Challenge Sessions, subject's oxygen saturation, respiratory rate, and overall safety profile will be reviewed by the research/nursing staff (as described in Section 7.1.2.1) to determine whether it is safe to proceed with administration of the next dose of hydromorphone.** **Vital signs assessments will be performed at the visits and time points defined in Table 4.** ▪ Section 10.4.5, pp.54 and 55	This section was updated to include additional safety precautions prior to dosing with hydromorphone as part of the challenge session.
Language describing cardiac monitoring was updated to include measurement from inpatient check-in to the end of the Treatment Phase (or Early Termination). Language was also added to allow cardiac monitoring and pulse oximetry equipment to be removed briefly (for hygiene purposes), as needed. ▪ Section 10.4.7, pp. 55	Based on equipment available at the CRUs, the term "Continuous" was removed and language was added to allow subjects to remove the equipment when necessary for brief periods.
Language updated to remove rationale for unipolar VAS administration. Language updated to include alertness/drowsiness VAS not sedation VAS. ▪ Section 10.5, pp. 56 and 57	Based on FDA feedback, the Drug Liking VAS will be administered as a bipolar scale; therefore, rationale for use of unipolar Drug Liking VAS was removed. Alertness/Drowsiness VAS was added and sedation VAS removed, this was an error in the original protocol.
Additional safety measures and withdrawal section separate into 2 subsections, Section 10.6.1 Opioid Effects and Section 10.6.2 Treating Opioid Withdrawal. The following details on treating opioid withdrawal were added as follows: If opioid withdrawal occurs after dosing with CAM2038 q1w (precipitated withdrawal), the following assessments will be collected every 4 hours while the subject is awake for at least 24 hours after dosing to include: 1) COWS, 2) OOWS, 3) VAS assessment of opioid withdrawal severity. Treatment will be based upon clinical judgment of the medically responsible physician at each site. To ensure the safety of subjects, incidences of precipitated withdrawal in response to CAM2038 q1w will be followed carefully and an amendment of the protocol to ensure subjects are	

Change and Location Within the Protocol	Rationale
in a more advanced state of opioid withdrawal e.g., increase required COWS score from 8 to 12, to reduce the risk of BPN-related precipitated withdrawal, will be considered if more than one incidence occurs. Ancillary medications that will be made available for symptomatic relief of all episodes of withdrawal (precipitated by CAM2038 q1w and other) are summarized in Table 5. ▪ Section 10.6.2, pp. 58	
Statistical analysis was updated to further define the way in which TEAEs would be displayed. The following text was updated: During the Qualification Phase subjects TEAEs will be displayed by IR morphine 30 mg treatment or by hydromorphone treatment groups i.e., 0 mg 6 mg or 18 mg - on the days of hydromorphone challenges. **During the Treatment Phase, TEAEs will be displayed by CAM2038 q1w relevant dose and hydromorphone relevant dose i.e., 0 mg 6 mg or 18 mg – on the days of hydromorphone challenges. TEAEs will be displayed** by SOC and preferred term. Additionally, TEAEs will be tabulated for each treatment group by severity and by relationship to the study drug. A listing of SAEs will be provided if applicable. ▪ Section 12.3.4.1, pp. 64 and 65	Based on additional review by the statistics group it was determined that the TEAEs would be displayed by CAM2038 dose and by hydromorphone relevant dose since specific time of AE may not be available.
Copies of the COWS, OOWS, C-SSRS, and MADRS were added in Appendices 17.2 to 17.6, respectively ▪ Appendix 17.2, pp 76 (COWS) ▪ Appendix 17.3, pp. 77 (OOWS) ▪ Appendix 17.4, pp. 78-81 (C-SSRS Baseline) ▪ Appendix 17.5, pp. 82-85 (C-SSRS Since Last Visit) ▪ Appendix 17.6, pp. 66-91 (MADRS)	Details for COWS, OOWS, MADRS, and C-SSRS were added to appendices for reference purposes.
Stylistic changes including updates to text, correcting minor typos, formatting errors, and added abbreviations ▪ Text updated throughout document	To ensure consistency and remove errors.

1. SPONSOR AND KEY PERSONNEL CONTACT INFORMATION

ROLE IN STUDY	NAME	CONTACT INFORMATION
Study Sponsor	Braeburn Pharmaceuticals, Inc.	47 Hulfish Street, Suite 441 Princeton, NJ 08542
Medical Monitor	Charles Laudadio MD	pharmmd@gmail.com (610) 812-3477
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Primary Investigator	Sharon Walsh PhD	sharon.walsh@uky.edu Robert Straus Behavioral Science Building 845 Angliana Avenue Lexington, KY 40508

2. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Braeburn Pharmaceuticals, Inc.

Name of Investigational Product:
CAM2038 q1w (buprenorphine FluidCrystal® once-weekly subcutaneous (SC) injection depot)

Name of Active Ingredient: buprenorphine (BPN)

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

Objectives:

The primary objective of this study is:

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

The secondary objectives of this study are:

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

Methodology:

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

Within 4 weeks of initiating screening, subjects will be admitted to a clinical research unit (CRU) for the Qualification Phase. Following check in to the CRU, subjects will be transitioned to an oral immediate-release (IR) opioid, morphine 30 mg (administered 4 times daily [QID]), for a minimum of 3 days and a maximum of 7 days. After stabilization on IR morphine 30 mg, all subjects will complete a 3-day Qualification/Baseline Hydromorphone Challenge Session which will involve IM administration of 3 doses of hydromorphone (Treatment A: 0 mg [placebo], Treatment B: 6 mg and Treatment C: 18 mg) administered once daily (Day -3, Day -2, and Day -1) in a randomized, double blind, crossover manner, with each hydromorphone administration separated by approximately 24 hours.

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Following the Qualification/Baseline Hydromorphone Challenge Session, eligible subjects will be randomized in a 1:1 ratio to 1 of 2 groups, stratified by gender, to receive CAM2038 q1w at doses of 24 mg or 32 mg. Subjects will receive once weekly SC injections of CAM2038 q1w for 2 weeks (injections on Day 0 and Day 7) and will remain inpatient in the CRU for up to 25 days (including Qualification Phase), during which time 4 Hydromorphone Challenge Sessions (3 consecutive days each) will be conducted on Days 1 to 3, Days 4 to 6, Days 8 to 10, and Days 11 to 13, respectively. Safety and pharmacodynamic assessments will be performed on each day of the Hydromorphone Challenge Sessions at multiple timepoints beginning at pre-dose until approximately 5 hours post-dose. Plasma samples to quantify BPN and obtain norbuprenorphine levels will also be collected approximately 60 minutes prior to hydromorphone dosing on each day of the Hydromorphone Challenge Sessions.

Subjects will be discharged on Day 14 and a follow-up phone interview will be conducted on approximately Day 21.

The degree of hydromorphone dose tolerability will be determined based on the site-specific study Investigator's review of the subject's oximetry data, vital signs, behavior, and physical demeanor.

Number of Subjects (Planned):

The study will enroll a sufficient number of subjects to ensure that at least 48 subjects complete the study (24 subjects per treatment group with at least 16 females in total). Replacement subjects may be added at the discretion of the sponsor with the agreement of the Investigator(s).

Criteria for Inclusion/Exclusion:

Subjects must meet each one of the following inclusion criteria in order to be eligible for participation in the study:

1. Subject must provide written informed consent prior to the conduct of any study-related procedures.
2. Male or female, 18-55 years of age, inclusive.
3. Subjects with a diagnosis of moderate or severe opioid use disorder (Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition [DSM-V]) who are currently physically dependent on IV or insufflated opioids, and who are willing to undergo short-term BPN treatment.
4. Self-reported opioid-use of a minimum of 21 days in the 30 days prior to Screening.
5. Positive urine drug screen (UDS) for opioids at Screening or at check-in. If UDS is not positive, subjects must present with physical signs of withdrawal, as determined by the Investigator. The Investigator may administer a naloxone challenge, in order to confirm opioid dependence at the Investigator's discretion.

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CAM2038 q1w (buprenorphine FluidCrystal® once-weekly subcutaneous (SC) injection depot)

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6. Female subjects of childbearing potential must be willing to use a reliable method of contraception during the entire study (Screening Visit to Follow-Up phone call).
7. Female subjects of non-childbearing potential should be surgically sterile (i.e., have undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation) or in a menopausal state (at least 1 year without menses), as confirmed by follicle stimulating hormone (FSH) levels.
8. Male subjects with female partners of childbearing potential must agree to use a reliable method of contraception from Screening Visit through at least 3 months after the last dose of study drug. Male subjects must also agree not to donate sperm during the study through at least 3 months after the last dose of study drug.
9. Subject is willing and able to comply with the study requirements (including blood sampling), complete study assessments, visit the clinic and remain confined in the CRU for up to 25 consecutive days.

Subjects will not be eligible to participate in this study if any one of the following exclusion criteria is met:

1. History or presence of any clinically significant psychiatric, endocrine, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, renal, or other major disease or illness at Screening, which in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.
2. Opioid dependent subjects who are actively seeking treatment for their moderate to severe opioid use disorder.
3. Subjects with positive urine drug screens for buprenorphine, alcohol, barbiturates, or methadone on the day of check in to the CRU or breath alcohol.
4. Aspartate aminotransferase levels >3 X the upper limit of normal, alanine aminotransferase levels >3 X the upper limit of normal, total bilirubin >1.5 X the upper limit of normal, or creatinine >1.5 X upper limit of normal on the Screening laboratory assessments and at inpatient check-in, or other clinically significant laboratory abnormalities, which in the opinion of the Investigator, may prevent the subject from safely participating in the study.
5. Any clinically significant abnormality on the basis of medical history, vital signs, physical examination, 12-Lead electrocardiogram (QTcF ≥450 msec for males or ≥470 msec for females), and laboratory evaluation (including hematology, clinical chemistry, urinalysis, and optional serology) at Screening, in the opinion of the Investigator.
6. Significant symptoms, medical conditions, or other circumstances which, in the opinion of the Investigator, would preclude compliance with the protocol, adequate cooperation in the study or obtaining informed consent, or may prevent the subject from safely participating in study (including, but not limited to, the risks described as precautions,

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warnings, and contraindications in the current version of the Investigator's Brochure for CAM2038).

7. Subjects will be carefully screened to exclude individuals presenting with or a history of clinically significant seizure disorders, history of asthma or other respiratory disorders, head injury, hypertension or personal history of cardiovascular disease or clinically significant electrocardiogram (ECG).
8. Current diagnosis of Acquired Immune Deficiency Syndrome (AIDS).
9. Current diagnosis of chronic pain requiring opioids for treatment.
10. Subjects who currently meet the criteria for a diagnosis of moderate or severe substance use disorder according to DSM-V criteria for any other substances other than opioids, caffeine or tobacco.
11. Pregnant or lactating, or planning to become pregnant during the study.
12. Clinically significant history of or current evidence of suicidal ideation or active suicidal behavior as based on the Columbia-Suicide Severity Rating Scale (C-SSRS; grade 4 or 5).
13. Hypersensitivity or allergy to BPN or other opioids or excipients of CAM2038.
14. Intolerance to venipuncture and/or difficulty with venous access, as per the judgment of the Investigator/research staff.
15. Subject is currently using an investigational drug or monoamine oxidase inhibitor (MAOI) or has used such within the last 30 days (or 5-times the half-life of the drug, if known and longer) prior to first drug administration in the Qualification Phase (i.e., IR morphine sulfate).
16. Requires current use of agents that are strong inhibitors or inducers of cytochrome P450 3A4 (CYP 3A4), such as some azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., clarithromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir).
17. If the subject is currently on probation or has any pending legal action that could prohibit participation or compliance in the study.
18. A subject who, in the opinion of the Investigator, is considered unsuitable or unlikely to comply with the study protocol for any reason.

Investigational Product, Dosage and Mode of Administration:

- CAM2038 q1w, 50 mg/mL: 24 and 32 mg (BPN base), 0.48 and 0.64 mL SC injection, respectively. SC injections will be performed in the upper buttocks rotating between right and left buttocks.

Reference Therapy, Dosage and Mode of Administration:

- Hydromorphone (10 mg/mL; Dilaudid HP®) for IM administration in the deltoid muscle.

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CAM2038 q1w (buprenorphine FluidCrystal® once-weekly subcutaneous (SC) injection depot)

Name of Active Ingredient: buprenorphine (BPN)

Dilaudid HP® will be supplied as single dose vials for IM administration. Each 1 mL of sterile solution contains 10 mg/mL hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid solution. Hydromorphone 18 mg will be delivered via administration of 1.8mL of this solution. Hydromorphone 6 mg will be a combination of 0.6 mL Dilaudid HP solution + 1.2 mL ½ NS sodium and water for a total injection volume of 1.8 mL. Hydromorphone 0 mg (placebo) will be delivered via administration of 1.8 mL of a solution of 0.45% sodium and water.

- Morphine Sulfate will be supplied as 30 mg tablets.

Duration of Study:

Subjects will participate in the study for approximately 7 weeks, from Screening to Follow-up.

Criteria for Evaluation:

Study Endpoints:

Pharmacodynamic Endpoints

The primary endpoint of this study is the maximum effect (E_{max}) of Drug Liking VAS for hydromorphone.
In addition to the primary endpoint of E_{max} of Drug Liking VAS, the following secondary endpoints will be calculated:

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

Pharmacokinetic Endpoints

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

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

Statistical Methods (Data Analysis):

A sample size of 24 completed subjects will provide 90% power for the CAM2038 32 mg to demonstrate no significant difference in the mean E_{max} score of the Drug Liking VAS compared to 0 mg hydromorphone at a two-sided 0.05 significance level with a non-significant difference cutoff at

Name of Sponsor/Company: Braeburn Pharmaceuticals, Inc.

Name of Investigational Product:
CAM2038 q1w (buprenorphine FluidCrystal® once-weekly subcutaneous (SC) injection depot)

Name of Active Ingredient: buprenorphine (BPN)

<=11 points. In the sample size calculation, it was assumed that the true difference was less than or equal to 1.5 and the standard deviation was 9.8.

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

The plan will be to enroll a sufficient number of subjects to ensure that at least 48 subjects complete the study (24 subjects per treatment group) by over-enrollment as needed and replacement of subjects for those who drop out.

Three populations are defined for the study.

- Intent-to-treat (ITT) Population will consist of all subjects who receive study drug and provide some post-baseline efficacy values.
- Completer Population will include all subjects who complete the study (i.e., complete Day 14). The primary efficacy analyses will be based on the Completer Population.
- Safety Population will include all subjects who receive any SC dose of CAM2038. All safety analyses will be based on the Safety Population.

The primary efficacy variable will be E_{max} of Drug Liking VAS. This variable will be analyzed via a mixed model including subject, hydromorphone challenge dose (A=0 mg, B=6 mg, or C=18 mg), Period (1, 2, or 3 to indicate first, second, or third day of each challenge session), challenge session (1, 2, 3, or 4), where subject will be treated as random effects and the remaining parameters fixed effects. The estimated treatment effects, differences in treatment effects (hydromorphone test dose – the reference dose of 0 mg), and 95% confidence intervals of the differences will be presented. Blockade effects will be claimed if upper bound of the treatment difference is <=11.

Safety analyses will be based on the evaluation of reported adverse events or laboratory outcomes.

3. TABLE OF CONTENTS

Table of Tables

Table of Figures

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{inf}	AUC from time 0 to infinity
BPN	Buprenorphine
C_{av}	Average plasma concentration during a dosing interval
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
CRU	Clinical research unit
CS	Clinically significant
CSR	Clinical study report
$C_{ss,av}$	Average plasma concentration during a dosing interval at steady state
$C_{ss,max}$	Maximum plasma concentration at steady state
$C_{ss,t}$	plasma trough concentration at steady state
C_t	Plasma concentration at time t;
CTA	Clinical Trial Agreement
C_{trough}	Plasma concentration level 7 days after the latest injection
DSM-V	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
E_{max}	Maximum effect
FC	FluidCrystal®
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice

HIV	Human Immunodeficiency Virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IM	Intramuscular
INR	International normalized ratio
IR	Immediate-release
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
MedDRA	Medical Dictionary of Regulatory Activities
mIU/ml	milli international units per milliliter
MOP	Manual of Procedures
NCS	Not clinically significant
OOWS	Objective Opioid Withdrawal Scale
PK	Pharmacokinetic
PO	By mouth
PRN	As needed
PT	Prothrombin time
q1w	Once weekly
q4w	Once monthly
QID	4 times daily
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SL	Sublingual
SOC	System Organ Class
TID	Three times daily
UDS	Urine Drug Screen
US	United States

5. INTRODUCTION

5.1. Background

Buprenorphine (BPN) is an opioid with mixed agonist-antagonist properties that, together with appropriate counseling and psychotherapy, has been shown to be effective in the treatment of opioid dependence. Treatment with BPN has been demonstrated to significantly reduce opioid-positive urines, i.e., to reduce illicit drug use, and increase retention of patients in outpatient treatment programs (Johnson et al., 1992; Strain et al., 1994; Schottenfeld et al.,1997; Ling et al., 1998).

