FDA ADVISORY COMMITTEE MEETING BRIEFING DOCUMENT

CAM2038

(buprenorphine) subcutaneous injection

JOINT MEETING OF THE
PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE AND
THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

NOVEMBER 1, 2017

Available for public disclosure without redaction

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
AUC	Area under the plasma concentration-time curve
AUC_{inf}	AUC extrapolated to infinity
AUC_{ss}	AUC during a dosing interval at steady state
AUC_{τ}	AUC during a dosing interval
BA	Bioavailability
BMI	Body mass index
BPN	Buprenorphine
CAM2038	CAM2038 is collectively used for CAM2038 q1w and CAM2038 q4w
CDF	Cumulative distribution function
CI	Confidence interval
CMC	Chemistry manufacturing controls
C_{max}	Maximum plasma concentration
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
CSR	Clinical study report
$C_{ss,av}$	Average plasma concentration at steady state
C_{trough}	Trough plasma concentration
CV	Coefficient of variation
CYP	Cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
ECG	Electrocardiogram/electrocardiographic
EMA	European Medicines Agency
E_{max}	Maximum effect
EU	European Union
FC	FluidCrystal®

Abbreviation	Definition
FDA	Food and Drug Administration
GDO	Glycerol dioleate
HCP	Healthcare provider
HED	Human equivalent dose
IM	Intramuscular
IR	Immediate-release
ITT	Intent-to-treat
IV	Intravenous
LLOQ	Lower limit of quantification
LSM	Least squares mean
MAT	Medication assisted treatment
NCA	Non-compartmental analysis
NDA	New Drug Application
NMP	N-methyl-2-pyrrolidone
NOAEL	No-observed-adverse effect level
norBPN	Norbuprenorphine
NX	Naloxone
OOWS	Objective Opioid Withdrawal Scale
OUD	Opioid use disorder
PD	Pharmacodynamic(s)
PDUFA	Prescription Drug User Fee Act
PFS	Pre-filled syringe
PK	Pharmacokinetic(s)
q1w	Once-weekly
q4w	Once-monthly
QTcF	Fridericia's correction formula for QT interval
REMS	Risk Evaluation and Mitigation Strategy
RR	Response rate
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation

Abbreviation	**Definition**
SL	Sublingual
SMQ	Standardized MedDRA Queries
SOWS	Subjective Opiate Withdrawal Score
SPC	soy phosphatidylcholine
$t_{½}$	Half-life
TEAE	Treatment-emergent adverse events
T_{max}	Time to C_{max}
US	United States
VAS	Visual analog scale

1. EXECUTIVE SUMMARY

1.1. Background

Opioid use disorder (OUD) is an escalating global health problem (Hedegaard, 2017; Rudd, 2016). OUD is a chronic and life-threatening disorder characterized by compulsive opioid use causing significant mental, physical, and social problems, including transmission of infectious diseases, unintentional overdose, criminal activity, and incarceration (Schwartz, 2007; Strathdee, 2015; Surya Prasad, 2014). More than 2.4 million people in the United States currently have OUD, which includes the use of both illicit and prescription opioid agents (Mattson and Lynch, 2015).

Buprenorphine (BPN) is widely used to treat OUD as part of medication assisted therapy (MAT). It is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Importantly, the pharmacological properties confer a ceiling effect on the respiratory depression that is typically associated with opioids (Dahan, 2006). Several BPN medications are currently approved by the Food and Drug Administration (FDA) for treatment of OUD. They include sublingual (SL) tablets /transmucosal films (e.g., Subutex®, Suboxone®, Bunavail®, Zubsolv®) which are taken daily in outpatient or supervised settings, and Probuphine®, an implantable long-acting BPN product. Both Suboxone and Bunavail contain naloxone (NX) to prevent abuse by the intravenous (IV) or intranasal route of administration. When given orally as prescribed, the NX does not provide any therapeutic benefit.

CAM2038 is intended for the treatment of OUD. The novel extended-release BPN formulation utilizes FluidCrystal® (FC) technology which is comprised of lipid components, a solvent, and BPN. Upon injection, CAM2038 absorbs interstitial aqueous body fluid and transforms from a liquid to a highly viscous, liquid crystalline gel that encapsulates BPN and releases it at a steady rate as the depot, comprised of the formulations' lipid components, biodegrades. This formulation was designed to maintain therapeutic plasma BPN levels for 1 week (weekly depot, CAM2038 q1w) or 1 month (monthly depot, CAM2038 q4w), reducing the likelihood of symptom emergence between doses. This property may aid in improving treatment retention over currently available BPN therapies by ensuring medication adherence and thus, improving effectiveness in the treatment of OUD.

However, BPN and other oral medications have important limitations that contribute to limited treatment, abuse, misuse, and diversion, and unintended exposures particularly in children. SL BPN must be administered daily and is dispensed directly to the consumer, the resulting limitations are an increased risk for unintended exposures and lack of adherence. These limitations may diminish effectiveness, contribute to negative perceptions and stigma, and represent barriers to treatment. CAM2038 is expected to overcome many of the shortcomings of SL BPN by providing sustained exposure to BPN throughout the weekly (CAM2038 q1w) or monthly (CAM2038 q4w) dosing interval, which may improve treatment outcomes and medication adherence. CAM2038 will not be dispensed directly to the consumer; rather, it will be administered by qualified healthcare providers (HCPs) in office settings. CAM2038's formulation using FC technology in conjunction with the setting of administration may help to diminish the

inherent risks of diversion, misuse, and pediatric exposure as compared to currently available daily BPN medications.

CAM2038 represents a novel formulation of a drug already approved by the FDA. The New Drug Application (NDA) was submitted under the 505(b)(2) pathway which relies in part on the FDA's previous findings of safety and efficacy for the previously approved drug (the reference product) and further supported by new studies conducted by the Sponsor and/or published literature to demonstrate safety and effectiveness. Appropriate bridging studies are conducted to provide an adequate basis for reliance upon FDA's previous findings of safety and effectiveness of the reference product(s). The reference products for the CAM2038 application are Subutex (SL BPN) tablets and Suboxone (SL BPN/ and NX) tablets.

1.2. Proposed Indication and Dosing

CAM2038 is indicated for the initiation, stabilization, and maintenance treatment of OUD and is provided as once-weekly or once-monthly extended-release solution for injection in a pre-filled syringe (PFS). Dose volumes range from 0.16 to 0.64 mL and are administered using a 23-gauge needle.

- Weekly formulations for OUD treatment include 8, 16, 24, and 32 mg, which deliver 0.16, 0.32, 0.48, and 0.64 mL respectively
- Monthly formulations for OUD treatment include 64, 96, 128, and 160 mg which deliver 0.18, 0.27, 0.36, and 0.45 mL, respectively

CAM2038 is injected into the subcutaneous tissue of the buttock, thigh, abdomen, or upper arm. Injection is administered by a HCP. CAM2038 administration should be in a single injection and not divided. Injection sites should be alternated/rotated at each injection. The dose should not be administered intravascularly, intramuscularly (IM), or intradermally.

Proposed transitions from daily doses of SL BPN to initial weekly doses of CAM2038 q1w or monthly doses of CAM2038 q4w are presented below. Weekly and monthly dosing options allow treating physicians the ability to individualize dosing based on patients evolving needs from initiation through maintenance

Proposed Transfer from Daily Doses of SL BPN to Initial Weekly or Monthly Doses of CAM2038 q1w or CAM2038 q4w

Dose of daily SL BPN	Dose of weekly CAM2038 q1w
2-6 mg	8 mg
8-10 mg	16 mg
12-16 mg	24 mg
18-24 mg	32 mg
Dose of daily SL BPN	**Dose of monthly CAM2038 q4w**
8-10 mg	64 mg
12-16 mg	96 mg
18-24 mg	128 mg
26-32 mg	160 mg

Abbreviation: SL BPN, sublingual buprenorphine

Source: Extracted from Summary of clinical pharmacology, Table 28

1.3. Nonclinical

1.3.1. Nonclinical Safety

A comprehensive nonclinical safety assessment of BPN is provided by reference to the Subutex label as well as studies conducted by Braeburn (here after referred to as the Sponsor). The Sponsor conducted appropriate toxicokinetic bridging studies to demonstrate comparable BPN exposures with CAM2038 and SL BPN in relevant species. In addition, the Sponsor conducted a 9-month chronic toxicology study with CAM2038 in dogs, both formulations were tested and were well tolerated. The principal finding was reversible injection site reactions for both drug and their respective vehicle placebo.

The toxicological assessment of the FC vehicle and its components rely on Sponsor-conducted studies and published literature. This data package provides for adequate safety margins for the FC vehicle and its components.

1.3.2. Nonclinical Pharmacokinetics

The release profiles for BPN for weekly and monthly CAM2038 in dogs and rats were characterized by rapid absorption of BPN (within 30 minutes). Maximum plasma concentrations (C_{max}) occurred within 24 hours for CAM2038 q1w in rat and dog, and for CAM2038 q4w within 3 to 24 hours in dogs and 5-8 days in rats. Release from the depot matrix appeared constant over the weekly and monthly dosing intervals. No gender-related differences were observed, and no accumulation was apparent with repeated dosing. BPN exposure was not affected by injection site manipulation.

Mean exposure for a one-month period ($AUC_{0\text{-}672h}$ [area under the plasma concentration-time curve]) of CAM2038 q4w was comparable to, or slightly lower than, the theoretical $AUC_{0\text{-}672h}$ for CAM2038 q1w based on the $AUC_{0\text{-}168h}$ value (i.e., 4 x $AUC_{0\text{-}168h}$). This result provides a bridge between weekly and monthly administration and supports the transition from weekly to monthly CAM2038 dose regimens in humans.

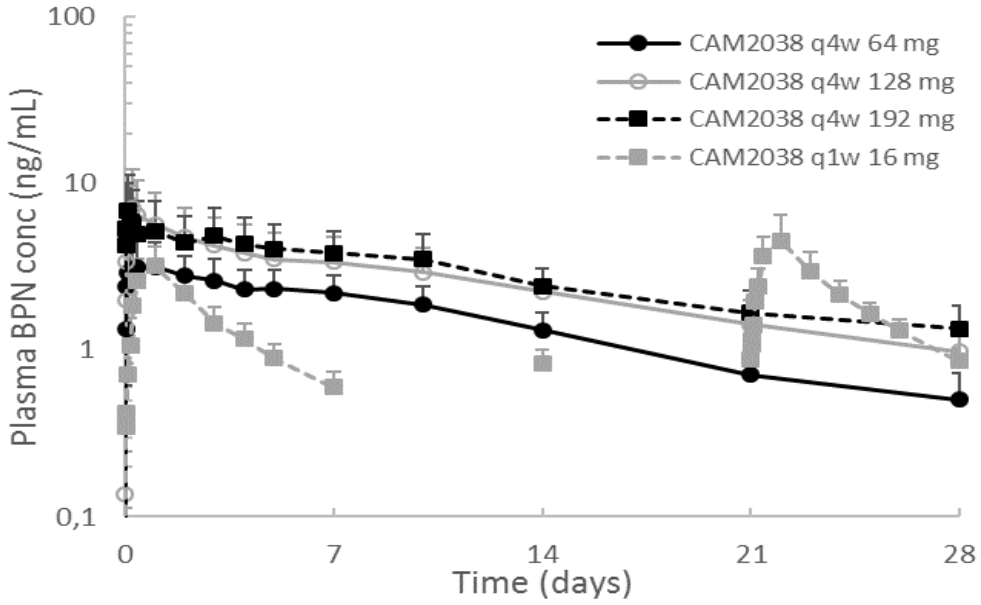
1.4. Clinical Pharmacology

The pharmacokinetic (PK) properties of CAM2038 were evaluated in 5 clinical pharmacology studies (HS-11-426, HS-13-487, HS-07-307, HS-13-478, and HS-15-549) to support the proposed dosing and bridging of clinical pharmacology data from SL BPN (Subutex) to CAM2038.

In study HS-11-426, single SC doses of 8, 16, and 32 mg CAM2038 q1w provided dose-proportional extended release of BPN, suitable for once-weekly dosing. The bioavailability of CAM2038 was 6- to 9-fold higher than SL BPN. CAM2038 q1w was well tolerated in healthy subjects under naltrexone blockade. PK findings for CAM2038 q1w were consistent across all studies.

Study HS-13-487 of CAM2038 q4w showed dose-proportional extended BPN release suitable for monthly dosing (dose range 64 to 192 mg). BPN exposure with CAM2038 q4w supported reference to Subutex (8 to 24 mg). Further, similar BPN and norbuprenorphine (norBPN) exposures were observed for a matching dose of CAM2038 q4w and 4 repeated weekly doses of CAM2038 q1w. PK findings for CAM2038 q4w were consistent across all studies.

Plasma BPN concentrations versus time are shown below. Comparable BPN exposures were achieved whether CAM2038 was injected SC in the abdomen, arm or thigh.



Plasma Concentration Time Profiles of BPN After Single SC injection of CAM2038 q4w and at First and Fourth Repeated Weekly SC injections of CAM2038 q1w in study HS-13-487

Values are mean (+SD)
Source: Table 14.2.1.2.2 in CSR HS-13-487

CAM2038 q1w and q4w formulations provided plasma levels comparable to those with daily SL BPN, but with only ~20% to 30% of total BPN dose administered over the same time period, and with lower variation in BPN plasma concentration over time.

BPN is primarily metabolized by CYP3A4 to norBPN, and norBPN is further metabolized by CYP3A and UDP-glucuronosyltransferase. Therefore, drug interaction information from the Subutex label recommends caution when using agents that impact CYP3A4. These precautions will be relevant for CAM2038 when co-administered with CYP3A4 inhibitors (e.g., ketoconazole) or inducers (e.g., carbamazepine) and will be incorporated into product labeling.

Dose adjustments are not considered necessary for patients with renal impairment based on prior studies of BPN (Boger 2006). In patients with mild hepatic impairment, no significant changes in PK parameters were observed. For patients with moderate and severe hepatic impairment, mean C_{max}, AUC_{last} and half-life ($t_{½}$) values of BPN were increased, and dose adjustments of BPN (and CAM2038) may be needed (Nasser 2015).

1.5. Clinical Efficacy

The clinical study program was designed to evaluate CAM2038 efficacy across treatment phases from initiation through maintenance. The clinical program evaluated both treatment-seeking adults with OUD, and subjects transferred from treatment with daily SL BPN and SL BPN/NX products. One Phase 2 and two Phase 3 studies incorporated efficacy endpoints:

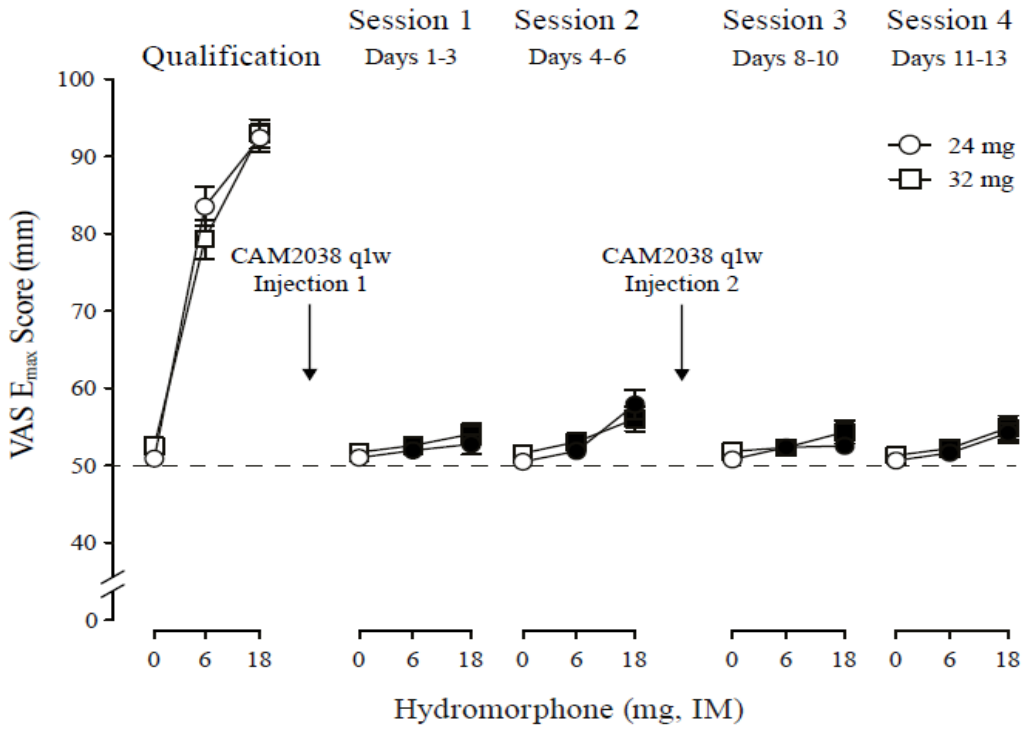
- HS-13-478: 7-week opioid challenge study; multicenter, double-blind, randomized within-patient study conducted at 3 controlled inpatient research facilities
- HS-11-421: 24-week efficacy and safety pivotal study; randomized, double-blind, double-dummy study against standard treatment with daily SL BPN/NX in treatment-seeking adults
- HS-14-499: Additional safety and efficacy findings from a 48-week open-label study that included both treatment-seeking adults and subjects transferred from SL BPN or SL BPN/NX treatment

Information from the Subutex and Suboxone reference product labels provide further support of clinical efficacy since BPN exposure levels were comparable in the CAM2038 clinical program and the referenced studies.

1.5.1. Phase 2 Study HS-13-478

Study HS-13-478 demonstrated the pharmacodynamic activity of CAM2038 by evaluating blockade of hydromorphone effects in patients with OUD. CAM2038 q1w at doses of 24 and 32 mg produced rapid and sustained opioid blockade and withdrawal suppression throughout the dosing intervals. Complete hydromorphone blockade based on a Visual Analog Scale (VAS) rating was achieved for BPN plasma concentrations between 1 to 2 ng/mL. These findings showed that both doses of CAM2038 q1w were effective at blocking the positive subjective effects (see figure below). Additionally,

higher plasma BPN concentrations were not associated with appreciable increases in the blockade.



Study HS-13-478: Mean (±SD) Maximum Effect Visual Analog Scale Scores for the Primary Outcome Measure of Drug Linking by Challenge Session for CAM2038 q1w at 24 and 32mg in Study HS-13-478

Abbreviations: E_{max}: maximum effect; IM, intramuscular; VAS, visual analog scale

Source: Extracted from summary of clinical efficacy, Figure 1
Abbreviations: BPN, buprenorphine; CI, confidence interval; E_{max}: maximum effect; LSM, least squares mean
Values are mean (95% CI). LSM, least squares mean
Source: Extracted from summary of clinical pharmacology, Figure 16

1.5.2. Phase 3 Study HS-11-421

Study HS-11-421 evaluated CAM2038 compared to an existing standard of care (SL BPN/NX; Suboxone tablets) in initiation and maintenance treatment of patients with OUD. The prespecified primary endpoint was responder rate (RR), with a responder defined as a patient with opioid-negative urine samples confirmed with self-report at:

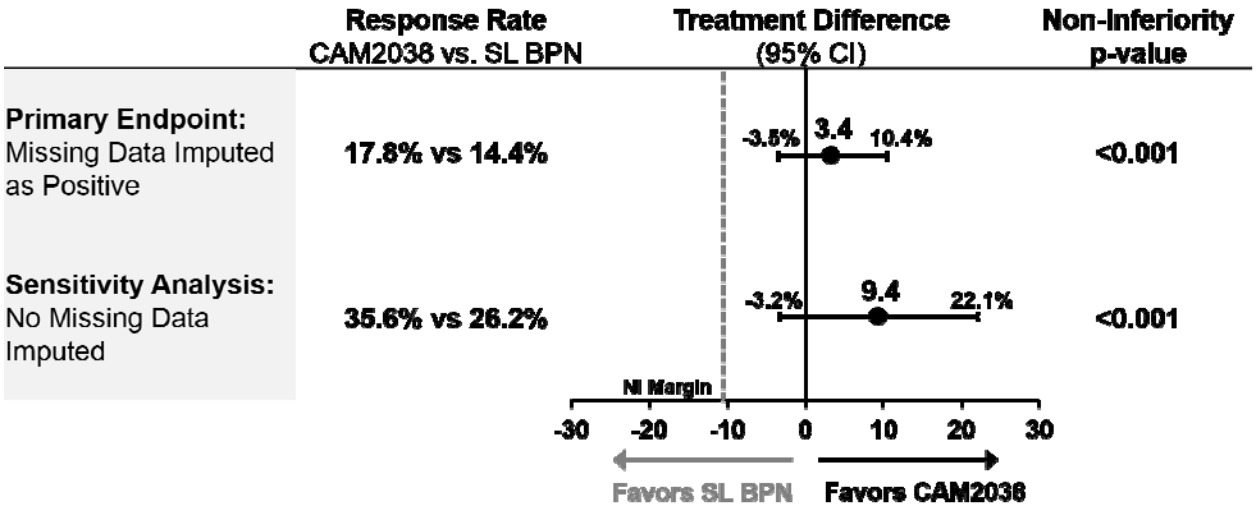
- Phase 1: Treatment Week 12, and for at least two of the three assessments between Treatment Weeks 9,10, and 11, AND
- Phase 2: Treatment Week 24, and for at least four of the five additional assessments between Weeks 13 and 23

There were 12 urine samples during Phase 1 (one per week for each weekly visit) and 6 urine samples in Phase 2 (3 monthly visits and 3 random urines). Therefore, to be a responder, at least 8 out of 10 urine samples from Weeks 9 to 24 needed to be negative

for illicit opioids (80% negative urine samples). Additionally, specific weeks, Week 12 and Week 24, needed to have urine negative for illicit opioids, to be a responder.

Secondary endpoints were ranked for statistical testing: superiority for cumulative distribution function (CDF) of percent samples that were negative for illicit opioids (Treatment Weeks 4- 24), supported by self-reports of illicit opioid use; superiority for the primary efficacy variable, RR (Treatment Weeks 1-24); superiority of active treatment over the control for time to sustained abstinence after 8 weeks of treatment; non-inferiority with margin of 15% for retention rate; and superiority of active treatment over the control for retention rate. The analyses considered all doses of CAM2038 together, because dose titrations, adjustments, and transitions (weekly to monthly and vice versa) are integral components of CAM2038 use in a treatment setting.

CAM2038 met the primary endpoint and demonstrated non-inferiority to SL BPN/NX for the primary endpoint of RR for opioid-negative urine samples (80% of urine samples from Weeks 9-24 negative for illicit opioids, with negative urines at specific weeks 12 and 24). The treatment difference was 3.4% with the lower bound of the confidence interval at -3.5%, which was well above the pre-specified 10% non-inferiority margin. A sensitivity analysis was conducted where missing data was not imputed, which supported the results of the primary analysis.



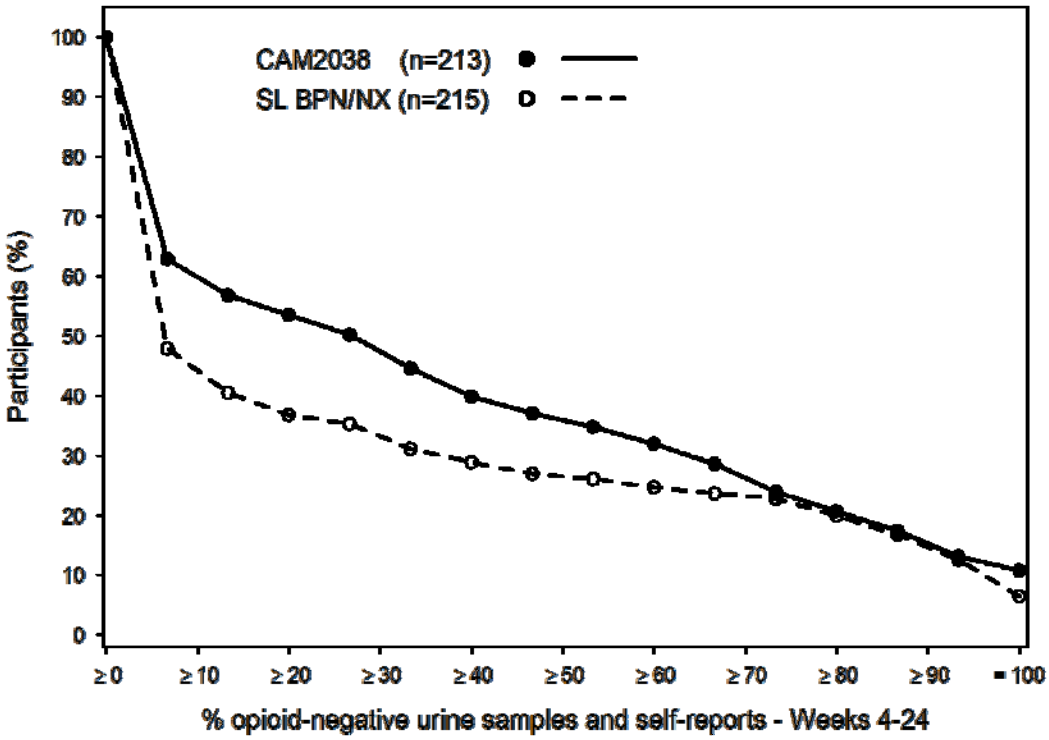
HS-11-421: Primary Endpoint Non-inferiority Analyses and Sensitivity Analysis with No Imputation of Missing Data

Abbreviations: CI, confidence interval; ITT, intent-to-treat; NI, noninferiority, SL BPN/NX, sublingual buprenorphine/naloxone

Additional post-hoc sensitivity analyses were also conducted to determine the responder rate in various subgroups. Subgroup analyses for age, sex, race, as well as patterns of illicit opioid use by injection route, heroin as primary opioid of use, and poly-drug use

(including cocaine, amphetamines, marijuana, and benzodiazepines) all provide supportive results demonstrating non-inferiority of CAM2038 to SL BPN.

CAM2038 also achieved superiority to SL BPN/NX for the CDF of the proportion of confirmed opioid-negative urine samples during Treatment Weeks 4–24 (see figure below). Formal statistical testing was halted when the subsequent endpoint was not met. Sensitivity analyses of the CDF of opioid negative urines over Treatment Weeks 1–24 (without a grace period, defined in Clinical Efficacy Section 8.2.3) and other grace periods were consistent with the main findings; CAM2038 was always superior to SL BPN/NX. Study retention was similar between groups, as was suppression of opioid craving and withdrawal. Outcome measures that evaluated desire or need to use opioids, subjective and objective rated withdrawal supported the efficacy of CAM2038.



Study HS-11-421: CDF of Percent of Urine Samples Negative for Illicit Opioids with Self-reports – Treatment Weeks 4 to 24 (ITT Population)

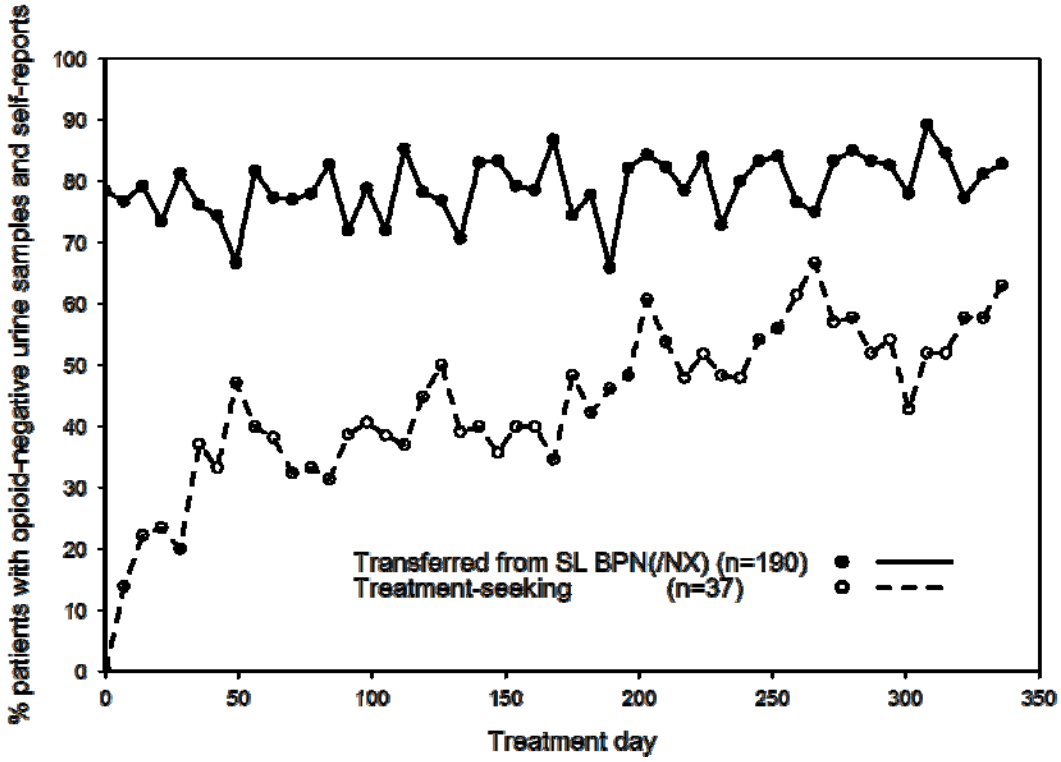
Abbreviations: CDF, cumulative distribution function; ITT, intent-to-treat; SL BPN/NX, sublingual buprenorphine/naloxone. Source: Extracted from summary of clinical efficacy, Figure 14

1.5.3. Phase 3 Long-term Safety Study HS-14-499

HS-14-499 was an open-label, 48-week safety study of CAM2038 q1w and q4w in adult patients with OUD. The study included subjects taking SL BPN/NX for OUD at study entry, and subjects who were actively seeking BPN treatment but had not yet begun treatment. In addition to evaluating the safety, this study assessed efficacy measures to

support the results of Study HS-11-421. These parameters included illicit opioid-negative urine samples, self-reported illicit opioid use, signs and symptoms of withdrawal, and cravings. Study HS-14-499 also evaluated efficacy measures during the transition from SL BPN to CAM2038, and from CAM2038 q1w to CAM2038 q4w.

Subjects receiving SL BPN (or SL BPN/NX) at entry remained stable after the transition to CAM2038, with a tendency toward improvements in most measures. Subjects new to BPN treatment had improvements in opioid withdrawal, desire/need to use opioids and, proportion of opioid negative urine samples (see figure below).



Study HS-14-499: Illicit Opioid Negative Samples Over Time

Abbreviations: BPN/NX: buprenorphine/naloxone; SL, sublingual

Source: Extracted from summary of clinical efficacy, Figure 6

1.6. Clinical Safety

Except for mild to moderate injection site reactions, the CAM2038 safety profile was comparable to the well-established safety profile of BPN. CAM2038 exposure in 729 subjects (of which 594 are patients with OUD) for up to 1 year supported the safety profile of CAM2038.