CAM2038 (BPN FluidCrystal® [FC] subcutaneous [SC] injection depot) once weekly (hereafter referred to as CAM2038 q1w) extended release BPN products developed for opioid dependence treatment with a target of once-weekly or once-monthly SC dosing, respectively.

CAM2038 q1w was developed using the proprietary lipid-based and ambient responsive FC Injection depot technology. The principle behind the FC Injection depot is a liquid-to-gel phase transition, occurring immediately as the lipid based FC system is exposed to *in vivo* conditions of SC tissue. The phase transition proceeds from the outside towards the center of the injected FC by absorption of minute quantities of water. Thus, injection of CAM2038 q1w into SC tissue results in an immediate and spontaneous formation of controlled BPN release matrix providing long-acting release *in vivo* with a minimum initial burst release. The dual nature of the FC system, i.e., a true liquid drug product *in vitro* before injection and stable gel *in vivo* after injection, enables a ready-to-use drug product in a prefilled syringe. CAM2038 q1w is designed for convenient and safe SC injection using a prefilled syringe including a needle safety device and with no need for mixing or temperature adjustment prior to administration. In addition, the injection volume for CAM2038 q1w is relatively low (from 0.15 to 0.6 mL volume, depending on dose and product) and can be administered using a fine gauge needle (23 G). CAM2038 depots have been designed with a focus on enabling easy administration, dosing flexibility, and importantly, minimizing risks of misuse, diversion and poor patient adherence.

5.2. Clinical Data

5.2.1. CAM2038 q1w (Once Weekly)

SC CAM2038 q1w has so far been investigated after single and repeated doses in 3 clinical trials, where a total of 176 human subjects (patients and healthy volunteers) have been exposed to the CAM2038 drug products. An initial trial assessed pharmacokinetics, pharmacodynamics and safety in opioid dependent patients (Trial HS-07-307). The results showed that CAM2038 q1w was well tolerated, both locally and systemically. Importantly, no treatment emergent serious adverse events (SAEs) were observed and drug-related local tolerability findings were limited to 4 of 42 patients (9.5%). Three patients experienced mild injection site pain and 1 patient exhibited transient injection site inflammation (mild) and injection site pruritus (moderate).

Two additional clinical trials were subsequently performed in healthy volunteers (under naltrexone blockade) to assess the pharmacokinetics and bioavailability of single and repeat doses of CAM2038 q1w versus repeated doses of sublingual (SL) BPN (i.e., at steady state) and single dose of intravenous (IV) BPN (Trials HS-11-426 and HS-13-487). These two trials demonstrated that after administration of the studied doses of CAM2038 q1w, the plasma concentrations corresponded to those obtained after administration of SL BPN at approved doses (i.e. 8 mg, 16 mg, or 24 mg doses). The BPN levels after administration of CAM2038 q1w were furthermore similar in healthy volunteers and patients with opioid dependence. The systemic tolerability of CAM2038 q1w was good in both trials and similar to the references, IV and SL BPN products, respectively. Local tolerability was very good with no local adverse events (AEs) reported in Trial HS-11-426 (N_{safety}=60) related to injection site tolerability. Similarly, local tolerability was also very good in Trial HS-13-487, featuring 4 repeat SC injections of CAM2038 q1w into the buttock site.

Based on these trials, the following main conclusions were drawn regarding clinical properties of CAM2038 q1w:

- Extended BPN release over one week at target plasma concentrations
- Dose proportionality and flexible/multiple dosing options
- 6- to 8-fold higher bioavailability versus SL BPN
- BPN plasma concentrations over 7 days within ranges of those produced by corresponding SL BPN doses at steady-state (i.e., approved 8 mg, 16 mg, or 24 mg doses)
- Observed and predicted (repeated dose), $C_{max,}$ C_{av} and C_{trough} values for CAM2038 q1w within established therapeutic plasma levels of SL BPN (Subutex®)
- Good safety and systemic tolerability in patients
- Safety in healthy volunteers comparable to reference IV and SL BPN treatments
- Good local tolerability in patients and healthy volunteers

The clinical pharmacokinetic profile and good systemic and local tolerability of CAM2038 q1w evidenced in subjects in these 3 trials is also supported by a large body of data generated in non-clinical pharmacokinetic and toxicology studies in the dog, mini-pig and rat of single and repeat SC doses of CAM2038 q1w, including repeat weekly doses of the FC vehicle formulation for 6 months. SC administration of CAM2038 q1w has been shown to be well tolerated both systemically and locally in the non-clinical studies. The treatment-related findings have been limited to clinical observations in agreement with and considered related to known pharmacological effects of the drug substance BPN, and to reversible, local inflammatory reactions at the SC site of injection. The latter findings were similar to the physiological response to a foreign body. The FC related injection site findings appeared to be reversible and self-limiting, and only apparent at the immediate vicinity of test article deposition. In summary, non-clinical data have indicated no systemic toxicity associated with CAM2038 q1w or the FC injection depot vehicle.

Additional information about CAM2038 can be found in the Investigator's Brochure.

5.2.1.1. Pharmacokinetics

Plasma concentrations of BPN (geometric mean) for the first 36 hours post-dose after single SC administration of CAM2038 q1w are presented in Table 1, respectively (Study HS-11-426 and HS-13-487). Although, the BPN release following CAM2038 q1w SC depot injections have a relatively smooth gradual onset relative to SL BPN formulations, BPN peak plasma concentrations (C_{max}) across doses were observed within the first 24 hours post-dose for both the q1w formulation.

Table 1 Plasma concentrations of buprenorphine (geometric mean) after single subcutaneous administration of CAM2038 q1w to healthy subjects under naltrexone blockade

Time after dose (h)	Plasma concentrations of buprenorphine (ng/mL)		
	CAM2038 q1w 8 mg	CAM2038 q1w 16 mg	CAM2038 q1w 32 mg
Pre-dose	<0.025	<0.025	<0.025
0.5	0.0759	0.253	0.220
1	0.119	0.396	0.391
2	0.257	0.722	0.748
4	0.568	1.39	1.83
6	0.767	1.63	2.61
10	1.40	2.84	4.42
24	1.65	2.84	5.00
36	1.11	2.02	3.76

Source: Study HS-11-426
h = hour; q1w = once weekly

Table 2 and Table 3 summarize observed and predicted BPN after single dose (Table 2) and repeat administration (Table 3) of CAM2038 q1w SC injection and SL BPN (administered as Subutex®) in healthy volunteers under naltrexone blockade. Although there are inherent differences in the pharmacokinetic profiles for daily-, weekly-, and monthly-administered products, pharmacokinetic results from Study HS-11-426 (Study Report HS-11-426) and Study HS-13-487 (Interim Study Report HS-13-487) presented below, suggest that the pharmacokinetic profiles of the q1w formulation are similar with respect to steady state C_{max} and C_{trough} of BPN after SL administration. Based on these similarities, the current study will examine the opioid-blocking effects of only the CAM2038 q1w formulation.

Table 2 Observed and predicted buprenorphine exposure after single administration of SC CAM2038 q1w, SC CAM2038 q4w, and SL Subutex® in healthy subjects

Treatment	Study	Geometric Mean (geometric CV%)		
		C_{max} (ng/mL)	C_t (ng/mL)[a]	AUC_{inf} (ng*h/mL)
SC CAM2038 q1w				
8 mg	HS-11-426	1.7 (36)	0.30 (26)	166 (20)
16 mg	HS-11-426	3.1 (49)	0.61 (25)	335 (13)
16 mg	HS-13-487	3.1 (46)	0.58 (25)	NC
24 mg		4.2[b]	0.86[b]	487[b]
32 mg	HS-11-426	5.3 (45)	1.1 (24)	638 (12)
SC CAM2038 q4w				
64 mg	HS-13-487	3.8 (60)	0.45 (57)	1360 (33)
96 mg		5.2[b]	0.69[b]	1960[b]
128 mg	HS-13-487	6.6 (68)	0.93 (33)	2550 (26)
160 mg		7.9[b]	1.2[b]	3120[b]
SL Subutex				
8 mg	HS-11-426	4.3 (32)	0.25 (38)	NC
16 mg	HS-11-426	6.7 (62)	0.38 (36)	NC
24 mg	HS-11-426	7.1 (19)	0.49 (39)	NC
8 mg	HS-13-487	4.4 (41)	0.26 (35)	NC
16 mg	HS-13-487	5.9 (31)	0.37 (44)	NC
24 mg	HS-13-487	8.2 (60)	0.54 (44)	NC

AUC_{inf} = are under the plasma concentration-time curve from time 0 to infinity; C_{max} = maximum plasma concentration; C_t = plasma concentration at time t; CV = coefficient of variation; NC = Not calculated; SL = sublingual

a. C_t at 7 days for SC CAM2038 q1w, C_t at 1 day (24 hours) for SL Subutex®
b. Predicted from linear regression analysis of logarithmic pharmacokinetic variable vs. logarithmic dose

Table 3 Observed and predicted buprenorphine exposure after steady state administration of SC CAM2038 q1w, SC CAM2038 q4w, and SL Subutex® in healthy subjects

Treatment	Study	Geometric Mean (geometric CV%)		
		$C_{ss,max}$ (ng/mL)	$C_{ss,av}$ (ng/mL)	$C_{ss,t}$ (ng/mL)
SC CAM2038 q1w				
8 mg		1.7[a]	1.0[b]	0.45[a]
16 mg	HS-13-487	4.3 (44)	2.1 (24)	0.84 (22)
24 mg		5.2[a]	2.9[b,c]	1.4[a]
32 mg		6.9[a]	3.8[b]	1.8[a]
SC CAM2038 q4w				
64 mg		3.9[a]	2.0[b]	1.1[a]
96 mg		5.8[a]	2.9[b,c]	1.6[a]
128 mg		7.8[a]	3.8[b]	2.1[a]
160 mg		9.8[a]	4.6[b,c]	2.7[a]
SL Subutex				
8 mg	HS-11-426	4.7 (29)	1.1 (34)	0.61 (46)
16 mg	HS-11-426	6.3 (49)	1.6 (37)	0.79 (58)
24 mg	HS-11-426	7.8 (37)	2.3 (29)	1.2 (44)
8 mg	HS-13-487	4.7 (36)	1.2 (33)	0.68 (52)
16 mg	HS-13-487	6.7 (47)	1.9 (33)	1.1 (46)
24 mg	HS-13-487	8.5 (54)	2.7 (34)	1.6 (40)

$C_{ss,max}$ = maximum plasma concentration at steady state; $C_{ss,av}$ = average plasma concentration during a dosing interval at steady state; $C_{ss,t}$ = plasma trough concentration at steady state; CV = coefficient of variation; PK = pharmacokinetic

a. Predicted by simulation from a nonlinear mixed effects pharmacokinetic model describing observed pharmacokinetic data.
b. Predicted and calculated from AUC_{inf} after single dosing and assuming time-independent pharmacokinetic.
c. Predicted from linear regression analysis of logarithmic pharmacokinetic variable vs. logarithmic dose.

Figure 1 below provides graphical illustrations of observed and predicted plasma BPN concentrations for different doses of CAM2038 q1w, CAM2038 q4w, and SL BPN (Subutex®) over 28 days.

Figure 1 **Observed steady state arithmetic mean C_{max} and C_{trough} of buprenorphine after sublingual administration of Subutex®, and observed and predicted steady state plasma concentration profiles after subcutaneous administration of CAM2038 q1w and CAM2038 q4w based on data from Studies HS-11-426 and HS-13-487 (semi-logarithmic scales)**

Figure 1A

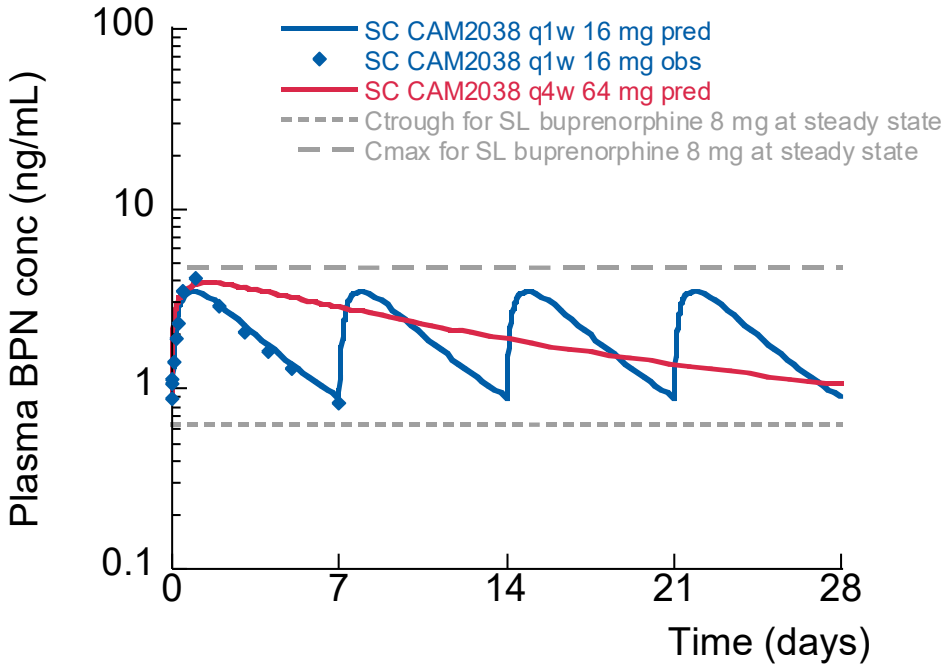


Figure 1B

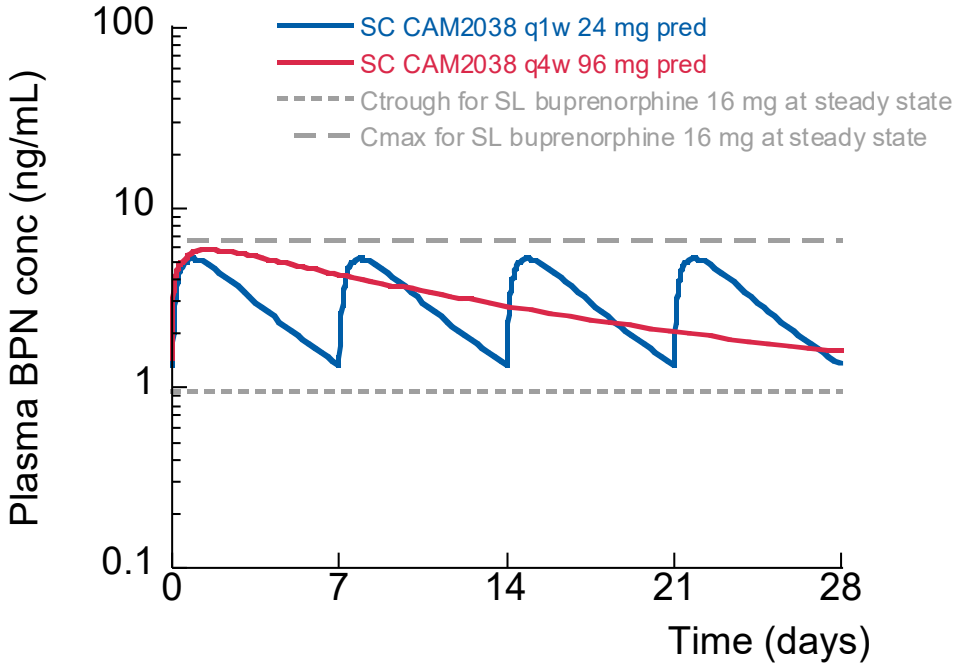
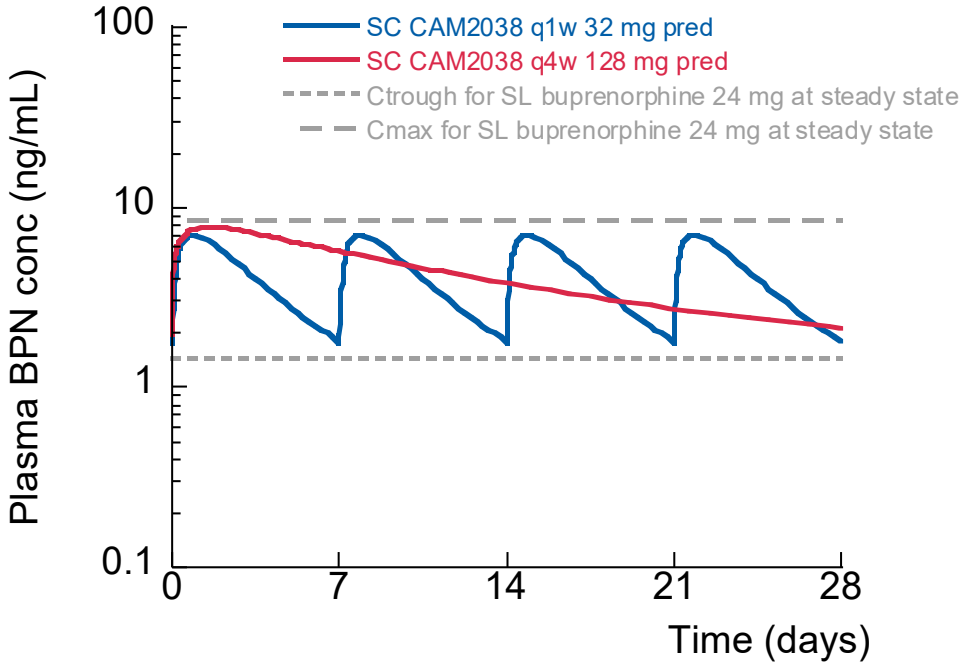


Figure 1C



C_{max}= maximum plasma concentration; C_{trough}= trough plasma concentrations; q1w= once weekly dosing
Geometric mean observed steady state C_{max} and C_{trough} for Subutex® from HS-11-426 and HS-13-487
Predicted plasma concentration versus time profiles for CAM2038 q1w from single and repeat dose data in HS-13-487
Observed steady state plasma concentration versus time profiles for CAM2038 q1w 16 mg from HS-13-487
Predicted steady state plasma concentration versus time profiles for CAM2038 q4w from single-dose data in HS-13-487

5.3. Study Rationale

Opioid drug dependence is a major health and social issue and is often a chronic medical condition that requires long-term maintenance treatment. An important aim of the treatment programs for opioid drug dependence is to reduce illicit drug use, reduce the associated harms and stabilize patients pharmacologically to allow them to engage in psychosocial interventions to assist in their recovery. Successful treatment can decrease morbidity and mortality, improve patients' quality of life, and reduce the burden on society. Moreover, individuals with opioid use disorder often engage in higher risk behaviors such as injecting with used syringes and needles, and thus expose themselves to high risk of transmission of infectious diseases, including human immunodeficiency virus (HIV) and hepatitis C.

Clinical studies have reported that BPN is effective at attenuating the effects of subsequently administered opioids, including those of acute doses of morphine up to 120 mg for up to 29.5 hours (Jasinski et al., 1978). Buprenorphine has also demonstrated the ability to dose-dependently decrease the effects of hydromorphone (Walsh et al., 1995; Bickel et al., 1988). These studies indicate that BPN (at doses ranging from 2 to 32 mg SL BPN) can attenuate the effects of hydromorphone, including subjective effects and euphoria in a dose-dependent manner. Furthermore, it was suggested that some therapeutic benefit of opioid attenuation was evident after the first dose.

The present study will investigate the presence, duration, and degree of full mu-opioid agonistic effect blockade provided by CAM2038 q1w administered at therapeutic doses for opioid maintenance therapy in patients with opioid use disorder.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of the study is:

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

6.2. Secondary Objectives

The secondary objectives of this study are:

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

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

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

Within 4 weeks of initiating screening, subjects will be admitted to a clinical research unit (CRU) for the Qualification Phase. Following check in to the CRU, subjects will be transitioned to a short-acting oral opioid, IR morphine 30 mg, (administered 4 times daily [QID]), for a minimum of 3 days and a maximum of 7 days (Qualification Phase described in detail in Section 7.1.2). One additional dose of IR morphine 30 mg may be administered for the first 3 days of stabilization, as needed, at the investigator's discretion. After stabilization on IR morphine 30 mg, all subjects will complete a 3-day Qualification/Baseline Hydromorphone Challenge Session which will involve IM administration of 3 doses of hydromorphone (Treatment A: 0 mg [placebo], Treatment B: 6 mg and Treatment C: 18 mg) administered once daily (Day -3, Day -2, and Day -1) in a randomized, double blind, crossover manner, with each hydromorphone administration separated by approximately 24 hours (described in detail in Section 7.1.4).

Following the Qualification/Baseline Hydromorphone Challenge Session, eligible subjects will receive CAM2038 q1w at doses of 24 mg or 32 mg (randomized in a 1:1 ratio to 1 of 2 groups). Subjects will receive once weekly SC injections of CAM2038 q1w for 2 weeks (injections on Day 0 and Day 7) and will remain inpatient in the CRU for up to 25 days (including Qualification Phase), during which time 4 Hydromorphone Challenge Sessions (3 consecutive days each) will be conducted on Days 1 to 3, Days 4 to 6, Days 8 to 10, and Days 11 to 13, respectively. Safety and pharmacodynamic assessments will be performed on each day of the Hydromorphone Challenge Sessions at multiple timepoints beginning at pre-dose until approximately 5 hours post-dose. Plasma samples to quantify BPN and norbuprenorphine levels will also be obtained approximately 60 minutes prior to hydromorphone dosing on each day of the Hydromorphone Challenge Sessions.

Subjects will be discharged on Day 14 and a follow-up phone interview will be conducted on approximately Day 21.

The degree of hydromorphone dose tolerability will be determined based on the site-specific study Investigator's review of the subject's oximetry data, vital signs, behavior, and physical demeanor.

To ensure adequate enrollment and address potential inconvenience to subjects, all subjects will receive appropriate compensation for time and travel expenses related to attendance at study visits. All costs of study participation, including study medications will be covered.

7.1.1. Screening Visits (Day -31 to Day -11):

Medical and eligibility screening will occur within roughly 3 weeks of check in to the inpatient Qualification Phase (Day -10, Day -9, Day -8, Day -7, or Day -6). At the first Screening Visit, subjects will provide written informed consent to participate in the study before any protocol-specified procedures or assessments are completed. Screening will include standard medical screening procedures, complete medical/psychosocial history, urine drug screen (UDS) and detailed substance use and treatment, using timeline follow-back methods (Fals-Stewart et al., 2000), as outlined in Table 4. Screening may occur over several outpatient visits. Subjects may be rescreened at the Investigator's discretion.

7.1.2. Qualification Phase

7.1.2.1. Day -10 to Day -1

During the Qualification Phase, subjects will be admitted to a CRU for a stabilization period starting on Day -10 during which all subjects will be stabilized on a short-acting oral opioid (i.e., morphine) to suppress opioid withdrawal. Subjects will receive IR morphine 30 mg, QID for a total daily dose of 120 mg; subjects will be permitted to receive an additional dose of IR morphine 30 mg dose (total daily dose of 150 mg), as needed (PRN) for the first 3 days only. At inpatient check-in, ancillary medications will be made available for symptomatic relief of withdrawal (see Table 5**Error! Reference source not found.Error! Reference source not found.** for the list of allowed medications). Subjects will receive IR morphine 30 mg (as outlined above) for a minimum of 3 days and a maximum of 7 days prior to entering the Qualification/Baseline Hydromorphone Challenge Session, dependent on the individual's underlying level of dependence.

During this stabilization period, subjects will be monitored carefully for safety. Before each scheduled IR morphine 30 mg dose is administered, research/nursing staff will record oxygen saturation and respiratory rate and assess the subject for sedation and/or intoxication. If respiratory rate drops to <12 breaths per minute or oxygen saturation is <95%, the measurements will be repeated and recorded. If either oxygen saturation or respiratory rate remains outside the pre-specified parameters or the subject appears sedated or intoxicated, the oral maintenance dose of IR morphine 30 mg will be withheld and a study Investigator notified. The withheld dose may be administered later (and the administration time recorded) once it is determined that the subject's status has returned to within a safe range.

On the evening prior to and on the morning of each Qualification/Baseline Hydromorphone Challenge Session day i.e., Day -3, Day -2 and Day -1, subjects will not receive their IR morphine 30 mg dose; therefore, the last active dose of IR morphine 30 mg will be administered a minimum of 12 hours before administration of hydromorphone during the Hydromorphone Challenge Session (see sample IR morphine 30 mg administration schedule in Section 17.1).

On Days -3 to -1, a Qualification/Baseline Hydromorphone Challenge Session will be completed (described in Section 7.1.4). The purpose of the Qualification/Baseline Hydromorphone Challenge Session is to ensure that subjects can discriminate and show positive subjective effects of 6 mg and 18 mg IM hydromorphone compared to IM hydromorphone 0 mg (placebo). After completion of each day of the Hydromorphone Challenge Session, subjects will be assessed by

research or nursing staff, based upon the same respiratory rate and oxygen saturation criteria described above, to determine if it is safe to resume administration of IR morphine 30 mg maintenance dosing, with dosing time documented. In the event that IR morphine 30 mg dosing is withheld in the afternoon, oral IR morphine 30 mg for the evening dose will be scheduled for no later than the original scheduled administration time in order to maintain consistency between time of last active dose and hydromorphone dose administration the following day. Subjects who are not eligible to continue to the Treatment Phase i.e., do not meet Qualification criteria (Section 8.3) will be discharged from the CRU at approximately 24 hours after administration of the Day -1 IM hydromorphone dose. Prior to discharge, subjects may be offered additional treatment, as needed, per the standard practices of the investigational site. Those subjects who meet Qualification criteria will proceed to the Treatment Phase.

7.1.3. Treatment Phase

7.1.3.1. Days 0 to 6

On the morning of Day 0 of the Treatment Phase, subjects will receive one of the following treatments (based on randomization in a 1:1 ratio, stratified by gender) to:

- Group A: CAM2038 q1w 24 mg SC injection
- Group B: CAM2038 q1w 32 mg SC injection

Maintenance IR morphine 30 mg will be withheld for at least 12 hours prior to CAM2038 q1w dosing; therefore, the Day -1 evening dose and the Day 0 morning dose of IR morphine 30 mg will be withheld. The Clinical Opiate Withdrawal Scale (COWS; See Section 17.2) will be administered prior to dosing with CAM2038 q1w; in order to be dosed on Day 0, subjects will be required to have a COWS score of ≥ 8, indicative of mild withdrawal.

CAM2038 q1w treatment will be administered at approximately 9:00 am; CAM2038 q1w administration instructions for user (IFU) will be provided in the Manual of Procedures (MOP).

On Days 1 to 3 and Days 4 to 6, subjects will undergo 2 separate Hydromorphone Challenge Sessions (described in Section 7.1.4), with each daily challenge dose of IM hydromorphone administered at approximately 9:00 am (i.e., approximately 24, 48, 72, 96, 120, and 144 hours following Day 0 CAM2038 q1w injection). Safety and pharmacodynamic assessments will be conducted immediately following each dose of hydromorphone administered in each Hydromorphone Challenge Session (maximum 5 hours after Hydromorphone Challenge Session). Plasma samples will also be collected prior to hydromorphone dosing on each day of the Hydromorphone Challenge Sessions.

7.1.3.2. Days 7 to 14:

On the morning of Day 7 (approximately 9:00 am) of the Treatment Phase, each Group (A and B) will receive a second dose of CAM2038 q1w according to their assigned treatment group. On Days 8 to 10 and Days 11 to 13, subjects will undergo 2 separate Hydromorphone Challenge Sessions, with each daily challenge dose of IM hydromorphone administered at approximately 9:00 am (i.e., approximately 24, 48, 72, 96, 120, and 144 hours following Day 7 CAM2038 q1w injection). As in previous sessions, each Hydromorphone Challenge Session will consist of subjects receiving 3 doses of IM hydromorphone (0 mg [placebo], 6 mg and 18 mg) in a

randomized, crossover manner. Safety and pharmacodynamic assessments will be conducted immediately following each dose of hydromorphone administered in each Hydromorphone Challenge Session (maximum 5 hours after Hydromorphone Challenge Session).

Subjects will be discharged on Day 14, if medically acceptable according to the investigator or designee.

7.1.4. Hydromorphone Challenge Sessions

Each Hydromorphone Challenge Session in the Qualification Phase and Treatment Phase will consist of the injection of 3 doses of IM hydromorphone 10 mg/mL (0 mg [placebo], 6 mg and 18 mg) administered once daily over 3 consecutive days in randomized order. Subjects will be randomized in a 1:1:1:1:1:1 ratio to 1 of 6 treatment sequences according to two 3 × 3 William squares. The following treatment sequences will be used: ABC, ACB, BAC, BCA, CAB, and CBA, where A, B, and C are IM Hydromorphone Challenge Sessions with 0 mg (placebo), 6 mg, and 18 mg, respectively. The volume of the 0 mg and 6 mg doses of IM hydromorphone will be the same as the volume of the 18 mg hydromorphone dose. Safety and pharmacodynamic assessments will be performed immediately following each dose of hydromorphone administered on each day of the Hydromorphone Challenge Session for a maximum 5 hours after Hydromorphone Challenge Session. Plasma BPN and norbuprenorphine levels will also be obtained approximately 60 minutes prior to hydromorphone dosing on each day of the Hydromorphone Challenge Sessions. After each dose of hydromorphone, subject's oxygen saturation, respiratory rate, and overall safety profile will be reviewed by the research/nursing staff (as described in Section 7.1.2.1) to determine whether it is safe to proceed with administration of the next dose of hydromorphone.

7.1.5. Follow-up Phase

Following the last day of the Treatment Phase (i.e., Day 14), plasma BPN levels are expected to be approximately 1.4 to 1.8 ng/mL and to gradually taper off; therefore, subjects are not expected to experience immediate withdrawal effects at the time of discharge. A follow-up telephone interview will be conducted approximately 7 days after discharge from the CRU to obtain information on any safety issues including withdrawal effects.

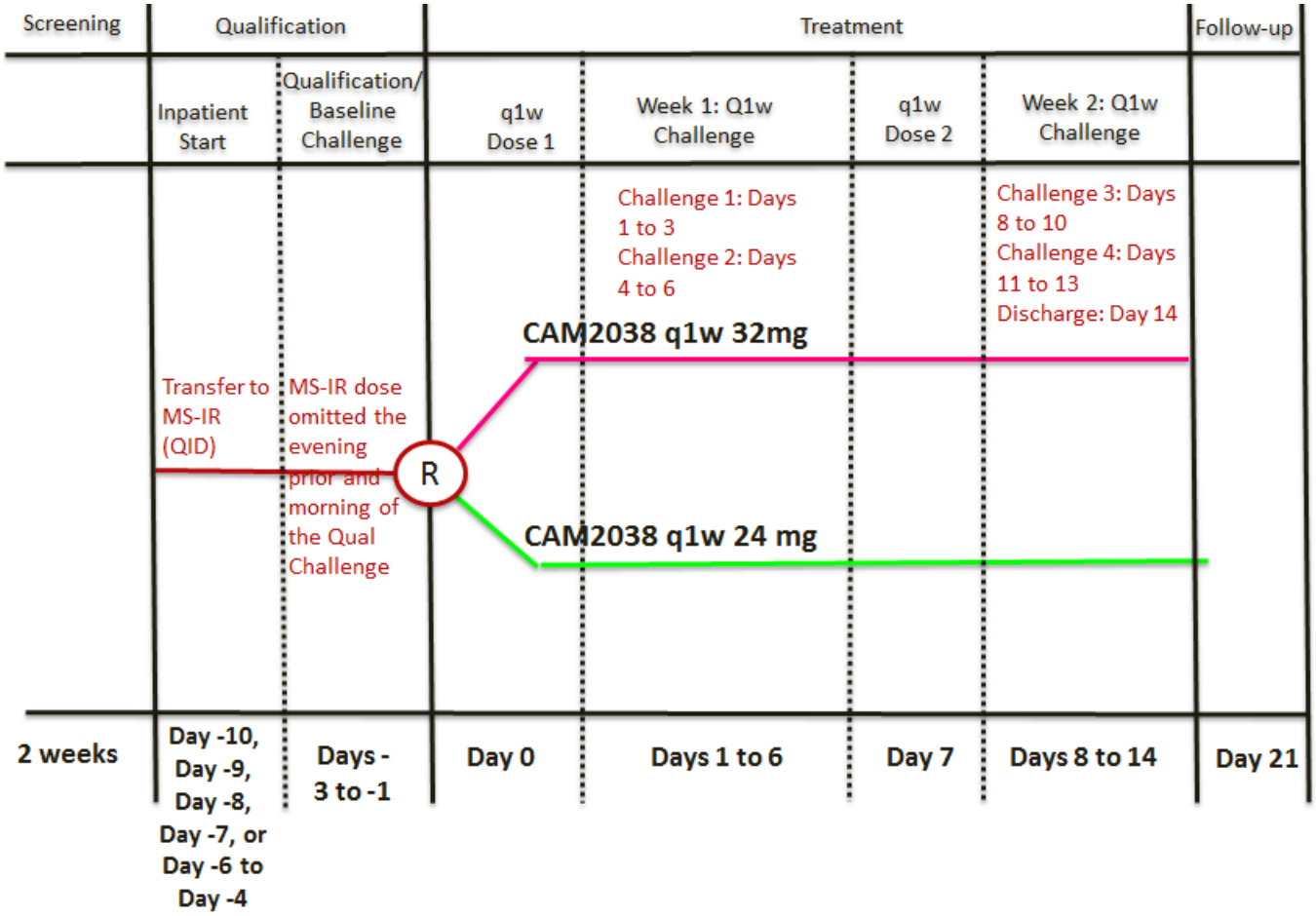
Subjects will participate in the study for approximately 7 weeks, from Screening to Follow-up.