The most commonly reported adverse events (AEs) with CAM2038 in the Phase 3 studies included injection site pain (12.3%), injection site swelling (8.2%), headache (7.7%), injection site erythema (7.5%), and nausea (7.0%). Across all studies, a total of 17 subjects (2.3%) receiving CAM2038 experienced 20 serious adverse events (SAEs). Road traffic accident and seizure were reported in 2 subjects each; all other SAEs were

reported in 1 subject each. One death occurred during the clinical studies; a subject on CAM2038 was involved in a fatal road traffic accident deemed unrelated to the study medication.

In study HS-11-421, 181 subjects (42.3%) discontinued the study early: 92 (43.2%) in the CAM2038 group and 89 (41.4%) in the SL BPN/NX group. In study HS-14-499 (open-label study), 70 subjects (30.8%) receiving CAM2038 discontinued. The most common (≥5% of subjects) reasons for study discontinuation across all studies were withdrawal by subject/withdrawal of consent (CAM2038 overall: 11.9%; SL BPN/NX: 21.4%) and lost to follow-up (CAM2038 overall: 5.9%; SL BPN/NX: 13.5%).

Adverse events of special interest (AESIs) were specified by the Sponsor based on the labeling of the reference product and taking the different route of administration into account. In the controlled study, HS-11-421, the incidence rates of these AESI were generally comparable in the CAM2038 and SL BPN/NX groups, with the possible exception being drug abuse and dependence (i.e. overdoses), which occurred more commonly in the SL BPN/NX group.

1.7. Abuse Potential

CAM2038 was not developed specifically to be abuse deterrent, however, the inherent extended-release properties of the FC technology and the requirement that CAM2038 will only be administered by a HCP mitigate the abuse potential of this product. The Sponsor is in discussions with FDA regarding a Risk Evaluation and Mitigation Strategy (REMS). The REMS will be designed to ensure that only HCPs who are DATA 2000-waived are able to order CAM2038 for their patients, and only HCPs can administer CAM2038.

1.8. Benefit-Risk Conclusion

The clinical efficacy and safety data offers strong evidence that CAM2038 provides clinical benefit in the treatment of OUD that is comparable to, or better than, that provided by SL BPN/NX. The safety profile is manageable, as has been demonstrated for other BPN products and other injectable agents. The risk of injection site reactions, which represents the only identified risk not shared by SL BPN, is outweighed by the benefits provided by the convenient dosing regimen and potential for improved adherence imparted by the novel extended-release formulation. CAM2038 is intended to be administered by a HCP only, which could reduce the potential for abuse, misuse, accidental pediatric exposure, as well as diversion.

2. INTRODUCTION

- Opioid Use Disorder (OUD) and opioid-related overdose deaths are escalating global health problems.
- OUD is often chronic and life-threatening disorder characterized by compulsive opioid use causing significant mental, physical, and social problems, including transmission of infectious diseases, unintentional overdose, criminal activity, and incarceration.
- OUD can be effectively managed with approved pharmacotherapies, including buprenorphine (BPN), a partial mμ-opioid receptor agonist, along with psychosocial support/counseling.
- Currently approved daily sublingual (SL) and buccal BPN formulations are demonstrated to be safe and effective, but also have limitations:
    - Suboptimal medication adherence and treatment retention
    - Diversion, abuse, and misuse
    - Potential for accidental pediatric exposure

  The above limitations may diminish effectiveness, contribute to negative perceptions and stigma, and represent barriers to treatment.
- Novel extended-release BPN formulations provide sustained exposure, which may improve treatment outcomes and medication adherence. In addition, administration by healthcare professionals may also help to diminish the inherent risks of diversion, misuse, and pediatric exposure of currently available daily oral BPN medications.
- CAM2038 is provided in weekly and monthly regimens
    - Multiple fixed doses with dose proportional BPN exposure
    - Enables individualized dosing for OUD from initiation to maintenance treatment

2.1. Background

2.1.1. Opioid Use Disorder

OUD and opioid-related overdose deaths are escalating global health problems (Hedegaard, 2017; Rudd, 2016). According to the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association fifth edition (DSM-5), an opioid-use disorder is defined as the repeated occurrence within a 12-month period of 2 or more of 11 problems, such as experiencing withdrawal, giving up important life events in order to use opioids, and excessive time spent using opioids (Table 1). OUD is often a chronic and life-threatening disorder characterized by compulsive opioid use causing significant mental, physical, and social problems, including transmission of infectious diseases, unintentional overdose, criminal activity, and incarceration (Schwartz, 2007;

Strathdee, 2015; Surya Prasad, 2014). There are currently more than 2.4 million people in the US suffering from OUD, which includes the use of both illicit and prescription opioids (Mattson and Lynch, 2015). In fact, 99% of the world's hydrocodone and 80% of global opioid consumption occurs in the US (International Narcotics Control Board, 2016). Currently, the number of medication overdose deaths surpass the number due to traffic accidents, with half of these deaths attributable to prescription opioids (Rudd, 2016).

As previously mentioned, OUD is a diagnosis applied to a person who uses opioids and who meets at least two of 11 specified criteria within a 12-month period (Table 1). The total number of criteria met is summed to give a total score that indicates level of severity. Specifically, 2-3 criteria is mild, 4-5 is moderate, 6 or more is severe severity. A summarized list of the 11 criteria are: failure to fulfill responsibilities due to opioid use, use in physically hazardous situations, opioid craving, social and interpersonal problems caused by opioid use, using larger amounts or for longer periods than intended, inability to cut down or quit despite desiring to do so, increasing time spent to acquire and use opioids and recover from their effects, giving up or decreasing involvement in other important parts of the person's life, ongoing use despite problems, tolerance and withdrawal. The last two criteria are not counted if the person is receiving opioid medication under appropriate medical care. Persons with OUD can have varying combinations of clinically significant signs and symptoms, levels of functioning in different domains, comorbidities and psychosocial situations. Consequently, a flexible multi-modal approach is needed. The treatment goal is to reduce the frequency, severity and consequences of opioid use and relapse, improve patients' overall level of functioning, placing the OUD into full remission, ideally accompanied by opioid abstinence. A careful assessment and development of a comprehensive treatment plan that addresses each patient's unique needs is required. It is critical to address comorbid psychiatric and medical illness as well as psychosocial problems such as food insecurity and housing problems that can impact opioid use.

Table 1: DSM-5 Diagnostic Criteria for Opioid Use Disorder

- Use of an opioid in increased amounts or longer than intended
- Persistent wish or unsuccessful effort to cut down or control opioid use
- Excessive time spent to obtain, use, or recover from opioid use
- Strong desire or urge to use an opioid
- Interference of opioid use with important obligations
- Continued opioid use despite resulting interpersonal problems, social problems (e.g., interference with work), or both
- Elimination or reduction of important activities because of opioid use
- Use of an opioid in physically hazardous situations (e.g., while driving)
- Continued opioid use despite resulting physical problems, psychological problems, or both
- Need for increased doses of an opioid for effects, diminished effect per dose, or both
- Withdrawal when dose of an opioid is decreased, use of drug to relieve withdrawal or both

2.1.2. Treatment of Opioid Use Disorder using Buprenorphine

Treatment for OUD may have multiple components, not only medication prescription and monitoring. For instance, the patient assessment may indicate needs for additional counseling, ancillary social services, peer and recovery support services, and treatment of other medical and psychiatric illnesses in order to facilitate remission of OUD and long-term recovery. Treatment may occur in a variety of settings - inpatient or outpatient clinical settings as well as settings outside the health care systems such as within the criminal justice system. OUD can be effectively managed with approved pharmacotherapies, which are often used in combination with counseling and behavioral therapies and referred to as Medication Assisted Treatment (MAT).

Buprenorphine has several important pharmacologic actions that contribute to its clinical effectiveness because of its long half-life, partial mu-opioid agonist action and tight binding to the mu-opioid receptor in several areas within the brain. These clinically relevant actions include reduction of opiate drug cravings and suppression of painful opioid withdrawal as well as blockade of the rewarding effects of opioids (i.e., waste of money to use heroin or a prescription opioid while taking buprenorphine), and blockade of other physiologic effects (like respiratory depression that contributes to risk of overdose death). Furthermore, as a partial agonist, it can also induce very uncomfortable opioid withdrawal (rather than euphoria or feeling high) if taken by someone who is physically dependent on opioids but not yet in opioid withdrawal. Treatment employing buprenorphine pharmacotherapy can reduce illicit opioid use, the risks of infectious-disease transmission and criminal activities allowing for improvement in psychosocial functioning and engagement in long term recovery.

BPN is widely used to treat OUD. It is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Importantly, the pharmacological properties confer a ceiling effect on the respiratory depression that is typically associated with opioids (Dahan, 2006). The status of BPN as a critical component in OUD treatment is underscored by its inclusion in the World Health Organization's essential medications list (Mattick, 2014; Schuckit, 2016).

The treatment course with BPN for OUD includes initiation or induction, stabilization, and maintenance phases (SAMSHA TIP 40). Treatment with all daily (SL and buccal, or transmucosal) BPN formulations involves an initial induction phase. This is the period and process of initial dosing, which typically involves the patient coming to the healthcare provider's (HCP's) office in opioid withdrawal. Current guidance recommends the patient be given 2-4 mg of SL BPN/naloxone (NX) under HCP supervision; this dose can be repeated approximately every 60-90 minutes in the HCP office if withdrawal persists. A typical day 1 dose is 8 mg and target dose is often 16 mg, which can be achieved often by the end of day 2 as long as there is no sedation or other adverse effects.

Supervised inductions with lengthy day 1 HCP office visits and subsequent office visits for day 2 and subsequent days if needed for dose adjustment have been reported as barriers to providing OUD treatment with BPN by HCPs. To address this barrier, there are a growing number of published reports of conducting inductions at home rather than at the HCP office. While this practice is not specifically recommended in any published

clinical guidance, clinically significant adverse events (AEs) have not been reported. Home inductions inherently involve less direct medical supervision and may increase the risk for incorrect use of the medication (i.e., patients not taking their dose correctly – swallowing their saliva rather than holding the saliva in the mouth), misuse (escalating their dose, injecting or snorting the dose, taking it multiple times daily when intended for daily dosing) and diversion. There is a difficult balancing act with daily BPN between making it feasible for providers to incorporate BPN treatment into their practice so it is accessible to patients while simultaneously trying to minimize the potential for the behaviors of misuse and diversion which can cause patient and public health harm but which are also common behaviors among persons with OUD (Walley, 2008; Lee 2014).

Stabilization on BPN occurs when there is evidence of a marked reduction in illicit opioid use, cravings and suppression of opioid withdrawal. Stabilization can occur at a range of doses. Maintenance on the medication refers to providing the treatment without a specified endpoint as is done with other medical illnesses (e.g., asthma, COPD). The typical course of illness and treatment are difficult to predict and varied, like other often chronic medical illnesses such as diabetes mellitus and bipolar affective disorder.

2.2. Limitations in Current Standard of Care and Barriers to Use

Although efficacious for OUD treatment, currently approved daily SL and buccal BPN formulations have limitations. These limitations include general barriers to MAT as well as inherent limitations of the SL and buccal formulations. Indeed, of the 2.5 million Americans 12 years of age or older who abused or were dependent on opioids in 2012 (according to the National Survey on Drug Use and Health conducted by the Substance Abuse and Mental Health Services Administration [SAMHSA]), fewer than 1 million received MAT (Volkow, 2014). The reasons for underuse are manifold and include negative perceptions, misunderstanding, and stigma around the medical treatment of OUD (Lofwall and Walsh 2014, Volkow, 2014). HCPs and patients may also be discouraged by suboptimal treatment retention (often ≤ 50% after 3–6 months) or non-adherence with the daily SL/buccal BPN agents, since treatment success depends in part on continuous exposure to BPN, and treatment dropout is strongly associated with relapse (Fiellin, 2006; Hser, 2017; Weiss, 2011).

In addition, oral BPN itself is susceptible to diversion and misuse, and has become the primary opioid of abuse in some countries (Alho, 2007; Lofwall and Walsh, 2014; Winstock, 2008). SL and buccal formulations of BPN can be injected or snorted to enhance euphoric effects (Fiellin, 2006; Middleton, 2011; Comer, 2002). This potential for abuse raises the risks of misuse and diversion.

Importantly, accidental exposure of children with SL and buccal BPN has been reported, leading to toxicity and fatality in children (Lovegrove, 2014; CDC 2012). These accidental exposures are enabled by direct-to-patient dispensing, which places the medication in home settings that may include children.

2.3. CAM2038 Addresses Clinical Need in Opioid Use Disorder Treatment

CAM2038 was developed to address limitations of existing daily dosing of BPN with SL and buccal BPN formulations. Specifically, the novel extended-release BPN formulation may improve medication adherence and increase treatment retention. Further, the CAM2038 extended-release formulation is designed to maintain therapeutic plasma BPN levels for 1 week (weekly depot, CAM2038 q1w) or 1 month (monthly depot, CAM2038 q4w), reducing the likelihood of symptom emergence between doses. Finally, the extended-released subcutaneous FluidCrystal® (FC) depot technology (Tiberg, 2012) and its proposed distribution paradigm are designed to minimize the potential for abuse, misuse, diversion and accidental pediatric exposure. The injection depot is designed to provide treatment over extended periods. It has the potential to reduce the burden of daily medication while increasing adherence to therapy.

CAM2038 contains a lipid-based liquid and dissolved BPN that is injected SC using a conventional syringe with a thin needle. Once injected, the liquid drug product spontaneously transforms from a low viscous solution to a highly viscous liquid crystalline gel that encapsulates BPN and releases it at a steady rate as the depot biodegrades.

2.4. Regulatory History

2.4.1. Regulatory Pathway 505(b)(2)

CAM2038 represents a novel formulation of an FDA-approved medication, and the New Drug Application (NDA) was submitted under the abbreviated Section 505(b)(2) regulatory pathway. This pathway allows a Sponsor to reference one or more FDA-approved products, relying in part on studies not conducted by or for the Sponsor to demonstrate safety and effectiveness. Appropriate bridging studies are conducted to provide an adequate basis for reliance upon FDA's previous findings of safety and effectiveness of the reference product(s). The reference products for the CAM2038 application are Subutex (BPN; up to 24 mg daily) SL tablets and Suboxone (BPN/NX; up to 24 mg/6 mg daily) SL tablets.

The Sponsor conducted a clinical development program, nonclinical studies and a full chemistry manufacturing controls (CMC) development program to bridge from the FDA's previous findings of safety and efficacy for the reference products.

2.4.2. Fast Track and Priority Review Designation

Fast Track Designation was granted on July 10, 2015. This status may be conferred for an investigational drug "if it is intended, whether alone or in combination with one or more other drugs, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition" (FDA Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, 2014). On September 15, 2017, the file was accepted and a Priority Review was granted. The Prescription Drug User Fee Act (PDUFA) date is January 19, 2018.

3. PROPOSED INDICATION, DOSAGE, AND ADMINISTRATION

CAM2038 is indicated for the initiation, stabilization, and maintenance treatment of OUD and should be used as part of a complete treatment plan to include counseling and psychosocial support. It is provided as once-weekly or once-monthly extended-release solution for injection in a pre-filled syringe (PFS). Dose volumes range from 0.16 to 0.64 mL and are administered using a 23-gauge needle.

- Weekly formulations for OUD treatment include 8, 16, 24, and 32 mg, delivered in 0.16, 0.32, 0.48, and 0.64 mL respectively
- Monthly formulations for OUD treatment include 64, 96, 128, and 160 mg delivered in 0.18, 0.27, 0.36, and 0.45 mL, respectively

CAM2038 is injected into the SC tissue of the buttock, thigh, abdomen, or upper arm. Injection is administered by a HCP. CAM2038 administration should be in a single injection and not divided. Injection sites should be alternated/rotated at each subsequent injection. The dose should not be administered intravascularly, intramuscularly (IM), or intradermally.

Proposed transitions from daily doses of SL BPN to initial weekly or monthly doses of CAM2038 are presented in Clinical Pharmacology Section 7.5.2, Table 5. Weekly and monthly dosing options allow treating physicians the ability to individualize dosing based on patients evolving needs from initiation through maintenance.

4. DRUG PRODUCT

CAM2038 is a novel, extended-release solution for SC injection containing BPN and utilizing FC technology. The FC formulation is comprised of lipid components, a solvent, and BPN. Upon injection, CAM2038 absorbs interstitial aqueous body fluid and transforms from a liquid to a highly viscous, liquid crystalline gel that encapsulates BPN and releases it at a steady rate as the depot, comprised of the formulation's lipid components, biodegrades. This formulation was designed to maintain therapeutic plasma BPN levels for 1 week (weekly depot, CAM2038 q1w) or 1 month (monthly depot, CAM2038 q4w), reducing the likelihood of symptom emergence between doses.

Figure 1 below provides a schematic summarizing the formulation, concentration, and available doses for each CAM2038 drug product.

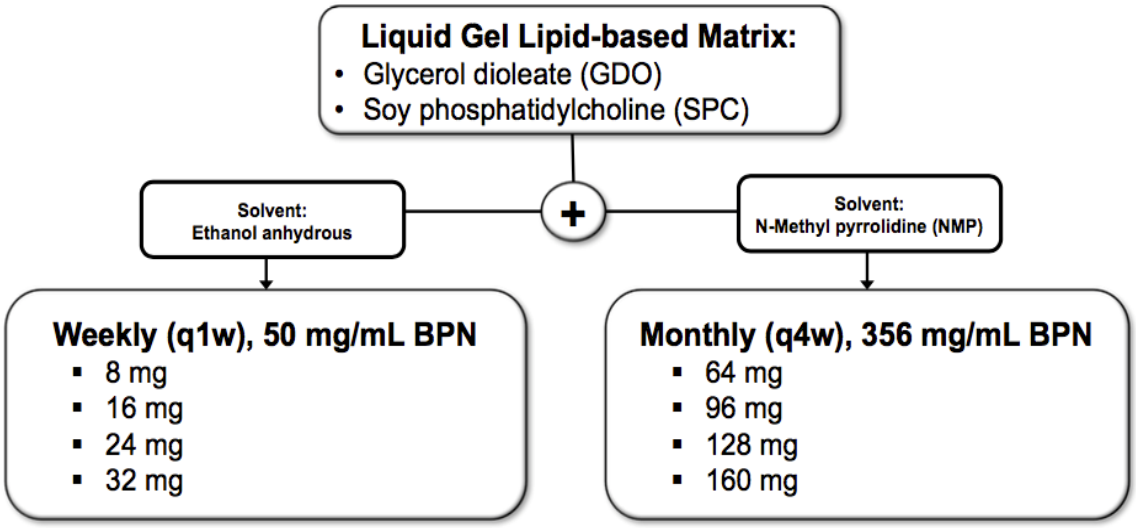


Figure 1: CAM2038 Weekly and Monthly Formulations

CAM2038 is provided ready for use in a PFS equipped with a needle stick prevention safety device and can be stored at room temperature, with no need for mixing prior to SC injection. Injection volumes are 0.16 to 0.64 mL and CAM2038 is administered through a thin 23-gauge needle (Figure 2).

Figure 2: CAM2038 Drug Product in Pre-filled Syringes

5. NONCLINICAL SAFETY

- In animal models, CAM2038 produced quantifiable concentrations of BPN throughout one week (CAM2038 q1w) or month (CAM2038 q4w), with no dose dumping.
- No systemic toxicity following a 9-month chronic toxicity study in dogs (32 mg q1w, up to 192 mg q4w).
- The principal finding for CAM2038 in animals was a reversible injection site inflammatory response.
- Multiple injections into the same site did not enhance the inflammatory response or alter the pharmacokinetics (PK) of BPN.
- QT prolongation observed only after the initial dose in dogs, with no QT findings following repeated dosing of CAM2038 (up to 32 mg q1w, up to 192 mg q4w).
- Based on PK bridging studies, BPN safety exposure margins of ~ 7-fold and higher were established for carcinogenicity, and ~ 11-fold and higher for developmental and reproductive toxicity.
- Qualification of Excipients:
    - No systemic toxicity attributed to the FC vehicle following chronic treatment in rats (6 months) and dogs (9 months).
    - No systemic toxicity, genotoxicity or reproductive toxicity observed for GDO, a lipid component of FC
        - Safety margins of 67-fold and higher were derived for carcinogenicity and 13-fold and higher for developmental and reproductive toxicity
    - Systemic exposure was limited for NMP, a component in CAM2038 q4w, following injection in rats and rabbits and based on retrospective analysis of human plasma samples.
        - Safety margins of 46-fold and higher derived for carcinogenicity and 3-fold and higher for developmental and reproductive toxicity based on data from PK bridging studies
    - Toxicological evaluations of the lipid excipient SPC and ethanol (both components of the FC) were based on approved parenteral pharmaceutical products and published data and determined to be safe in the CAM2038 drug products.

5.1. Overview

The nonclinical testing of CAM2038 included a combination of Sponsor-conducted studies and cross-referencing to nonclinical safety data in the reference product (Subutex) label and to data on BPN described in the scientific literature.

The nonclinical studies conducted with CAM2038 characterized the PK profiles for weekly (CAM2038 q1w) and monthly (CAM2038 q4w) SC BPN formulations, and provided long-term safety and local tolerability data. For the nonclinical carcinogenicity, mutagenicity, impairment of fertility and pregnancy, reference is made to the Subutex label. BPN exposures achieved with the SC or dietary administration in nonclinical studies, and human BPN exposure from CAM2038 injection were used to generate safety margins of systemic exposure that support the nonclinical safety of CAM2038.

Risk assessments of the FC vehicle and each of the components were performed, including developing toxicological and toxicokinetic data for the FC vehicle, the excipient GDO and the solvent NMP. In addition, a toxicological assessment of the other components of the FC vehicle (ethanol and SPC) was performed.

The pivotal nonclinical studies were conducted in accordance with Good Laboratory Practice (GLP) regulations, and the nonclinical studies were conducted consistent with ICH M3(R2).

5.2. Pharmacology and Safety Pharmacology

The primary pharmacology of BPN is well-established based on nonclinical studies and extensive clinical experience. The pharmacological activity of BPN is not expected to differ when administered SC in CAM2038 compared to the SL administration of Subutex. No stand-alone *in vivo* safety pharmacology studies in animals were conducted for CAM2038. However, potential effects on cardiovascular, respiratory and central nervous system (CNS) were evaluated within repeated dose toxicity studies in dogs that included a pivotal 9-month study. No effects on respiratory function were observed.

Effects related to the nervous system, such as reduced activity level, sedation, stereotypic behavior, trembling, and vocalization were observed in rats and dogs treated by subcutaneous injection with CAM2038. These effects are expected based on the known pharmacology of BPN. The clinical signs were mainly observed following the first CAM2038 administration, after which the frequency and severity decreased or abated, suggesting acclimation to BPN.

Cardiovascular changes such as a mild decrease in heart rate and moderate QT prolongation were observed at the start of the treatment, but not after 4 weeks or 9 months of treatment with CAM2038 in dogs.

Electrocardiographic (ECG) QT interval prolongation by BPN is described in the literature and has been associated with C_{max}. Therefore, *in vitro* evaluations of the effect of BPN and the metabolite nor-BPN on ion channels relevant for human cardiovascular function were conducted. BPN and nor-BPN blocked ion-channels (sodium, calcium, and potassium) at similar concentrations (IC_{50}) as reported in the literature (Katchman, 2002).

In published studies, BPN had less of an effect than methadone on the ion channels *in vitro* (Katchman, 2002), and was associated with less QTc prolongation in a randomized clinical study (Wedam, 2007). The ratio between the CAM2038 IC_{50} from the *in vitro* assays and the maximum plasma concentration (C_{max}) in subjects following administration of CAM2038 ($IC_{50}/C_{max;}$ Study HS-15-549) was determined. The margins (ratio) calculated for BPN and nor-BPN were ≥200-fold suggesting a limited risk of QT prolongation in subjects treated with CAM2038.

5.3. Nonclinical Pharmacokinetics

5.3.1. CAM2038 Pharmacokinetics in Dog and Rat

The PK profile of BPN following SC administration of CAM2038 was characterized in the rat, minipig, and dog.

The release profiles for BPN for weekly and the monthly CAM2038 were similar across species and were characterized by rapid absorption of BPN. Plasma BPN concentration levels were demonstrated at 30 minutes in both rat and dog following injection. C_{max} was established within 24 hours after dosing with CAM2038 q1w in rat and dog. For CAM2038 q4w, C_{max} was established after 3-24 hours in dogs, and 5-8 days in rats. The plasma concentration-over-time profiles showed sustained release from the depot matrix across weekly and monthly time intervals. No gender-related differences were observed.

Following repeated administrations of weekly (32 mg) or monthly (up to 192 mg) CAM2038 for 9 months in dogs, no apparent accumulation was observed. Steady state was achieved within 2 to 3 weekly repeated doses for CAM2038 q1w, and within 2 to 3 monthly repeated doses for CAM2038 q4w, based on trough plasma concentrations (C_{trough}). Exposures (AUC) following CAM2038 q1w (32 mg) and CAM2038 q4w (128 mg) in the 9-month toxicity study in dogs were comparable (Table 2). Mean exposure for a one-month period ($AUC_{0\text{-}672h}$) of CAM2038 q4w was comparable to, or slightly lower than, the theoretical $AUC_{0\text{-}672h}$ for CAM2038 q1w based on the $AUC_{0\text{-}168h}$ value (i.e., 4 x $AUC_{0\text{-}168h}$). This result provides a bridge between weekly and monthly administration and supports the transition from weekly to monthly CAM2038 dose regimens in humans.

Table 2: Toxicokinetics for BPN Following Doses of 32 mg CAM2038 q1w and 128 mg CAM2038 q4w in 9-month Toxicity Study in Dogs[a]

	CAM2038 q1w			CAM2038 q4w			Ratio 128 mg CAM2038 q4w: 32 mg CAM2038 q1w	
Day	C_{max} (ng/mL) Mean	AUC_{0-168h} (ng*d/mL) Mean	Theoretical AUC_{0-672h}[b] (ng*d/mL) Mean	C_{max} (ng/mL) Mean	AUC_{0-168h} (ng*d/mL) Mean	AUC_{0-672h} (ng*d/mL) Mean	AUC_{0-168h}	AUC_{0-672h}
1	16.4	68.3	273	21.9	82.5	218	1.21	0.79
141	19.7	77.1	308	38.3	77.5	275	1.01	0.89
225	19.4	86.7	347	21.1	67.5	283	0.779	0.81

[a] Blood was sampled on Days 1, 141 and 225 of the study. TK parameters are presented for males and females combined.
[b] Theoretical AUC_{0-672h} for CAM2038 q1w was derived by multiplying the AUC_{0-168h} with 4.
Source: Extracted from nonclinical overview, Table 2.4.2.2.1-4

To address the potential effect of external manipulation, such as what may occur through belts or clothing rubbing or intentional rubbing, a study of external manipulation of the injection site was conducted in the rat. In this PK study, the SC injection site was subjected to manipulation (rubbing and squeezing) at different time points following injection. The time points were selected to challenge the depot immediately post injection when the formulation is just starting to form the gel, or at 24-hour post-dose when the depot is assumed to be completely gelled, and also at 8 and 14 days post dose when the depot matrix is completely formed. The release performance of BPN from CAM2038 was not impacted by injection site manipulation compared to injection at a site that was not manipulated.

5.4. Nonclinical Toxicology

5.4.1. Toxicology Information Referenced from Subutex Label

Toxicology information provided in the reference product label (Subutex) with the relative margin of safety for SL use is described:

- Lifetime carcinogenicity studies in rats and mice: In rats, a dose-related increase in testicular interstitial (Leydig) cell tumors was observed at doses up to an estimated exposure of 35 times the recommended human SL dose of 16 mg (body surface area basis). In mice, BPN was not carcinogenic at doses providing estimated exposures 30 times the recommended human SL dose of 16 mg (body surface area basis).
- Mutagenicity testing: BPN was not genotoxic. Results were negative in a panel of tests including mammalian cells.
- Fertility: No impairment was observed at doses providing exposures up to 50 times the recommended human SL dose of 16 mg (body surface area basis).
- Reproductive toxicology: Not teratogenic in rats or rabbits at exposures up to 6 times the recommended human SL dose of 16 mg (body surface area basis).

Importantly, the doses tested in the referenced toxicology studies are relevant to CAM2038 because comparable BPN exposures were achieved with CAM2038 and Subutex (Section 7.5.1.2). At slightly higher C_{ss} and AUC during a dosing interval at steady state (AUC_{ss}) values projected for the highest doses of CAM2038 in subjects as compared with clinical doses of SL BPN (see Clinical Pharmacology Section 7.5.1.2, Table 4), safety exposure margins noted above for the referenced studies are adequate.

5.4.2. Toxicology Studies Conducted by the Sponsor

The potential for the CAM2038 drug products to induce toxicity was characterized in single dose, repeated dose and chronic toxicology studies in the dog, and a single dose study in minipig. These studies provide both long-term safety and local tolerability data. The excipients of the FC technology were also evaluated in dedicated toxicology studies.

In general, clinical signs observed following administration of CAM2038 were consistent with the known pharmacology of BPN, e.g., reduced activity, sedation, etc.

5.4.2.1. Chronic 9-Month Dog Study

In a chronic (9-month) toxicity study in dogs, no systemic toxicity was evident for 32 mg CAM2038 q1w, which represents ~3.3 times the highest recommended weekly human dose of 32 mg (body surface area basis), and the corresponding safety margin of exposure (AUC basis) is 2.9 times higher than the systemic exposure in patients. Similarly, no systemic toxicity occurred at doses up to 192 mg CAM2038 q4w representing ~4-fold safety margin to the highest recommended monthly human dose of 160 mg (body surface area basis) with a corresponding safety margin of exposure (AUC basis) being ~3 times higher than systemic exposure in subjects.

The principal finding in the 9-month dog study was reversible injection site inflammatory reactions. Small raised areas the approximate size of the formed depot in the tissue was observed. Rare events of erythema were observed. Microscopic findings in the skin were characterized as a continuum of a localized inflammatory response consistent with the physiological foreign body reaction occurring in response to the injection of any biodegradable material (Anderson 2008). Multiple injections into the same site did not enhance the inflammatory response.

5.4.2.2. Pharmacokinetic Bridging Studies to the Reference Compound

To bridge to the nonclinical data provided in the Subutex Label (Section 5.4.1), PK studies were conducted with CAM2038. BPN exposure was determined in female and male rats and mice and pregnant rats and rabbits at the highest doses tested in the carcinogenic and reproduction toxicity studies described in the Subutex label. The exposure data were used to determine margins of safety to the systemic exposure of BPN in humans following administration of the highest doses of CAM2038 (32 mg CAM2038 q1w and 160 mg CAM2038 q4w).

The systemic exposures in the animal studies were 8-21 times the potential human exposure for the weekly 32 mg CAM2038 q1w, and 7-17 times the monthly 160 mg CAM2038 q4w. These estimated margins of safety support reference to the Subutex Label for the risk evaluation of CAM2038. Hence, no additional carcinogenicity studies

or developmental and reproductive toxicity studies for CAM2038 are warranted. Furthermore, there is a sufficient margin of safety for the CAM2038 drug products and would not represent any additional risk to subjects.