An overview of the study design is provided in Figure 2.

Study assessments and procedures will be performed at the visits and time points outlined in the Schedule of Assessments.

Section 10 provides additional information on the baseline, safety, and pharmacodynamic procedures and assessments included in the study. Pharmacodynamic endpoints are described in Section 10.7. Statistical analysis is described in Section 12.

Figure 2 Overview of Study Design



IR = immediate-release; MS = morphine sulfate; q1w = once weekly dosing; R = randomization

Table 4 Schedule of Assessments

	Screening	Inpatient Qualification Phase			Inpatient Treatment Phase					Follow-up Phone Call
Visit:	**1**	**2**								
Day:	**-39 to -11**	**-10, -9, -8, -7, OR -6**	**-9, -8, -7, -6, OR -5 to -4**	**-3 to -1**	**0**	**1 to 3 & 4 to 6**	**7**	**8 to 10 & 11 to 13**	**14/ ET**	**21**
Assessment										
Informed Consent[a]	X									
Eligibility Criteria Review[b]	X	X								
Medical and Medication History	X	X[c]								
DSM-V	X									
Physical Examination (including BMI)	X[d]	X[e]							X[e]	
Serology panel (optional)	X									
Concomitant Meds/Procedures	X	X	X	X	X	X	X	X	X	X
ECG	X	X			X[f]		X[f]		X	
Urine Drug Screen[g]	X	X								
Breath Alcohol Test	X	X								

[a] Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.
[b] Prior to enrollment in the Qualification Phase of this study, all Inclusion and Exclusion criteria must be met.
[c] Brief update on the subject's medical and medication history since Screening at inpatient check-in only.
[d] A complete physical exam of all major body systems will be performed during Screening including height, weight and BMI.
[e] Abbreviated (symptom-directed) physical examination performed at the investigator's discretion (height will not be measured)
[f] ECGs performed prior to dosing with CAM2038 q1w
[g] Urine drug screen will be administered at Screening and inpatient check-in. Additional urine drug screens may be performed at the investigator's discretion.

	Screening	Inpatient Qualification Phase			Inpatient Treatment Phase					Follow-up Phone Call
Visit:	**1**	**2**								
Day:	**-39 to -11**	**-10, -9, -8, -7, OR -6**	**-9, -8, -7, -6, OR -5 to -4**	**-3 to -1**	**0**	**1 to 3 & 4 to 6**	**7**	**8 to 10 & 11 to 13**	**14/ ET**	**21**
Pregnancy Test	X[h]	X[h]		Xi	X[i]		Xi			
FSH Test[j]	X									
Laboratory Tests[k]	X	X							X	
Pulse Oximetry/Cardiac monitoring/Respiratory Rate Monitoring		X[l]	X	X[m]	X	X[m]	X	X[m]		
Vital Signs[n]	X	X	X	X[o]	X[p]	X[o]	X[p]	X[o]	X	

[h] A serum pregnancy test will be performed for all females of childbearing potential during Screening and at inpatient check-in. Following inpatient check-in and throughout the duration of confinement, urine pregnancy tests may be administered at the Investigator's discretion.

[i] A urine pregnancy test will be performed for all females of child-bearing potential only prior to IM hydromorphone injection on Day -3 and prior to dosing with CAM2038 q1w on Day 0 and Day 7.

[j] If post-menopausal females do not have a record of a FSH test, post-menopausal females will have a FSH test at Screening.

[k] Includes chemistry, hematology, urinalysis and coagulation profile.

[l] Before each scheduled IR morphine 30 mg dose is administered, research/nursing staff will record oxygen saturation and respiratory rate and assess the subject for sedation and/or intoxication. If respiratory rate drops to <12 breaths per minute or oxygen saturation is <95%, the measurements will be repeated and recorded. If either oxygen saturation or respiratory rate remains outside parameters or the subject appears sedated or intoxicated, the oral maintenance dose will be withheld and a study Investigator notified. The withheld dose may be administered later (and the administration time recorded) once it is determined that the subject's status has returned to within a safe range. Continuous pulse oximetry and telemetry can be implemented at the Investigator's discretion.

[m] Pulse oximetry/Cardiac monitoring/Respiratory rate monitoring will be included on each Hydromorphone Challenge Session day (i.e., Days -3, -2, -1, 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, and 13). Monitoring will be continuous from pre-dose up to 5 hours post-dose or longer, if clinically indicated. After each dose of hydromorphone, subject's oxygen saturation, respiratory rate, and overall safety profile will be reviewed by the research/nursing staff to determine whether it is safe to proceed with administration of the next dose of hydromorphone.

[n] Includes temperature, blood pressure, pulse rate, respiratory rate.

[o] On each Hydromorphone Challenge Session day (i.e., Days -3, -2, -1, 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, and 13), vital signs will be collected predose and at 15, 30, 45, 60, 90, 120 and 180 minutes post-dose and then hourly up to 5 hours post-dose.

[p] On CAM2038 q1w dosing days (i.e., Days 0 and 7), vital signs will be collected at pre-dose and at 15, 30, and 60 minutes post-dose, then hourly up to 6 hours post-dose.

	Screening	Inpatient Qualification Phase			Inpatient Treatment Phase					Follow-up Phone Call
Visit:	**1**	**2**								
Day:	**-39 to -11**	**-10, -9, -8, -7, OR -6**	**-9, -8, -7, -6, OR -5 to -4**	**-3 to -1**	**0**	**1 to 3 & 4 to 6**	**7**	**8 to 10 & 11 to 13**	**14/ ET**	**21**
Adverse Events[q]	X	X	X	X	X	X	X	X	X	X
C-SSRS (baseline/screening)	X									
C-SSRS (since last visit)[r]			X		X		X		X	
MADRS[s]	X		X		X		X		X	
COWS[t]	X	X	X	X	X[u]	X	X[u]	X	X	
OOWS				X	X[u]	X	X[u]	X	X	
CAM2038 Injection Site Examination					X	X	X	X	X	
Oral IR Morphine 30 mg Dosing[v]		X	X	X						
CAM2038 q1w SC Injection[w]					X		X			
Hydromorphone Challenge Session[x]				X		X		X		

[q] Any spontaneously reported adverse events will be recorded after the subject signs the informed consent form.
[r] C-SSRS (since last visit) will be administered on Day -4, prior to dosing with CAM2038 q1w on Day 0 and Day 7, and prior to discharge on Day 14/ET.
[s] MADRS will be administered at Screening, Day -4, prior to dosing with CAM2038 q1w on Day 0 and Day 7, and prior to discharge on Day 14/ET.
[t] COWS will be administered on each CAM2038 q1w dosing day, prior to dosing. In order to be dosed on Day 0, subjects must have a COWS score ≥ 8. If opioid withdrawal occurs after dosing with CAM2038 q1w (precipitated withdrawal), COWS and OOWS will be collected every 4 hours while the subject is awake for at least 24 hours after dosing. COWS and OOWS will be administered prior to dosing on each Hydromorphone Challenge Session day.
[u] COWS and OOWS will be administered prior to dosing on each Hydromorphone Challenge Session and as needed, if a subject experiences precipitated withdrawal following administration of CAM203 q1w.
[v] Subjects will be given a short-acting oral opioid, IR morphine 30 mg, QID, for a minimum of 3 days and a maximum of 7 days prior to the Qualification/Baseline Hydromorphone Challenge Session. One additional dose of IR morphine 30 mg may be administered for the first 3 days of stabilization, as needed, at the investigator's discretion. Subjects will not receive their dose of oral IR morphine 30 mg for approximately 12 hours prior to dosing with CAM2038 q1w on Day 0.
[w] Subjects will be dosed with either CAM2038 q1w 24 mg or 32 mg SC injection depending on the subject's treatment group assignment. A second dose of CAM2038 q1w will be administered on Day 7.
[x] Subjects will be scheduled to receive 3 doses of hydromorphone (0 mg [Placebo], 6 mg, and 18 mg) in a randomized crossover manner over 3 consecutive days.

	Screening	Inpatient Qualification Phase			Inpatient Treatment Phase					Follow-up Phone Call
Visit:	**1**	**2**								
Day:	**-39 to -11**	**-10, -9, -8, -7, OR -6**	**-9, -8, -7, -6, OR -5 to -4**	**-3 to -1**	**0**	**1 to 3 & 4 to 6**	**7**	**8 to 10 & 11 to 13**	**14/ ET**	**21**
Pharmacokinetic sampling					X[y]	X[z]	X[y]	X[z]	X[aa]	
Pharmacodynamic training/practice		X[bb]								
VAS[cc]				X		X		X		
Severity of Opioid Withdrawal VAS					X[dd]		X			
Check-in		X								
Discharge									X[ee]	

BMI=body mass index; COWS=Clinical Opiate Withdrawal Scale; C-SSRS=Columbia-Suicide Severity Rating Scale; DSM-V = Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition; ECG=electrocardiogram; ET=Early Termination; FSH=Follicle Stimulating Hormone; HIV= Human Immunodeficiency Virus; MADRS=Montgomery-Asberg Depression Rating Scale; OOWS=Objective Opioid Withdrawal Scale; PD=pharmacodynamic VAS= visual analog scale.

[y] Blood samples will be taken pre-dose and 1, 4, 6 and 8 hours after CAM2038 q1w injection
[z] Blood samples will be taken approximately 60 minutes prior to administration of hydromorphone on each of the 3 Hydromorphone Challenge Session days during the Treatment Phase (i.e., Days 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, and 13).
[aa] Blood samples will be taken approximately 168 hours after CAM2038 q1w injection
[bb] Pharmacodynamic training may be administered as frequently as required, but all subjects must complete at least one training session prior to the Qualification/Baseline Hydromorphone Challenge Session. Training can only occur prior to or after, but not during the Hydromorphone Challenge Sessions.
[cc] On Hydromorphone Challenge Session days (i.e., Day -3, -2, -1, 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, and 13), subjective measures (Drug Liking, Feeling High, Any Drug Effects, Good Drug Effects, Bad Drug Effects, Sedated, Desire to Use Opioids VAS) assessments will be performed at predose (up to 15 minutes prior to dosing) and at 5, 10, 15, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 270 and 300 minutes post-dose.
[dd] Severity of Opioid Withdrawal VAS will be administered, as needed, if a subject experiences precipitated withdrawal following administration of CAM203 q1w.
[ee] Subjects will be discharged on Day 14, if medically acceptable.

7.2. Discussion of Study Design

Subjects with opioid physical dependence and moderate to severe opioid use disorder (based on criteria defined in the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition [DSM-V]) will be enrolled in this study. Because this is the intended patient population, results from this study will be directly applicable to the therapeutic use of CAM2038 q1w in clinical practice (i.e., determine the ability of CAM2038 q1w to block illicit opioid effects, which is one dimension of opioid maintenance treatment). These subjects are also likely to provide meaningful ratings of subjective opioid effects based on their prior opioid use experience. For ethical and safety reasons, non-dependent opioid users will not be included, as they are less likely to tolerate the higher CAM2038 q1w doses (i.e., no naltrexone blockade) and because it would be unethical to produce opioid dependence in an opioid abuser who are not currently physically dependent. In addition to the requirement that subjects are "history-qualified" (i.e., history of regular opioid use), this study will use a pharmacologic qualification to ensure that subjects who meet the drug use history criteria can also distinguish and demonstrate "liking" of the subjective euphoric experience of both doses of hydromorphone compared to placebo. Therefore, the pharmacologic qualification procedure provides a more objective confirmation of drug use history and ensures that subjects can respond appropriately in a laboratory setting as well as tolerate the doses of hydromorphone.

Subjects will be carefully screened to eliminate those presenting with a clinically significant history of seizure disorders, history of asthma or other respiratory disorders, head injury, hypertension or personal history of cardiovascular disease or clinically significant electrocardiogram (ECG). Subjects must not have clinically significant chronic illness (e.g., diabetes, liver or kidney disease). Subjects with a known hypersensitivity to any of the study drugs or to specific opioids will not be enrolled.

Studies with opioid-dependent subjects have used a wide array of opioid maintenance drugs and doses to stabilize subjects. In the current study, all subjects will be stabilized on a 30 mg dose of IR morphine, administered QID (with the option of adding one additional dose of IR morphine during the first 3 days of stabilization, as needed) prior to enrollment in the Treatment Phase. Administration of IR morphine 30 mg will ensure that any opioids that the subject may have recently used will be washed out and will also establish a consistent schedule of opioid administration, thereby shortening the duration of opioid washout period required prior to administration of the Qualification/Baseline Hydromorphone Challenge Session. Therapeutically, patients will be induced with CAM2038 q1w immediately after a short period of abstinence (approximately 12 hours) from opioid use as is typical for induction onto buprenorphine; therefore, to remain consistent with how the product will be administered clinically, a short-acting opioid (morphine sulfate) has been selected for stabilization purposes.

In addition, the 3 to 7 day IR morphine 30 mg stabilization phase will ensure that any opioids used prior to check-in will be sufficiently washed out, while also increasing the likelihood that subjects will have a similar level of physical dependence to opioids prior to beginning the Qualification/Baseline Hydromorphone Challenge. The intention of stabilizing all subjects on IR

morphine 30 mg is to attempt to decrease the severity of and discomfort associated with opioid withdrawal (Walsh et al., 2015). This will increase the validity of baseline measurement of "drug liking" collected after the first administration of hydromorphone (i.e., baseline scores will be less likely to be skewed in either direction due to severe withdrawal effects).

Many studies have evaluated the conditions under which buprenorphine can be administered to opioid dependent individuals to avoid the precipitation of withdrawal. Collectively, these studies have shown that BPN-precipitated withdrawal is dependent on the following: 1) duration of action of the maintenance opioid (whereby precipitated withdrawal is more likely to occur in those maintained on long-acting opioids (e.g., methadone) than short-acting opioids (e.g., heroin), 2) the time since last opioid maintenance dose (whereby precipitated withdrawal is more likely to occur when opioid dosing is recent and more opioid is on board than when time for opioid wash-out has occurred and the individual is showing signs of opioid withdrawal, and 3) the absolute dose of BPN (whereby a higher BPN dose is more likely to precipitate withdrawal compared to a lower dose of BPN). The strategy proposed here addressed each of these principles in the following manner: 1) Subjects will be maintained on a short-acting opioid, morphine, rather than a long-acting opioid, 2) Morphine will be omitted for a period of ~12 hours and withdrawal signs and symptoms are expected to emerge during this interval prior to CAM2038 q1w administration (subjects will be required to score 8 points or greater on the COWS prior to being dosed with CAM2038 q1w on Day 0 (Walsh et al., 2015), and 3) while the absolute depot dose of CAM2038 q1w at 24 and 32 mg is high, the more relevant factor is the initial concentration exposures following the injection and the rate of onset, whereby a slower rate of BPN delivery is associated with decreased likelihood of precipitated withdrawal (Rosado et al., 2007). The standard recommended approach (although not necessarily the most commonly used in clinical practice) is to begin dosing with 4 mg, wait for 2 hours and, in the absence of precipitated withdrawal, administer an additional 4 mg. A 4 mg sublingual tablet of BPN will produce a concentration of approximately 2 ng/mL (C_{max}) at approximately 1 hour post-dose (Ciraulo et al., 2006), while an 8 mg initial dose would produce ~4.3 ng/mL (C_{max}) at approximately 1.5 hour post-dose (HS-11-426). With respect to the CAM2038 q1w doses proposed for testing here, even at the highest dose (32 mg), BPN plasma levels will not exceed 2 ng/mL until approximately ~4 hours after administration. Thus, the initial BPN concentration exposure is predicted to be lower than the exposure typically seen during the first 2-4 hours of initial induction with SL products. Moreover, with CAM2038 q1w, concentrations will continue to slowly rise, reaching C_{max} at approximately 24 hours post-dose. While BPN-precipitated withdrawal is a relatively rare occurrence in clinical practice, one strategy employed for treatment is to give more BPN. Given the pharmacokinetics of CAM2038 q1w, this potential approach for treating BPN-precipitated withdrawal is built into the product design and may serve to ameliorate any potential withdrawal effects. However, if withdrawal does occur, specific procedures have been included to ensure that subjects are assessed and receive treatment for symptoms (See Section 10.6).

The overall design of the current study is consistent with previously published opioid agonist challenge studies, which have investigated the opiate blocking effects of BPN (Jasinski et al., 1978; Walsh et al., 1995). Based on the pharmacokinetic profile of CAM2038 q1w, specifically that BPN peak plasma concentrations are observed within the first 24 hours post-dose,

Hydromorphone Challenge Sessions will begin a minimum of 24 hours following the first dose of CAM2038 q1w. An additional Hydromorphone Challenge Session will be administered after 48, 72, 96, 120, and 144 hours post-dose in order to investigate the full duration and magnitude of opioid-blockade of the CAM2038 q1w formulation. In order to improve subject retention, the study drug will be administered for two weeks with two sets of three Hydromorphone Challenge Sessions per week; thereby reducing the inpatient Treatment Phase and the overall duration of the study.

In the current study, subjective "at the moment" assessments using VAS for Drug Liking, Feeling High, Any Drug Effects, Good Drug Effects, Bad Drug Effects, Sedated, and Desire to Use Opioids will be included to measure the degree and time course of the CAM2038 q1w-induced blockade of subjective effects. In addition, pharmacokinetic samples will be collected on each Hydromorphone Challenge Session day to measure plasma levels of BPN and norbuprenorphine prior to the challenge session.

Randomization will be used to avoid bias in the assignment of treatment for all the Hydromorphone Challenge Sessions and in the assignment of subjects to the 24 mg or 32 mg CAM2038 q1w dose groups during the Treatment Phase. Prior to the Qualification/Baseline Hydromorphone Challenge Session, subjects will be randomized to 1 of 6 challenge sequences, according to two 3 x 3 William squares (ABC, ACB, BAC, BCA, CAB, CBA), and will receive one dose of hydromorphone daily over 3 consecutive days, including 2 doses of hydromorphone and 1 dose of placebo. This approach has previously been shown to be sensitive to identifying dose-related agonist effects, while ensuring that both subjects and staff remain blinded to the dose of hydromorphone or placebo being administered, thereby reducing the risk of potential expectancy effects. As an additional precaution, subjects will be housed in inpatient research units for the duration of the study both for safety monitoring and to ensure that the subjects do not use other illicit opioids while enrolled in the study, as this may affect the Hydromorphone Challenge Session results.

Randomization increases the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) will be evenly balanced across dose groups and enhance the validity of statistical comparisons across dose groups. It was not possible to include a placebo control group (CAM2038 SC Placebo injection) in the current study because the enrolled population will be physically dependent on opioids and would go into opioid withdrawal with placebo administration. Therefore, this study includes a Qualification/Baseline Hydromorphone Challenge Session to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of CAM2038 q1w.

8. SELECTION OF STUDY POPULATION

The study will enroll a sufficient number of subjects to ensure that at least 48 subjects complete the study (24 subjects per group with at least 16 females in total). Replacement subjects may be added at the discretion of the sponsor with the agreement of the Investigator(s).

8.1. Inclusion Criteria

Subjects must meet each one of the following inclusion criteria in order to be eligible for participation in the study:

1. Subject must provide written informed consent prior to the conduct of any study-related procedures.
2. Male or female, 18-55 years of age, inclusive.
3. Subjects with a diagnosis of moderate or severe opioid use disorder (DSM-V) who are currently physically dependent on IV or insufflated opioids, and who are willing to undergo short-term BPN treatment.
4. Self-reported opioid-use of a minimum of 21 days in the 30 days prior to Screening.
5. Positive UDS for opioids at Screening or at check-in. If UDS is not positive, subjects must present with physical signs of withdrawal, as determined by the Investigator. The Investigator may administer a naloxone challenge, in order to confirm opioid dependence at the Investigator's discretion.
6. Female subjects of childbearing potential must be willing to use a reliable method of contraception during the entire study (Screening Visit to Follow-Up phone call), as defined in Section 10.1.6.
7. Female subjects of non-childbearing potential should be surgically sterile (i.e., have undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation) or in a menopausal state (at least 1 year without menses), as confirmed by follicle stimulating hormone (FSH) levels.
8. Male subjects with female partners of childbearing potential must agree to use a reliable method of contraception from Screening Visit through at least 3 months after the last dose of study drug. Male subjects must also agree not to donate sperm during the study through at least 3 months after the last dose of study drug.
9. Is willing and able to comply with the study requirements (including blood sampling), complete study assessments, visit the clinic and remain confined in the CRU for up to 25 consecutive days.

8.2. Exclusion Criteria

Subjects will not be eligible to participate in this study if any one of the following exclusion criteria is met:

1. History or presence of any clinically significant psychiatric, endocrine, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, renal, or other major disease or illness at Screening, which in the opinion of the Investigator would jeopardize the safety of the subject or the validity of the study results.
2. Opioid dependent subjects who are actively seeking treatment for their moderate to severe opioid use disorder.
3. Subjects with positive urine drug screens for buprenorphine, alcohol, barbiturates, or methadone or breath alcohol on the day of check in to the CRU.
4. Aspartate aminotransferase levels >3 X the upper limit of normal, alanine aminotransferase levels >3 X the upper limit of normal, total bilirubin >1.5 X the upper limit of normal, or creatinine >1.5 X upper limit of normal on the Screening laboratory assessments and at inpatient check-in, or other clinically significant laboratory abnormalities, which in the opinion of the Investigator may prevent the subject from safely participating in study.
5. Any clinically significant abnormality on the basis of medical history, vital signs, physical examination, 12-lead electrocardiogram (QTcF ≥450 msec. for males or ≥470 msec. for females), and laboratory evaluation (including hematology, clinical chemistry, urinalysis, and serology [optional]) at Screening, in the opinion of the Investigator.
6. Significant symptoms, medical conditions, or other circumstances which, in the opinion of the Investigator, would preclude compliance with the protocol, adequate cooperation in the study or obtaining informed consent, or may prevent the subject from safely participating in study (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the Investigator's Brochure for CAM2038).
7. Subjects will be carefully screened to exclude individuals presenting with a clinically significant history of seizure disorders, history of asthma or other respiratory disorders, head injury, hypertension or personal history of cardiovascular disease or clinically significant ECG abnormalities.
8. Current diagnosis of Acquired Immune Deficiency Syndrome (AIDS).
9. Current diagnosis of chronic pain requiring opioids for treatment.
10. Subjects who currently meet the criteria for a diagnosis of moderate or severe substance use disorder according to DSM-V criteria for any other substances other than opioids, caffeine or tobacco.
11. Pregnant or lactating, or planning to become pregnant during the study.
12. Clinically significant history of or current evidence of suicidal ideation or active suicidal behavior as based on the Columbia-Suicide Severity Rating Scale (C-SSRS; grade 4 or 5).

13. Hypersensitivity or allergy to BPN or other opioids or excipients of CAM2038.
14. Intolerance to venipuncture and/or difficulty with venous access, as per the judgment of the Investigator/research staff.
15. Subject is currently using an investigational drug or monoamine oxidase inhibitor (MAOI) or has used such within the last 30 days (or 5-times the half-life of the drug, if known and longer) prior to first drug administration in the Qualification Phase (i.e., IR morphine sulfate).
16. Requires current use of agents that are strong inhibitors or inducers of cytochrome P450 3A4 (CYP 3A4), such as some azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., clarithromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir).
17. If the subject is currently on probation or has any pending legal action that could prohibit participation or compliance in the study.
18. A subject who, in the opinion of the Investigator, is considered unsuitable or unlikely to comply with the study protocol for any reason.

8.3. Qualification Criteria

In addition to the inclusion and exclusion criteria, subjects must meet each one of the following criteria in order to be eligible for participation in the Treatment Phase:

- Maximum effect (E_{max}) in response to IM hydromorphone 6 mg greater than that of placebo on Drug Liking bipolar VAS (response to hydromorphone 6 mg should be greater than 55 mm in the VAS and a difference of at least 15 mm between placebo and 6 mg) and acceptable overall responses to hydromorphone and placebo on the subjective measures, as judged by the Investigator or designee.
- E_{max} in response to IM hydromorphone 18 mg greater than that of placebo on Drug Liking bipolar VAS (greater than 60 mm and a difference of at least 20 mm between placebo and 18 mg) and E_{max} score of at least 20 points, and acceptable overall responses to hydromorphone and placebo on the subjective measures, as judged by the Investigator or designee.
- Acceptable placebo response based on Drug Liking bipolar VAS (score between 40 and 60 mm, inclusive).
- Subject is able to tolerate IM hydromorphone 6 mg and 18 mg, as judged by the Investigator, including ability to complete most pharmacodynamic assessments administered within 5 hours post-dose.
- General behavior suggests that the subject could successfully complete the study, as judged by the research site staff.

8.4. Removal of Subjects from Therapy or Assessment

A subject is free to withdraw his/her consent and discontinue participation in the study at any time for any reason. A subject's participation must therefore be terminated immediately upon his/her request, and the reason(s) for discontinuation appropriately documented.

A subject must be discontinued from the study for any of the following reasons:

- Safety reasons, including AEs or significant concomitant illness, injury, or urgent surgeries/procedures that would, in the judgment of the Investigator, affect assessments of clinical status to a significant extent, require discontinuation of study drug, or both
- At the request of the Sponsor, regulatory agency, or Institutional Review Board (IRB)
- Subject is lost to follow-up
- Subject treatment allocation is unblinded during the Treatment Phase (i.e., individual code break; Section 9.6)
- Death of subject

A subject may also be discontinued from the study, at the discretion of the Investigator and/or Sponsor, for any of the following reasons:

- Subject refuses or is unable to adhere to the study protocol
- Protocol violation
- Pregnancy
- Requirement for continual use of opioid analgesics >7 days or requirement for general anesthesia for surgery

The Investigator must maintain a record of all subjects who discontinue from the study prior to completion; the reason(s) for study discontinuation will be documented. In the event that a subject chooses to withdraw from the study, the Investigator should make a reasonable attempt to obtain and record the reason(s) for withdrawal, if possible, although the subject is not obligated to provide such a reason.

All efforts should be made by the Investigator to continue collection of safety assessments at the protocol-defined intervals, including concomitant medications and AEs in subjects that discontinue study drugs, unless the subject withdraws his/her consent at the time of early discontinuation. The Investigator should also ask the subject to complete Follow-up phone-call, provided that the subject has not withdrawn consent. If a subject refuses to complete Early Termination procedures and/or Follow-up, this information will be recorded.

8.5. Study Restrictions

In addition to the inclusion/exclusion criteria described in Sections 8.1 and 8.2, the subject must agree to abide by the following study restrictions:

- Subjects will be required to abstain from alcohol for 24 hours prior to Screening and before check in to the CRU. Alcohol abstinence will be confirmed with a breath alcohol test.
- Subjects will be asked to abstain from recreational drug use throughout the study, from check-in to the CRU until after discharge following the last hydromorphone administration in the Treatment Phase.
- Subjects will not be permitted to consume caffeine-containing beverages on Hydromorphone Challenge Session days.
- Subjects will be asked to abstain from the following foods from 1 week prior to first drug administration in the Treatment Phase until after study discharge: grapefruit or grapefruit-containing products, pomegranate, pomelo, and star fruit juice/products, as well as foods containing poppy seeds,
- On Hydromorphone Challenge Session days, subjects will be required to abstain from smoking for at least 30 minutes prior to hydromorphone dosing. At other times, smoking will be permitted at short breaks (approximately 5-10 minutes in duration) at the discretion of the CRU staff. If a smoking break is permitted, it must not interfere with study procedures. Subjects will be permitted to use a nicotine-containing transdermal system as needed, at the discretion of the Investigator.
- Subjects will be required to abstain from blood donation for 30 days following the Follow-up visit.
- Subjects will be required to follow the informed consent form (ICF) and any clinic rules and requirements.
- Male subjects should refrain from donating sperm for 3 months after the subjects follow up visit.

9. TREATMENTS

9.1. Treatment Administration

Subjects will be given a short-acting oral opioid, IR morphine 30 mg, QID, for a minimum of 3 days and a maximum of 7 days prior to the Qualification/Baseline Hydromorphone Challenge Session. One additional dose of IR morphine 30 mg may be administered for the first 3 days of stabilization, as needed, at the investigator's discretion. Subjects will not receive IR morphine 30 mg on the evening and morning prior to hydromorphone dosing in the Qualification/Baseline Hydromorphone Challenge Session (Day -3, Day -2, Day -1) and the evening prior to and morning of CAM2038 q1w dosing (Day 0).

Subjects will receive one of the following weekly doses of CAM2038 q1w (BPN FluidCrystal® Injection depot for once weekly administration), 24 mg or 32 mg (BPN base), on two separate days in the study (Day 0 and Day 7). CAM2038 q1w will be administered by SC injection in the subject's buttocks while rotating between right and left buttocks (0.48 mL or 0.64 mL, respectively).

Hydromorphone (10 mg/mL) will be administered in a randomized manner (placebo, 6 mg and 18 mg) once daily during each 3-day Hydromorphone Challenge Session. Hydromorphone will be administered by 1.8 mL IM injection (described below).

9.2. Identity of Investigational Products

The following treatments will be used during the study:

- CAM2038 q1w, 50 mg/mL: 24 and 32 mg (BPN base), 0.48 mL and 0.64 mL SC injection. Subcutaneous injections will be performed in the upper buttocks rotating between right and left buttocks.
- Hydromorphone, 10 mg/mL (Dilaudid HP®): 6 and 18 mg for IM administration. Intramuscular injections will be performed in the deltoid muscle.
- Morphine IR 30 mg tablet for oral administration.

CAM2038 q1w will be supplied as pre-filled syringe with safety device and plunger containing the following: BPN, soybean phosphatidylcholine, glycerol dioleate, and ethanol. More information regarding the CAM2038 q1w can be found in the Study MOP.

Dilaudid HP® will be supplied as single dose vials for IM administration. Each 1 mL of sterile solution contains 10 mg/mL mg hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid solution.

- For the hydromorphone 18 mg dose, 1.8 mL of this solution will be used.
- Hydromorphone 6 mg dose will be a combination of 0.6 mL Dilaudid HP solution + 1.2 mL ½ NS sodium and water for a total injection volume of 1.8 mL.
- Hydromorphone 0 mg (placebo) will be administered using 1.8 mL of a solution of 0.45% sodium and water (1/2 NS).

Morphine Sulfate will be supplied as 30 mg tablets.

Each container of study drug will be clearly labeled with study-specific information meeting all the applicable regulatory requirements.

9.2.1. Handling, Storage, and Accountability

All study drugs will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions provided to the research site, and applicable regulations.

CAM2038 products must be stored according to the requirements outlined in the Study MOP. Storage requirements for hydromorphone are provided in the product label (a copy is provided in the Study MOP).

Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed, the running inventory, and the unused quantities returned to the Sponsor's drug supply vendor at the end of the trial. All unused supplies will be checked against the drug accountability records during the study and/or at the end of the study. Additional details are provided in the Study MOP.

Buprenorphine (Schedule III), morphine sulfate and hydromorphone (Schedule II) are controlled substances and study drugs must be handled and stored strictly in accordance with restrictions related to controlled substances. Study drugs must be kept securely locked with access limited to appropriate study personnel, according to applicable regulations.

9.2.2. Dispensing and Administration

Only eligible subjects participating in the study will receive the study drug. Only authorized research site staff may administer the study drugs. Once dispensed, study drug may not be relabeled or reassigned for use by other subjects.

CAM2038 q1w SC injections, hydromorphone IM injections, and IR morphine 30 mg tablets will be administered by designated healthcare professional(s) at the CRU. Detailed instructions for use will be provided in the Study MOP.

Investigators will be instructed to treat AEs as they would usually, including pharmacological interventions. Any pharmacological interventions provided by the Investigators will be recorded, along with the reasons for determining the need for these interventions. Further instructions on handling precipitated withdrawal is addressed in Section 10.6.

9.3. Method of Assigning Subjects to 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 will be randomized in a 1:1 ratio to 1 of 2 groups (CAM2038 q1w at doses of 24 mg or 32 mg) stratified by gender. If a subject discontinues from the study, that subject may be replaced at the discretion of the Sponsor. The replacement subject will receive the same treatment

(CAM2038 q1w) and will follow the same treatment sequence in the Hydromorphone Challenge Sessions as the original subject in the Treatment Phase.

For the Hydromorphone Challenge Sessions, subjects will be randomized in a 1:1:1:1:1:1 ratio to 1 of 6 treatment sequences according to two 3 × 3 William squares. The following treatment sequences will be used: ABC, ACB, BAC, BCA, CAB, and CBA, where A, B, and C are IM hydromorphone doses of 0 mg (placebo), 6 mg, and 18 mg, respectively

9.4. Selection of Doses

The full mu opioid agonist hydromorphone will be used for the opioid challenge sessions. Hydromorphone has been commonly employed for this purpose as it has favorable pharmacokinetics and is similar to heroin in its time course and pharmacodynamic profile. It has a high abuse liability and obviates the challenges of using a Schedule I agent (i.e., heroin). Numerous opioid challenge studies have used hydromorphone specifically to examine the ability of putative opioid dependence treatments to produce opioid blockade (Walsh et al., 1995; Bickel et al., 1988; Strain et al., 1997; Sobel et al., 2004; Ciraulo et al., 2006; Walsh et al., 2006; Lanier et al., 2010) so there is a strong precedent for the choice of this compound.