5.4.2.3. Toxicological Testing of FluidCrystal Vehicle and Excipients

The FC vehicle of CAM2038 was evaluated in chronic studies in rodent and dogs. Weekly SC administration of 1000 mg/kg (approximately 16 times the FC dose in 32 mg CAM2038 q1w and 31 times the FC dose in 160 mg CAM2038 q4w) for 6 months in rat produced no systemic toxicity. In dogs, weekly SC administration of up to 0.64 mL (612 mg/kg; human equivalent dose [HED] 340 mg/kg) FC vehicle for 9 months showed no systemic toxicity. At this dose of the FC vehicle, there is a 35-fold and greater margin of safety for subjects.

Each component of the FC vehicle was also evaluated.

GDO has limited use as pharmaceutical excipient; thus, a package of primary toxicology studies was conducted. GDO induced no systemic toxicity at doses up to 1000 mg/kg (HED 162 mg/kg) in rats for 6 months. GDO was not genotoxic and did not affect pre- and post-natal development in the rat at 350 mg/kg (HED 56.5 mg/kg). There is approximately a 13- to -69-fold margin of safety for humans at these no-observed-adverse effect level (NOAEL) nonclinical doses for GDO.

In addition, available published toxicity data for diglycerides, an analogous substance to GDO, results in safety margins of 70-fold and greater than human dose based on NOAEL determined in repeated dose toxicity, developmental and reproduction toxicity and carcinogenicity studies in animals.

NMP is part of the CAM2038 q4w formulation, but not the CAM2038 q1w formulation. Systemic exposure to NMP was limited after CAM2038 q4w administration. A retrospective analysis of clinical samples from subjects treated with CAM2038 q4w indicated a relatively rapid release of NMP from the injected CAM2038 q4w, fast absorption of NMP and rapid elimination from the circulation. The half-life of elimination for NMP was ~1.5 hour, consistent with the PK data in animals.

Published reproduction and developmental toxicity data and carcinogenicity data for NMP were identified and used for a toxicological risk assessment. Safety margins of approximately 46-fold and higher were derived for the doses of NMP in the CAM2038 based on carcinogenicity studies and 3-fold and higher for developmental and reproduction toxicity studies (SCCS 2011 and WHO 2001). Based on these data, NMP does not represent a human health concern for patients treated with CAM2038 q4w.

For the SPC and ethanol components, previous use in marketed pharmaceutical products and literature safety data establish that they pose no safety risk to humans as used in CAM2038 (AmBisone Label; Intralipid Label).

5.4.2.4. Intramuscular Injection

Potential effects on BPN release and local injection site reaction were evaluated after intramuscular (IM) injections in rat and dog. In rat, BPN release was similar after IM and SC administration. No local reactions were seen at the IM injection site in rat or dog.

Histopathology evaluation showed inflammatory reactions similar to those observed after SC injection in dogs. The data suggest that inadvertent IM injection is unlikely to affect the systemic exposure to BPN or result in additional local AEs.

5.4.3. Nonclinical Safety Conclusion

In conclusion, a robust nonclinical package, comprised of data from the Sponsor-initiated nonclinical studies with CAM2038, from the reference drug label (Subutex Label), and from published nonclinical data for BPN provide a thorough safety assessment of the doses that will be delivered as CAM2038 weekly or monthly injections. Nonclinical data for the FC vehicle and the components of the FC vehicle provide additional support for the safety of CAM2038 used in patients.

The primary finding with SC injection in the nonclinical studies was a reversible local inflammatory response. In general, clinical signs observed following administration of the CAM2038 drug product were consistent with an exaggerated pharmacological response to BPN, e.g., sedation. The excipients and FC components of CAM2038 have been qualified, and exhibit adequate safety margins and/or produce minimal systemic exposure.

6. CLINICAL DEVELOPMENT PROGRAM

The clinical program with CAM2038 for the treatment of OUD comprises 7 clinical studies (Table 3), including 2 Phase 1 naltrexone blockade studies in healthy volunteers and 5 studies in patients with OUD.

Weekly (CAM2038 q1w) and monthly (CAM2038 q4w) SC BPN FC injection depot treatments are intended to provide continuous delivery of BPN for 1 week (CAM2038 q1w) and 1 month (CAM2038 q4w) for the initiation, stabilization, and maintenance treatment of OUD.

The clinical study program evaluated efficacy and safety of CAM2038 in treatment-seeking adults with OUD, and subjects transferred from treatment with daily SL BPN or SL BPN/NX products. Efficacy measures included illicit opioid-negative urine samples, evidence of no opioid use, study retention, signs and symptoms of withdrawal, and cravings. A Phase 2, opioid-challenge study (HS-13-478) was conducted to evaluate the effects of CAM2038 on blocking euphorigenic effects using a drug liking VAS score when subjects were given doses of hydromorphone. The pivotal 24-week efficacy study (HS-11-421) was a randomized, double-blind, double-dummy study comparing CAM2038 against standard treatment with daily SL BPN/NX in treatment-seeking adults representative of the real-world setting, including patients with heroin use, poly-drug abuse, and injection route of administration.

A 48-week open-label Phase 3 study (HS-14-499) evaluated the long-term safety and additional findings of efficacy of CAM2038. This study included both treatment-seeking adults and subjects transferred from SL BPN or SL BPN/NX treatment.

Additional studies included two PK studies in healthy volunteers (HS-11-426 and HS-13-487) and two PK studies in participants with OUD (HS-07-307 and HS-15-549).

Table 3: Completed Clinical Studies with CAM2038 for Treatment of Opioid Use Disorder

Study Identifier	Study Objectives	Study Design and Type of Control	Duration of Treatment	No. of Subjects Enrolled/ Completed	Healthy Subjects or Diagnosis of Patients
HS-11-426	PK, BA, and Safety	Phase 1, randomized, open-label, single dose study assessing 3 different SC doses of CAM2038 q1w Control: IV Temgesic and SL Subutex	1 Week	60 subjects enrolled/ 54 subjects completed	Healthy volunteers under naltrexone blockage
HS-13-487	PK, BA, and safety	Phase 1, randomized, open-label, single and repeated dose study of CAM2038 q4w and CAM2038 q1w Control: IV Temgesic and SL Subutex	4 Weeks	87 subjects enrolled/ 75 subjects completed	Healthy volunteers under naltrexone blockage
HS-07-307	PK, PD, and safety	Phase 1/2, single-center, single-blind, single dose, dose-escalation, first-time-in-man study investigating 4 different doses of CAM2038 q1w Control: NA	1 Week	41 subjects were enrolled (of which 1 subject was treated in both Group B and Group D)	Adult patients with OUD on stable maintenance treatment with SL BPN for ≥6 months
HS-13-478	PK, efficacy, and safety	Phase 2, randomized, double-blind, multicenter, repeated-dose opioid challenge study of CAM2038 q1w (24 and 32 mg) Control: IM Hydromorphone IR Morphine Sulphate Tablets	7 Weeks	47 subjects enrolled and 46 subjects completed the study.	Adult patients with moderate to severe OUD based on DSM-5 criteria
HS-15-549	PK, efficacy, and safety	Phase 2, open-label, partially randomized, multi-center study assessing PK and administration of repeated doses of CAM2038 q1w (32 mg in Group 1) and CAM2038 q4w (128 mg in Group 2 and 160 mg in Group 3) at different injection sites Control (Group 3 only): 24 mg SL BPN/NX	Group 1: 7 to 13 weeks Group 2: 16 to 22 weeks Group 3: 17 weeks	Group 1[a]: 28/23 Group 2[a]: 20/16 Group 3: 18/12	Adult patients with moderate to severe OUD based on DSM-5 criteria
HS-11-421	Efficacy and safety	A Phase 3, randomized, double-blind, double-dummy, active-controlled, parallel group, multi-center study. Active: 12 weeks SC injections with 16, 24 or 32 mg CAM2038 q1w + daily SL placebo tablets, followed by 12 weeks SC injections with 64, 96, 128 or 160 mg CAM2038 q4w + daily SL placebo tablets.	24 weeks	428 subjects enrolled (213 subjects on CAM2038 and 215 subjects on SL BPN/NX). 247 subjects completed	Adult patients with moderate to severe OUD based on DSM-5 criteria

Study Identifier	Study Objectives	Study Design and Type of Control	Duration of Treatment	No. of Subjects Enrolled/ Completed	Healthy Subjects or Diagnosis of Patients
		Control: Daily SL BPN/NX tablets at 8 or 24 mg/day (up to 32 mg during the last 12 weeks) + SC placebo injections			
HS-14-499	Safety and efficacy	Phase 3, open-label multicenter study of CAM2038 q1w and CAM2038 q4w Control: NA	48 weeks	228 subjects enrolled/157 subjects completed[b]	Adult patients with moderate to severe OUD based on DSM-5 criteria (taking SL BPN or SL BPN/NX, or actively seeking BPN treatment before enrollment)

Abbreviations: BA: bioavailability; BPN: buprenorphine; BPN/NX: buprenorphine/naloxone; DSM-5: Diagnostic and Statistical Manual of Mental Disorders – 5th Edition; IM: intramuscular; IR, immediate-release; IV: intravenous; OUD; opioid use disorder; PD: pharmacodynamic; PK: pharmacokinetic; SC: subcutaneous; SL: sublingual
[a] Treatment Period was completed by 23 subjects in Group 1, 16 subjects in Group 2. Open-Label Safety Extension Period was completed by 14 subjects in Group 1 and 12 subjects in Group 2.
[b] 156 subjects completed 48 weeks of treatment.
Source: Extracted from clinical overview, Table 1

7. CLINICAL PHARMACOLOGY

- The PK properties of CAM2038 were evaluated in 5 clinical pharmacology studies (HS-11-426, HS-13-487, HS-07-307, HS-13-478, and HS-15-549) to support the proposed dosing and bridging of clinical pharmacology data from SL BPN (Subutex) to CAM2038.
- PK assessment of weekly dosing in healthy subjects (HS-11-426)
    - Single SC doses of 8, 16 and 32 mg CAM2038 q1w provided dose-proportional extended release of BPN suitable for once-weekly dosing.
    - Bioavailability of CAM2038 was 6- to 9-fold higher than SL BPN (Subutex).
    - CAM2038 was well tolerated in healthy subjects under naltrexone blockade.
- PK assessment of monthly dosing in healthy subjects (HS-13-487)
    - Single SC doses of 64, 96, 128, and 192 mg CAM2038 q4w provided approximately dose-proportional systemic exposure with extended BPN release suitable for monthly dosing.
    - Similar BPN and norbuprenorphine (norBPN) exposures were observed for a matching dose of CAM2038 q4w and 4 repeated weekly doses of CAM2038 q1w.
- PK properties and initial dose selection in a dose escalating study in OUD patients (Study HS-07-307) confirmed pre-specified dose conversion between SL BPN and CAM2038 q1w.
- PK assessment of weekly and monthly dosing of CAM2038 in OUD patients (HS-15-549)
    - Steady-state was reached at approximately the 4th repeated dose of both weekly and monthly dose groups.
    - Geometric mean plasma trough concentrations at steady state were between 2-3 ng/mL for 32 mg weekly dose; 128 mg and 160 mg monthly doses.
    - Injections at alternative or different sites resulted in similar PK profiles.
- CAM2038 q1w and q4w formulations provided plasma levels comparable to those with daily SL BPN, but with only 20% to 30% of total BPN dose administered over same time period, and with lower variation in BPN plasma concentration over time.

7.1. Key Pharmacokinetic Properties of Reference Drug Sublingual Buprenorphine

Absorption, distribution, metabolism, and excretion have been extensively characterized for the reference product SL BPN (Subutex). Based on Subutex labeling, absorption time to C_{max} (T_{max}) was 1.2-1.8 hours. Exposure increased with dose but in a non-proportional

fashion. At the labeled therapeutic dose of 16 mg, SL BPN produced C_{max} of 4.7 ng/mL, and AUC_{inf} of 47 ng*hr/mL (US Subutex Label).

BPN is highly bound to plasma proteins (96%), mainly to alpha and beta globulin (Heel 1979).

BPN is primarily metabolized by CYP3A4 to norBPN, and norBPN is further metabolized by CYP3A and UDP-glucuronosyltransferase. NorBPN has biological activity, exhibiting high affinities for mu-, delta-, and kappa-opioid receptors. NorBPN is also a potent full agonist at the delta-receptor and a potent partial agonist with moderate efficacy at the mu- and kappa-receptors.

BPN is primarily excreted in the feces (68% of the dose), and 27% is excreted in the urine. (Heel 1979). Renal function impairment is not expected to influence the elimination of BPN (Boger 2006). The PK of BPN was evaluated after administration of Suboxone (BPN/NX) SL tablet in subjects with hepatic impairment and compared to that of subjects with normal hepatic function (Nasser 2015). In subjects with mild hepatic impairment, the changes in PK parameters were not clinically significant. For subjects with moderate and severe hepatic impairment, mean C_{max}, AUC_{last} and $t_{½}$ values of BPN were increased, and dose adjustments of BPN may be needed.

It is important to note that the 505(b)(2) NDA pathway does not require a demonstration of bioequivalence between the investigational product and the reference product. Indeed, given that CAM2038 is specifically designed as a depot form of BPN, bioequivalence should not be expected. Rather, the PK characterization of CAM2038 should demonstrate that the BPN exposures achieved are relevant to the non-clinical and clinical studies of SL BPN to which the CAM2038 NDA refers.

7.2. Pharmacokinetics

Five clinical studies evaluated the PK of CAM2038. The studies included single- and repeated-dose PK for the weekly and monthly formulations; comparison of CAM2038 PK to that of SL BPN (Subutex), or SL BPN/NX (Suboxone) and a single intravenous (IV) injection of BPN (Temgesic) to assess absolute and relative bioavailability of BPN; PK of the primary metabolite norBPN; and dose-proportionality.

The PK parameters were estimated using standard non-compartmental analysis (NCA) methods, and are summarized across all studies in Appendix A- 1 for BPN and Appendix A-2 for norBPN.

A population PK model of BPN was developed to evaluate the influence of covariates on the PK of BPN and simulations of different treatment schedules with CAM2038 q1w, CAM2038 q4w and SL BPN (Subutex) were developed. The population PK model was developed based on the data obtained in the HS-11-426, HS-13-487, HS-13-478 and HS-15-549 studies.

7.2.1. Plasma Concentration

The PK studies of CAM2038 provided consistent and reproducible data; hence, selected study results are shown graphically as examples.

BPN release following SC injection of CAM2038 had a median T_{max} of about 24 hours for CAM2038 q1w (HS-11-426, HS-13-487, HS-07-307, HS-13-478, and HS-15-549; Figure 3) and between 4 and 10 hours after single doses of CAM2038 q4w (HS-13-487 and HS-15-549; Appendix A- 1 and Figure 4). The median T_{max} was 10 hours after repeated monthly administration of 128 mg CAM2038 q4w and 24 hours after 160 mg CAM2038 q4w (HS-15-549). For the comparator SL BPN, C_{max} was reached approximately 50 minutes to 1.5 hours after administration (HS-11-426 and HS-13-487).

The terminal t½ was 3 to 5 days for CAM2038 q1w (HS-11-426) supporting once-weekly administration, and 19 to 25 days for CAM2038 q4w (HS-13-487) supporting once-monthly administration. The daily administered SL BPN product Subutex had a terminal t½ of 36 to 43 hours (HS-11-426 and HS-13-487), which is consistent with the Subutex label (US Subutex Label).

The estimated apparent volume of distribution of BPN was large (1900 L) and plasma clearance was low (68 L/h) based on NCA (HS-13-487).

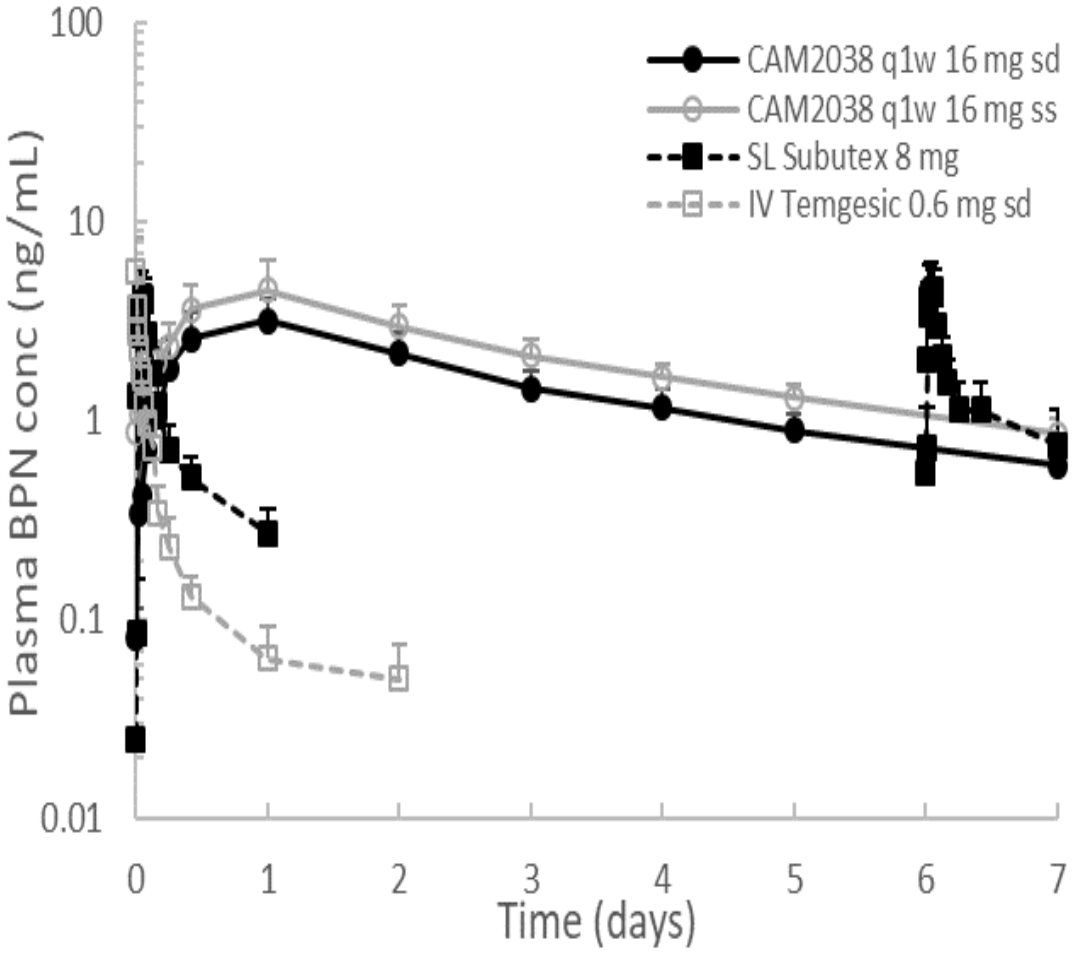


Figure 3: Plasma Concentration-Time Profiles of BPN after single IV injection of 0.6 mg Temgesic, Single and Repeated Daily SL doses of 8 mg Subutex and Weekly SC injections of 16 mg CAM2038 q1w in study HS-13-487

Abbreviations: BPN, buprenorphine; IV, intravenous; SC, subcutaneous; sd, single dose; SL, sublingual; ss, steady state
Values are mean (+SD)

Source: Extracted from summary of clinical pharmacology, Figure 17

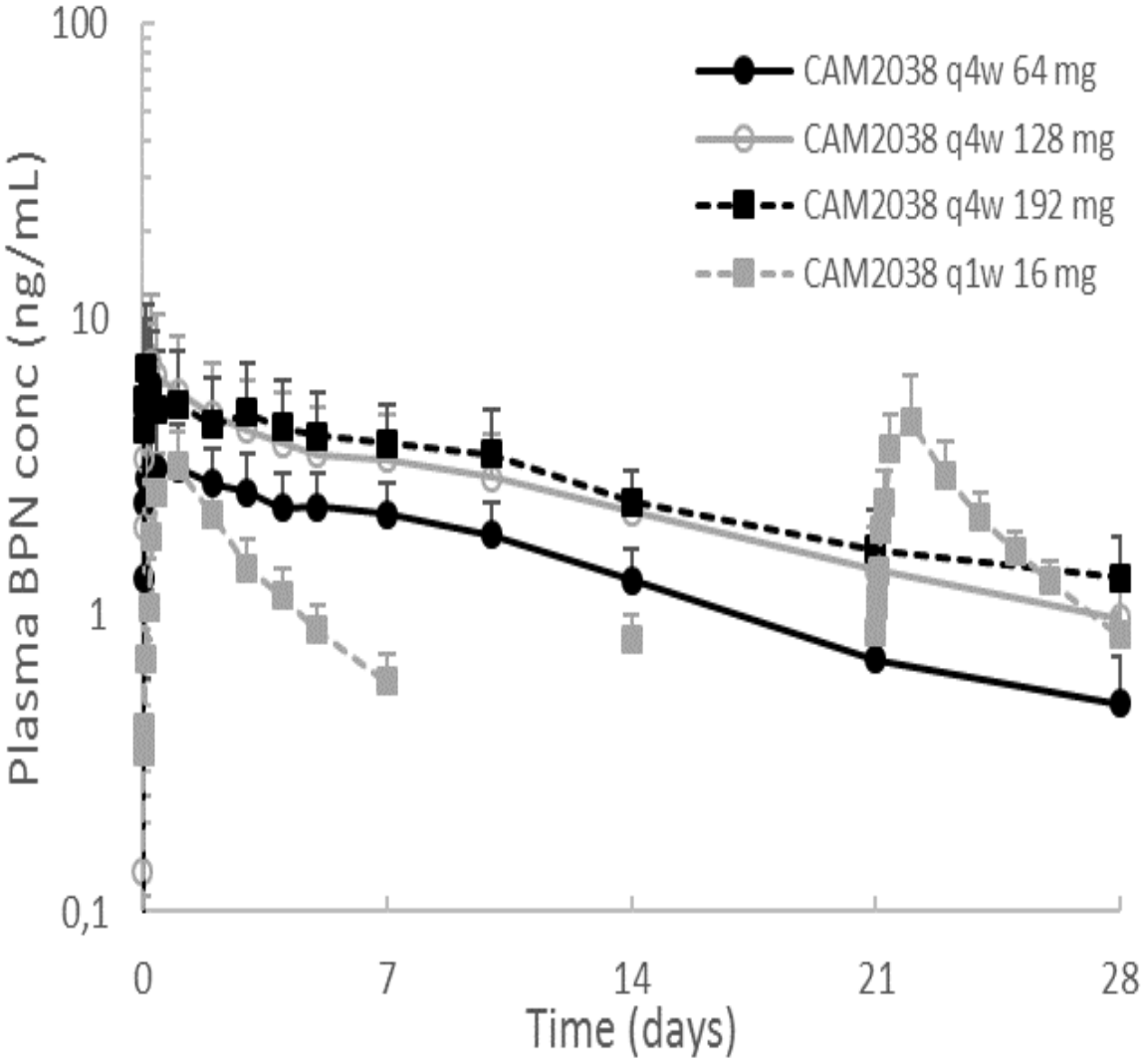


Figure 4: Plasma concentration-Time Profiles of BPN After Single SC Injection of CAM2038 q4w and at First and Fourth Repeated Weekly SC Injections of CAM2038 q1w in Study HS-13-487

Abbreviations: BPN, buprenorphine; SC, subcutaneous
Values are mean (+SD)
Source: Table 14.2.1.2.2 in CSR HS-13-487

7.2.2. Dose Proportionality

BPN C_{max} and AUC_{inf} increased in a dose-proportional manner after a single administration of CAM2038 q1w within the dose range 8 to 32 mg (Figure 5). Following single doses of 64 to 192 mg CAM2038 q4w, BPN AUC_{inf}, and C_{max} also increased proportionally to dose within the product dose range, while C_{max} increased in a slightly less than dose-proportionally manner for the 192-mg dose. Population PK analysis for both CAM2038 q1w and CAM2038 q4w showed no dose proportionality in PK parameters. CAM2038 q4w 192 mg dose was an exploratory dose in Phase 1 and was not taken further into development.

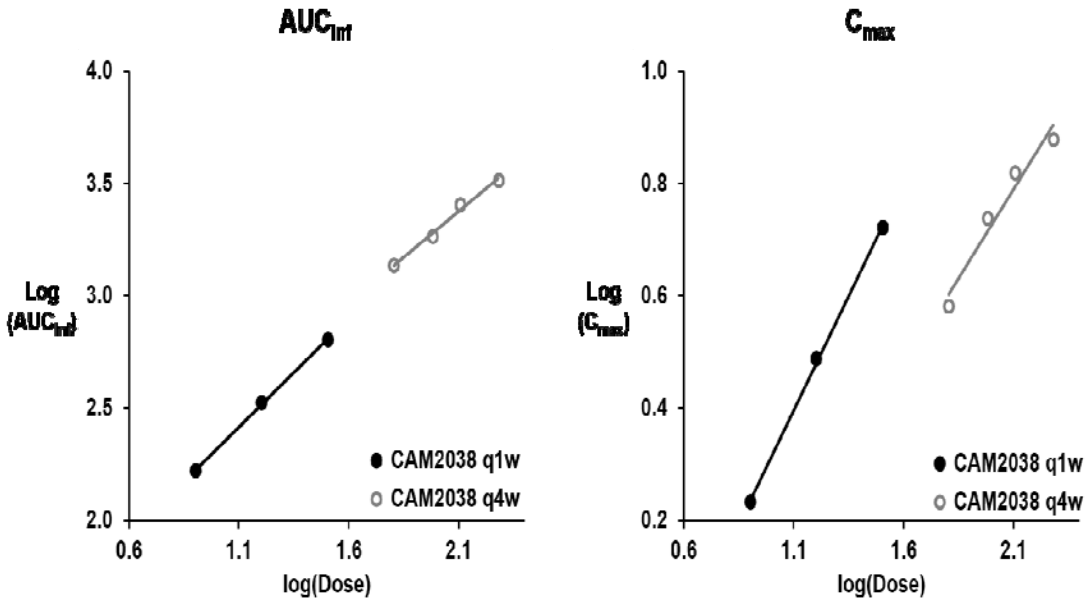


Figure 5: Dose Proportionality of CAM2038 q1w and q4w

Abbreviations: AUC_{inf}, AUC extrapolated to infinity: C_{max}, maximum plasma concentration

7.2.3. Steady-state

Steady-state conditions were achieved at approximately the 4th repeated weekly dose of CAM2038 q1w and the 4th repeated monthly dose of CAM2038 q4w. No time-dependent PK of BPN was apparent in the population PK analysis for the repeated weekly administration of CAM2038 q1w, repeated monthly administration of CAM2038 q4w, or repeated daily administration of SL BPN. Thus, no unexpected accumulation was observed after administration of CAM2038 or SL BPN. The fluctuation in plasma concentrations of BPN at steady state was smaller and occurred less frequently after CAM2038 q1w and CAM2038 q4w than after daily administration of SL BPN. Plasma geometric mean trough concentrations at steady-state was 1.6 ng/mL for 32 mg CAM2038 q1w, 1.8 ng/mL for 128 mg CAM2038 q4w, and 2.3 ng/mL for 160 mg CAM2038 q4w (Table 4).

7.2.4. Bioavailability

7.2.4.1. Comparison to Reference Drugs

The bioavailability of CAM2038 both weekly and monthly was 6 to 9 times higher as compared to Subutex at comparable BPN exposure levels.

Importantly, the CAM2038 q1w and CAM2038 q4w formulations provided steady state plasma levels comparable to those of daily SL BPN (Subutex) but with only 20% to 30% of total BPN dose administered over the same time period. The variation in BPN plasma concentration levels over time was also smaller for CAM2038 compared to SL BPN (Appendix A-1).

7.2.4.2. Comparison of Anatomical Injection Sites

Comparable BPN steady-state exposures were observed after repeated SC injections of CAM2038 q1w in the buttock, abdomen, thigh and upper arm (Figure 6). The BPN peak concentration was potentially slightly lower after injection in the thigh compared to the buttock, abdomen and upper arm, as indicated by the population PK analysis. These findings are considered generalizable across CAM2038 doses and durations, as they are based on the same FC injection depot formulation technology. Thus, no meaningful differences in BPN exposure are expected for the CAM2038 product after SC administration in the buttock, abdomen, thigh or upper arm.

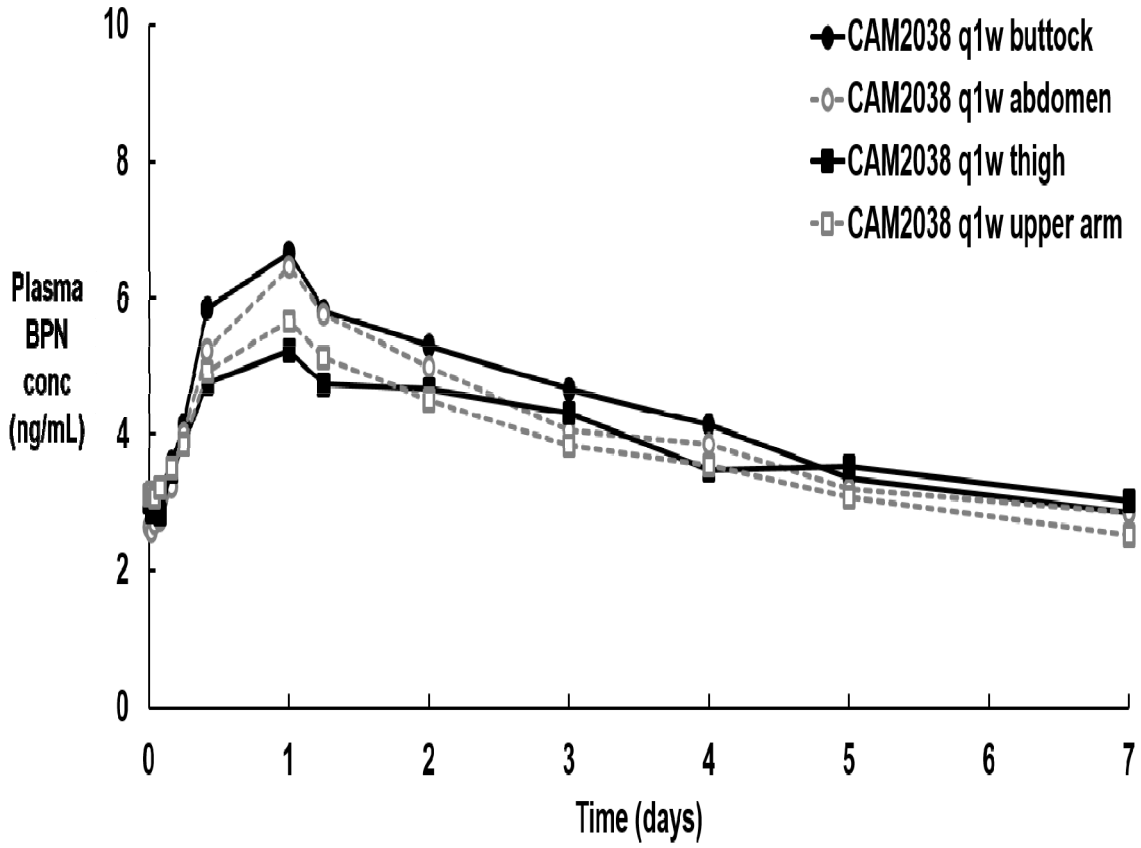


Figure 6: Plasma Concentration-Time Profiles of BPN After SC Injection of the 4th to 7th dose of 32 mg CAM2038 q1w in the Buttock, Abdomen, Thigh and Upper Arm in Study HS-15-549

Abbreviations: BPN, buprenorphine; SC, subcutaneous
Source: Extracted from summary of clinical pharmacology, Figure 8

7.2.5. Drug-drug Interactions

Drug interaction information from the Subutex label recommends caution when using agents that impact CYP3A4: "Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when Subutex sublingual tablet is given concurrently with agents that affect CYP3A4 activity. The concomitant use of Subutex sublingual tablet with CYP3A4 inhibitors (e.g., azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors) should be monitored and may require dose-reduction of one or both agents." These precautions will also be relevant for CAM2038 when co-administered with CYP3A4 inhibitors or inducers and will be incorporated into product labeling (Section 9.13).

7.2.6. Subgroups

Population PK analyses showed that intrinsic factors (age, sex, race, body weight and renal function) did not have a clinically meaningful effect on BPN exposure; therefore, no dose adjustment is recommended. Additionally, there was no difference between patients and healthy subjects. Importantly, subjects with OUD will be titrated to the optimal dose of CAM2038.

7.3. Metabolism to Norbuprenorphine

The AUC_{ss} ratio of norBPN to BPN was 3 to 7 times lower after SC administration of CAM2038 as compared to SL BPN. The higher exposure of norBPN after SL BPN treatment suggests high first-pass metabolism of BPN following SL administration. Further, the substantially lower norBPN exposure in subjects receiving CAM2038 than SL BPN provides robust bridging to the clinical and non-clinical safety findings relevant to norBPN for the reference drug Subutex.

Given that norBPN appears to contribute to respiratory depression (Mégrabane, 2006), the reduced norBPN exposure with CAM2038 formulations may translate into a more predictable safety profile and expand the safety margin for CAM2038.

7.4. Pharmacodynamics

CAM2038 is expected to have pharmacological activity similar to that described for BPN in published literature and in the reference product label. BPN is a partial opioid agonist at the mu-opioid receptor and an antagonist at the kappa opioid receptor. In addition to its partial agonist action, it also has a long half-life and high affinity for and slow dissociation from the mu-opioid receptor giving it a prolonged duration of PD activity. Overall, buprenorphine has an improved safety profile compared to full opioid agonists. For example, BPN exhibits a ceiling effect such the opioid agonist effects plateau at higher doses, resulting in a low risk of overdose, sedation or respiratory depression compared with full opiate agonists (Kahan 2011; Alhaddad, 2012; Dahan, 2006; Walsh, 1994; Walsh, 1995).

7.5. Rationale for Selection of Doses and Dose Interval

Dose selection for Phase 3 studies was based on several factors: tolerability and safety in Phase 1 and phase 2 clinical studies, PK characteristics that support once weekly (CAM2038 q1w) or monthly (CAM2038 q4w) dosing, plasma BPN exposure approximating that of the reference drug Subutex, and pharmacodynamic (PD) assessments in Phase 1 and 2 studies. An additional goal for dose selection was to establish matching doses (with respect to exposure) of weekly and monthly CAM2038 that will enable transitioning from one formulation to the other.

The recommended initiation dose for subjects new to BPN treatment of 24 mg CAM2038 q1w during the first week of treatment was determined to be an effective illicit opioid blocking dose from the Phase 2 opioid challenge study.

7.5.1.1. Dose Selection Based on Tolerability and Safety

CAM2038 was well tolerated systemically and locally in PK studies at each dose tested. No dose-limiting AEs were identified.

7.5.1.2. Dose Selection Based on Pharmacokinetic Properties

CAM2038 provided dose-proportional long-acting release of BPN over the intended weekly and monthly treatment intervals. Data from individual PK studies showed that the plasma BPN exposures achieved with CAM2038 doses of 8, 16, 24, 32, 64, 96, 128 or 160 mg were comparable in terms of C_{max} and C_{min} range to those across the range of currently used daily SL BPN doses with slightly higher values for the 160-mg dose (Appendix A- 1). Additionally, the studies showed the dose-proportional extended release of BPN, suited for once weekly dosing (CAM2038 q1w) or monthly dosing (CAM2038 q4w). The studies also met the goal of matching weekly and monthly doses, showing average plasma exposure for CAM2038 q1w and CAM2038 q4w doses (32 mg and 128 mg) that were comparable.

The population PK analysis of studies HS-11-426, HS-13-487, HS-13-478 and HS-15-549 confirmed that doses of 8, 16, 24 and 32 mg CAM2038 q1w and 64, 96, 128 and 160 mg CAM2038 q4w appropriately bridge to BPN exposure for Subutex (Table 4). Across the dose range, CAM2038 derived BPN exposures based on $C_{ss,max}$ were comparable to the steady state BPN exposures derived from SL BPN. Exposure based on AUC_{ss} was somewhat higher with CAM2038 than with corresponding SL BPN.

Table 4: Steady State PK Parameters from Population PK Analysis of BPN Provided as CAM2038 or SL BPN

Regimen/Dose	AUC_{ss} (ng*hr/mL)		$C_{ss,max}$ (ng/mL)		$C_{ss,\ trough}$ (ng/mL)	
	Geometric Mean	Geometric CV%	Geometric Mean	Geometric CV%	Geometric Mean	Geometric CV%
SL BPN three times daily						
8 mg	25.9	32.5	5.51	31.3	2.2	39.9
SL BPN once daily						
8 mg	26.0	33.2	3.92	36.8	0.54	45.9
12 mg	34.1	34.4	5.15	37.9	0.71	44.7
16 mg	40.6	33.3	6.09	36.1	0.85	44.6
24 mg	53.0	35.0	7.94	38.0	1.1	46.7
CAM2038 q1w						
8 mg	150	21.7	1.69	24.9	0.39	44.5
12 mg	224	22.2	2.49	25.0	0.59	42.9
16 mg	300	22.0	3.38	24.2	0.78	45.4
24 mg	447	21.4	4.97	25.4	1.2	44.8
32 mg	599	20.9	6.75	24.4	1.6	43.1
CAM2038 q4w						
64 mg	1220	20.8	3.81	37.6	0.92	35.0
96 mg	1830	20.2	5.86	37.8	1.4	34.7
128 mg	2400	20.9	7.51	37.2	1.8	35.3
160 mg	3010	21.1	9.38	36.2	2.3	36.3
192 mg	3600	21.3	11.5	37.5	2.7	37.1

Abbreviations: AUCss: area under the curve for a dosing interval at steady state; BPN: buprenorphine; Css,max: maximum observed plasma concentration at steady state; Css,trough: observed concentration before the next actual or intended dose at steady state; CV%: coefficient of variation percentage; SC: subcutaneous; SL: sublingual; SC doses are administered in the buttock.
Source: Table 9 in Report REP-2-CAM-2038-PMX-1

7.5.1.3. Dose Selection Based on Pharmacodynamic Activity and Efficacy

Initial dose selection was assessed in a dose escalating study in patients with OUD (HS-07-307). Four CAM2038 q1w doses were assessed against patients' pre-study maintenance doses of SL BPN and evaluated based on PD response (e.g., Clinical Opiate Withdrawal Scale [COWS; see Section 8.2.2.3] and time-to-rescue medication) after switching subjects to CAM2038 q1w. CAM2038q1w (dose range 7.5 to 30 mg) controlled opiate withdrawal symptoms for up to 10 days after single injection. Minor adjustments were made to the doses following this early study (new dose range 8-32 mg).

The opioid challenge study HS-13-478 demonstrated that CAM2038 q1w at doses of 24 and 32 mg produced rapid and sustained opioid blockade and withdrawal suppression throughout the dosing intervals (Section 8.1). Complete hydromorphone blockade (i.e., visual analog scale [VAS] maximum effect [E_{max}] difference to hydromorphone placebo including the 95% CI upper bound ≤11 mm points; see Section 8.2.2.3) was achieved at the group level for BPN plasma concentrations above approximately 1 ng/mL.

The clinical relevance to the proposed dose ranges were verified by measures of withdrawal (e.g., COWS, Subjective Opiate Withdrawal Scale [SOWS], and Objective

Opiate Withdrawal Scale (OOWS; see Section 8.2.2.3), cravings (e.g. desire to use and need to use VAS) and/or blockade of opioid effects (drug liking, high, good effects, any drug effect and bad drug effects, alertness/sedation VAS E_{max}) across 5 clinical studies HS-07-307, HS-13-478, HS-15-549, HS-11-421, and HS-14-499). Furthermore, the selection of these doses was confirmed by the clinical efficacy and safety outcome in the pivotal Phase 3 efficacy study HS-11-421 (Section 8.2)and the supporting long-term Phase 3 study HS-14-499 (Section 8.3).

In summary, safety, PK, and PD parameters support doses of 8, 16, 24, and 32 mg CAM2038 q1w; and 64, 96, 128, and 160 mg CAM2038 q4w.

7.5.2. Dose Transitions

As part of the anticipated clinical use of CAM2038, the ability to transition from SL BPN to CAM2038, or from weekly to monthly CAM2038, or vice versa, will be important.

Proposed transitions from daily doses of SL BPN to initial weekly (q1w) doses of CAM2038 or monthly (q4w) doses of CAM2038 are presented in Table 5. The aim is to maintain comparable steady-state BPN exposure during the transfer from SL BPN to CAM2038 q1w or CAM2038 q4w. The proposed transitions are based on observed and predicted steady-state BPN systemic exposure for SL BPN, CAM2038 q1w, and CAM2038 q4w.

Table 5: Proposed Transfer from Daily Doses of SL BPN to Initial Weekly or Monthly Doses of CAM2038 q1w or CAM2038 q4w

Dose of daily SL BPN	Dose of CAM2038 q1w
2-6 mg	8 mg
8-10 mg	16 mg
12-16 mg	24 mg
18-24 mg	32 mg
Dose of daily SL BPN	**Dose of CAM2038 q4w**
8-10 mg	64 mg
12-16 mg	96 mg
18-24 mg	128 mg
26-32 mg	160 mg

Abbreviation: SL BPN, sublingual buprenorphine

Source: Extracted from Summary of clinical pharmacology, Table 28

The overall steady state systemic exposure of BPN for a monthly dose of CAM2038 q4w was comparable to the same total dose administered as 4 weekly doses of CAM2038 q1w (Section 7.5.1.2). Simulated steady-state BPN plasma concentration-time profiles are shown for the transitions between 8 mg SL BPN and 16 mg CAM2038 q1w; 24 mg SL BPN and 32 mg CAM2038 q1w in Figure 7 and between 8 mg SL BPN and 64 mg CAM2038 q4w; 24 mg SL BPN and 128 mg CAM2038 q4w in Figure 8.

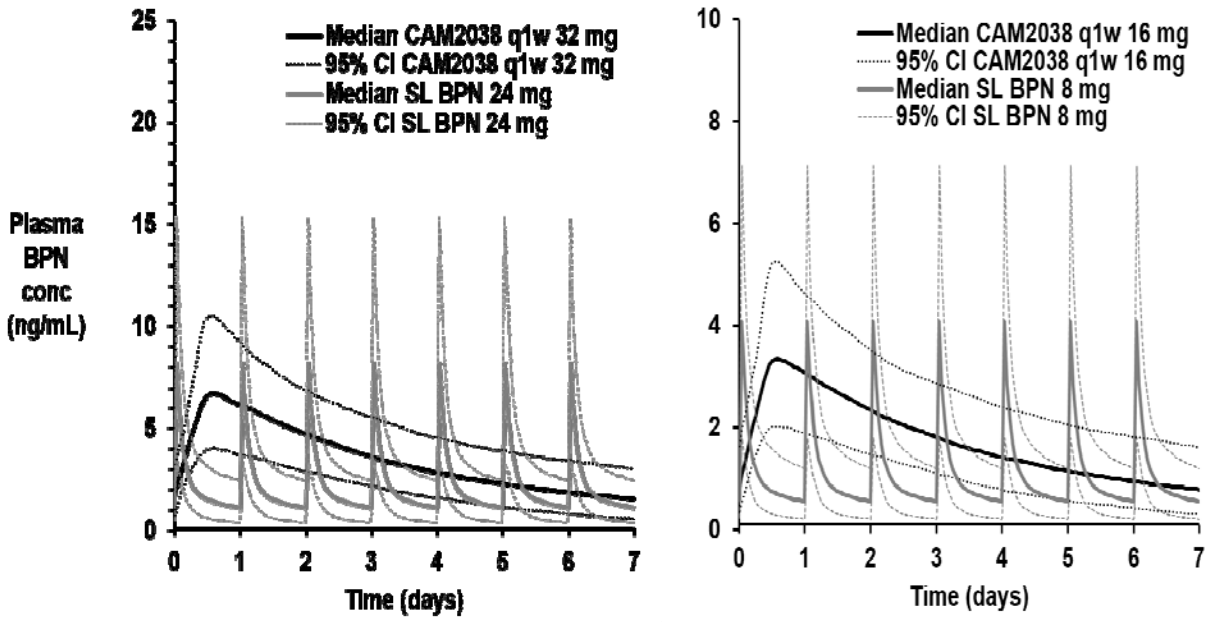


Figure 7: Simulated Steady-state Plasma Concentration-time Profiles of BPN by Population PK Analysis after Weekly CAM2038 q1w and Daily SL BPN

Abbreviations: BPN, buprenorphine; CI, confidence interval; PK, pharmacokinetic; SL, sublingual
Source: Simulations based on base population PK model

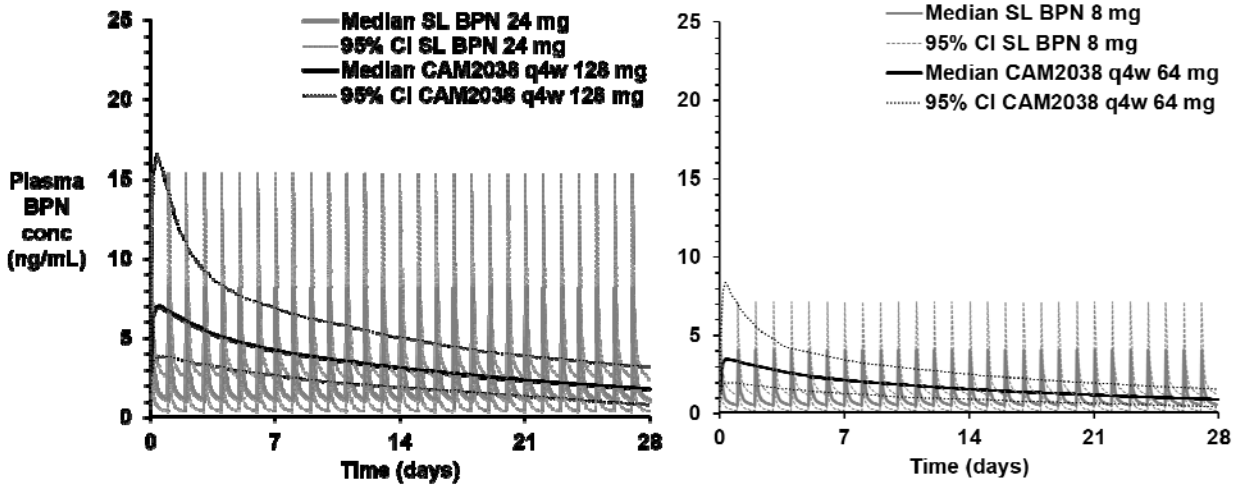


Figure 8: Simulated Steady-state Plasma Concentration-time Profiles of BPN by Population PK Analysis, after Daily SL BPN and Monthly CAM2038 q4w

Abbreviations: BPN, buprenorphine; CI, confidence interval; PK, pharmacokinetics
Source: Simulations based on base population PK model

7.6. Clinical Pharmacology Conclusions

The CAM2038 clinical pharmacology program has demonstrated that CAM2038 provides dose proportional profiles suitable for weekly and monthly dosing allowing individualized treatment and switching between sublingual and CAM2038 depot products. Additionally, a PK bridge was established with the approved reference product (Subutex). The higher bioavailability of CAM2038 allows for comparable exposure to sublingual buprenorphine with 20-30% of the total buprenorphine dose.

8. CLINICAL EFFICACY

- Opioid Challenge Phase 2 Study (HS-13-478)
  - CAM2038 doses of 24 mg and 32 mg demonstrated complete opioid blocking of euphorigenic effects of hydromorphone (i.e., drug liking VAS E_{max} score and 95% CI difference to Placebo <11mm points) from the first dose and across the entire dosing interval.
  - Evaluation of the relationship between PK and PD after weekly doses of CAM2038 24 mg and 32 mg suggested that complete blockade was achieved at BPN concentrations above approximately 1 ng/mL.
  - Higher plasma BPN concentrations were not associated with appreciable increases in the blockade.
- Pivotal Phase 3 Efficacy Study (HS-11-421)
  - CAM2038 was non-inferior to SL BPN/NX for the primary endpoint of responder rate (RR) for opioid-negative urine samples in a randomized, placebo-controlled, double-blind, double-dummy Phase 3 study.
  - CAM2038 was superior to SL BPN/NX for the cumulative distribution function (CDF) of the proportion of opioid-negative urine samples verified by self-reports during Treatment Weeks 4–24.
    - Sensitivity analysis of the CDF over Weeks 1–24 (entire treatment period) also demonstrated statistical superiority.
  - Study retention was similar between groups, as expected with a double-blind, double-dummy design.
- Long-term Safety Phase 3 Study (HS-14-499)
  - Open-label, 48-week study of CAM2038 q1w and CAM2038 q4w demonstrated the ability to individualize doses and dosing intervals based on subject's needs.
  - Subjects receiving SL BPN at entry remained stable after the transition to CAM2038, with a tendency toward improvements in most efficacy measures.
  - Subjects new to BPN treatment showed improvements in opioid withdrawal, desire/need to use opioid, and proportion of opioid negative urine samples.
- Dosing Recommendations
  - New to treatment: The recommended initiation dose for patients new to BPN treatment is CAM2038 q1w 24 mg starting on Day 1 of treatment. CAM2038 24 mg dose was demonstrated to be an effective initiation dose providing complete blockade of illicit opioids. This dose is equivalent to the combined dose of 16 mg and 8 mg during Week 1 used in the Phase 3 studies (HS-11-421 and HS-14-499), which provides comparable BPN exposure during the first week.
  - Switching from SL BPN: There are 4 weekly and 4 monthly doses of CAM2038 corresponding to doses of SL BPN, providing the ability to individualize treatment as done in current clinical practice.

The clinical study program was designed to evaluate CAM2038 efficacy across treatment phases from initiation through maintenance. The clinical program evaluated both treatment-seeking adults with OUD, and subjects transferred from treatment with daily SL BPN and SL BPN/NX products. One Phase 2 and Two Phase 3 studies incorporated efficacy endpoints:

- HS-13-478: 7-week opioid challenge study; multicenter, double-blind, randomized within-patient study conducted at 3 controlled inpatient research facilities
- HS-11-421: 24-week efficacy and safety pivotal study; randomized, double-blind, double-dummy study against standard treatment with daily SL BPN/NX in treatment-seeking adults
- HS-14-499: 48-week open-label study that included both treatment-seeking adults and subjects transferred from SL BPN or SL BPN/NX treatment. Efficacy results are presented separately for the two studies.

8.1. Opioid Challenge Study, HS-13-478

Study HS-13-478 was a multicenter, double-blind, randomized within-patient study conducted at 3 controlled inpatient research facilities. It involved 47 adults with moderate-to-severe OUD (based on DSM-5). Five 3-day test sessions evaluated the response to hydromorphone (0, 6, and 18mg IM in random order; 1 dose/session/day). After the first 3-day session (qualification phase), participants were randomized to CAM2038 q1w at 24mg (n = 22) or 32mg (n = 25); the assigned CAM2038 dose was given twice, 1 week apart (Day 0 and 7). Four sets of sessions were conducted after randomization (Days 1-3, 4-6, 8-10, and 11-13).

The primary objective was to evaluate the ability of CAM2038 q1w to block euphorigenic opioid effects and suppress opioid withdrawal in non-treatment seeking individuals with OUD. The primary endpoint was the difference between the E_{max} on the bipolar VAS-scale for drug liking between IM hydromorphone and placebo. Secondary endpoints included other VAS assessments (e.g., high and desire to use), opioid withdrawal scales, and physiological and PK outcomes.

8.1.1.1. Efficacy Results

Mean plasma BPN concentrations following administration of 24 mg and 32 mg CAM2038 q1w are shown in Figure 9. PK parameters are summarized in (Table 6). Exposure, as indicated by both C_{max} and AUC, was higher with the 32-mg dose than with the 24-mg dose. With both doses, exposure was higher after the second dose than after the first dose.

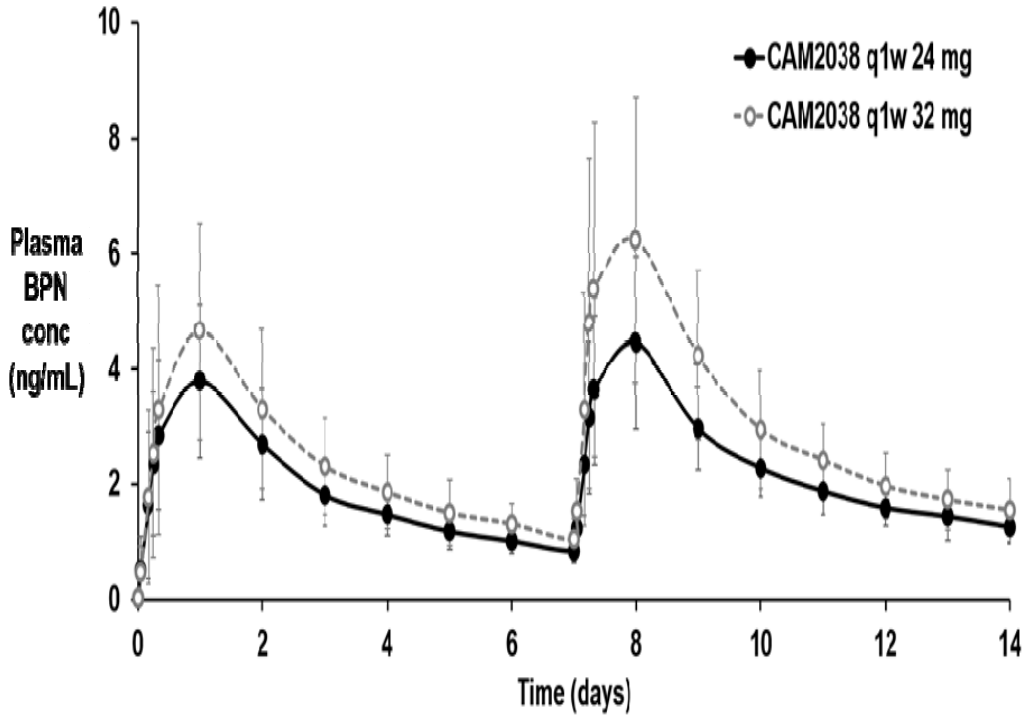


Figure 9: Plasma Concentration-Time Profiles of BPN After 2 Repeated Weekly SC injections of CAM2038 q1w in Study HS-13-478

Abbreviations: BPN, buprenorphine; SC, subcutaneous
Values are mean (+SD)
Source: Table 14.2.12.1a-b in CSR HS-13-478

Table 6: PK Parameters of BPN after SC CAM2038 q1w in Study HS-13-478

Dose (mg)	Dose Number	Parameter [geometric mean (geometric CV%)]			
		C_{max} (ng/mL)	T_{max} (h)	AUC_{τ} (ng*hr/mL)	C_{trough} (ng/mL)
24 (n=24)	1	3.64 (39)	24.0 (4.0-48.0)	304 (30)	0.822(25)
	2	4.37 (35)	24.0 (7.9-24.4)	385 (23)	1.23 (23)
32 (n=24)	1	4.39 (43)	24.0 (8.0-48.3)	376 (31)	0.993 (32)
	2	6.01 (45)	24.0 (6.0-48.0)	512 (29)	1.47 (32)

Abbreviations: AUCτ, AUC during a dosing interval; C_{max}, maximum plasma concentration; C_{trough}, observed concentration before the next actual or intended dose; CV%, coefficient of variation percentage; PK, pharmacokinetic; SC, subcutaneous; T_{max}, time to C_{max}.
[a] Median (minimum-maximum)
Source: Table 14.2.12.2a and 14.2.12.2b in CSR HS-13-478

The primary outcome, drug liking E_{max}, is shown in Figure 10. During qualification, mean E_{max} scores for placebo were within the a priori-specified neutral range of approximately 50 mm, while hydromorphone at 6 and 18 mg produced dose-related increases in the scores. Treatment with CAM2038 q1w 24 and 32 mg, suppressed the response to hydromorphone as evidenced by:

- No active hydromorphone dose yielded a mean drug liking VAS E_{max} score ≥11 compared with placebo (the a priori definition for complete blockade, including upper bounds of the 95% CI).
- Statistically significant differences between pre- and post-treatment hydromorphone matched-dose comparisons. Some individual scores exceeded the 11-point margin. One subject was qualified in error but was included in the analysis. A sensitivity analysis demonstrated no difference in outcomes with or without this subject.

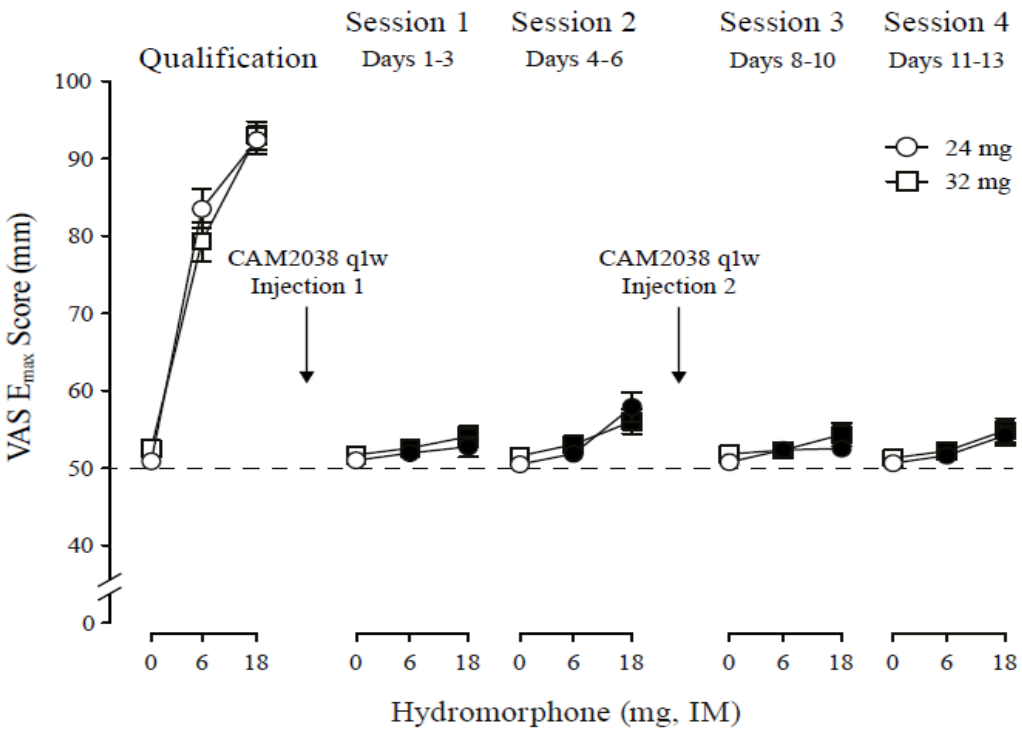


Figure 10: Study HS-13-478: Mean (±SD) Maximum Effect Visual Analog Scale Scores for the Primary Outcome Measure of Drug Linking by Challenge Session for CAM2038 q1w at 24 and 32mg in Study HS-13-478

Abbreviations: E_{max}: maximum effect; IM, intramuscular; VAS, visual analog scale
Source: Extracted from summary of clinical efficacy, Figure 1

On secondary measures, CAM2038 q1w 24 mg and 32 mg blocked hydromorphone effects, producing <11 mm difference on most E_{max} scores between placebo and hydromorphone doses (Table 7). In general, the lower CAM2038 q1w 24 mg dose produced slightly greater suppression during the second dosing period than during the first. In summary, these findings suggest that both doses of CAM2038 q1w were effective at blocking the positive subjective effects associated with the administration of hydromorphone.

Table 7: Study HS-13-478: Blocking Effects of 18-mg and 6-mg Hydromorphone Challenges with CAM2038 Weekly, 24 mg and 32 mg

Dosage	Time, d	Geometric Buprenorphine Concentration, Mean (SD), ng/mL	Drug Liking VAS Scores/ Change from Placebo, Mean (95% CI) [Range], mm	
			18 mg vs 0 mg	6 mg vs 0 mg
CAM2038, 24 mg				
Qualification	-3 to -1	0[a]	41.5 (37.8 to 45.2)	32.5 (27.2 to 37.9)
Session 1	1 to 3	2.3 (0.92)	1.8 (-1.1 to 4.6)	1.0 (-0.3 to 2.2)
Session 2	4 to 6	1.49 (0.38)	7.4 (3.4 to 11.4)	1.4 (-0.1 to 2.8)
Session 3	8 to 10	2.66 (0.76)	1.8 (-0.2 to 3.4)	1.6 (-0.4 to 3.6)
Session 4	11 to 13	1.91 (0.37)	3.6 (0.9 to 6.2)	1.0 (-0.3 to 2.3)
CAM2038, 32 mg				
Qualification	-3 to -1	0[a]	40.4 (36.3 to 44.4)	26.8 (20.8 to 32.7)]
Session 1	1 to 3	2.77 (1.37)	2.4 (0.5 to 4.53)	0.9 (-05 to 2.2)
Session 2	4 to 6	1.91 (0.63)	4.5 (2.0 to 7.0)	1.5 (-0.3 to 3.2)
Session 3	8 to 10	3.79 (1.56)	2.5 (-0.3 to 5.3)	0.5 (-0.2 to 1.2)
Session 4	11 to 13	2.44 (0.71)	3.6 (0.5 to 6.7)	0.9 (-0.1 to 1.9)

Abbreviation: CI, confidence interval; d, day; SD, standard deviation; VAS, visual analog scale.
Note: No samples were collected on Days -3 to -1. This value is from baseline just prior to CAM2038 injection on Day 0.
Source: Extracted from Summary of Clinical Efficacy, Table 4

8.1.1.2. Pharmacokinetic/Pharmacokinetic Relationship

Evaluation of a potential relationship between PK and PD of CAM2038 q1w suggested that BPN concentrations between 1 to 2 ng/mL were sufficient to block the subjective effects of hydromorphone 18 mg (Figure 11). Higher plasma BPN concentrations were not associated with appreciable increases in the blockade.