Initial parenteral doses of hydromorphone for analgesia are 1 to 2 mg subcutaneously or IM every 2 to 3 hours PRN (Handelsman et al., 1987; Hydromorphone, 1984). However, supratherapeutic doses are needed for challenge studies in opioid abusers. Typically, a lower range of supratherapeutic doses can be employed in opioid abusing individuals without physical dependence and still produce robust dose-related effects. However, higher supratherapeutic doses are needed when investigating responses in active opioid abusers with physical dependence (and hence, higher levels of tolerance). Studies that have examined the ability of BPN maintenance treatment to produce blockade of hydromorphone effect have varied. For example, one open-label trial of a depot BPN formulation examined hydromorphone doses of 0 mg and 3 mg (on the low end), but this product produced BPN plasma concentrations of under 2 ng/mL (a target range generally accepted as the lower therapeutic concentration for blockade, but effective for withdrawal suppression). Other studies have employed higher hydromorphone doses during BPN and methadone maintenance treatment ranging between 10 mg to 18 mg. In one early study, BPN SL solution (estimated to have approximately 30% higher bioavailability over the currently marketed tablets) (Handelsman et al., 1987; Hydromorphone, 1984) examined blockade with BPN maintenance doses ranging from 2 mg to 16 mg/day using a cumulative SC hydromorphone dosing procedure of 0 mg, 6 mg, and 12 mg, for a total challenge dose of 18 mg. A recent study examining blockade with another sustained-release BPN product (RBP 6000, Clinical Trials.gov, NCT02044094) examined single acute doses of 0 mg, 6 mg and 18 mg. Based upon prior studies of methadone and BPN maintenance, the proposed doses are appropriate for opioid challenge studies, should be safely tolerated during the Qualification Phase and should reflect attenuated responses after stabilization on BPN.

CAM20138 q1w doses of 24 mg and 32 mg were selected to represent a range of therapeutic doses that are being evaluated in Phase III efficacy studies.

9.5. Selection and Timing of Dose

During the Treatment Phase, Hydromorphone Challenge Session doses will be administered as single IM doses once daily over 3 days, with each daily dose administered at approximately 9:00 am. CAM2038 q1w SC injections will be administered on Days 0 and 7 at approximately 9:00 am. The drug administration time should remain consistent (±10 minutes), if possible, on all dosing days (CAM2038q q1w and hydromorphone) of the Treatment Phase.

All subjects will receive standard meals at specified times. Dietary restrictions are described in Section 8.5.

9.6. Blinding

In order to reduce the potential for bias in the study, Hydromorphone Challenge Session treatment sequences and CAM2038 q1w treatment group assignments will be double-blinded. The subjects will not be aware of the treatment group assignments. The randomization scheme will be provided to the site's unblinded personnel for preparation of the individual subject doses. If necessary, personnel from the bioanalytical laboratory will have access to the randomization scheme.

Upon completion of each double-blind, Qualification/Baseline Hydromorphone Challenge Session cohort of subjects, the randomization codes for the completed subjects will be unblinded to the designated personnel, and the eligibility of subjects to participate in the Treatment Phase will be assessed as described in Section 8.3. In order to maintain the blind, unblinded staff not otherwise involved in the study will prepare the hydromorphone doses so that they are volume-matched (1.8 mL, See Section 9.2).

There is a slight difference in fill volume between the different doses of CAM2038 q1w; however, the viscosity is the same. In order to maintain the blind given the differences in color fill volume, the following procedures will be implemented:

- The Injecting staff member and any other staff involved in the injection process will not participate in subject evaluations, nor discuss any information regarding the injections with the subjects or other study staff.
- To keep the subjects blinded, appropriate steps will be taken to ensure that the subject is unable to view the syringe at any time.

Under normal circumstances, the blind will not be broken until all subjects have completed treatment. In case of emergency, and only if the information is required by the Investigator to manage a subject's medical condition, a subject's treatment may be unblinded at the site with the approval of the Sponsor. Whenever a treatment 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 subject from the study.

9.7. Prior and Concomitant Therapy

All non-study medications, including prescription, over-the-counter, or herbal therapies, used by the subject will be documented for the 30 days prior to Screening and throughout the study. The Investigator will determine if the prior/concomitant medication(s) affect the subject's eligibility to participate or continue to participate in the study. The following restrictions on concomitant medications will be in place during the study:

- Opioid receptors are likely to be occupied by BPN, which may reduce the analgesic effects of an opioid. The dissociation of BPN from the receptors may take up to 2 weeks following the last CAM2038 q1w injection. Therefore, subjects requiring analgesic emergency treatment or anesthesia for surgery should ideally be treated with a non-opioid analgesic. Opioids may be used with caution, but as higher doses may be required for analgesic effect, there may be a higher potential for toxicity with opioid administration. The clinical course should be carefully evaluated and fully documented for subjects who have a requirement for any opioid analgesic for >7 days continually or general anesthesia for surgery within 2 weeks of the final dose of CAM2038 q1w.
- Buprenorphine is metabolized via CYP3A4. Because CYP3A4 inhibitors may increase plasma concentrations of BPN, if CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir) are required, the Medical Monitor must be consulted. Interactions with CYP3A4 inducers have not been investigated; therefore, it is recommended that the use of agents such as phenobarbital, carbamazepine, phenytoin and rifampicin be avoided in subjects receiving study treatment. The Medical Monitor must be consulted prior to starting subjects on any of these agents.
- Concomitant use of other narcotic anesthetics, benzodiazepines, phenothiazines, other tranquilizers, or other central nervous system (CNS) depressants (including alcohol and sedative/hypnotics) may cause respiratory and CNS depression. Use of these substances should be minimized during treatment with CAM2038. If these sedatives are required during the study, the Medical Monitor must be consulted. Subjects should be advised of the danger of concomitant use of sedatives while participating in in the study.
- Ancillary medications (PRNs) will be allowed as needed throughout the study (see Table 5), with the exception of Hydromorphone Challenge Session days starting from midnight (i.e., approximately 9 hours prior to dosing) through to the end of the Hydromorphone Challenge Session (i.e., approximately 5 hours after dosing). Once the session has ended, PRNs will be permitted. Ancillary medications will also not be permitted from midnight on Day -1 (i.e., approximately 9 hours prior to dosing) until after administration of the first dose of CAM2038 on Day 0.

Table 5 Ancillary Medications (PRNs) for Relief of Withdrawal Symptoms

Symptom	Treatment	Dose	Route of Administration	Dosing Schedule
Anxiety/restlessness	hydroxyzine	50-100 mg	Oral	Q6H, PRN
Diarrhea	bismuth subsalicylate (e.g., Pepto-Bismol®)	30 mL	Oral	Q4H, PRN
Hypotension/sedation	clonidine	0.1 mg	Oral	Q6H, PRN
Insomnia	Zolpidem (i.e., Ambien®)	5 mL	Oral	PRN
Musculoskeletal pain/general body aches/discomfort	acetaminophen (e.g., Tylenol®)	650 mL	Oral	QID, PRN
	ibuprofen	400 mg	Oral	Q4-6H, PRN
Nausea/dyspepsia	alumina, magnesia, simethicone	30 mL	Oral	QID, PRN
Vomiting/severe nausea	promethazine	25 mg	Oral or IM	Q3-4H, PRN

IM=intramuscular; PRN=as needed; QID=4 times/daily; Q3-4H= every 3 to 4 hours; Q4H=every 4 hours; Q4-6=every 4 to 6 hours; Q6H=every 6 hours

On a case-by-case basis, the Investigator is permitted to allow the use of some additional concomitant medications not outlined in Table 5**Error! Reference source not found.**, for example, to treat an AE, as long as the Investigator determines that the medication will not affect the subject's safety or study integrity (e.g., topical medications). Whenever possible, the Investigator should obtain approval from the sponsor's Medical Monitor prior to administering the medication.

9.8. Treatment Compliance

Study drugs will be administered by study personnel, thus no subject compliance procedures are necessary.

10. STUDY PROCEDURES AND ASSESSMENTS

All study assessments will be performed at the visits and time points outlined in the Schedule of Assessments (Table 4); the following sections outline the details and procedures associated with the assessments.

10.1. Demographics and Other Baseline Characteristics

10.1.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the subject by the Investigator or designated study personnel. The subject must voluntarily provide written informed consent on an ethics-approved ICF, prior to performing any study-related procedures. The subject's medical records must document that the consent process has been completed and that written informed consent has been obtained from the subject prior to the initiation of any study-specific procedures. Documentation that the subject was given adequate time to ask the Investigator (or designee) questions about their participation in the study and that a signed and dated copy of the ICF was provided to the subject should also be included in the medical records or clinical chart.

10.1.2. Demographics

The following demographics will be recorded: age (birthdate), sex, race, and ethnicity. A complete psychosocial history will be obtained including: education, employment status, marital/significant other status, residential status and legal status/arrest history.

10.1.3. Medical History

The complete medical history will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems that have occurred within the last five years or that the Investigator deems clinically significant that should be included in the subject's medical history. All findings on medical history will be evaluated by the Investigator for clinical significance. Medical histories will be obtained according to the site's standard operating procedures.

10.1.4. Medication History

All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) taken by the subjects during the 30 days prior to Screening will be recorded in the source documentation as medication history. Substance Abuse History and Treatment History (Section 10.1.5) will be collected separately and stored in the subject's file.

10.1.5. Substance Use and Treatment History

A complete history of previous and current illicit drug use, substance abuse/dependence, and treatments for any substance use disorders (pharmacologic as well as non-pharmacologic) will be obtained. This will include drugs used, type, frequency and patterns of abuse, routes of administration, doses, and drug preferences, using a timeline follow-back type of interview (Fals-Stewart et al., 2000).

10.1.6. Contraceptive Requirements

Female subjects of childbearing potential must be using and willing to continue using medically acceptable contraception during the study. Examples of medically acceptable forms of contraception include true abstinence, hormonal contraceptives (combined oral pill, patch or vaginal ring, intrauterine device or system, progestin implant or injection), bilateral tubal ligation, or double-barrier methods (e.g., male condom with spermicide in addition to a diaphragm or a contraceptive sponge).

Female subjects of non-childbearing potential are not required to use contraception and to undergo pregnancy tests; however, they must have documentation supporting that they are surgically sterile (hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy, as determined by subject medical history) or congenitally sterile, or must be post-menopausal. Post-menopausal is defined as being amenorrheic for at least 2 years without another cause or amenorrheic for at least 1 year without another cause and a documented FSH level ≥50 mIU/mL.

Male subjects with female partners of childbearing potential must agree to use a medically acceptable method of contraception from Screening Visit through at least 3 months after the last dose of study drug. Male subjects must also agree not to donate sperm during the study through at least 3 months after the last dose of study drug.

10.2. Eligibility Review

Prior to receiving the first dose of hydromorphone on Day -3, subjects must meet all inclusion and not meet any exclusion criteria as outlined in Sections 8.1 and 8.2.

The Investigator or designee must document that the subjects meet each individual criterion via a signed note or eligibility and clinical stability checklist during Screening. Signatures on these documents must be dated on or before the date of Day -10.

10.3. Pharmacodynamic Assessments

All subjects will undergo a scripted training and practice regimen prior to completion of the paper and pen subjective measures as outlined in Table 6.

Testing conditions for pharmacodynamic assessments should remain as consistent as possible throughout the Treatment Phase. Subjects will be monitored carefully to ensure that they are completing the pharmacodynamic assessments appropriately. Study staff are encouraged to provide additional subject training as needed, to ensure that the subjects comprehend the differences between different types of VASs. Training dates/times will be documented in the subject's files. Subject training can only occur before VAS administration or after the 5 hour Challenge session is completed. The training script will be provided to the sites.

10.3.1. Visual Analog Scales

Each VAS will be scored as an integer from 0 to 100. When appropriate, VASs will be administered as bipolar measures, meaning that the neutral point equals 50 (i.e., Drug Liking and Alertness/Drowsiness VAS). The neutral point will also be labeled with an anchor, such as

"neither like nor dislike." Unipolar VASs (i.e., High, Good, Bad, and Any Effects VAS) are presented with anchors such as "not at all" (score = 0) to "extremely" (score = 100), where the neutral point equals 0. The use of a unipolar or bipolar scale is determined by the nature of the subjective effect being measured.

If precipitated withdrawal occurs after administration of CAM2038 q1w, subjects will be requested to complete a unipolar VAS assessment of opioid withdrawal severity.

Table 6 lists the subjective effects VAS question text and response anchors.

Table 6 Visual Analog Scale Descriptions

Scale Interpretation	Description	Question Text	Response Anchors
Balance	Drug Liking	At this moment, my liking for this drug is	0: Strong disliking 50: Neither like nor dislike 100: Strong liking
Other effects	Any Drug Effects	At this moment, I feel any drug effects	0: Not at all 100: Extremely
Positive	High	At this moment, I feel high	
Positive	Good Drug Effects	At this moment, I feel good drug effects	
Negative	Bad Drug Effects	At this moment, I feel bad drug effects	
Other Effects	Desire to use opioids	At this moment, I desire opioids	0: Definitely not 100: Definitely so
Other Effects	Alertness/Drowsiness	At this moment, my mental state is	0: Very drowsy 50: Neither drowsy nor alert 100: Very alert
Other Effects	Opioid Withdrawal Severity	I feel opioid withdrawal	0: Not at all 100: Extremely

10.4. Safety Assessments

Safety monitoring will be performed throughout the study for all subjects. All AEs, regardless of causality or severity, will be recorded on the AE CRF. CAM2038 injections may be discontinued as clinically indicated.

10.4.1. Adverse Events and Serious Adverse Events

The following definitions, developed in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Clinical Safety

Data Management Guidance for Industry, E2A, will be used for the purpose of identifying AEs in this clinical study.

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or increase in severity of a preexisting abnormality, temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

10.4.1.1. Adverse Event Reporting

All AEs (except for withdrawal symptoms, see below) must be entered on the AE CRF, regardless of causality or severity. AEs include new AEs, worsening baseline conditions, clinically significant laboratory findings, disease-related signs and symptoms that were not present at baseline, and any events or findings that the Investigator feels are clinically significant. Withdrawal symptoms will be captured via specified assessments and should not be recorded as AEs.

Disease-related signs and symptoms that are present at baseline should not be recorded as AEs unless they worsen in severity or increase in frequency, but rather should be considered and recorded as pre-existing conditions.

Information collected concerning AEs will include the following:

- Name of the event
- Onset date
- Resolution date
- Severity (i.e., mild, moderate, or severe)
- Relationship to study drug
- Action and outcome
- Seriousness of event

All AEs will be documented and followed from the time the subject has signed the ICF until 14 days after the Follow-up Visit (or 30 days after Early Termination). Serious AEs and AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization. At least 3 attempts will be made to contact the subject and after 3 unsuccessful attempts, a certified letter will be sent to the subject address that was provided to the site.

10.4.1.2. Serious Adverse Event

A SAE or reaction is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization,

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in an offspring)
- An Important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All AEs requiring hospitalization or prolongation of a pre-existing hospitalization should be reported as SAEs unless they occur greater than 14 days after the Follow-up phone call (or 30 days after Early Termination) AND are not considered to be drug-related by the Investigator.

Hospitalizations meeting the following criteria will not be reported as an SAE but must be recorded on the appropriate CRF: study specified hospitalization, short-term administrative hospitalization for procedures, tests or treatments of conditions that would not otherwise constitute an SAE, elective hospitalizations.

10.4.1.2.1. Serious Adverse Event Reporting

Serious AEs must be reported to the Sponsor or designee within 24 hours of knowledge of the event. All SAEs that occur while a subject is receiving study drug and within 14 days following the Follow-up phone call (or 30 days after Early Termination) are reportable within 24 hours. During the follow-up period beyond 14 days from Follow-up (or 30 days after Early Termination), only those SAEs that are considered to be possibly related to study drug should be reported within 24 hours.

The procedure for reporting a SAE is as follows:

- Within 24 hours of knowledge of the event, the site must contact the Sponsor (or designee) by telephone or facsimile to report the event.
- The initial report should include all information known at the time of the report (additional information can be reported as discovered). Do not delay the initial reporting in order to obtain resolution or follow-up information.
- The site will complete the provided SAE report form that includes the following information, as available:
    - Subject ID
    - Basic demographic information (age, gender, weight)
    - Outcomes attributed to the event (death, life-threatening hospitalization [new or prolonged], disability, congenital anomaly, required medical intervention to prevent permanent impairment/damage, etc.)
    - Onset date and severity of the event
    - Brief description of the event including frequency and severity of symptoms leading to diagnosis
    - List of relevant test results and laboratory data
    - Any other relevant history

- Whether the study drug was discontinued
- Whether the assigned treatment oral or injectable therapy was discontinued and/or dose titration discontinued, as applicable
- Investigator's assessment of causality
- Other concomitant medication and medical history

The SAE report form should then be emailed to the Sponsor (or designee) or faxed per instructions in the SAE Reporting and Management Plan.

The Medical Monitor or another representative of the Sponsor may contact the Investigator to request additional information regarding the event or to confirm information. All SAEs will be entered on the AE CRF. The same nomenclature should be used on both the SAE report and the AE CRF.