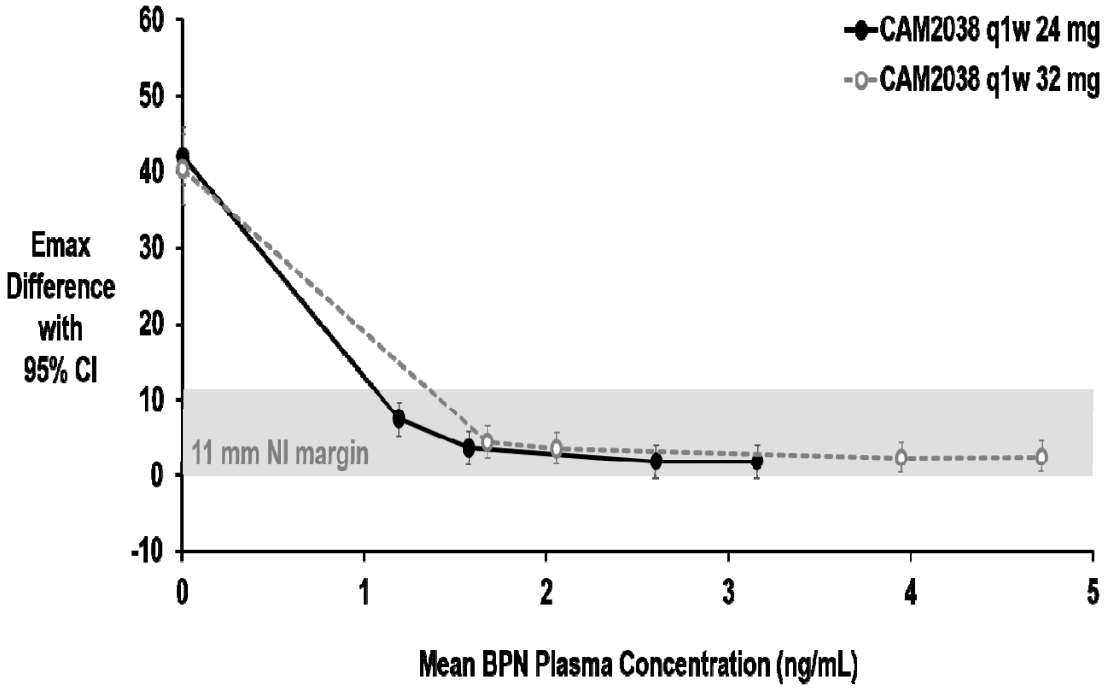


Figure 11: Mean BPN Concentration *vs.* LSM Estimates of Treatment Difference (18 mg hydromorphone vs. placebo) for Drug-Liking VAS E_{max} in Study HS-13-478

Abbreviations: BPN, buprenorphine; CI, confidence interval; E_{max}: maximum effect; LSM, least squares mean
Values are mean (95% CI). LSM, least squares mean
Source: Extracted from summary of clinical pharmacology, Figure 16

8.2. Pivotal Phase 3 Study, HS-11-421

8.2.1. Study Design

HS-11-421 was a Phase 3, double-blind, double-dummy, active-controlled, parallel-group multicenter study, designed to evaluate CAM2038 compared to an existing standard of care (SL BPN/NX) in initiation and maintenance treatment of patients with OUD. The study involved 4 phases: Screening, Phase 1, Phase 2, and Follow-up (Figure 12).

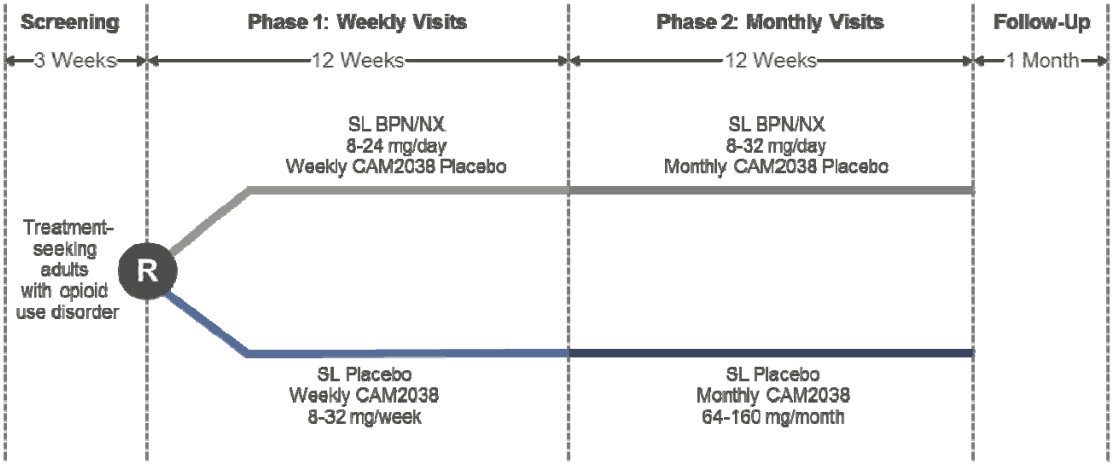


Figure 12: Study Design

Abbreviations: BPN/NX, buprenorphine/naloxone; R, randomization; SL, sublingual

Eligible participants were adults seeking treatment for moderate-to-severe OUD. Those receiving pharmacotherapeutic treatment for OUD within 60 days or having a current moderate-to-severe substance use disorder other than opioids, caffeine, or nicotine were excluded.

Eligible subjects were randomized to one of two treatment groups in a 1:1 ratio:

- Group 1: SL BPN/NX tablets + placebo SC injections
- Group 2: CAM2038 SC injections + SL placebo tablets

Randomized subjects underwent initiation of BPN treatment with either SL BPN/NX or SC CAM2038 q1w and participated in weekly visits for 12 weeks (Phase 1). Subjects then transitioned to Phase 2 with monthly visits. Subjects in Group 1 continued treatment with daily SL BPN/NX (dispensed monthly) and monthly placebo SC injections; subjects in Group 2 transferred to monthly injections of CAM2038 q4w and daily SL placebo (dispensed monthly). Six visits were scheduled during the 12 weeks of Phase 2: 3 monthly visits and 3 random urine toxicology visits. At each visit, efficacy and safety measures were assessed. Subjects who completed the 24 weeks of treatment (i.e., Phase 1 and Phase 2) were transitioned to the standard of care (e.g., SL BPN/NX) and followed up for 4 weeks.

During Phases 1 and 2, 18 urine toxicology samples for illicit opioids were collected; 12 of these samples were collected at the scheduled weekly visits during Phase 1 and 6 were collected during Phase 2 (3 scheduled and 3 random). A self-report of drug use accompanied every urine toxicology test.

Supplemental doses of CAM2038 q1w 8 mg were allowed only in Phase 2 at the discretion of the Investigator. All subjects received manual-guided drug counseling during the study on a weekly basis during Phase 1 and monthly during Phase 2. Additional counseling was allowed as clinically indicated.

8.2.2. Endpoints

8.2.2.1. Primary Endpoint

The prespecified primary endpoint was RR. The responder was defined as a subject with opioid-negative urine samples confirmed with self-report at:

- Phase 1: Treatment Week 12, and for at least two of the three assessments between Treatment Weeks 9, 10, and 11, AND
- Phase 2: Treatment Week 24, and for at least four out of the five additional assessments between Treatment Weeks 13 and 24.

There were 12 urine samples during Phase 1 (one per week for each weekly visits) and 6 urine samples in Phase 2 (3 monthly visits and 3 random urines).

Therefore, to be a responder, at least 8 out of 10 urine samples from Weeks 9 to 24 needed to be negative for illicit opioids (80% negative urine samples). Additionally, there was a requirement for opioid negative urines at specific weeks, Week 12 and Week 24 in order to be a responder. All urine samples were verified by subject's self-reported use.

8.2.2.2. Ranked Secondary Endpoints

Ranked secondary endpoints included CDF over Treatment Weeks 4-24 for illicit opioid-negative urine samples with and without self-reports and study retention (see Section 8.2.3).

8.2.2.3. Additional Outcome Measures

Exploratory outcomes included opioid-negative urine samples by time point, desire- and need-to-use opioid VAS, Clinical and Subjective Opiate Withdrawal Scales (COWS and SOWS) (Rosenthal, 2013), use of supplemental 8 mg CAM2038, additional psychosocial counseling, and quantitative urine morphine concentrations. All opioid-negative urine samples were confirmed negative with self-reports of no illicit opioid use.

8.2.2.3.1. Description of Questionnaires and Scales

- VAS for Opioid Desire to Use and Need to Use: Subject-rated assessment of the degree of cravings experienced since the previous visit using a VAS of 0 (no craving) to 100-mm (maximum possible).
- COWS: This validated instrument contains 11 common opioid withdrawal signs or symptoms that are physically observable, rated on a numerical scale and based on a time period of observation of the subject by the rater. Total score interpretation is as follows (maximum=48; Tompkins, 2009):
  - 5-12 = mild;
  - 13-24 = moderate;
  - 25-36 = moderately severe;
  - > 36 = severe withdrawal

- SOWS: This validated form contains 16 questions that rate the intensity of withdrawal on a 0 (not at all) to 4 (extremely) scale. Maximum score is 64 (Dijkstra, 2007).

8.2.3. Statistical Testing

A sample size of 190 per group was chosen to achieve approximately 82% power to establish non-inferiority.

Analysis sets were as follows:

- Intent-to-Treat (ITT) Population: All randomized subjects. Analyses were according to assigned treatment, regardless of actual treatment received. The primary efficacy analysis was based on this ITT population.
- Safety Population: All randomized subjects randomized who received any dose of SL BPN/NX/placebo or CAM2038/placebo in the treatment phase. All safety analyses used the safety population.
- Per Protocol (PP) Population: All subjects in the ITT population with no major protocol violations.

To control overall Type I error rate at 5%, a closed testing procedure was employed. A pre-determined order was specified for testing of secondary endpoints. A comparison was eligible for non-inferiority or superiority testing only if all previous comparisons, if any, were successfully established at the two-sided 5% significance level. The prespecified testing order was as follows:

1. Non-inferiority with a margin of 10% for the primary efficacy variable RR (Treatment Weeks 1-24)
2. Superiority for CDF of percent samples that were negative for illicit opioids (Treatment Weeks 4- 24), supported by self-reports of illicit opioid use
3. Superiority for the primary efficacy variable, RR (Treatment Weeks 1-24)
4. Superiority of active treatment over the control for time to sustained abstinence after 8 weeks of treatment
5. Non-inferiority with margin of 15% for retention rate
6. Superiority of active treatment over the control for retention rate

Efficacy analyses considered subjects who received any dose of CAM2038 as a single group. Similarly, the comparator group pooled all subjects who received any dose of SL BPN(/NX).

The secondary efficacy analysis compared the CDF of the percentage of urine samples negative for opioids in the two treatment groups using a stratified Wilcoxon rank sum test.

Additionally, patients may require some time to engage in treatment. Therefore, the analysis included a “grace period” where drug use during the initial grace period is not included in the calculations. In this secondary analysis of CDF, a 3-weeks of grace period was used. Additional sensitivity analyses were also conducted with no grace period and various other grace periods.

All analysis of urine samples incorporated self-reported use, where if a patient reported the illicit use of opioids in between scheduled visits, urine samples collected during that timeframe were considered positive, even if a urine sample tested negative.

All missing urine samples were considered positive (imputed as positive urine samples).

8.2.4. Demographics and Baseline Disease Characteristics

Subject demographics were comparable between treatment groups. Four hundred and twenty-eight subjects were enrolled in the study, 213 patients were randomized to the CAM2038 treatment group and 215 patients to the SL BPN/NX treatment group. The only notable difference was a higher proportion of male subjects in the SL BPN/NX group than in the CAM2038 group (Table 8).

Table 8: Study HS-11-421: Summary of Demographic Characteristics

Category	CAM2038 N=213	SL BPN/NX N=215	Total N=428
Age (years)			
Mean (SD)	38.7 (11.17)	38.0 (10.89)	38.4 (11.02)
Min, max	19.0 - 65.0	18.0 - 65.0	18.0 - 65.0
Sex, n (%)			
Male	121 (56.8)	142 (66.0)	263 (61.4)
Female	92 (43.2)	73 (34.0)	165 (38.6)
Race, n (%)			
White	159 (74.6)	164 (76.3)	323 (75.5)
Black or African American	47 (22.1)	48 (22.3)	95 (22.2)
Asian	1 (0.5)	0 (0.0)	1 (0.2)
American Indian or Alaska native	2 (0.9)	1 (0.5)	3 (0.7)
Native Hawaiian or other Pacific Islander	1 (0.5)	0 (0.0)	1 (0.2)
Other	3 (1.4)	2 (0.9)	5 (1.2)
Ethnicity, n (%)			
Hispanic or Latino	25 (11.7)	24 (11.2)	49 (11.4)
Not Hispanic or Latino	188 (88.3)	191 (88.8)	379 (88.6)
BMI (kg/m^2)			
Mean (SD)	25.6 (5.03)	26.2 (5.55)	25.9 (5.30)
Min, max	14.9 - 42.8	15.8 - 53.2	14.9 - 53.2

Abbreviations: BMI, body mass index; Max, maximum; Min, minimum; SD, standard deviation; SL BPN/NX, sublingual buprenorphine/naloxone
Source: Extracted from summary of clinical efficacy, Table 5

Baseline characteristics were similar between two treatment groups (Table 9). The history of opioid use was comparable between the two treatment groups, as were positive screening results

for amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, and phencyclidine. Heroin was the primary opioid of abuse (70.8%) and 52.3% used injection as the route of administration.

A post hoc analysis demonstrated 93.7% subjects had opioid-positive urine samples at baseline. Heroin was the most common opioid in baseline urine samples, fentanyl was also common (22.8%, SL BPN/NX; 29.1%, CAM2038). These characteristics are consistent with new-to-treatment subjects seen in the general population.

Table 9: Study HS-11-421: Other Baseline Characteristics

Category	CAM2038 N=213	SL BPN/NX N=215
Primary Opioid of Use n (%)		
Heroin	152 (71)	151 (70)
Prescription Opioids	61 (29)	64 (30)
Injection Opioid Use	114 (54)	110 (51)
Non-opioid Drug use at Screening		
Total non-opioid drug use	155 (73)	149 (69)
Amphetamine	38 (18)	32 (15)
Benzodiazepine	30 (14)	35 (16)
Cocaine	53 (25)	53 (25)
Marijuana	57 (27)	64 (30)
Fentanyl at Baseline, n (%)	62 (29.1)	49 (22.8)
History of Hepatitis C, n (%)	81 (38)	81 (40)
Medical History of Depression (mean [SD])	25 (12)	28 (13)
Opioid Craving: Need-to-use VAS (mean [SD])	77 (25.4)	76 (24.9)
Opioid Craving: Desire-to-use VAS (mean [SD])	77 (26.2)	77 (25.4)
COWS Score (mean [SD])	12 (5.4)	12 (6.0)
SOWS Score (mean [SD])	32 (15.4)	31 (16.1)

Abbreviations: COWS, Clinical Opiate Withdrawal Score; GED, General Education Development; Max, maximum; Min, minimum; SD, standard deviation; SL BPN/NX, sublingual buprenorphine/naloxone; SOWS, Subjective Opiate Withdrawal Score; VAS, Visual analog scale
Source: Extracted from summary of clinical efficacy, Table 6

8.2.5. Subject Disposition

Of the 428 participants who were randomized, all received at least one medication dose, and 69% (147/213) of CAM2038 and 73% (156/215) of SL BPN/NX subjects completed the 24-week treatment period. Including the 4 weeks of study follow-up, 57% (121/213) of CAM2038 and 59% (126/215) of SL/BPN/NX subjects finished 28 weeks of the study (treatment difference -1.8% [95% CI: -11.2%, 7.6%]). Duration of medication exposure was also comparable between treatment groups (mean [SD]: SL BPN/NX, 131 [60.7] days and CAM2038, 127 [62.9] days).

As shown in Figure 13, study discontinuations occurred throughout the study and were similar in both groups.

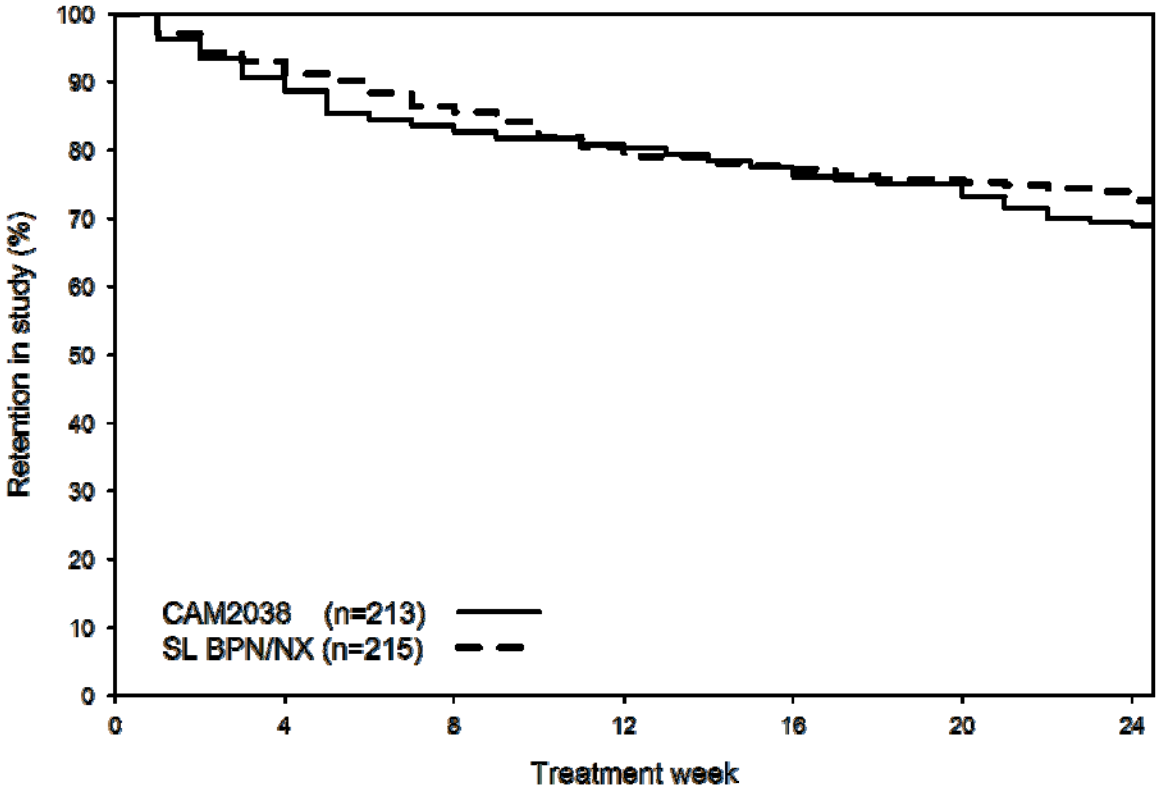


Figure 13: HS-11-421: Study Retention by Treatment Week (ITT Population)

Abbreviations: ITT, intent-to-treat; SL BPN/NX, sublingual buprenorphine/naloxone
Source: Extracted from summary of clinical efficacy, Figure 8

8.2.6. Efficacy Results, Pivotal Phase 3 Study HS-11-421

Analyses included all randomized participants (intent to treat [ITT]) and followed the statistical analysis plans (finalized before database lock). All opioid-negative urine samples were confirmed negative with self-reports of no illicit opioid use.

8.2.6.1. Primary Endpoint: Responder Rate

CAM2038 met the primary endpoint and demonstrated non-inferiority to SL BPN for the primary endpoint of RR for opioid-negative urine samples (80% of urine samples from Weeks 9-24 negative for illicit opioids, with negative urines at specific Weeks 12 and 24). The treatment difference was 3.4% with the lower bound of the confidence interval at -3.5%, which was well above the pre-specified 10% non-inferiority margin (Table 10).

Table 10: Study HS-11-421: Primary Efficacy Endpoint Responder Rate (ITT Population)

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference[a] (95% CI)	P-value[b] 2-sided
Responder, n (%)	38 (17.8)	31 (14.4)	3.4 (-3.5, 10.4)	< 0.001
Non responder, n (%)	175 (82.2)	184 (85.6)		

Abbreviations: CI, confidence interval; ITT, intent-to-treat; SL BPN/NX, sublingual buprenorphine/naloxone
[a] Proportion difference = CAM2038 – SL BPN/NX.
[b] The p-value was based on the chi-square test for noninferiority with the margin of -10% point.
Source: Extracted from summary of clinical efficacy, Table 7

Sensitivity analyses were conducted to determine the robustness of the primary endpoint. Figure 14 illustrates the primary endpoint shown in a forest plot as well as a sensitivity analysis of those subjects who provided all the urine samples. This analysis also demonstrated non-inferiority.

Additionally, subjects who discontinued the study were compared to subjects who completed the study to determine any variances between the two groups. This comparison shows that those who discontinued the study were similar in demographic and opioid use pattern and history as those who completed the study (Table 11).

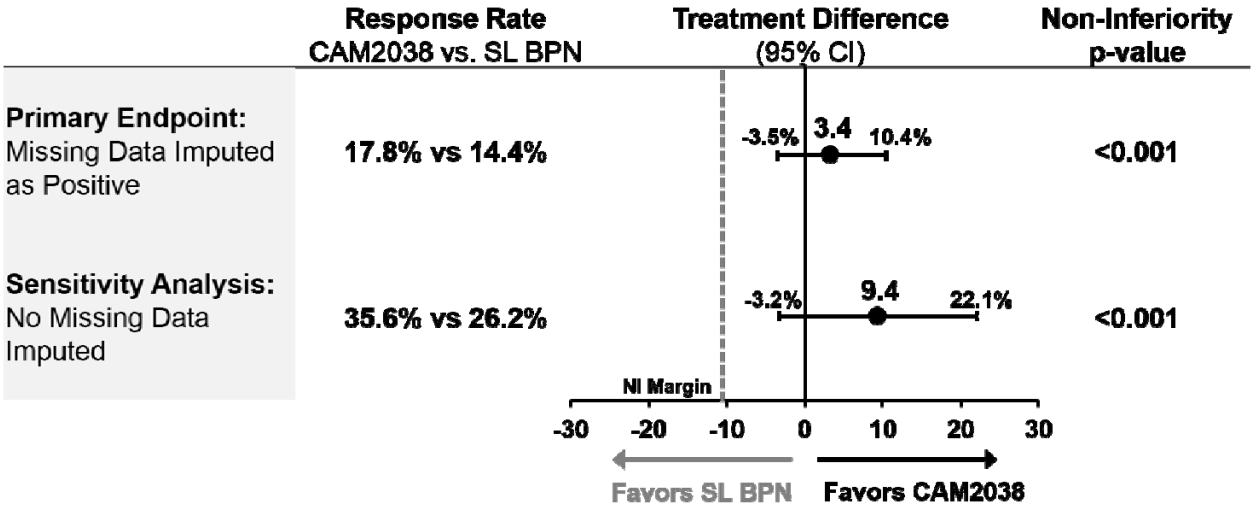


Figure 14: HS-11-421: Primary Endpoint Non-inferiority Analyses and Sensitivity Analysis with No Imputation of Missing Data

Abbreviations: CI, confidence interval; ITT, intent-to-treat; NI, noninferiority, SL BPN, sublingual buprenorphine

Source: HS-11-421 study, BB tables

Table 11: Study HS-11-421: Demographics of Completed Versus Discontinued Subjects

		Completed		Discontinued	
		CAM2038 N=121	SL BPN N=126	CAM2038 N=92	SL BPN N=89
Mean age		40 years	40 years	37 years	36 years
Sex (female)		47%	34%	38%	34%
Race	White	69%	73%	83%	81%
	Black / Afr. American	28%	26%	14%	17%
	Other	3%	2%	3%	2%
Primary opioid	Heroin	71%	65%	72%	78%
	Rx opioids	29%	35%	28%	23%
Injection opioid use		55%	43%	52%	63%
Poly-drug user at baseline		68%	66%	79%	74%

Source: HS-11-421 study, BB tables

8.2.6.1.1. Subgroup Analyses

Additional post-hoc sensitivity analyses were also conducted to determine the RR in various subgroups. Subgroup analyses for age, sex, race, as well as patterns of illicit opioid use by injection route, heroin as primary opioid of use, and poly-drug use (including cocaine, amphetamines, marijuana, and benzodiazepines) all provided supportive results demonstrating non-inferiority of CAM2038 to SL BPN. One subgroup, those who chose heroin as their primary opioid of use showed trends of higher treatment difference for CAM2038 compared to SL BPN (Figure 15). The highest RRs among these groups were observed for patients that were not poly-drug users at screening.

		CAM2038 N=213		SL BPN N=215		Treatment Difference (95% CI)
Category		N	Responders	N	Responders	
Age	< 36 years	99	20.2%	100	11.0%	
	≥ 36 years	114	15.8%	115	17.4%	
Sex	Male	121	14.9%	142	12.7%	
	Female	92	21.7%	73	17.8%	
Race	White	159	20.1%	164	17.1%	
	Black	47	6.4%	48	4.2%	
	Other	7	42.9%	3	33.3%	
Injection User		114	15.8%	110	7.3%	
Heroin as Preferred		152	15.8%	151	4.6%	
Poly-Drug Use		155	11.6%	149	9.4%	
No Poly-Drug use		58	34.5%	66	25.8%	

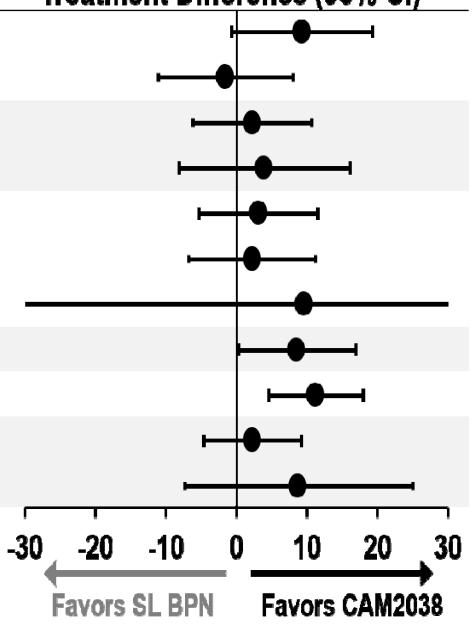


Figure 15: HS-11-421: Subgroup Analysis by Age, Sex, Race, Injection and Non-Injection Users, Heroin and Opioid Users

Abbreviations: CI, confidence interval; SL BPN, sublingual buprenorphine

8.2.6.2. Secondary Endpoint: Cumulative Distribution Function

The secondary efficacy analysis compared the cumulative distribution function (CDF) of the percentage of urine samples negative for opioids in the two treatment groups using a stratified Wilcoxon rank sum test. The urine samples incorporated self-reported use, where if a patient reported illicit use of opioids in between scheduled visits, urine samples collected during that timeframe were considered positive, even if a urine sample tested negative. Missing urine samples were considered positive.

Additionally, patients may require some time to engage in treatment, therefore the analysis included a "grace period" where drug use during the initial grace period is not included in the calculations. In this secondary analysis of CDF, a 3-weeks of grace period was used. Additional sensitivity analyses were also conducted with no grace period and various other grace periods.

The demonstration of non-inferiority for the primary endpoint of RR allowed testing for the superiority of CAM2038 versus SL BPN/NX on the CDF of the proportion of confirmed (self-report) opioid-negative urine samples, during Treatment Weeks 4-24. Superiority was demonstrated with p=0.004 (Figure 16 and Table 12).

Post hoc sensitivity analyses using different initial treatment periods (different number of grace period weeks) supported the pre-specified endpoint for the CDF, including retention of superiority when the entire treatment period was analyzed (no grace period; Table 13).

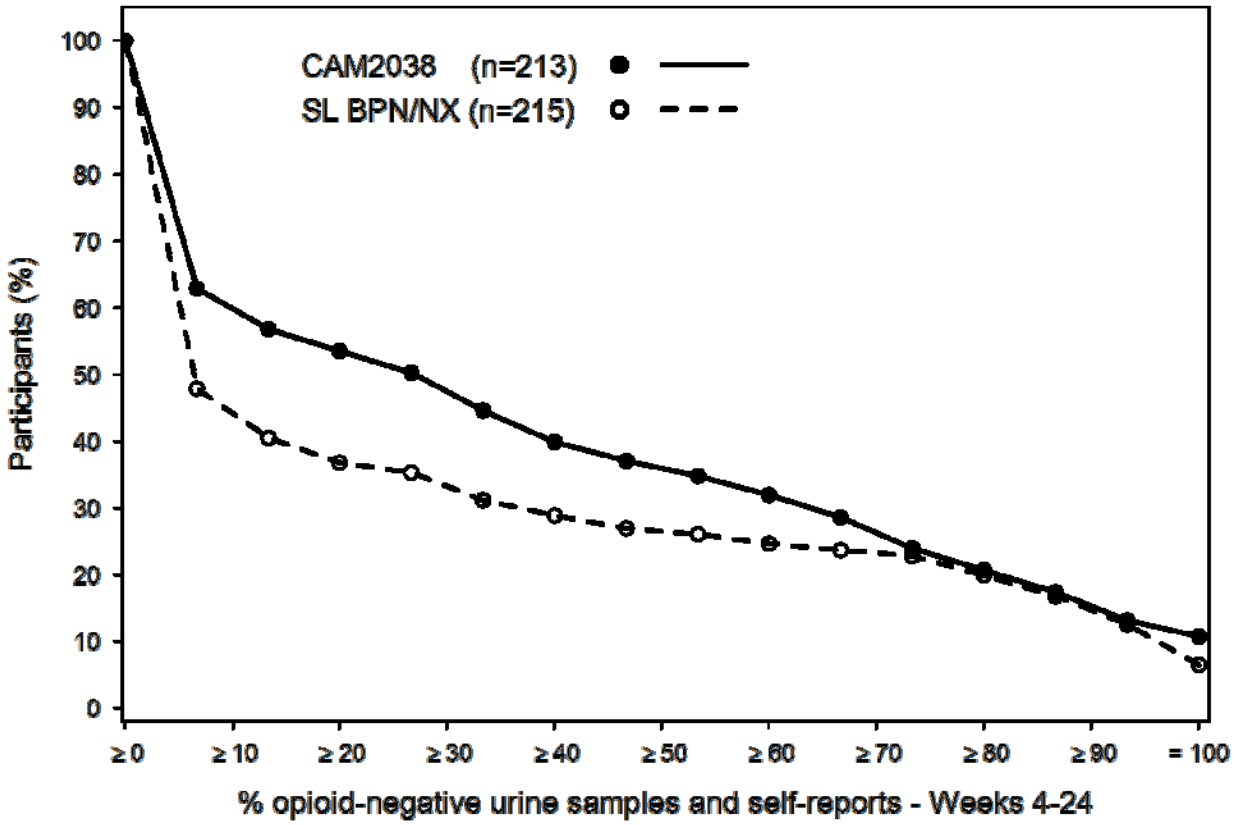


Figure 16: Study HS-11-421: CDF of Percent of Urine Samples Negative for Illicit Opioids with Self-reports – Treatment Weeks 4 to 24 (ITT Population)

Abbreviations: CDF, cumulative distribution function; ITT, intent-to-treat; SL BPN/NX, sublingual buprenorphine/naloxone. Source: Extracted from summary of clinical efficacy, Figure 3

Table 12: Study HS-11-421: Percent of Negative Urine Samples for Illicit Opioids with Self Reports (ITT Population)

Percentage of Opioid Negative Urine Samples	CAM2038 Participants (%)	SL BPN/NX Participants (%)
≥30	44.6	31.2
≥50	34.7	26.0
≥75	20.7	20.0
≥80	20.7	20.0
≥85	17.4	16.7
≥90	13.1	12.6
≥95	10.8	6.5

Abbreviations: CDF, cumulative distribution function; ITT, intent-to-treat; SL BPN/NX, sublingual buprenorphine/naloxone
Source: Extracted from HS-11-421 clinical study report

Table 13: Study HS-11-421: Comparison of CAM2038 to SL BPN/NX Across Various Grace Period Weeks

Grace Period (Weeks)	Treatment Weeks Included in CDF	Mean % Urine Negative % (SD)		Median % Urine Negative %		
		CAM2038	SL BPN/ NX	CAM2038	SL BPN/ NX	Nominal P Value[1]
0	1-24	34.2 (35.5)	27.4 (36.3)	22.2	5.6	0.006
1	2-24	34.7 (36.3)	27.3 (36.8)	23.5	0.0	0.005
3	4-24	35.1 (37.2)	26.7 (37.2)	26.7	0.0	0.004
4	5-24	35.2 (37.4)	26.2 (37.3)	21.4	0.0	0.001

Abbreviations: CDF, cumulative distribution function; ITT, intent-to-treat; SD, standard deviation; SL BPN/NX, sublingual buprenorphine/naloxone
[1] Exploratory analyses not included in pre-specified closed testing procedure
Source: Extracted from summary of clinical efficacy, Table 8

8.2.6.3. Additional Secondary Efficacy Measures

The third prespecified ranked analysis was a test of the superiority of CAM2038 over SL BPN/NX for the RR endpoint. Because this endpoint did not meet the hypothesis for superiority, ordered hypothesis testing was stopped after this endpoint was tested. All subsequent statistical analyses should be considered exploratory.

8.2.6.4. Additional Outcome Measures

The following additional outcome measures are presented:

1. Mean percentages of negative urine samples (Phase 1, 2, and overall) verified by self-report.
2. Mean percentages of negative urine samples verified by self-report and represented over time
3. Opioid withdrawal and craving
4. Supplemental use

8.2.6.4.1. Opioid Negative Urine Samples Verified by Self-Report by Phase 1, Phase 2, and Overall

Analyses of mean percentage of negative urine samples by Phase 1, Phase 2, and overall demonstrated higher mean percent of negative urines in CAM2038 compared to SL BPN/NX (Figure 17)

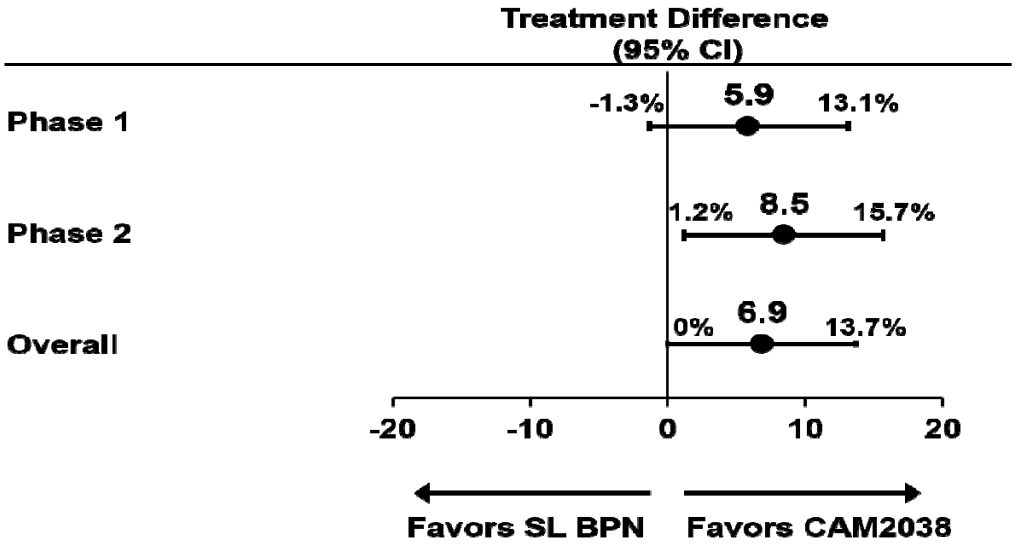


Figure 17: Study HS-11-421: Mean Percent of Negative Urine Samples Verified with Self Reports by Phase 1, Phase 2, and Overall

Abbreviations: CI, confidence interval; SL BPN/NX, sublingual buprenorphine/naloxone
Source: Extracted from clinical study report, HS-11-421

8.2.6.4.2. Opioid Negative Urine Samples Verified by Self-Report by Time Point

Exploratory analyses of opioid negative urine samples supported the primary and secondary treatment outcomes in HS-11-421 (Figure 18). The proportion of negative opioid urine tests was consistently higher in the CAM2038 group than in the SL BPN/NX group after the first four treatment weeks. The results were consistent regardless of whether missing urine samples were counted as positive or excluded. These results support a conclusion that opioid use was decreased by CAM2038 relative to SL BPN/NX.

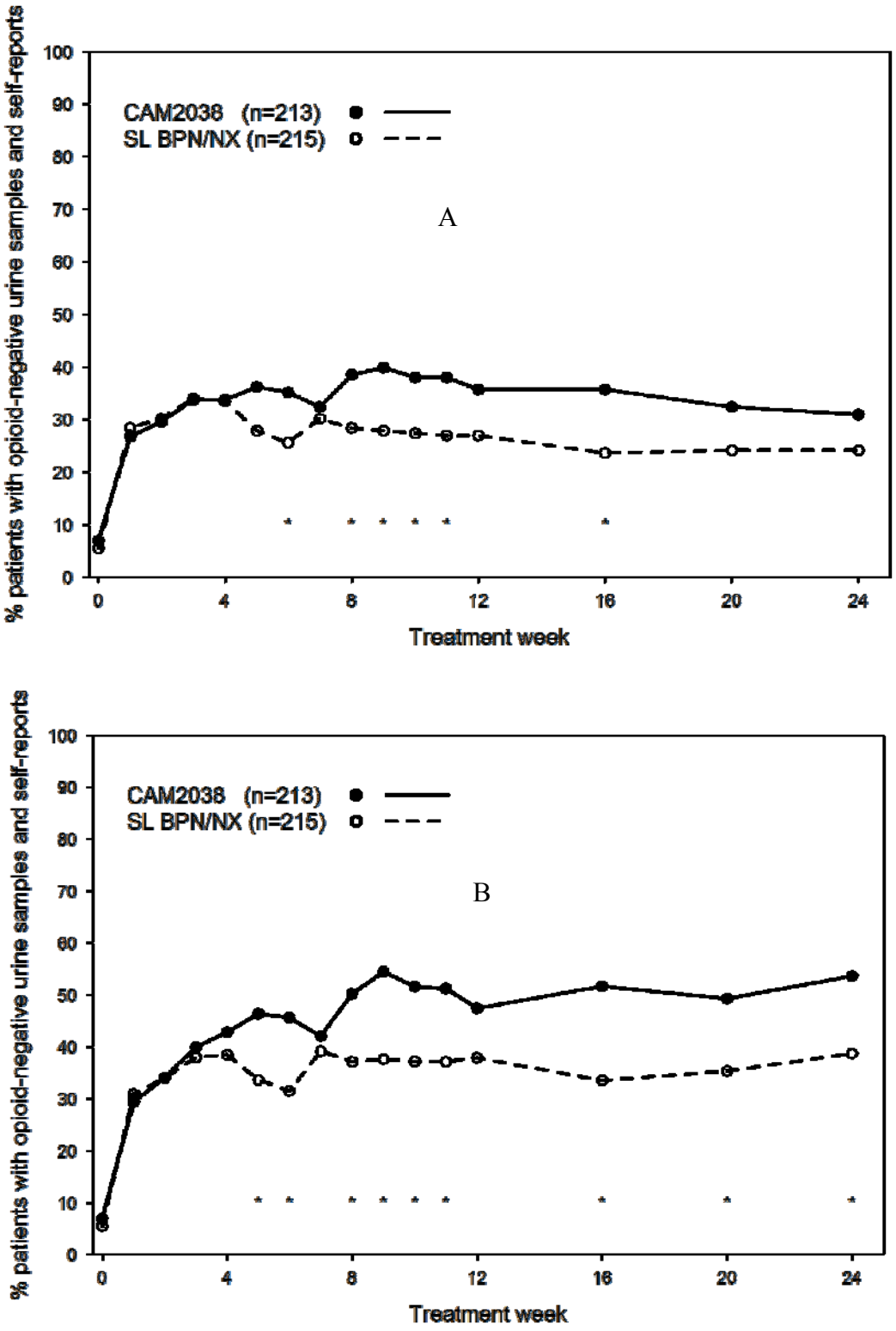


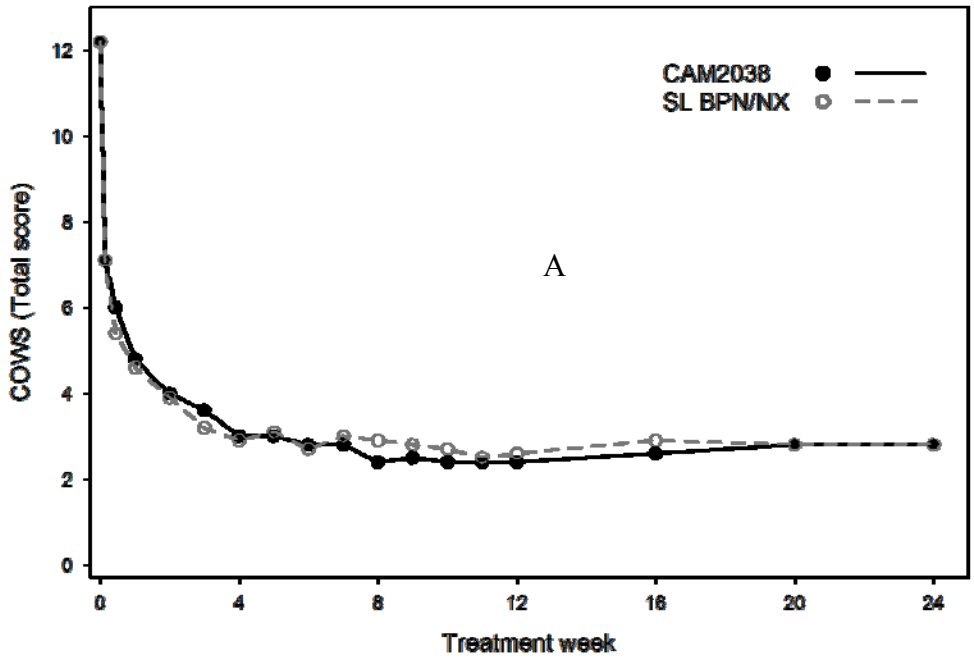
Figure 18: HS-11-421: Opioid Negative Urine Samples Verified by Self-Report by Time Point. A: Missing Imputed as Positive; B: Non-Imputed (ITT Population)

Abbreviations: SL BPN/NX, sublingual buprenorphine/naloxone

Source: Extracted from summary of clinical efficacy, Figure 9

8.2.6.4.3. Opioid Craving and Withdrawal: Exploratory Endpoints

Opioid craving, as measured by the Need to Use VAS item, and withdrawal (COWS and SOWS) were suppressed immediately and throughout the study in both treatment groups (Figure 19). No treatment differences were evident. Importantly, continuous suppression of craving and withdrawal was evident and persisted during the transition from weekly to monthly CAM2038 treatment phases.



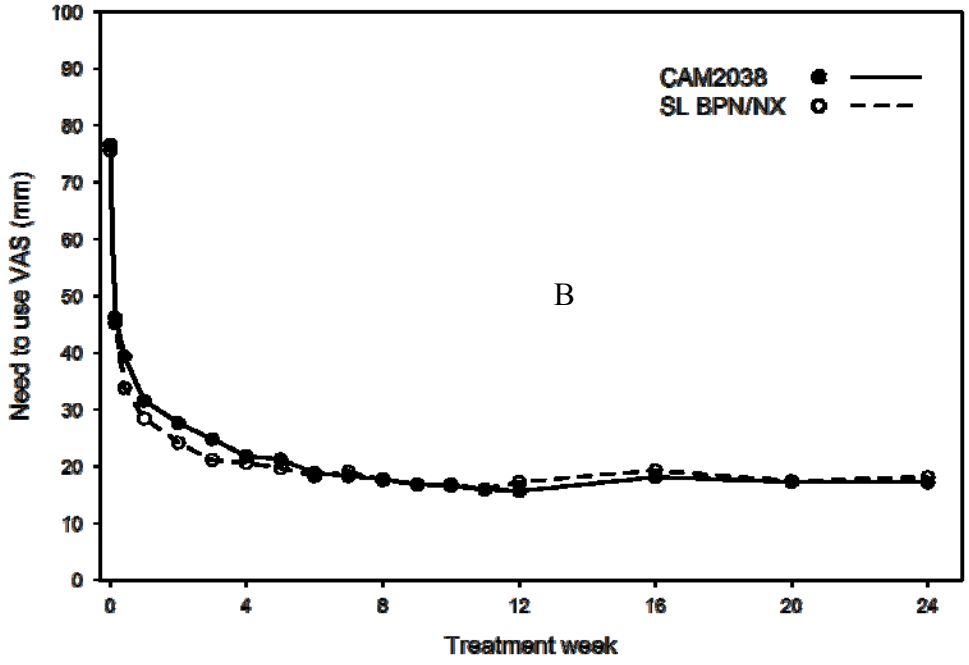


Figure 19: HS-11-421: Opioid Withdrawal and Craving, COWS (A) and VAS (B) (ITT Population)

Abbreviations: COWS, Clinical Opiate Withdrawal Scale; ITT, intent-to-treat; SL BPN/NX, sublingual buprenorphine/naloxone; VAS: visual analog scale
Source: Extracted from summary of clinical efficacy, Figure 10

8.2.6.4.4. Supplemental BPN Use and Counseling: Exploratory Endpoints

Supplemental dosing with CAM2038 8mg q1w was allowed only once per month during Phase 2. Supplement doses were administered to a total of 18 subjects (8.4%) in SL BPN/ NX, in total 30 doses, and 16 subjects (7.5%) in the CAM2038 treatment group, in total 24 doses.

Additional supplemental counseling was provided to 14 subjects (6.5%) in SL BPN/ NX treatment group and 15 subjects (7.9%) in the CAM2038 treatment group.

8.2.6.5. Summary of Efficacy Findings for Pivotal Phase 3 Study HS-11-421

CAM2038 met the pre-specified outcome of non-inferiority to SL BPN/NX for RR based on confirmed opioid negative urine samples. Subsequent analysis of secondary outcomes, following the pre-specified test order, demonstrated the superiority of CAM2038 versus SL BPN/NX on the CDF of the proportion of confirmed opioid-negative urine samples during Treatment Weeks 4–24. Superiority of RR, was not confirmed; hence, other efficacy analyses should be considered exploratory. Sensitivity analyses of the CDF were consistent with the main findings, indicating robustness of efficacy results. Study retention was similar between groups, as was suppression of opioid craving and withdrawal.

8.3. Supportive Efficacy Findings from Phase 3 Long-Term Safety Study, HS-14-499

8.3.1. Study Design

HS-14-499 was an open-label multicenter, 12-month (48-week) safety study of CAM2038 once-weekly (q1w) and once-monthly (q4w) in adult patients with OUD. The study had 3 phases: Screening Phase (within 1-3 weeks of Day 1 of the Treatment Phase), Treatment Phase (Weeks 1 to 48), and Follow-up Phase (Weeks 49 to 53).

The primary objective of the study was to demonstrate long-term safety and tolerability of CAM2038 in adult patients with OUD. The secondary objective was to evaluate the efficacy of CAM2038 through efficacy parameters that included illicit opioid-negative urine samples, self-reported illicit opioid use, signs and symptoms of withdrawal, and cravings.

The inclusion criteria differed from HS-11-421 study. HS-11-499 study included both subjects who were on SL BPN(/NX) treatment and subjects who were actively seeking BPN treatment but had not yet begun treatment. Following Screening and confirmation of eligibility, subjects initiated or transitioned to CAM2038 q1w or q4w based on their current treatment status:

- For treatment-seeking subjects not receiving SL BPN or SL BPN/NX, treatment with 16 mg CAM2038 q1w was initiated
- For subjects taking SL BPN or SL BPN/NX, treatment was transitioned to the corresponding CAM2038 q1w or q4w dose (Table 14)

Table 14: Doses of CAM2038 q1w and q4w for Subjects Transitioning from SL BPN or SL BPN/NX in Study HS-14-499

Weekly SL BPN or SL BPN/NX Category	Once-weekly CAM2038 q1w SC Injection[a]
≤ 6 mg	8 mg (0.16 mL)
8-10 mg	16 mg (0.32 mL)
12-16 mg	24 mg (0.48 mL)
18-24 mg	32 mg (0.64 mL)
Monthly SL BPN or SL BPN/NX Category	**Once-monthly CAM2038 q4w SC Injection[b]**
8-10 mg	64 mg (0.18 mL)
12-16 mg	96 mg (0.27 mL)
18-24 mg	128 mg (0.36 mL)
26-32 mg	160 mg (0.45 mL)

Abbreviations: BPN, buprenorphine; BPN/NX, buprenorphine/naloxone; SC, subcutaneous; SL, sublingual

a. Subjects could return to the clinic for additional dose adjustments with CAM2038 q1w at scheduled visits or 8 mg SC supplemental injections at unscheduled visits, as needed, up to a maximum weekly dose of 40 mg per week (the maximum dose was increased in Protocol Amendment 2).

b. Subjects who needed additional temporary BPN while receiving CAM2038 q4w could receive a maximum of 2 supplemental injections of CAM2038 q1w 8 mg SC injections per week (i.e., unscheduled visits) (the number of supplemental doses was increased from 1 to 2 in Protocol Amendment 2). Dose adjustments could be made at the discretion of the Investigator at scheduled visits.

Source: Extracted from HS-14-499 clinical study report, Table 3

Subjects were allowed to receive supplemental SC injections of CAM2038 q1w 8 mg, at the discretion of the Investigator. Dose adjustments were also allowed at scheduled visits. Subjects on CAM2038 q1w could transfer to CAM2038 q4w (and vice versa) under prespecified conditions:

- Subject was on a stable dose of CAM2038 q1w without fluctuations in dose for 4 weeks
- Subject had minimal subjective and no objective withdrawal symptoms, based on SOWS and COWS scores (SOWS ≤7 and COWS ≤5)
- Subject exhibited diminished desire/need to use, based on visual analogue scale (VAS)
- Subject had diminished use of illicit opioids, assessed by the Investigator's discretion

Dose adjustments were allowed up to a maximum weekly dose of 40 mg for patients receiving CAM2038 q1w. For patients receiving CAM2038 q4w, a maximum of 2 supplemental injections with 8 mg CAM2038 q1w were allowed per week.

During the Treatment Phase, subjects received CAM2038 treatment for up to 48 weeks, as agreed with the Agency. All subjects were transitioned back to usual care and followed for an additional 4 weeks (i.e., up to Week 53) during the Follow-up Phase.

8.3.2. Demographics and Baseline Disease Characteristics

A total of 227 patients received treatment with CAM2038 in the study. The demographic characteristics are shown in Table 15. Notable parameters include a higher proportion of African American subjects in the new to treatment subgroup as compared to the prior BPN subgroup, the preponderance of US subjects in the new to treatment subgroup, and the greater heroin use among new to treatment versus prior BPN users. Overall, most of the subjects (55.9%) were enrolled in the US, with 33.5% of subjects enrolling in the European Union (EU) and 10.6% enrolling in Australia. The population demographics were generally similar to those in Study HS-11-421.

Table 15: HS-14-499: Demographics and Baseline Clinical Characteristics

Characteristics	Receiving SL BPN at Entry N=190	New to BPN Treatment N=37	Total CAM2038 N=227
Age (years)			
Mean (SD)	41.3 (9.64)	41.8 (9.41)	41.4 (9.59)
Min, max	24.0, 66.0	24.0, 61.0	24.0, 66.0
Sex, n (%)			
Male	119 (62.6)	24 (64.9)	143 (63.0)
Female	71 (37.4)	13 (35.1)	84 (37.0)
Race, n (%)			
White	183 (96.3)	20 (54.1)	203 (89.4)
Black or African American	3 (1.6)	17 (45.9)	20 (8.8)
Other	4 (2.1)	0 (0.0)	4 (1.8)
Ethnicity, n (%)			
Hispanic or Latino	2 (1.1)	2 (5.4)	4 (1.8)
Not Hispanic or Latino	187 (98.4)	35 (94.6)	222 (97.8)
Unknown	1 (0.5)	0 (0.0)	1 (0.4)
Region			
Australia	23 (12.1)	1 (2.7)	24 (10.6)
Europe	76 (40.0)	0	76 (33.5)
US	91 (47.9)	36 (97.3)	127 (55.9)
BMI (kg/m^2)			
Mean (SD)	26.7 (5.84)	25.3 (5.33)	26.5 (5.77)
Min, max	16.9, 50.4	18.2, 46.4	16.9, 50.4
Primary Opioid of Use n (%)			
Heroin	97 (51.1)	37 (100.0)	134 (59.0)
Prescription Opioids	81 (42.6)	0	81 (35.7)

Abbreviations: BMI, body mass index; Max, maximum; Min, minimum; US, United States
Source: Extracted from summary of clinical efficacy, Table 9

8.3.3. Study Retention

A total of 228 subjects were enrolled. One subject withdrew consent prior to receiving the first dose of CAM2038; therefore, 227 subjects received at least one dose of CAM2038 and were

included in the Overall Safety Population. This population was also considered the efficacy population for this study. A total of 156 patients (68.4%) completed the 48-week treatment period. Median duration of exposure in the Overall Safety Population was 48 weeks in both groups, with mean (SD) durations of exposure of 38.3 (16.9) weeks for patients receiving SL BPN at entry and 43.6 (11.5) weeks for patients new to BPN treatment (Figure 20).

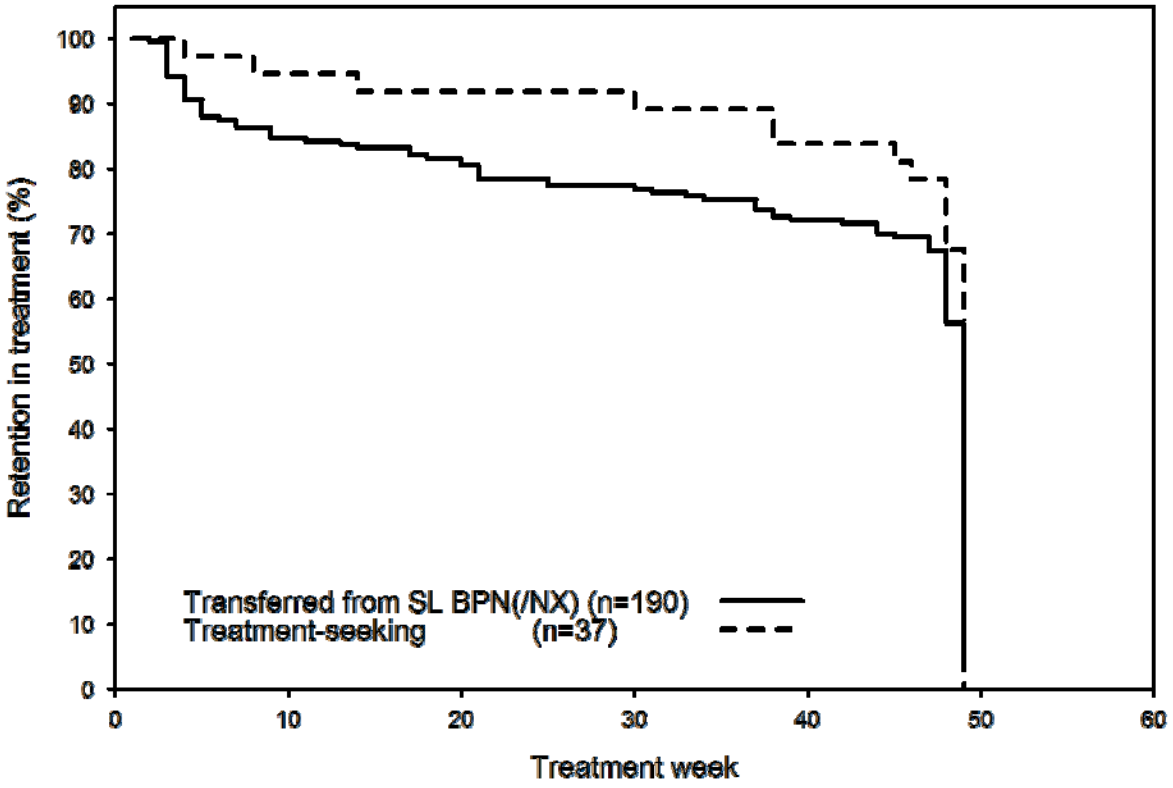


Figure 20: Study HS-14-499: Retention in Treatment by Treatment Week

Abbreviations: SL BPN/NX, sublingual buprenorphine/naloxone

Source: Extracted from summary of clinical efficacy, Figure 5

8.3.4. Efficacy Results

In the absence of a placebo or active comparator, efficacy measures are considered supportive of those from controlled Phase 2 and 3 studies.

At baseline, urine toxicology results were negative in 78.4% of subjects on SL BPN at entry, and 0% of those new to BPN treatment (Figure 21). At the end of treatment, these values were 82.8% and 63.0%, respectively (Table 16). In general, negative urine toxicology results remained stable and high throughout the study among subjects who transitioned from prior SL BPN to CAM2038, while in subjects new to BPN, the proportion of subjects with negative urines increased continuously from baseline to end of the study. Similar results were obtained when urine toxicology results were supported by self-reports of illicit opioid use.

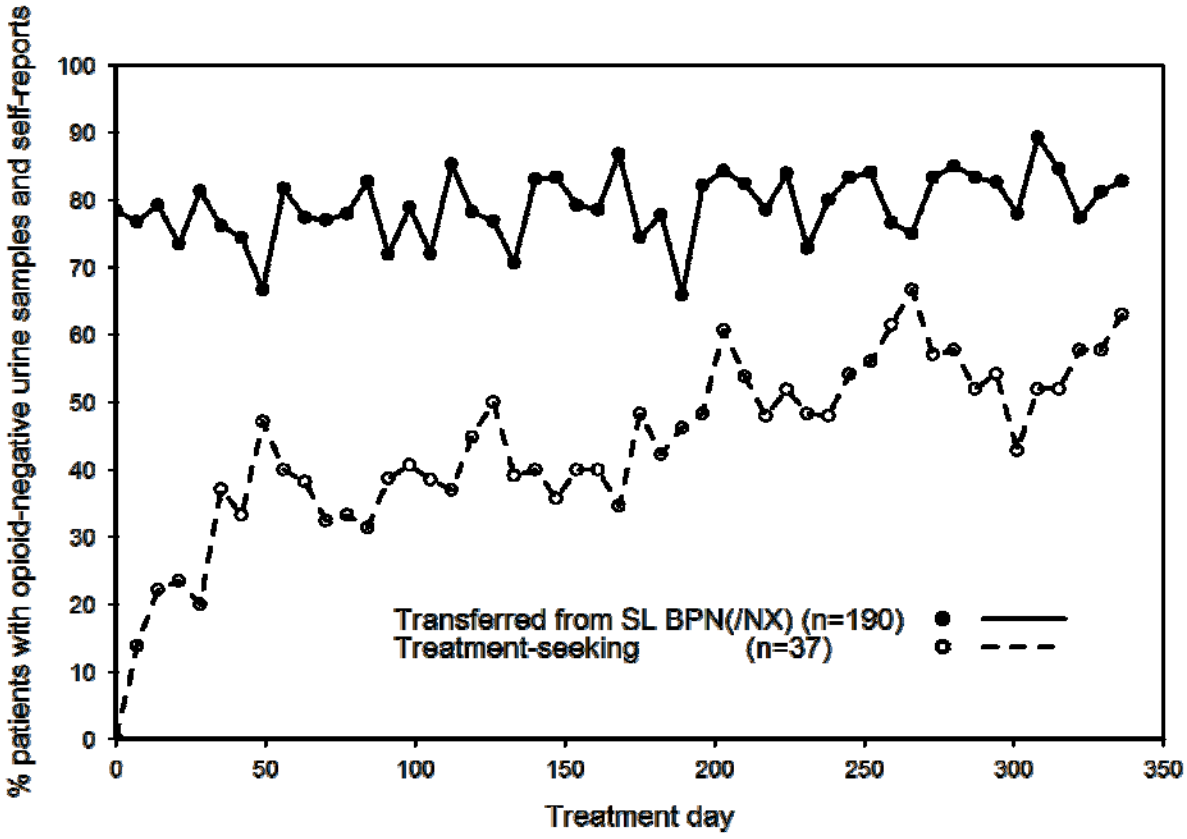


Figure 21: Study HS-14-499: Illicit Opioid Negative Samples Over Time

Source: Extracted from summary of clinical efficacy, Figure 6

Opioid withdrawal symptoms were assessed using the COWS and SOWS questionnaires. Withdrawal symptoms for both subjects receiving SL BPN at entry and new to treatment subjects were mild to moderate at baseline and decreased over the course of the study. Consistent with the measures of withdrawal symptoms, desire to use and need to use measurements were low at Baseline and decreased over the course of the study (Table 16).

Table 16: Study HS-14-499: Illicit Opioid Negative Samples and Withdrawal Over Time

	At Baseline[a]	At End of Treatment[a]
Urine Toxicology (% Negative for Opioids)[b]		
Subjects Receiving SL BPN at Entry (%)	78.4	82.8
Subjects New to Treatment (%)	0.0	63.0
Cravings: Need to use VAS (mm)		
Subjects Receiving SL BPN at Entry	11.7 (23.8)	5.4 (14.3)
Subjects New to Treatment	76.3 (24.9)	5.3 (15.9)
Cravings: Desire to use VAS (mm)		
Subjects Receiving SL BPN at Entry	11.7 (24.2)	6.4 (16.5)
Subjects New to Treatment	74.8 (24.8)	2.8 (6.2)
COWS (0-48)		
Subjects Receiving SL BPN at Entry	2.0 (2.7)	1.4 (2.3)
Subjects New to Treatment	10.6 (3.7)	0.3 (0.5)
SOWS (0-64)		
Subjects Receiving SL BPN at Entry	4.7 (8.1)	3.3 (6.3)
Subjects New to Treatment	27.1 (15.3)	3.9 (8.0)

[a]Mean (SD) values are presented for VAS, COWS, and SOWS. Urine Toxicology results are presented in percentage.