Specific instructions for SAE reporting and a copy of an SAE report form are provided in the MOP.

The Investigator is responsible for the complete and timely reporting of all SAEs to the Sponsor (or designee), reporting pertinent follow-up information on the SAE, and notifying the appropriate IRB/Independent Ethics Committee (IEC) of the occurrence of and details surrounding the event. In the event there is a question as to whether the AE is serious, the event should be reported.

10.4.2. Pregnancy

Pregnancies among trial subjects should be reported to the Sponsor or designee as soon as possible after learning of the event. Subjects who become pregnant will be withdrawn from the study and be referred back to the care of their usual provider or continue in the study after discussion with and documentation by the Principal Investigator or his/her designee. Pregnancies will be recorded as an AE in the eCRFs. Follow-up information will be obtained where possible (with the consent of the subject or their partner) regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant.

10.4.3. Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood and urine samples will be performed by each CRU's local laboratory. The local laboratory will generate laboratory reports and forward them to the clinical site in a timely manner. It is the responsibility of the local medically responsible investigator to review and sign all lab reports expeditiously, in order to document appropriate safety monitoring of study subjects. The Investigator should sign and date each lab report concurrent with her or his review, and should indicate the clinical significance of each abnormal/flagged value by noting "NCS" (not clinically significant) or "CS" (clinically significant), for example. Notations indicating that a value is clinically significant should also include a brief description of the underlying disease or condition that is associated with the value, e.g., "CS/mild anemia." In general, abnormal, clinically significant laboratory values are expected to be associated with an item recorded in medical history or with an AE.

Table 7 Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count RBC Morphology Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Total and differential (absolute) white blood cell count Platelets	Sodium Potassium Magnesium Calcium Glucose (random) Bicarbonate Chloride Creatinine Total protein Blood urea nitrogen Albumin Total bilirubin Alanine transferase Aspartate transferase Lactic dehydrogenase Amylase Lipase Gamma-glutamyl transferase Alkaline phosphatase Creatine phosphokinase Total cholesterol (non-fasting) FSH	Dipstick illicit drug screen including buprenorphine, barbiturates, benzodiazepines or methadone Color pH Specific gravity Ketones Protein Glucose Bilirubin Nitrite Urobilinogen Occult blood Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*
Coagulation		
Prothrombin time (PT), International normalized ratio (INR)		
Serology testing (optional)		
HIV-1 and HIV-2 Hepatitis B surface antigen Hepatitis C Antibody (HCVAb)		

Blood and urine samples will be collected, processed, and shipped according to instructions from the local laboratory. Additional laboratory samples may be taken at the discretion of the Investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety. Blood volumes required per draw, laboratory test will be determined by each site's local laboratory. Specific hematology, coagulation, biochemistry, and urinalysis assessments are listed in Table 7. It is up to the investigator to review lab results and determine if the abnormal lab results are clinically significant.

In addition to the clinical laboratory tests, pregnancy testing for the presence of β-human chorionic gonadotropin in serum will be performed at the visits defined in Table 4. Results of serum pregnancy tests will be reported and determined to be negative prior to study continuation and/or dosing. Urine pregnancy testing will be performed prior to the Qualification Phase challenge. As an additional precaution, urine pregnancy tests will be administered weekly (on Day 0 and Day 7) prior to CAM2038 q1w dosing.

10.4.4. Urine Drug Screen and Breath Alcohol Testing

Qualitative UDS will be utilized to test for the following drugs of abuse: buprenorphine, methadone, tetrahydrocannabinol, oxycodone and other opioids, methamphetamines, amphetamines, phencyclidine, oxycodone, propoxyphene, cocaine, barbiturates, and benzodiazepines.

Breath alcohol testing will be performed according to the sites' standard operating procedures. If there is any doubt or concern regarding alcohol use, research site staff may request a breath test for alcohol measures at any time during the study.

Tests will be performed at the visits defined in Table 4.

10.4.5. Vital Signs

Vital signs will consist of oral body temperature (°C), blood pressure (systolic and diastolic blood pressure, mmHg), pulse rate (beats per minute), and respiratory rate (breaths/min) collected while sitting with legs uncrossed and feet flat on floor, following a rest period of at least 3 minutes.

10.4.5.1. Qualification Phase Vital Signs Safety Monitoring

Before each scheduled IR morphine 30 mg dose is administered during the Qualification Phase, research or nursing staff will record oxygen saturation and respiratory rate and assess the subject for sedation and/or intoxication. If respiratory rate is <12 breaths per minute or oxygen saturation is <95% (Section 10.4.7), the measurements will be repeated and recorded. If either oxygen saturation or respiratory rate remain outside parameters or the subject appears sedated or intoxicated, the oral IR morphine 30 mg maintenance dose will be withheld and a study Investigator notified. The withheld dose may be administered later (and recorded) once it is determined that the subject's status has returned to within the safety dosing criteria.

After the Qualification/Baseline Hydromorphone Challenge Session, subjects will be assessed based upon the same safety criteria described above (i.e., respiratory rate, oxygen saturation and sedation or intoxication) to determine if it is safe to resume administration of oral IR morphine 30 mg maintenance dosing. This assessment will be documented. In the event that morphine dosing is withheld in the afternoon, evening administration of oral IR morphine 30 mg will be scheduled for no later than the original scheduled administration time in order to maintain consistency between time of last dose of morphine and Hydromorphone Challenge Session dosing the following day.

10.4.5.2. Treatment Phase Vital Signs Safety Monitoring

After each dose of IM hydromorphone during the Treatment Phase Hydromorphone Challenge Sessions, subject's oxygen saturation, respiratory rate, and overall safety profile will be reviewed by the research/nursing staff (as described in Section 7.1.2.1) to determine whether it is safe to proceed with administration of the next dose of hydromorphone.

Vital signs assessments will be performed at the visits and time points defined in Table 4.

10.4.6. 12-Lead Electrocardiograms

12-Lead ECGs will be performed 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, 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. In general, abnormal, clinically significant ECGs are expected to be associated with an item recorded in medical history or with an AE.

Assessments will be performed at the visits and time points defined in Table 4.

10.4.7. Cardiac Monitoring (including Pulse Oximetry)

Cardiac monitoring (cardiac rhythm, heart rate) and pulse oximetry will be performed from inpatient check-in to the end of the Treatment Phase (or Early Termination) of the study. Data will not be recorded in the database, but will be used for real-time safety monitoring. Occurrences of oxygen saturation <95%, the measurements will be repeated and recorded as AEs. Pulse oximetry/cardiovascular monitoring will be included on each Hydromorphone Challenge Session day (i.e., Day -3, -2, -1, 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, and 13). Monitoring will be from pre-dose until at least 5 hours post-dose or longer, if clinically indicated. Cardiac monitoring and pulse oximetry equipment may be removed briefly (for hygiene purposes), as needed.

Continuous pulse oximetry and telemetry can be performed if the Investigator deems it is necessary.

10.4.8. Physical Examination

A complete physical examination including all major body systems will be performed at Screening. At select subsequent study visits, an abbreviated review of systems will be performed to capture changes since Screening.

Height, weight and BMI will be assessed as described in Table 4.

10.4.9. Injection Site Examination

CAM2038 injection sites will be examined daily, after each injection, during the Treatment Phase for any signs of adverse site reactions. The injection site will be visually inspected daily for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing and any other abnormalities. Injection sites will be examined daily after each injection to determine if any site related adverse reactions have occurred.

10.4.10. Clinical Opiate Opioid Withdrawal Scale (COWS)

The COWS contains 11 physically observable signs, rated present or absent, based on a timed period of observation of the patient by a rater. This scale is a valid and reliable indicator of the severity of opiate withdrawal over a wide range of common signs and symptoms (Appendix 17.2; Wesson, 2003).

10.4.11. Objective Opioid Withdrawal Scale (OOWS)

The Objective Opioid Withdrawal Scale (OOWS) contains 13 physically observable signs, rated present or absent, based on a timed period of observation of the patient by a rater (Appendix 17.3; Handelsmen et. al. 1987).

10.4.12. Columbia-Suicide Severity Rating Scale

The C-SSRS will be used to assess both behavior and ideation that tracks all suicidal events, and provides a summary of suicidal ideation and behavior. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation, and deterrents), all of which are significantly predictive of completed suicide.

Two versions of the C-SSRS will be used in this study: the Baseline/Screening version (6 months and lifetime history; Appendix 17.4) and the Since Last Visit version (Appendix 17.5). The Screening version of the C-SSRS will be administered at Screening. The Since Last Visit version of the C-SSRS will be administered at all subsequent assessment times, as indicated in Table 4, by the Investigator or his/her qualified designee (qualified designee is defined as someone that has completed the C-SSRS training within the last 2 years). The survey should be administered by the same assessor, where possible, throughout the study.

10.4.13. Montgomery-Asberg Depression Rating Scale (MADRS)

The Montgomery-Asberg Depression Rating Scale (MADRS) will be used to assess subjects for the presence of symptoms that are most frequently observed in patients with major depression. The scale will be conducted as a clinical interview in which subjects will be required to respond to 10 questions. The items will be rated with regards to how the patient has done over the past week (Appendix 17.6; Montgomery, 1979).

10.5. Appropriateness of Measures

As the primary objective of this study is to demonstrate CAM2038 q1w-induced blockade of hydromorphone effects; Drug Liking VAS has been chosen as the primary pharmacodynamic variable.

The Drug Liking VAS assesses the response to the question “At this moment, I like this drug.” Values for this scale range from 0 (“Strong disliking”) to 100 (“Strong liking”), with 50 as the neutral point (“Neither like nor dislike”). This scale has been included to understand the time course of CAM2038 q1w-induced blockade of subjective effects of hydromorphone. Additional subjective effects VASs will be collected to support findings on the primary measure. The subjective effects VAS items will measure positive (Good Drug Effects and High), negative (Bad

Drug Effects), and other subjective effects (Any Drug Effects, Desire to Use Opioids, and Alertness/Drowsiness VAS) to further assess the pharmacologic response to the Hydromorphone Challenge Session injection.

Pharmacokinetic measures are included to confirm exposure, explore potential relationships between pharmacokinetic and subjective measures, and if necessary, to aid in the interpretation of unusual responses.

Standard safety outcomes, such as AEs, ECG, vital signs and clinical laboratory testing will be assessed during the study. In addition, respiratory rate and oxygen saturation safety monitoring will be included prior to dosing with IR morphine 30 mg and after dosing with hydromorphone.

10.6. Additional Safety Measures and Withdrawal

10.6.1. Opioid Effects

Buprenorphine and hydromorphone can produce the typical side effect profile of mu opioid agonists, and these may include nausea, vomiting, headache, dry mouth, itchiness, drowsiness, sweating, dizziness, stimulation, somnolence, lightheadedness, restlessness, a feeling of well-being, talkativeness, urinary retention and constipation. More serious side effects may include allergic reaction and respiratory depression. However, subjects will be opioid-dependent and, thus, familiar with these common side effects, and not likely to experience the severe side effects such as allergic reaction.

Physiological and behavioral effects, as well as the emergence of possible side effects, will be monitored daily during Hydromorphone Challenge Sessions. Subjects who exhibit hypersensitivity (i.e., experience a SAE) following administration of any of the drugs will be excluded from further research participation. Heart rate, blood pressure, oxygen saturation and respiratory rate will be monitored frequently throughout sessions. However, if a subject experiences an allergic reaction, diphenhydramine will be available for oral administration.

While the risk of significant respiratory depression may be decreased in opioid-dependent individuals (due to greater tolerance), standardized criteria for nursing staff and research personnel will be employed during the monitoring of individuals. If respiratory rate drops below 12 breaths/min accompanied by sedation, subjects will be prompted verbally to breathe. This approach of physical and verbal stimulation is often sufficient to prompt breathing and restore a normal respiratory rate. Subjects will be monitored carefully with a watch-and-wait approach and will be accompanied continuously by nursing personnel and evaluated by the staff physician. If clinical evaluation determines that a subject's level of sedation is increasing, naloxone will be promptly administered parenterally to produce immediate reversal of the hydromorphone effects. Naltrexone will also be available if longer blockade is necessary.

The study will be conducted in CRUs with trained nursing staff available on site. A crash-cart with naloxone will be on site as well. Emergency response will be available by a physician code-team if needed.

10.6.2. Treating Opioid Withdrawal

If opioid withdrawal occurs after dosing with CAM2038 q1w (precipitated withdrawal), the following assessments will be collected every 4 hours while the subject is awake for at least 24 hours after dosing to include:

1) COWS,
2) OOWS,
3) VAS assessment of opioid withdrawal severity.

Treatment will be based upon clinical judgment of the medically responsible physician at each site. To ensure the safety of subjects, incidences of precipitated withdrawal in response to CAM2038 q1w will be followed carefully and an amendment of the protocol to ensure subjects are in a more advanced state of opioid withdrawal e.g., increase required COWS score from 8 to 12, to reduce the risk of BPN-related precipitated withdrawal, will be considered if more than one incidence occurs.

Ancillary medications that will be made available for symptomatic relief of all episodes of withdrawal (precipitated by CAM2038 q1w and other) are summarized in Table 5**Error! Reference source not found.Error! Reference source not found.**.

10.7. Pharmacodynamic Variables

10.7.1. Primary Pharmacodynamic Endpoint

The primary endpoint of this study is the E_{max} of Drug Liking VAS.

10.7.2. Secondary Endpoints

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

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

10.8. Drug Concentration Measurements

Venous blood samples (6 mL each) will be collected, as indicated in Table 4. Samples will be collected, processed, and shipped according to instructions provided in the Study MOP. The actual date and time of each blood sample collection will be recorded.

Up to 138 mL of total blood volume will be required from subjects for pharmacokinetic sampling. Analysis of the plasma samples will be detailed in the Study MOP.

Plasma samples will be shipped frozen on dry ice from the research site to the designated bioanalytical laboratory, as outlined in the Study's MOP.

Samples will not be shipped without prior arrangement with the bioanalytical laboratory and/or notification to the Sponsor.

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

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

Details of the pharmacokinetic evaluation will be presented in the SAP.

11. DATA QUALITY ASSURANCE

This study will be conducted under Good Clinical Practice (GCP) and all applicable regulatory requirements. To ensure compliance, the sponsor or designee may conduct a quality assurance audit, as outlined in Section 11.2.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers; the review of protocol procedures with the Investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use (where applicable); the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as the periodic site monitoring by the sponsor. The sponsor or designee will review source documents for accuracy and completeness during on-site monitoring visits and after their return to the sponsor; any discrepancies will be resolved with the Investigator, as appropriate.

Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator site termination and regulatory authority notification.

11.1. Data Collection

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This study will use electronic data capture (EDC) or paper CRFs. At a minimum, all data required by the protocol should have supporting source documentation for entries in the EDC system, unless that data can be recorded directly in the EDC system or other device.

All CRFs will be completed by the site staff prior to review by the sponsor's monitor or designated representative. The sponsor's monitor or designated representative will review all source records on-site and compare them to the data collected on the CRF. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture system maintains a full audit trail.

11.2. Study Auditing and Monitoring

Monitoring of the study site (including, but not limited to, reviewing CRFs for accuracy and completeness) will be performed by the sponsor's monitor. The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the sponsor, a regulatory authority, and/or an IRB may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, subject charts and source documents, and other records

related to study conduct. The purpose of the sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether the study-related activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, the site's standard operating procedures, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The following sections describe the statistical methods to be used to analyze the efficacy and safety. These methods may be revised and updated due to reasons such as regulatory requirements or need for further clarifications. The final analysis plan will be documented in a formal statistical analysis plan (SAP) that must be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how data will be presented as well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report (CSR) will discuss deviations from the SAP, if any.

12.1. Sample Size Determination

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

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

The plan will be to enroll a sufficient number of subjects to ensure that at least 48 subjects complete the study (24 subjects per treatment group) by over-enrollment as needed and replacement of subjects for those who drop out.

12.2. Analysis Populations

Three populations are defined for the study:

- Intent-to-treat (ITT) Population will consist of all subjects who receive study drug and provide some post baseline efficacy values.
- Completer Population will include all subjects who complete the study (i.e., complete Day 14). The primary efficacy analyses will be based on the Completer Population.
- Safety Population will include all subjects who receive study drug. All safety analyses will be based on the Safety Population.

12.3. Statistical Analyses

Unless otherwise indicated, all testing of statistical significance will be 2-sided, and a difference resulting in a *P* value of less than or equal to 0.05 will be considered statistically significant.

Furthermore, the baseline will be the last assessment before the first dosing of the study medication.

Summary statistics will be provided for the variables described in the following sections. For continuous variables, these statistics will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of subjects in each category.

12.3.1. Study Subjects and Demographics

12.3.1.1. Subject Disposition and Discontinuations

The numbers of subjects randomized, completing, and discontinuing, along with reasons for discontinuation, will be tabulated overall and by CAM2038 treatment group (24 mg and 32 mg groups) and sequence. The number of subjects in each analysis population will be reported.