[b]Urine toxicology results on Day 1 is presented as baseline value and Day 337 is presented as end of treatment value

Abbreviations: BPN, buprenorphine; COWS, clinical opiate withdrawal scale; SOWS, subjective opiate withdrawal scale; SD, standard deviation; SL, sublingual; VAS, visual analog scale

Source: Extracted from HS-14-499 clinical study report, Table 14.2.1.1.1, Table 14.2.6, Table 14.2.7, Table 14.2.8, and Table 14.2.9

8.3.4.1. Supplemental CAM2038 Injections and Additional Supplemental Counseling

Supplemental 8 mg weekly CAM2038 doses accounted for 301 injections (5.8%) of the total number of 5,196 injections throughout 12 months of treatment. Overall, the time of first use of supplemental 8 mg CAM2038 occurred mostly within 28 days from dosing during the 12 months of treatment. Of which, 76% of the subjects received 3 or less supplemental doses (Table 17). Only 5 supplemental doses were used by new-to-treatment participants across the study.

Supplemental counseling was also provided throughout the study. The need for additional supplemental counseling was higher among subjects who were new to BPN treatment (34 subjects, 91.9%) compared with subjects who were receiving SL BPN at entry (84 subjects, 44.2%)

Table 17: Study HS-14-499: Number of Supplemental Use per Patient Distribution

Number of Supplemental Doses	% of Patients Who Received Supplemental BPN
1-3	76
4-6	12
≥ 7	12

Abbreviations: BPN, buprenorphine

Source: Extracted from HS-14-499 clinical study report

8.4. Efficacy Conclusions

Across treatment phases, CAM2038 was as effective as SL BPN for response rate based on opioid negative urine samples. In addition, CAM2038 demonstrated superiority compared to SL BPN/NX in reducing overall use of illicit opioids. CAM2038 rapidly suppressed withdrawal symptoms and the need or desire to use opioids. Importantly, no loss of efficacy was observed during transitions from SL BPN/NX to CAM2038, of from weekly to monthly CAM2038. The results comprise a key component of the bridge to reference drug SL BPN.

The rapid onset of CAM2038 effects was illustrated by near complete opioid blockade within 1 hour of dosing in phase 2 study HS-13-478. This finding eliminated any concern that the depot formulation would delay the onset of action.

CAM2038 was superior to SL BPN/NX for the CDF of the proportion of confirmed opioid-negative urine samples during treatment Weeks 4–24. Sensitivity analyses of the CDF that employed a range of grace periods supported the main analyses. It is notable that the CDF over Weeks 1–24 (no grace period) showed less illicit opioid use in the CAM2038 group than in the SL BPN/NX group. Treatment retention rates were 72.6% for the SL BPN/NX group and 69.0% for the CAM2038 group.

The long-term safety study, HS-14-499 supported the efficacy findings of the pivotal study. Continuous treatment effects across the 48-week treatment period were observed and were not diminished during transitions from weekly to monthly CAM2038 dosing. Among subjects receiving SL BPN at study entry, CAM2038 maintained suppression of withdrawal and desire/need to use opioids. The numbers of opioid-negative urine samples were also maintained through the treatment period. These results support the proposed dosing paradigm for transitions from SL BPN to CAM2038 and between weekly and monthly CAM2038. Among subjects new to BPN treatment, CAM2038 rapidly and continuously reduced withdrawal and opioid cravings and increased the numbers of opioid negative urine samples. The results of study HS-14-499 supported the proposed starting and maintenance doses.

Taken together, the Phase 2 and Phase 3 studies demonstrate that CAM2038 is efficacious and that the proposed doses and dosing paradigms are appropriate:

- Primary efficacy was non-inferior to the reference drug SL BPN/NX (study 421), establishing a key component of the bridge to the reference drug
- Secondary and additional efficacy outcomes supported the primary result
- Efficacy was maintained during transitions from SL BPN(/NX) and between weekly and monthly CAM2038 (studies HS-11-421, HS-14-499)
- The distribution of doses reached by study end encompassed all available doses, with the intermediate doses used most often (Studies HS-11-421, HS-14-499); minimal supplemental BPN was used after the initial 2-3 weeks of study HS-14-499

9. CLINICAL SAFETY

- Except for mild to moderate injection site reactions, CAM2038 has a safety profile consistent with the well-established BPN safety profile.
- The safety profile of CAM2038 was similar in healthy volunteers and patients with OUD.
- The most common AEs with CAM2038 across Phase 3 studies were injection site pain (12.3%), injection site swelling (8.2%), headache (7.7%), injection site erythema (7.5%), nausea (7.0%), urinary tract infection (5.2%), constipation (5.0%), and nasopharyngitis (5.0%).
- Many AEs reported with CAM2038 (except injection site reactions) were known class effects of opioids.
- The majority of injection site AEs were mild or moderate, with no SAEs associated with injection site reactions.

9.1. Overview of Safety Evaluation

Except for mild to moderate injection site reactions, the CAM2038 safety profile was comparable to the well-established safety profile of BPN.

The safety evaluation of CAM2038 included 729 subjects; 604 received CAM2038 q1w and 408 received CAM2038 q4w.

Key safety assessments, including deaths, SAEs and study discontinuations, are presented for all clinical studies. For this briefing document, the presentation of general AE data and AESIs is focused on Phase 3 study data.

The safety evaluation in pivotal study HS-11-421 incorporated as comparator SL BPN/NX at doses in the range used in the treatment of OUD, i.e., 4 to 24 mg daily (Subutex US label).

In regards to abuse potential, the product design minimizes the potential for extracting or manipulating the product. Restricting administration to HCPs eliminates dispensing directly to patients, and will further minimize the potential for diversion, misuse, abuse or pediatric accidental exposure.

9.2. Population and Extent of Exposure

Across all studies, 594 patients with OUD were exposed to CAM2038, of which 299 subjects (50.3%) were exposed to CAM2038 for at least 24 weeks, and 132 subjects (22.2%) were exposed to CAM2038 for at least 48 weeks Table 18. Subjects may have switched between CAM2038 q1w and CAM2038 q4w and/or changed doses in the Phase 3 studies, as dose titration was allowed at the discretion of the Investigator.

Table 18: Overall Exposure to CAM2038 in Subjects with OUD

	CAM2038 q1w (N=531)	CAM2038 q4w (N=346)	CAM2038 (N=594)
Exposed for at least 4 weeks	369 (69.5%)	346 (100.0%)	445 (74.9%)
Exposed for at least 8 weeks	300 (56.5%)	316 (91.3%)	414 (69.7%)
Exposed for at least 12 weeks	262 (49.3%)	288 (83.2%)	400 (67.3%)
Exposed for at least 24 weeks	68 (12.8%)	116 (33.5%)	299 (50.3%)
Exposed for at least 48 weeks	42 (7.9%)	45 (13.0%)	132 (22.2%)

Note: The value in the CAM2038 column does not necessarily match the sum of the CAM2038 q1w and CAM2038 q4w columns since, for example, if a subject was treated for 3 weeks with 24 mg CAM2038 q1w, 5 weeks with 32 mg CAM2038 q1w and 40 weeks with 128 mg CAM2038 q4w, the subject was not included as treated for at least 48 weeks with CAM2038 q1w or CAM2038 q4w but in the total column for CAM2038. Thus, this subject would appear as treated for at least 8 weeks with CAM2038 q1w, at least 24 weeks with CAM2038 q1w and at least 48 weeks with CAM2038.

Source: Extracted from Summary of Clinical Safety, Table 7

The safety of CAM2038 was assessed in 7 clinical studies; in which 729 subjects received 8693 injections (mean: 11.9 injections per subject) of CAM2038 corresponding to 270.8 subject-exposure-years. Moreover, in the HS-11-421 study, 215 subjects received 2817 injections (mean: 13.1 injections per subject) of placebo corresponding to 77 subject-exposure-years. Exposure by regimen, age, sex, race, ethnicity, BMI, and region across all studies is presented in Table 19.

Table 19: Exposure by Regimen, Age, Sex, Race, Ethnicity, BMI and Region Across All Studies (Safety Population)

Category	Statistics	CAM2038 q1w (N=604)	CAM2038 q4w (N=408)	SL BPN/NX (N=215)	CAM2038 (N=729)
	No of injections	6780	1913	2817	8693
	No of injections per subject	11.2	4.7	13.1	11.9
	Subject exposure years	129.94	146.65	76.97	270.80
Age group (years)	18-64 years	601 (99.5%)	403 (98.8%)	214 (99.5%)	723 (99.2%)
	65-74 years	3 (0.5%)	5 (1.2%)	1 (0.5%)	6 (0.8%)
Sex	Female	232 (38.4%)	171 (41.9%)	73 (34.0%)	284 (39.0%)
	Male	372 (61.6%)	237 (58.1%)	142 (66.0%)	445 (61.0%)
Race	Asian	8 (1.3%)	7 (1.7%)	0	15 (2.1%)
	Black / African American	108 (17.9%)	57 (14.0%)	48 (22.3%)	120 (16.5%)
	Mixed	3 (0.5%)	1 (0.2%)	0	4 (0.5%)
	White	470 (77.8%)	327 (80.1%)	164 (76.3%)	569 (78.1%)
	All Others	15 (2.5%)	16 (3.9%)	3 (1.4%)	21 (2.9%)
Ethnicity	Hispanic or Latino	34 (5.6%)	18 (4.4%)	24 (11.2%)	38 (5.2%)
	Not Hispanic or Latino	527 (87.3%)	389 (95.3%)	191 (88.8%)	648 (88.9%)
	Unknown	1 (0.2%)	1 (0.2%)	0	1 (0.1%)

Category	Statistics	CAM2038 q1w (N=604)	CAM2038 q4w (N=408)	SL BPN/NX (N=215)	CAM2038 (N=729)
	Not collected	42 (7.0%)	0	0	42 (5.8%)
BMI group	<18.5 kg/m2	17 (2.8%)	11 (2.7%)	7 (3.3%)	18 (2.5%)
	18.5-30 kg/m2	488 (80.8%)	318 (77.9%)	166 (77.2%)	592 (81.2%)
	>=30 kg/m2	99 (16.4%)	79 (19.4%)	42 (19.5%)	119 (16.3%)
Region	Australia	19 (3.1%)	22 (5.4%)	0	24 (3.3%)
	EU	191 (31.6%)	96 (23.5%)	0	253 (34.7%)
	US	394 (65.2%)	290 (71.1%)	215 (100.0%)	452 (62.0%)

Abbreviations: BMI = body mass index, US = United States, EU = European Union
Source: Extracted from summary of clinical safety, Table 10

9.3. Deaths

One death occurred among the 729 subjects exposed to CAM2038, where the subject was a pedestrian hit by an oncoming car (a road traffic incident) assessed by the investigator as unlikely related to the investigational medicinal product (IMP). No other AEs were reported during the subject's participation in the study.

9.4. Serious Adverse Events

A total of 17 subjects (2.3%) among the 729 subjects receiving CAM2038 experienced 20 SAEs. Road traffic accident and seizure were reported in 2 subjects each; all other SAEs were reported in 1 subject each. One treatment-related SAE (vomiting) occurred within 30 days after the last dose of CAM2038 16mg q1w (Table 20). Summary of serious adverse events in CAM2038 subjects across all studies is presented in Table 21. In the pivotal study, HS-11-421, 13 subjects (6.0%) in the SL BPN/NX group and 5 subjects (2.3%) in the CAM2038 group experienced at least one SAE (Table 22). None of the SAEs occurred at the injection site or in association with an injection site reaction (Table 21).

Table 20: Overall Summary of Serious Adverse Events Across All Studies (Safety Population)

Category		TOTAL CAM2038 (N=729)
No. (%) of subjects with at least one SAE		17 (2.3%)
No. of SAEs		20
No. (%) of subjects with at least one related SAE		1 (0.1%)
Severity No. (%) of subjects with SAE	Mild	1 (0.1%)
	Moderate	6 (0.8%)
	Severe	11 (1.5%)
Outcome No. (%) of subjects with SAE	Recovered/resolved	14 (1.9%)
	Not recovered/not resolved	2 (0.3%)
	Recovered/resolved with sequelae	2 (0.3%)
	Fatal	1 (0.1%)
No. (%) of subjects with at least one SAE leading to withdrawal		3 (0.4%)
No. (%) of deaths with SAE		1 (0.1%)

Abbreviations: SAE, serious adverse event
Source: Extracted from summary of clinical safety, Table 26

Table 21: Summary of Serious Adverse Events in Subjects Receiving CAM2038 Across All Studies (N = 729)

Preferred Term	n (%)	Preferred Term	n (%)
Road traffic accident	2 (0.3)	Malignant melanoma	1 (0.1)
Seizure	2 (0.3)	Multiple injuries	1 (0.1)
Abortion spontaneous	1 (0.1)	Non-cardiac chest pain	1 (0.1)
Cellulitis	1 (0.1)	Pneumonia	1 (0.1)
Cholecystitis chronic	1 (0.1)	Psychotic disorder	1 (0.1)
Drug withdrawal syndrome	1 (0.1)	Substance-induced psychotic disorder	1 (0.1)
Duodenitis	1 (0.1)	Suicidal ideation	1 (0.1)
Follicular thyroid cancer	1 (0.1)	Ventricular tachycardia	1 (0.1)
Intervertebral disc degeneration	1 (0.1)	Vomiting	1 (0.1)

Abbreviations: SAE, serious adverse event

Source: Extracted from integrated summary of safety, Table 6.2.2

Table 22: Summary of Serious Adverse Events in Study HS-11-421

SAE	CAM2038 (N = 213)	SL BPN/ NX (N= 215)
Haemophilia	0	1
Vomiting	1	0
Non-cardiac chest pain	1	0
Abscess limb	0	1
Acute hepatitis C	0	1
Cellulitis	0	1
Localised infection	0	1
Osteomyelitis	0	1
Pneumonia	0	1
Sepsis	0	1
Subcutaneous abscess	0	1
Accidental overdose	0	3
Intentional overdose	0	1
Road traffic accident	1	0
Seizure	0	1
Abortion spontaneous	1	0
Bipolar disorder	0	1
Substance-induced mood disorder	0	1
Suicidal ideation	1	1
Chronic obstructive pulmonary disease	0	1

Abbreviations: SAE, serious adverse events

Source: Extracted from HS-11-421 CSR, Table 14.3.9.1

9.5. Common Adverse Events in Phase 3 Studies

Table 23 shows a summary of AEs by study and treatment in Phase 3 studies. The incidence and rates of these AEs were similar between treatments in study HS-11-421.

Table 23: Overall Summary of AEs by Study and Treatment in Phase 3 Studies (Safety Population)

Category		HS-11-421		HS-14-499	Total
		CAM2038 (N=213)	SL BPN/NX (N=215)	CAM2038 (N=227)	CAM2038 (N=440)
No. (%) of subjects with at least one AE		128 (60.1%)	119 (55.3%)	143 (63.0%)	271 (61.6%)
No. (%) of subjects with at least one related AE		70 (32.9%)	64 (29.8%)	60 (26.4%)	130 (29.5%)
Severity No. (%) of subjects	Mild	102 (47.9%)	97 (45.1%)	116 (51.1%)	218 (49.5%)
	Moderate	59 (27.7%)	67 (31.2%)	84 (37.0%)	143 (32.5%)
	Severe	6 (2.8%)	15 (7.0%)	15 (6.6%)	21 (4.8%)
Outcome No. (%) of subjects	Recovered/resolved	114 (53.5%)	111 (51.6%)	134 (59.0%)	248 (56.4%)
	Not recovered/not resolved	34 (16.0%)	46 (21.4%)	50 (22.0%)	84 (19.1%)
	Recovered/resolved with sequelae	3 (1.4%)	2 (0.9%)	2 (0.9%)	5 (1.1%)
	Fatal	1 (0.5%)	0	0	1 (0.2%)
	Unknown	3 (1.4%)	2 (0.9%)	0	3 (0.7%)
No. (%) of subjects with at least one SAE		5 (2.3%)	13 (6.0%)	12 (5.3%)	17 (3.9%)
No. of SAEs		5	18	15	20
No. (%) of subjects with at least one AE leading to withdrawal		7 (3.3%)	3 (1.4%)	3 (1.3%)	10 (2.3%)
No. (%) of deaths		1 (0.5%)	0	0	1 (0.2%)

Abbreviations: AE, adverse event; SAE, serious adverse event; SL BPN/NX, sublingual buprenorphine/naloxone

Source: Extracted from summary of clinical safety, Table 16

The most commonly reported AEs in the Phase 3 studies included injection site pain (12.3%), injection site swelling (8.2%), headache (7.7%), injection site erythema (7.5%), nausea (7.0%), urinary tract infection (5.2%), constipation (5.0%), and nasopharyngitis (5.0%). When looking at the 5 most commonly reported AEs, the rates were higher for CAM2038 q1w than for CAM2038 q4w. This observation may be explained by a visit frequency bias, as subjects receiving CAM2038 q1w had more frequent visits with AEs collected more often than did subjects receiving CAM2038 q4w (Table 24).

Table 24: AEs by Regimen, and PT (Incidence of ≥5%) in Phase 3 Studies (CAM2038 Safety Population)

Preferred Term	CAM2038 q1w (N=402)	CAM2038 q4w (N=309)
	n (%)	n (%)
Injection site pain	38 (9.5%)	20 (6.5%)
Injection site swelling	27 (6.7%)	10 (3.2%)
Headache	25 (6.2%)	11 (3.6%)
Injection site erythema	25 (6.2%)	9 (2.9%)
Nausea	20 (5.0%)	12 (3.9%)

Abbreviations: AE, adverse event;

Source: Extracted from summary of clinical safety, Table 18 and Table 19

9.6. Adverse Events Leading to Discontinuation

In study HS-11-421,181 subjects (42.3%) discontinued the study early: 92 (43.2%) in the CAM2038 group and 89 (41.4%) in the SL BPN/NX group (Table 25). In study HS-14-499, 70 subjects (30.8%) receiving CAM2038 discontinued. The most common (≥5% of subjects) reasons for study discontinuation across all studies were 'withdrawal by subject'/'withdrawal of consent' (CAM2038 overall: 11.9%; SL BPN/NX: 21.4%) and lost to follow-up (CAM2038 overall: 5.9%; SL BPN/NX: 13.5%).

Table 25: Reasons for Study Discontinuation by Study and Treatment Group Across All Studies (Safety Population)

Category	HS-11-426 (N=56)	HS-13-487 (N=79)	HS-07-307 (N=42)	HS-15-549 (N=65)	HS-13-478 (N=47)	HS-11-421 CAM2038 (N=213)	HS-11-421 SL BPN/NX (N=215)	HS-14-499 (N=227)	Total CAM2038 (N=729)	Total (N=944)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects who discontinued	2 (3.6)	4 (5.1)	42 (100.0)	15 (23.1)	1 (2.1)	92 (43.2)	89 (41.4)	70 (30.8)	226 (31.0)	315 (33.4)
Adverse event	0	1 (1.3)	0	0	1 (2.1)	6 (2.8)	1 (0.5)	4 (1.8)	12 (1.6)	13 (1.4)
After intake of BPN as rescue medication after Day 14	0	0	23 (54.8)	0	0	0	0	0	23 (3.2)	23 (2.4)
After intake of BPN as rescue medication before Day 14	0	0	15 (35.7)	0	0	0	0	0	15 (2.1)	15 (1.6)
Death	0	0	0	0	0	1 (0.5)	0	0	1 (0.1)	1 (0.1)
Development of exclusion criteria	0	0	1 (2.4)	0	0	0	0	0	1 (0.1)	1 (0.1)
Lack of efficacy	0	0	0	0	0	0	0	12 (5.3)	12 (1.6)	12 (1.3)
Lost to follow-up	0	0	0	3 (4.6)	0	27 (12.7)	29 (13.5)	13 (5.7)	43 (5.9)	72 (7.6)
Other	0	0	0	3 (4.6)	0	6 (2.8)	8 (3.7)	2 (0.9)	11 (1.5)	19 (2.0)
Physician decision	0	0	0	0	0	8 (3.8)	4 (1.9)	5 (2.2)	13 (1.8)	17 (1.8)
Pregnancy	0	0	0	0	0	0	1 (0.5)	1 (0.4)	1 (0.1)	2 (0.2)
Protocol violation	0	2 (2.5)	3 (7.1)	0	0	0	0	0	5 (0.7)	5 (0.5)
Study ended by Sponsor	0	0	0	2 (3.1)	0	0	0	0	2 (0.3)	2 (0.2)
Withdrawal by subject	2 (3.6)	1 (1.3)	0	7 (10.8)	0	44 (20.7)	46 (21.4)	33 (14.5)	87 (11.9)	133 (14.1)

Abbreviations: BPN, buprenorphine; SL BPN/NX, sublingual buprenorphine/naloxone
Source: Extracted from Summary of Clinical Safety, Table 9

9.7. Adverse Events of Special Interest

AESIs were specified by the Sponsor based on the labeling of the reference product and taking the different route of administration into account. The AESI included allergic reactions, CNS depression, device failure, drug abuse or dependence, drug withdrawal, elevated cerebrospinal fluid pressure, elevated intracholedochal pressure, gastrointestinal disorders, hepatic disorders, medication errors including overdose, orthostatic hypotension, psychiatric disorders, QT prolongation, reproductive or neonatal disorders, respiratory depression and severe injection site reactions. When available, predefined standardized MedDRA Queries (SMQs) were used to identify predefined potential AESIs.

The incidence rates of the pre-defined AESIs were similar between CAM2038 and SL BPN/NX in study HS-11-421, as expected given the similar BPN exposure ranges produced by CAM2038 and therapeutic SL BPN doses. A possible exception is the AESI drug abuse and dependence (i.e. overdoses), which occurred more commonly in the SL BPN/NX group (Table 26).

Table 26: Incidence of Potential AESIs by AESI, Study, and Treatment Group in Study HS-11-421 (Safety Population)

AESI	Preferred Term	CAM2038 (N=213)	SL BPN /NX (N=215)
		n (%)	n (%)
At least one AESI		**55 (25.8%)**	**57 (26.5%)**
Allergic reactions		**7 (3.3%)**	**12 (5.6%)**
	Cough	4 (1.9%)	2 (0.9%)
	Injection site urticaria	1 (0.5%)	0
	Ocular hyperaemia	1 (0.5%)	0
	Rash	1 (0.5%)	2 (0.9%)
	Chest discomfort	0	1 (0.5%)
	Dyspnoea	0	2 (0.9%)
	Erythema	0	1 (0.5%)
	Eye pruritus	0	1 (0.5%)
	Periorbital oedema	0	1 (0.5%)
	Pruritus	0	2 (0.9%)
	Swelling face	0	2 (0.9%)
	Wheezing	0	1 (0.5%)
Central nervous system		**4 (1.9%)**	**3 (1.4%)**
	Sedation	2 (0.9%)	1 (0.5%)
	Somnolence	2 (0.9%)	2 (0.9%)
Drug abuse and dependence		**0**	**5 (2.3%)**
	Accidental overdose	0	4 (1.9%)
	Intentional overdose	0	1 (0.5%)
	Substance-induced mood disorder	0	1 (0.5%)
Drug withdrawal		**0**	**3 (1.4%)**
	Drug withdrawal syndrome	0	3 (1.4%)
Gastrointestinal disorders		**38 17.8%)**	**36 (16.7%)**
	Constipation	16 (7.5%)	16 (7.4%)
	Nausea	15 (7.0%)	17 (7.9%)

AESI	Preferred Term	CAM2038 (N=213)	SL BPN /NX (N=215)
		n (%)	n (%)
	Vomiting	9 (4.2%)	8 (3.7%)
	Diarrhoea	6 (2.8%)	7 (3.3%)
	Abdominal pain upper	2 (0.9%)	3 (1.4%)
	Abdominal distension	1 (0.5%)	0
	Abdominal pain	1 (0.5%)	3 (1.4%)
	Flatulence	1 (0.5%)	0
	Non-cardiac chest pain	1 (0.5%)	0
Hepatic disorders		**0**	**1 (0.5%)**
	Acute hepatic failure	0	1 (0.5%)
Medication errors		**0**	**4 (1.9%)**
	Accidental overdose	0	4 (1.9%)
Psychiatric disorders		**18 (8.5%)**	**14 (6.5%)**
	Insomnia	12 (5.6%)	6 (2.8%)
	Anxiety	6 (2.8%)	7 (3.3%)
	Depression	3 (1.4%)	2 (0.9%)
QT prolongation		**0**	**1 (0.5%)**
	ECG QT prolonged	0	1 (0.5%)
Respiratory depression		**0**	**4 (1.9%)**
	Dyspnoea	0	2 (0.9%)
	Sleep apnoea syndrome	0	2 (0.9%)
Urinary retention		**1 (0.5%)**	**0**

Abbreviations: AESI, adverse event of special interest; SL BPN/NX, sublingual buprenorphine/naloxone

Source: Extracted from summary of clinical safety, Table 33

Table 27 presents a summary of AESIs, serious AESIs, and AESIs leading to withdrawal in both Phase 3 studies. The results were generally comparable to those in study HS-11-421 alone. With the addition of data from open-label study HS-14-499, the incidence rates of insomnia and depression were higher in the CAM2038 group than in the SL BPN/NX group (3.9% versus 2.8% for insomnia and 2.7% versus 0.9% for depression). The Columbia Suicide Severity Rating Scale (C-SSRS) was administered in Phase 3 Studies, and showed no meaningful differences between the CAM2038 and SL BPN/NX treatment groups.

One SAE of ventricular tachycardia occurred in the CAM2038 group under 'QT prolongation':

A female subject in study HS-14-499 SL BPN/NX at entry experienced ventricular tachycardia on Day 313. Relevant medical history included anxiety and essential hypertension. She reported a consuming caffeinated Red Bull drinks (possibly 3-5) prior to onset of the ventricular tachycardia. The event resulted in hospitalization and implantation of a defibrillator. Study drug was continued and she completed the study. The investigator considered the event not related to study drug.

Two non-serious AEs of loss of consciousness within the QT prolongation SMQ occurred in 2 subjects receiving CAM2038; these included 1 AE of 'alcohol induced blackout' (deemed by investigator to be not related to IMP), and 1 AE of 'blackout' deemed by investigator to be not related to IMP).

Table 27: Summary of AESIs in Phase 3 Studies (Safety Population)

	All AESIs		Serious AESIs		AESIs leading to withdrawal	
Adverse Event of Interest	CAM2038 N=440 n (%)	SL BPN/NX N=215 n (%)	CAM2038 N=440 n (%)	SL BPN/NX N=215 n (%)	CAM2038 N=440 n (%)	SL BPN/NX N=215 n (%)
Total (subjects with any AESI)	114 (25.9)	57 (26.5)	5 (1.1)	4 (1.9)	4 (0.9)	1 (0.5)
Allergic reactions	18 (4.1)	12 (5.6)	0	0	0	0
CNS depression	4 (0.9)	3 (1.4)	0	0	1 (0.2)	0
Drug abuse and dependence	2 (0.5)	5 (2.3)	1 (0.2)	4 (1.9)	0	0
Substance-induced psychotic disorder	1 (0.2)	0	1 (0.2)	0	0	0
Toxicity to various agents	1 (0.2)	0	0	0	0	0
Accidental overdose	0	4 (1.9)	0	3 (1.4)	0	0
Intentional overdose	0	1 (0.5)	0	1 (0.5)	0	0
Substance-induced mood disorder	0	1 (0.5)	0	1 (0.5)	0	0
Drug withdrawal	3 (0.7)	3 (1.4)	1 (0.2)	0	0	1 (0.5)
Gastrointestinal disorders	75 (17.0)	36 (16.7)	2 (0.5)	0	3 (0.7)	0
Hepatic disorders	0	1 (0.5)	0	0	0	0
Acute hepatic failure	0	1 (0.5)	0	0	0	0
Medication errors	0	4 (1.9)	0	3 (1.4)	0	0
Accidental overdose	0	4 (1.9)	0	3 (1.4)	0	0
Myxoedema/hypothyroidism	1 (0.2)	0	0	0	0	0
Psychiatric disorders	37 (8.4)	14 (6.5)	0	0	0	0
Insomnia	17 (3.9)	6 (2.8)	0	0	0	0
Anxiety	13 (3.0)	7 (3.3)	0	0	0	0
Depression	12 (2.7)	2 (0.9)	0	0	0	0
QT prolongation	4 (0.9)	1 (0.5)	1 (0.2)	0	0	0
Loss of consciousness	2 (0.5)[a]	0	0	0	0	0
Electrocardiogram QT prolonged	1 (0.2)[b]	1 (0.5)	0	0	0	0
Ventricular tachycardia	1 (0.2)[c]	0	1 (0.2)	0	0	0
Respiratory depression	0	4 (1.9)	0	0	0	0
Severe injection site reactions	1 (0.2)	0	0	0	0	0
Injection site pain	1 (0.2)	0	0	0	0	0
Urinary retention	1 (0.2)	0	0	0	0	0

[a]Subject IDs 20-01-005 and 50-02-012 (both subjects are from Study HS-14-499)
[b]Subject ID is 90-05-014 (Study HS-14-499)
[c]Subject ID is 90-08-002 (Study HS-14-499)
Abbreviations: AESI, adverse event of special interest; CNS, central nervous system; SL BPN/NX, sublingual buprenorphine/naloxone
Source: Extracted from summary of clinical safety, Table 34

9.8. Long-Term Safety

The long-term safety of CAM2038 was assessed in an open-label Phase 3 study HS-14-499. Mean duration of exposure to IMP was 48.1 (SD: 0.37) weeks (range: 46.9-49.9 weeks).

The most common AEs (≥ 5% of all subjects) were injection site pain (15.4%), injection site swelling (11.9%) injection site erythema (9.3%), nasopharyngitis (7.9%), headache (7.9%), nausea (7.0%), urinary tract infection (5.3%), and vomiting (5.3%) (Table 28). With the exception of urinary tract infection, incidences of these individual TEAEs were higher in subjects who were receiving SL BPN/NX at entry compared to subjects new to BPN treatment.

No unexpected AEs were observed. All injection site AEs associated with CAM2038, except one, were mild to moderate in intensity. One subject had a severe injection site AE (injection site pain); the event occurred on Day 1 and resolved the same day with no change in study drug.

With the exception of injection site AEs, the long-term safety profile observed with CAM2038 was consistent with the known systemic safety profile of BPN and mirrored the results of controlled phase 3 study HS-11-421. The results identified no new safety findings with CAM2038 treatment duration up to 1 year.

Table 28: Treatment Emergent Adverse Events that Occurred in ≥ 5.0% of Subjects (Overall Safety Populations)- Study HS-14-499

System Organ Class/Preferred Term	Currently Receiving SL BPN/NX N=190 n (%)	New to BPN Treatment N=37 n (%)	Total CAM2038 N=227 n (%)
Subjects with at least 1 TEAE	131 (68.9)	12 (32.4)	143 (63.0)
Infections and infestations	67 (35.3)	6 (16.2)	73 (32.2)
Nasopharyngitis	17 (8.9)	1 (2.7)	18 (7.9)
Urinary tract infection	9 (4.7)	3 (8.1)	12 (5.3)
General disorders and administration site conditions	60 (31.6)	2 (5.4)	62 (27.3)
Injection site pain	33 (17.4)	2 (5.4)	35 (15.4)
Injection site swelling	25 (13.2)	2 (5.4)	27 (11.9)
Injection site erythema	20 (10.5)	1 (2.7)	21 (9.3)
Gastrointestinal disorders	42 (22.1)	2 (5.4)	44 (19.4)
Nausea	16 (8.4)	0	16 (7.0)
Vomiting	12 (6.3)	0	12 (5.3)
Nervous system disorders	32 (16.8)	1 (2.7)	33 (14.5)
Headache	18 (9.5)	0	18 (7.9)

9.9. Laboratory Evaluations

Descriptive statistics of laboratory values (clinical hematology, clinical chemistry, and clinical coagulations) from baseline to end of treatment by treatment across all studies in subjects with OUD showed no meaningful differences between CAM2038 and SL BPN(/NX).