12.3.1.2. Protocol Deviations

Major protocol deviations will be classified and documented before database lock and will be discussed in the CSR. All protocol deviations, both minor and major, will be presented in a data listing.

12.3.1.3. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (including age, sex, race, weight, and height) will be summarized for each treatment group, sequence, and for the overall population by descriptive statistics. Medical history and clinical laboratory tests will be listed.

Prior and concomitant medications will be summarized by treatment group and sequence by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms.

12.3.2. Exposure

Study drug administration will be summarized in terms of exposure in day (last dose date – first dose date +1). Descriptive statistics for these quantities, including the mean, SD, minimum, and maximum, will be provided by treatment group.

12.3.3. Efficacy Analyses

Efficacy variables will be summarized and analyzed using both Completer and ITT Populations unless otherwise specified. The primary analyses will be based on the Completer Population.

12.3.3.1. Primary Efficacy Analyses

The primary efficacy variable will be E_{max} of Drug Liking VAS. This variable will be analyzed via a mixed model including subject, challenge dosing (A=0 mg, B=6 mg, or C=18 mg), Period (1, 2, or 3 to indicate first, second, or third day of each challenge session), challenge session (1, 2, 3, or 4), where subject will be treated as random effects and the remaining parameters fixed effects. The estimated treatment effects, differences in treatment effects (test dose – the reference

dose of 0 mg), 95% confidence intervals of the differences will be presented. Blockade effects will be claimed if upper bound of the treatment difference is ≤11.

12.3.3.2. Secondary Efficacy Analyses

The secondary endpoints will include:

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

These variables will be analyzed using the similar methods discuss for the primary efficacy variable analyses.

COWS and OOWS scores will be summarized.

12.3.4. Safety and Tolerability Analyses

Safety analyses will be conducted using data from the Safety Population (as defined in Section 12.2).

Safety and tolerability will be assessed through TEAEs; hematologic and laboratory parameters; and vital signs measurements.

No formal statistical comparisons will be performed for safety endpoints.

12.3.4.1. Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) reporting system. Treatment-emergent AEs are defined as any of the following:

- Non-serious AEs with onset on the date of first dose of treatment with the study drug through discharge or Early Termination, whichever occurs first;
- Serious AEs with onset on the date of first dose of treatment with the study drug through 30 days after discharge or Early Termination, whichever occurs first;
- AEs that start before the start of treatment but increase in severity or relationship at the time of or following the start of treatment through discharge or Early Termination, whichever occurs first.

The number and percentage of subjects with TEAEs will be displayed for each treatment group. During the Qualification Phase subjects TEAEs will be displayed by IR morphine 30 mg

treatment or by hydromorphone treatment groups i.e., 0 mg 6 mg or 18 mg - on the days of hydromorphone challenges. During the Treatment Phase, TEAEs will be displayed by CAM2038 q1w relevant dose and hydromorphone relevant dose i.e., 0 mg 6 mg or 18 mg – on the days of hydromorphone challenges. TEAEs will be displayed by SOC and preferred term. Additionally, TEAEs will be tabulated for each treatment group by severity and by relationship to the study drug. A listing of SAEs will be provided if applicable.

If an AE is considered to be caused by a drug, the Investigator will note which drug caused the AE.

12.3.4.2. Clinical Laboratory Evaluations

For continuous laboratory parameters, descriptive statistics will be presented for each visit and for the changes from Baseline to each subsequent visit by treatment group (CAM2038 q1w of 24 mg or 32 mg).

Additionally, clinical laboratory parameters will be categorized as low, normal, or high according to laboratory range specifications and the number and percentage of subjects in each category will be presented in shift tables.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges.

12.3.4.3. Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from Baseline will be calculated for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and oral body temperature.

12.3.4.4. Physical Examination Findings

Physical examination data will be presented in the listings.

12.3.5. Analysis of Pharmacokinetics

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

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

12.3.6. Multiple Comparisons

To control for multiple comparisons in the efficacy analyses, the treatment differences between Treatments B (hydromorphone 6 mg) and A (0 mg) will be tested at first at a 0.05 significance level, followed by the tests between Treatments C (18 mg) and A. Blockade effects for hydromorphone 18 mg cannot be claimed unless the blockade effects for 6 mg are established first.

Furthermore, the above tests will be performed for CAM2038 q1w 32 mg first followed by the tests for CAM2038 q1w 24 mg. To control for the Type I error rate, opioid agonist blocking effects for CAM2038 q1w 24 mg cannot be claimed unless blocking effects for CAM2038 q1w 32 mg are established.

12.3.7. Interim Analysis

No interim analyses are planned.

13. STUDY ADMINISTRATION AND INVESTIGATOR RESPONSIBILITIES

Additional details may be outlined in the Clinical Trial Agreement (CTA) between the sponsor and the investigational site.

13.1. Regulatory and Ethical Considerations

13.1.1. Ethical Conduct of the Study

The Investigator will conduct the study in accordance with GCP and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the sponsor's representatives and/or regulatory authority's representatives at any time.

13.1.2. Ethics Approval

The investigational site's IRB must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB prior to enrolling subjects into the study; written approval from the committee must be received by the sponsor before drug will be released to the Investigator. The Investigator is responsible for submitting all protocol or ICF changes and SAE reports to the IRB according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

In accordance with applicable local regulatory requirements, the Investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her research site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor. The sponsor will be provided with copies of all notifications sent to the IRB.

All relevant correspondence from the IRB will be forwarded by the respective study site to the sponsor in a timely fashion.

13.1.3. Subject Informed Consent

The Investigator (or authorized designee) will ensure that the subject (or the subject's legal representative) is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject will receive an IRB-approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided in a language understandable to the subject and must not include any language that waives the subject's legal rights. Prospective subjects must also be informed of their right to withdraw consent without prejudice at any time during the study. If the subject chooses to participate, he/she must sign the ICF before any study-related procedures are performed.

Significant changes to the protocol or product safety information may require a revision of the ICF, which must be reviewed and signed by all applicable study subjects.

The time that informed consent is obtained must be documented. The investigator must maintain the original, signed ICF in the subject's source documents. A copy of the signed ICF must be given to the study subject.

13.2. Privacy and Confidentiality

The Investigator is responsible for complying with applicable privacy regulations, per his or her jurisdiction. Only information identified in this protocol will be collected. The information collected will only be used for the purposes identified in this protocol.

To ensure anonymity and to limit disclosure, subjects will be assigned a unique identifier at their first assessment. This identifier will be cross-referenced in the subject's chart. The identifier will not contain any potentially identifiable information. An identifier log will be maintained, linking each subject's name to the corresponding identifier. This log will be stored at the research site in a secure location.

The knowledge gained through this study is the property of the sponsor. The Sponsor, representatives and affiliated companies of the sponsor, the IRB, and regulatory agencies (such as the United States Food and Drug Administration [FDA]) may inspect medical records related to the study to check the validity and accuracy of the data gathered in this study. Subject medical records (with subject's initials and/or date of birth) may be copied. Confidentiality of subject records will be maintained except where release of information is required by law.

The results of this study will be reported in such a manner that subjects will not be identifiable in any way. Published reports or presentations will refer to grouped data or coded individual data and not to any identifiable individuals. Study reports sent to the sponsor or drug regulatory agencies will not include subject names.

By signing the ICF, the subject consents to the collection, access, use, and disclosure of his or her information as described in the ICF document. If a subject withdraws consent, some of the subject's information may still be collected, used, and disclosed by those involved in this study, per applicable laws.

By signing this protocol, the Investigator affirms that he or she will maintain in confidence information furnished to him or her by the sponsor and will divulge such information to his or her respective IRB or IEC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of the sponsor. Please refer to the CTA for details.

13.3. Study and Site Closure

Upon completion of the study, all study data will be provided to the Sponsor following review of site study records for completeness, and data clarifications and resolutions. Accounting, reconciliation, and final disposition of used and unused study drugs, treatment codes, and emergency code break envelopes will be performed, as applicable.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the Sponsor will discuss this with

the Investigator (including the reasons for taking such action) at that time. The Sponsor will promptly inform any other investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons and will inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator will inform the IRB promptly and provide the study subjects with the reason for the suspension or termination. If the study is prematurely discontinued, all study data will be returned to the Sponsor.

13.4. Regulatory Documents and Records Retention

The Investigator(s) are responsible for creating and/or maintaining all study documentation required by 21 CFR 50, 54, 56 and 312, ICH E6 section 8, as well as any other documentation defined in the protocol or CTA. The Investigator(s) must provide key documents to the Sponsor prior to the start of the study. A complete list of required regulatory documents will be supplied by the Sponsor or its representative.

Federal and local regulations require that the Investigator(s) retain a copy of all regulatory documents and records that support the data for this study for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.

The Sponsor will notify investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by the sponsor that the entire clinical investigation (not merely the investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application/Clinical Trial Authorization or request for marketing approval (New Drug Application/Marketing Authorization Application).

If the Investigator(s) retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the sponsor.

13.5. Delegation of Responsibilities and Adequate Resources

The Investigator(s) should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study.

The term “Investigator” used throughout this protocol refers to the principal investigator and/or qualified sub-investigators. However, the Investigator(s) may delegate responsibilities to other investigational site personnel. The Investigator(s) shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator(s) shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator(s) is responsible for ensuring all delegated staff have been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the investigational site.

13.6. Protocol Amendments

Approval of a protocol amendment by the investigator’s IRB must be obtained before implementation of the protocol amendment, unless a change is necessary to eliminate an apparent immediate hazard to the subject or when the change involves logistical or administrative aspects of the study. The protocol amendment must be signed and dated by both the sponsor and the Investigator(s). The Sponsor or designee will submit protocol amendments to the appropriate regulatory authorities, if required.

13.7. Financial Disclosure

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR § 54.2, a clinical investigator is a listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

14. SPONSOR APPROVAL PAGE

A MULTIPLE DOSE OPIOID CHALLENGE STUDY TO ASSESS BLOCKADE OF SUBJECTIVE OPIOID EFFECTS OF CAM2038 Q1W (BUPRENORPHINE FLUIDCRYSTAL® SUBCUTANEOUS INJECTION DEPOTS) IN ADULTS WITH OPIOID USE DISORDER

Version: 2.0

Date: 17-NOV-2015

Braeburn Pharmaceuticals, Inc.

Sponsor Representative Full Title	Date

15. INVESTIGATOR PROTOCOL AGREEMENT PAGE

A MULTIPLE DOSE OPIOID CHALLENGE STUDY TO ASSESS BLOCKADE OF SUBJECTIVE OPIOID EFFECTS OF CAM2038 Q1W (BUPRENORPHINE FLUIDCRYSTAL® SUBCUTANEOUS INJECTION DEPOTS) IN ADULTS WITH OPIOID USE DISORDER

Version: 2.0

Date: 17-NOV-2015

I have read this protocol and I agree to conduct the study in accordance with the protocol and with all applicable government regulations and International Conference on Harmonisation/Good Clinical Practice guidances.

Principal Investigator's Name
(please print or type) _____

_____ _____

Principal Investigator's Signature | Date (DD-MMM-YYYY)

16. REFERENCES

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17. APPENDICES

17.1. Qualification Phase Sample Daily Short-Acting Opioid Administration Schedule

During the Qualification Phase, subjects will be administered IR morphine 30 mg QID for a minimum of 3 days and a maximum of 7 days. For the first 3 days of stabilization, subjects will be permitted to receive one additional dose of IR morphine 30 mg, as needed at the discretion of the Investigator. Therefore, subjects will be permitted to receive a maximum of 150 mg IR morphine per day for the first 3 days, after which the total daily dose will be reduced to 120 mg.

A sample schedule for the 3 Qualification/Baseline Hydromorphone Challenge Session days (Day -3, Day -2, and Day-1) is provided below.

Time	
8:30 am	Start of session (pre-dose Hydromorphone Challenge Session procedures)
9:00 am	Hydromorphone Challenge dose administered, IM
9:00 am – 2:00 pm	Hydromorphone Challenge Session study procedures
2:00 pm	Morphine IR 30 mg dose administered, orally (after all challenge procedures are completed)
8:00 pm	Morphine IR 30 mg dose administered, orally

Each morning prior to the start of the Hydromorphone Challenge Session, the COWS (Appendix 17.2) and OOWS (Appendix 17.3) will be administered and the score recorded to assess the degree of opioid withdrawal that the subject may be experiencing.

17.2. Clinical Opiate Withdrawal Scale (COWS)

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/_____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

Journal of Psychoactive Drugs 259 Volume 35 (2), April - June 2003

17.3. Objective Opioid Withdrawal Scale (OOWS)

Date ..... Time .....

OBSERVE THE PATIENT DURING A
5 MINUTE OBSERVATION PERIOD
THEN INDICATE A SCORE FOR EACH OF THE OPIOID WITHDRAWAL SIGNS LISTED BELOW (ITEMS 1-13). ADD THE SCORES FOR EACH ITEM TO OBTAIN THE TOTAL SCORE

	SIGN	MEASURES		SCORE
1	Yawning	0 = no yawns	1 = ≥ 1 yawn	
2	Rhinorrhoea	0 = < 3 sniffs	1 = ≥ 3 sniffs	
3	Piloerection (observe arm)	0 = absent	1 = present	
4	Perspiration	0 = absent	1 = present	
5	Lacrimation	0 = absent	1 = present	
6	Tremor (hands)	0 = absent	1 = present	
7	Mydriasis	0 = absent	1 = ≥ 3 mm	
8	Hot and Cold flushes	0 = absent	1 = shivering / huddling for warmth	
9	Restlessness	0 = absent	1 = frequent shifts of position	
10	Vomiting	0 = absent	1 = present	
11	Muscle twitches	0 = absent	1 = present	
12	Abdominal cramps	0 = absent	1 = Holding stomach	
13	Anxiety	0 = absent	1 = mild - severe	
	TOTAL SCORE			

Range 0-13
Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987) Two New Rating Scales for Opiate Withdrawal, *American Journal of Alcohol Abuse,* 13, 293-308

17.4. Columbia-Suicide Severity Rating Scale (C-SSRS)-Baseline/Screening

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Phase 1 study

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 6 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past 6 Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

17.5. Columbia-Suicide Severity Rating Scale (C-SSRS)- Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** **No** ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Completed Suicide:	**Yes** **No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

17.6. Montgomery Asberg Depression Rating Scale (MADRS)

Montgomery Åsberg Depression Rating Scale (MADRS)

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on predefined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

It is important to remember that it is only on rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patient all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice.

The scale may be used for any time interval between ratings, be it weekly or otherwise, but this must be recorded.

Item List

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

1. Apparent Sadness

Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0 No sadness.

1

2 Looks dispirited but does brighten up without difficulty.

3

4 Appears sad and unhappy most of the time.

5

6 Looks miserable all the time. Extremely despondent.

2. Reported sadness

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 Occasional sadness in keeping with the circumstances.

1

2 Sad or low but brightens up without difficulty.

3

4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.

5

6 Continuous or unvarying sadness, misery or despondency.

3. Inner tension

Representing feeling of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only fleeting inner tension.

1

2 Occasional feelings of edginess and ill-defined discomfort.

3

4 Continuous feelings of inner tension or intermittent panic which the

patient can only master with some difficulty.

5

6 Unrelenting dread or anguish. Overwhelming panic.

4. Reduced sleep

Representing the experience of reduced duration or depth of sleep compared with the subject's own normal pattern when well.

0 Sleeps as usual.

1

2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.

3

4 Sleep reduced or broken by at least two hours.

5

6 Less than two or three hours sleep.

5. Reduced appetite

Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite.

1

2 Slightly reduced appetite.

3

4 No appetite. Food is tasteless.

5

6 Needs persuasion to eat at all.

6. Concentration difficulties

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties in concentrating.

1

2 Occasional difficulties in collecting one's thoughts.

3

4 Difficulties in concentration and sustaining thought which reduces ability to read or hold a conversation.

5

6 Unable to read or converse without great difficulty.

7. Lassitude

Representing a difficulty getting started or slowness initiating and performing everyday activities.

0 Hardly any difficulty in getting started. No sluggishness.

1

2 Difficulties in starting activities.

3

4 Difficulties in starting simple routine activities which are carried out with effort.

5

6 Complete lassitude. Unable to do anything without help.

8. Inability to feel

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with

adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and in other people.

1

2 Reduced ability to enjoy usual interests.

3

4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.

5

6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. Pessimistic thoughts

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

0 No pessimistic thoughts.

1

2 Fluctuating ideas of failure, self-reproach or self-depreciation.

3

4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.

5

6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

10. Suicidal thoughts

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts and preparations for suicide.

Suicidal attempts should not in themselves influence the rating.

0 Enjoys life or takes it as it comes.

1

2 Weary of life. Only fleeting suicidal thoughts.

3

4 Probably better off dead. Suicidal thoughts are common and suicide is considered as a possible solution, but without specific plans or intention.

5

6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.