The most frequently observed hematological abnormalities included shifts from normal to low in hemoglobin (CAM2038: 7.8% of subjects; SL BPN/NX: 10.5%), shifts from normal to low in erythrocyte mean corpuscular hemoglobin concentration (CAM2038: 6.0%; SL BPN/NX: 7.1%), and shifts from normal to low in erythrocytes (CAM2038: 5.1%; SL BPN/NX: 4.8%). These changes in both treatment groups may have results from frequent study-related blood sampling.

Clinical chemistry changes appeared sporadic, and did not differ meaningfully between treatment groups. In particular, liver function shifts occurred in comparable proportions of patients in the CAM2038 and SL BPN/NX groups:

- Shift from normal to high in alanine aminotransferase (CAM2038: 5.6% of patients; SL BPN/NX: 4.2%)
- Shift from normal to high in albumin (CAM2038: 0.5%; SL BPN/NX: 0.0%)
- Shift from normal to high in alkaline phosphatase (CAM2038: 2.5%; SL BPN/NX: 3.7%)
- Shift from normal to high in aspartate aminotransferase (CAM2038: 6.0%; SL BPN/NX: 4.2%)
- Shift from normal to high in bilirubin (CAM2038: 1.3%; SL BPN/NX: 0.5%)
- Shift from normal to high in gamma glytamyl transferase (CAM2038: 3.1%; SL BPN/NX: 5.1%)

9.10. Vital Signs

There were no clinically relevant changes in vital signs and no consistent differences from baseline after administration of CAM2038.

9.11. Potential Effects on Electrocardiogram and QTc Interval

9.11.1. Electrocardiogram Assessments in Phase 1 and 2 Clinical Studies

CAM2038 was not associated with significant QTc interval prolongation in the clinical studies (HS-11-426, HS-13-487, HS-07-307, HS-13-478, and HS-15-549), which, in agreement with previous studies (Kao, 2015; Stallvik, 2013; Wedam, 2007), demonstrated no clinically meaningful trends in QTc prolongation across plasma concentrations of buprenorphine.

9.11.1.1. QTc Assessments in Studies HS-11-426 and HS-13-487, Healthy Subjects

QTc intervals were evaluated in single and repeated dose studies in healthy subjects (HS-11-426 and HS-13-487). These studies included single doses of 8, 16 and 32 mg CAM2038 q1w, and 64, 96, 128 and 192 mg CAM2038 q4w. Repeated doses included 4 weekly doses of 16 mg CAM2038 q1w. In these studies, CAM2038 was compared with 7 repeated daily doses of 8, 16 and 24 mg SL BPN (Subutex) and a single dose of 0.6 mg IV BPN (Temgesic).

ECGs were measured at baseline and as serial measurements (including at and around T_{max}) during the dosage intervals for CAM2038. The ECGs and plasma samples were also obtained simultaneously.

Absolute QTc interval prolongation for all subjects and treatments were below than 500 ms threshold as well as the 450 ms and 480 ms thresholds for males and females, respectively.

Changes from baseline were also less than 60 ms. No trends were observed between BPN plasma concentrations and absolute QTcF values or QTcF change from baseline (Figure 22) for any treatment, including the reference SL BPN or IV Temgesic. No significant or concentration dependent QTc interval prolongation with CAM2038 q1w or CAM2038 q4w was observed.

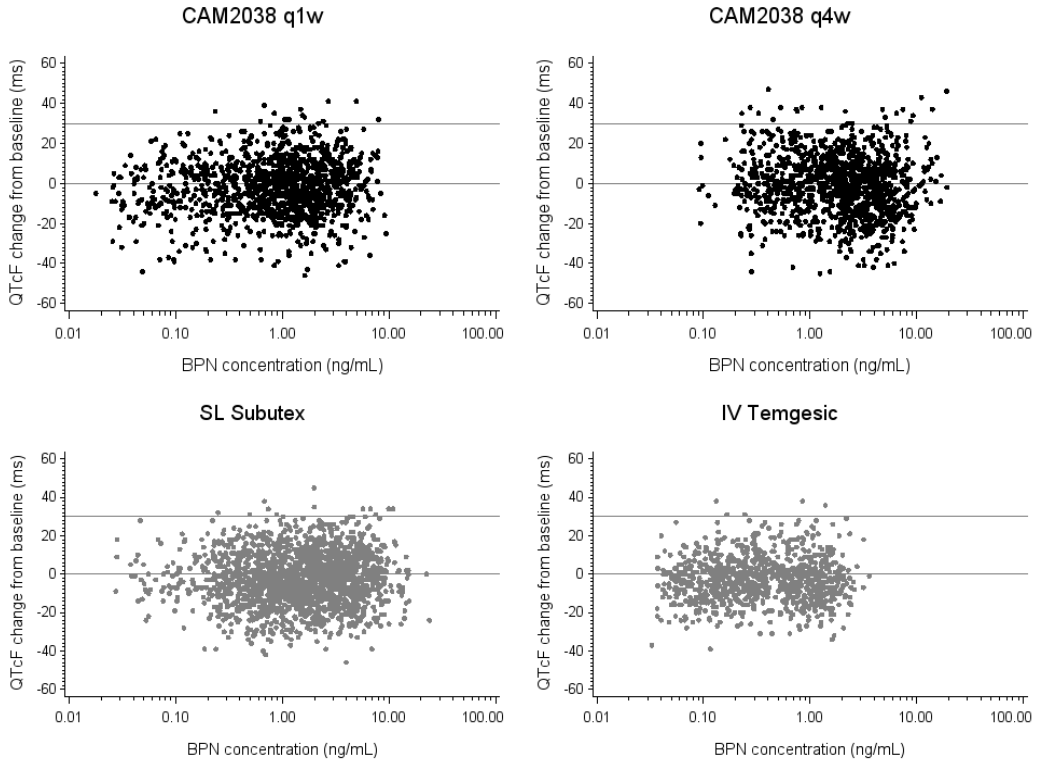


Figure 22: QTcF Change from Baseline *vs* BPN Plasma Concentration after Administration of CAM2038 q1w, CAM2038 q4w, Subutex or Temgesic to Healthy Volunteers

Abbreviations: BPN, buprenorphine; IV, intravenous; SL, sublingual
Source: Extracted from summary of clinical pharmacology, Figure 29

9.11.1.2. QTc Assessment in Study HS-15-549, Patients with Opioid Use Disorder

Patients with opioid dependence and a history of chronic noncancer pain received 7 repeated weekly doses of 32 mg CAM2038 q1w or 4 repeated monthly doses of 128 or 160 mg CAM2038 q4w (HS-15-549). Absolute QTcF interval prolongation was less than 500 ms for all patients. Increases from baseline were less than 60 ms for most patients; a few exceptions occurred at low BPN plasma concentrations (< 5 ng/mL), making a relationship with BPN unlikely.

Figure 23 shows no relationship between QTcF change from baseline and steady-state BPN concentrations after administrations of 32 mg CAM2038 q1w; or 128 or 160 mg CAM2038 q4w.

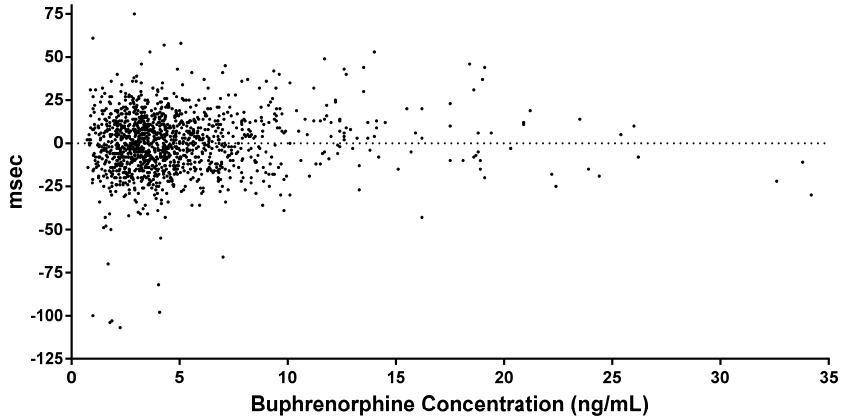


Figure 23: QTcF Change from Baseline *vs.* BPN Plasma Concentration after Repeated Administration of CAM2038 q1w or CAM2038 q4w to Patients with Opioid Use Disorder and Chronic Noncancer Pain in Study HS-15-549

Source: Extracted from summary of clinical pharmacology, Figure 31

9.11.1.3. Additional Supportive Nonclinical Evaluations on Cardiac Ion-Channels

In vitro evaluations of the effect of BPN and the metabolite nor-BPN on human ion channels relevant for cardiovascular function, stably expressed in human embryonic kidney (HEK293) cells or Chinese Hamster Ovary (CHO) cells were completed. The evaluated ion channels were: hERG (Ikr) and hKvLQT1/hmin K potassium, hNav1.5 sodium peak and late, and hCAV 1.2 calcium ion channels (Studies TO-17-589, TO-17-594).

BPN and nor-BPN blocked ion-channels at similar concentrations (IC50) as reported in the literature (Katchman, 2002). For the assessment of cardiovascular risk by subcutaneous administration of CAM2038, the ratio of the IC50 from the in vitro assay to the C_{max} in patients following administration of CAM2038 (clinical study HS-15-549) was determined, since induction of QT prolongation and possible Torsades de Pointe appear to be associated with Cmax plasma concentrations. The margins (ratio) calculated for BPN and nor-BPN were ≥200-fold suggesting a limited risk of QT prolongation in patients treated with CAM2038.

9.11.1.4. Clinical Laboratory Evaluation of ECG and QTc Interval from All Studies in Patients with OUD

In the studies of subjects with OUD, 1.8% subjects had a QTcF value ≥450 to <480 ms at Baseline; none had a value >500 msec. At the end of study, 2.6% of subjects had a QTcF interval of 450 ms or longer (Table 29).

In study HS-11-421, 1 subject taking CAM2038 had a QTcF ≥500 ms at end of study (EOS). The prolonged interval was an isolated occurrence, and no cardiac-related AEs (e.g., bradycardia or AV block) were reported in association with this prolonged QTcF interval. The subject was not taking a concomitant medication with a known risk of QT prolongation. One subject in the

SL BPN/NX group also experienced a a QTcF ≥500 ms during study HS-11-421 (Appendix B-1).

The percentage of subjects who had an increase from Baseline in QTcF value ≥60 ms at EOS was 0.6% (2 subjects in study HS-11-421; 1 subject in study HS-14-499). Comparable results were observed for the SL BPN/NX group in study HS-11-421.

A shift analysis showed that (Appendix B-2) one subject treated with CAM2038 had a shift from normal at Baseline to clinically significantly abnormal at EOS, and 2 subjects had shifts from not clinically significantly abnormal at Baseline to clinically significantly abnormal at end of study.

QTc prolongation is a known class effect of opioids. The QTcF profiles of CAM2038 were consistent with those observed for Subutex and Temgesic in study HS-13-487. Given the comparable BPN exposures achieved with therapeutic doses of SL BPN and at the proposed doses of CAM2038, no difference from SL BPN in ECG safety is expected.

Table 29: Summary of QTcF Intervals (Studies in Subjects with Opioid Use Disorder, Safety Population)

Timepoint/Category	Total CAM2038 n (%)
Baseline	
N	550
<450 ms	540 (98.2)
≥450 to <480 ms	10 (1.8)
≥480 to <500 ms	0
≥500 ms	0
End of Study Visit	
N	545
<450 ms	531 (97.4)
≥450 to <480 ms	12 (2.2)
≥480 to <500 ms	1 (0.2)
≥500 ms	1 (0.2)
Increase from Baseline to EOS Visit	
N	545
<30 ms	507 (93.0)
≥30 to <60 ms	35 (6.4)
≥60 ms	3 (0.6)

Source: Extracted from summary of clinical safety, Table 39

9.11.2. ECG-related AEs

ECG related AEs observed in subjects with OUD across all CAM2038 studies are presented below in Table 30.

Three subjects experienced ventricular tachycardia as an AE, of which one was an SAE reported in Study HS-16-499 while the other two were non-serious AEs reported in Study HS-13-478.

- Subject 90-08-002, a 55-year-old Caucasian female, enrolled in study HS-16-499 experienced severe ventricular tachycardia (SAE) on Day 313 which resulted in hospitalization and implantation of a defibrillator. Her study treatment was CAM2038, 96 mg q4w, and her last dose of study medication was on Day 309, 4 days prior to the onset of the event. Relevant medical history included anxiety and essential hypertension. The subject reported consumption of highly caffeinated beverages (3-5 Red Bull drinks) prior to the onset of the event.

  On day 313, the subject experienced sub-sternal chest pain and became unresponsive. A cardiopulmonary resuscitation was performed, defibrillation initiated and the subject intubated and transported to the hospital by emergency response personnel. Upon arrival in the ED, vital signs were as follows: BP of 163/102 mmHg, HR of 81 bpm, and temperature of 99.2°F. An ECG performed showed an atrial flutter (assessed as not clinically significant) and a 2:1 A-V block, possible right ventricular hypertrophy, inferolateral ST-T changes, HR of 152 bpm, QRS of 128 msec, and QTc of 479 msec. Laboratory testing revealed a blood lactic acid of 3.2 mmol/L (NR 0.7-2.1 mmol/L) and a markedly elevated WBC count of 26.4 × 1000/UL (NR 5.0-10.0 × 1000/UL). The subject was treated with medications including Zosyn (piperacillin and tazobactam), hydralazine, pantoprazole, hydromorphone, vancomycin). An ACID (automatic cardioverter implantable defibrillator) was inserted. The event resolved, and the subject was discharged 5 days later, on Day 318. Both the cardiologist attending to the patient and the principal investigator deemed the event unrelated to study medication and the subject continued with the study medication and completed the study.
- Subject 101-033, a 44-year-old black male enrolled in study HS-13-478 experienced a transient episode of ‘ventricular tachycardia, non-sustained), on Day 2 of the study. The event lasted less than 1 minute and was not associated with loss of consciousness. The event resolved without intervention and did not recur during the study. The subject’s reported QT, QTcF, QRS, and Heart Rate values were normal throughout the study.
- Subject 101-112, an 18-year-old Caucasian male enrolled in study HS-13-478 experienced a transient episode of ‘ventricular tachycardia, non-sustained), on Day 2 of the study. The event lasted less than 1 minute and was not associated with loss of consciousness. The event resolved spontaneously, without intervention and did not recur during the study. The subject’s reported QT, QTcF, QRS and Heart Rate values were all normal throughout the study.

In addition, four subjects discontinued treatment due to an ECG-related AE (three on CAM2038 and one on SL BPN). Of the subjects on CAM2038, the following provides more details:

- In HS-13-478, 1 subject (Subject ID: 101-053) received only one dose of CAM2038 q1w 32mg and was discontinued due to ventricular extra systoles AE, which is considered as not related to study drug.
- In study HS-14-499, the subject (Subject ID: 90-05-014) who experienced electrocardiogram QRS complex abnormal and electrocardiogram QT prolonged was withdrawn from the study at the investigator’s discretion on Day 44.

- In study HS-11-421, subject (Subject ID: 117-010) discontinued the study after a clinically significant ECG abnormality (moderate electrocardiogram abnormal) at Week 17. The subject had a normal ECG at baseline

Table 30: Summary of ECG-related Adverse Events

Study	Subject ID	CAM2038 or SL BPN/NX Dose Group	Event(s)	Relatedness	Study outcome
HS-15-549 (1 subject)	101-014	CAM2038 q4w 128 mg	Paroxysmal atrial fibrillation	Not related	Completed
HS-13-478 (4 subjects)	101-053	CAM2038 q1w 32mg	Ventricular extra systoles	Not related	Discontinued
	101-033 101-112	CAM2038 q1w 32mg	Ventricular tachycardia (2 subjects)	possibly related to study drug	Completed
	103-023	CAM2038 q1w 24mg	Electrocardiogram ST-T segment abnormal	Not related	Completed
HS-11-421 (CAM2038: 2 subjects)	117-008	CAM2038 q1w 32 mg	Atrial fibrillation	Not related	Completed
	117-010	CAM2038 96mg q4w	Electrocardiogram abnormal	Not related	Discontinued
HS-11-421 (SL BPN/ NX: 3 subjects)	117-004	SL BPN/NX 160 mg every 4 weeks	Myocardial infarction	Not related	Completed
	117-015	SL BPN/NX 96 mg every 4 weeks	Electrocardiogram abnormal	Not related	Completed
	125-009	SL BPN/NX 64 mg every 4 weeks	Bradycardia	Not related	Discontinued
HS-14-499 (3 subjects currently receiving SL BPN/NX treatment group)	90-05-014	CAM2038 q1w 32mg	Electrocardiogram QRS complex abnormal and electrocardiogram QT prolonged	Not related	Discontinued the study
	50-01-007	CAM2038 q4w 128 mg	Myocardial ischaemia	Not related	Completed
	90-08-002	CAM2038 q4w 64 mg	Ventricular tachycardia (SAE)	Not related	Completed

Abbreviations: SAE, serious adverse event; SL BPN/NX, sublingual buprenorphine/naloxone
Source: Extracted from summary of clinical efficacy, Section 4.3

9.12. Safety in Special Populations

Overall, intrinsic factors of sex, age, race, and BMI had little impact on the overall AE profile in the Phase 3 studies. Incidence of unsolicited injection site AEs, the most common preferred terms reported in subjects with OUD, appeared consistent across subgroups. Conclusions are limited by the relatively low number of subjects in some demographic subgroups.

9.12.1. Safety in Subjects with Hepatic Impairment

Information related to CAM2038 safety in subjects with hepatic impairment relies on reference to the Subutex label and published literature. The PK of BPN was evaluated after administration of Suboxone (BPN/NX) SL tablet in subjects with hepatic impairment and compared to that of subjects with normal hepatic function (Nasser 2015). In subjects with mild hepatic impairment, the changes in PK parameters were not clinically significant. For subjects with moderate and severe hepatic impairment, mean C_{max}, AUC_{last} and $t_{½}$ values of BPN were increased, and dose adjustments of BPN may be needed.

The current Subutex label reads:

> The effects of hepatic impairment on the PK of buprenorphine were evaluated in a PK study. Buprenorphine is extensively metabolized in the liver and buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment. For subjects with severe hepatic impairment, a dose adjustment is recommended, and subjects with moderate or severe hepatic impairment should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

9.12.2. Safety in Subjects with Renal Impairment

Information related to CAM2038 safety in subjects with renal impairment relies on reference to the Subutex label and published literature. The current Subutex label reads:

- No differences in buprenorphine PKs were observed between 9 dialysis-dependent and 6 normal subjects following IV administration of 0.3 mg buprenorphine.

In accordance with the label of the reference product and the proposed label for CAM2038, modification of the BPN dose is not generally required for subjects with renal impairment (Subutex Label). Caution is recommended when dosing subjects with severe renal impairment (creatinine clearance <30 mL/min), which may require dose adjustment.

9.13. Drug Interactions

For information related to potential drug-drug interactions (DDI), reference is made to the US Subutex Label. Key elements of DDI information are summarized in this section.

Alcohol

Concurrent intake of alcohol and BPN augments the sedative and depressive effects on the respiratory and central nervous system (reviewed in Nolan 2016; Soyka 2015). In accordance

with the label of the reference product and the proposed label for CAM2038, BPN should not be taken together with alcohol (Subutex Label).

Benzodiazepines

Benzodiazepines have not been reported to influence BPN exposure or PK profile, and the drug interaction at therapeutic doses appears to be a PD response to exacerbate the effects on sedation and depression of the respiratory and central nervous system (reviewed in Lintzeris 2010). Benzodiazepine use is very common in subjects with opioid dependence and is thought to contribute to the fatal overdoses with BPN (reviewed in Jones 2012). Although the Subutex label includes a warning for concomitant benzodiazepine use and for other opioid agonists used for MAT, co-prescriptions are common. This concurrent use may contribute to the mortality in this subject population, indicating a need for further education about the risks of respiratory depression with concomitant use of these medications (Abrahamsson 2017). The proposed label of CAM2038 will include a warning against the concomitant use of benzodiazepines.

CYP3A4 Inducers or Inhibitors

BPN is a substrate of CYP3A4; inhibitors of this enzyme (e.g., protease inhibitors like ritonavir, nelfinavir or indinavir, or azole antifungals such as ketoconazole and itraconazole, or macrolide antibiotics) may therefore increase BPN plasma concentrations. Conversely, CYP3A4 inducers (e.g., phenobarbital, carbamazepine, phenytoin or rifampicin) may decrease BPN plasma concentrations. The referenced Subutex describes these drug-drug interactions, and notes that Subutex should be used cautiously together with these medications (Subutex Label).

Cocaine

The literature safety search on drug-drug interactions with BPN identified two articles examining the effect of cocaine use on BPN plasma exposure in subjects with opioid dependence. One study in subjects treated with BPN/NX did not find any effect of cocaine on BPN plasma exposure (Tetrault 2015), while the other study indicated that cocaine use might lower BPN plasma concentrations (McCance Katz 2010).

Codeine

The literature safety search on drug-drug interactions with BPN identified one article examining the effect of codeine on BPN exposure without finding any clinically relevant effect on PK (Gelston 2012).

Drug Interactions with Antiviral Drugs

The majority of the articles identified in the literature safety search examine interactions between BPN and antiviral medications, mainly for treatment of HIV or HCV.

Studies of the 3 direct-acting (3D) antiviral regimen containing ombitasvir, paritaprevir, ritonavir, and dasabuvir, with and without ribavirin did not identify any clinically relevant effects on PK of BPN (King 2017; Menon 2015).

Studies of boceprevir (Hulskotte 2015), faldaprevir (Joseph 2015), daclatasvir (Garimella 2015), elvitegravir/cobicistat (Bruce 2013b), raltegravir (Bruce 2013c), telaprevir (Luo 2012), darunavir-ritonavir (Gruber 2012; Sekar 2011), fosamprenavir-ritonavir (Gruber 2012), atazanavir (Vergara Rodriguez 2011), lopinavir-ritonavir (Bruce 2010), didanosine, lamivudine, and tenofovir (Baker 2010), nevirapine (McCance Katz 2010), efavirenz, delavirdine, nelfinavir

and ritonavir (Moody 2009) did not identify any clinically relevant effects on BPN PK at therapeutic doses.

One study has found that treatment with rifampin, but not rifabutin, might require a higher BPN dose (McCance Katz 2011).

Two studies have found that tipranavir/ritonavir might require higher BPN doses (Bruce 2011; Bruce 2009).

One study has found that BPN treatment might influence the plasma concentrations of lopinavir-ritonavir (Moody 2009). Another study has reported that atazanavir or atazanavir/ritonavir may influence BPN PK and that a decreased BPN dose might be required (McCance Katz 2007).

Monoamine Oxidase Inhibitors

The label for the reference product Subutex (Subutex Label) states that the product should be taken cautiously together with monoamine oxidase inhibitors (MAOI) due to a possible exacerbation of the effects of opioids, based on experience with morphine. In the literature, there is one case report of a case of serotonergic syndrome triggered by BPN/NX for opioid dependence (Isenberg 2008).

Summary of Drug Interactions

In accordance with the label of the reference product and the proposed label for CAM2038, BPN should not be taken together with alcohol and should be used cautiously together with benzodiazepines, other central nervous system depressants, opioid analgesics, naltrexone, monoamine oxidase inhibitors, and CYP3A4 inhibitors and inducers (Subutex Label). Relevant published literature supports these recommendations.

9.14. Clinical Safety Conclusions

Except for mild to moderate injection site reactions, CAM2038 has a safety profile comparable to the well-established profile of BPN.

The safety profile of CAM2038 was consistent in healthy volunteers and in patients with OUD; AEs rarely interfered with the administration of therapy.

The most common adverse events (AEs) across the Phase 3 studies associated with the CAM2038 administration were injection site pain (12.3%), injection site swelling (8.2%), headache (7.7%), injection site erythema (7.5%), nausea (7.0%), urinary tract infection (5.2%), constipation (5.0%), and nasopharyngitis (5.0%).

All AEs in CAM2038 except injection site reactions are known class effects of opioids. All injection site AEs were mild and moderate, with the exception of a single transient severe injection site pain which resolved within a day. Across Phase 3 studies, 10 subjects (2.3%) receiving CAM2038 had an AE leading to withdrawal from treatment. These were mainly injection site AEs and gastrointestinal events. No injection site AEs were serious (SAE).

Adverse event of special interest (AESI), which were based on known effects of opioids including BPN, occurred with incidence rates and severities that compared favorably to the reference drug SL BPN(/NX). Despite slightly higher BPN exposures with the highest

CAM2038 doses as compared to SL BPN at therapeutic doses, the safety profile of CAM2038 did not differ meaningfully from that of the reference drug.

10. ABUSE POTENTIAL

The overall risk of misuse, abuse, and diversion of CAM2038 is expected to be minimized by the intrinsic properties of the CAM2038 long-acting formulation and the method of administration and treatment. The abuse potential relies primarily on the inherent properties of the proprietary FC extended-release formulation and is augmented by the combination of data from the following sources: published literature, information from the reference product, Subutex; and applicable data from nonclinical and clinical investigations of CAM2038. Additionally, a Controlled Distribution System will ensure that only prescribers who are DATA-2000 waived can order CAM2038 for their patients.

10.1. Abuse Liability of Buprenorphine

Abuse liability studies have been conducted with commercially available BPN products and are published in the literature (Walsh et al., 1994; Walsh et al., 1995). Briefly, these studies have shown that BPN did have abuse potential and repeated BPN administration could lead to both physical and psychological dependence, although withdrawal symptoms are generally milder compared with full mu opioid agonists such as oxycodone or morphine (Suboxone, 2016; Subutex, 2016). Buprenorphine causes morphine-like euphoric effects in non-dependent, polydrug users (Walsh et al., 1994) and recently detoxified opioid users (Jasinski et al., 1978; Comer et al., 2005), but it can precipitate withdrawal symptoms in opioid-dependent users (Walsh et al., 1995). Because of its unique pharmacological properties, it is generally accepted that the abuse potential of BPN is less than that of full μ-opioid agonists (for review, see Center for Substance Abuse and Treatment, 2007). Moreover, when BPN is administered concomitantly with naloxone, an opioid antagonist, as in the Suboxone formulation, abuse potential has been shown to be lower than BPN alone (e.g., Subutex) in the opioid-abusing population (Comer et al., 2005; Comer et al.,2008; Comer et al., 2010)

10.2. Inherent Properties of CAM2038

Injection products utilizing the lipid-based FC technology are relatively low viscosity liquids in which the drug substance is dissolved. When injected into the SC or IM tissue, the FC formulation absorbs interstitial aqueous body fluid and transforms from liquid to highly viscous liquid crystal (or gel-like) phases *in situ*. The liquid crystal phase (or gel) formation is a solely physical spontaneous process resulting from lipid self-assembly and takes place 'outside-in', as aqueous body fluids penetrate the formulation. The transformation starts instantaneously after injection. The immediate onset of gel formation after injection results in effective encapsulation of the drug compound in the depot matrix, resulting in a prompt and controlled initial release followed by a slow and consistent release of the drug from the depot matrix. Clinical and nonclinical assessments of different FC based products have demonstrated similar PK for IM and SC injection sites, as well as between different SC injection sites. The Sponsor is currently evaluating, in an exploratory rat study, the consequences of injecting CAM2038 intravenously. The Sponsor believes this risk (IV injection) to be very low, as the Limited Distribution System will significantly minimize the risk of patients having or handling the product.

Although an individual desiring to misuse or abuse the CAM2038 products could extract BPN from CAM2038, this should only occur if the product is diverted prior to injection. Application of heat or pressure does not affect the release of BPN from the injection site, thus limiting this as a possible method of misuse or abuse. Potential points of diversion prior to injection may include theft from the manufacturing plant, the distributor holding and shipping facilities, or from the prescribing DATA 2000 certified physician's office/facility. Unlike other BPN products approved for OUD treatment, CAM2038 will not be stored at retail pharmacies, thus eliminating this avenue of diversion.

10.3. Data from Clinical Studies

The Sponsor did an evaluation of AE terms possibly suggestive of abuse (e.g., suggestive of drug abuse, overuse, physical dependence, and withdrawal) from the integrated Phase 3 dataset, which included approximately 40 discreet AE terms. The AEs across the Phase 3 studies possibly suggestive of abuse was 17.6% in the CAM2038 group and 16.3% in the SL BPN/NX group. These findings from the CAM2038 Phase 3 clinical studies are consistent with finding from randomized studies of Suboxone (Suboxone Label) and Subutex (Subutex Label) that show that the overall rates of adverse events possibly suggestive of abuse potential are low across treatment groups.

Treatment compliance and drug accountability were evaluated in all Phase 3 studies in the CAM2038 development program. Injection sites were examined in all subjects at all study visits, including the end of study visit. All injection site AEs were recorded on the AE case report form and tabulated at the end of the studies. There were no attempts at removal of the injected CAM2038 in Phase 3 clinical studies, or in two healthy volunteer studies or the 3 Phase 2 studies in patients with OUD.

10.4. Risk Management – Administration by HCPs only

The Sponsor is in discussions with FDA regarding a Risk Evaluation and Mitigation Strategy (REMS) program. The goal of the REMS is to mitigate risks of potential abuse, misuse, and accidental pediatric exposure with buprenorphine. The Sponsor will address this risk by ensuring that only HCPs administer CAM2038 directly to appropriate patients. In order to accomplish this goal, the Sponsor will utilize a Limited Distribution System. The Sponsor developed the Limited Distribution Model for CAM2038 to ensure the controlled distribution of CAM2038 to appropriate treatment settings, while also providing sufficient access for patients. The Limited Distribution System was designed to ensure that **only healthcare providers will have access to CAM2038** for administration to patients in a healthcare setting. **Patients will neither handle nor self-administer CAM2038**. The Limited Distribution Model will comply with Schedule III drug distribution requirements defined in the Controlled Substances Act, and to support healthcare providers, distribution partners, and patients in administering, distributing, dispensing, and receiving treatment, respectively, of CAM2038.

Administration of CAM2038 will occur in one of two ways:

- DATA 2000 (Drug Addiction Treatment Act of 2000) waived prescribers can order and take title of CAM2038 from a Sponsor-associated Specialty Distributor for shipment directly to their facility for administration to their patients during a treatment visit.
- DATA 2000 certified prescribers can send a prescription to a Braeburn-associated Specialty Pharmacy for a named patient. The Specialty pharmacy will dispense CAM2038 and ship to the HCPs practice setting or a local healthcare clinic affiliated with a local pharmacy, both for only HCP administration. Similar to retail pharmacies, the Specialty Pharmacy would ensure the prescriber is DATA-2000 certified prior to shipment.

The CAM2038 Limited Distribution System will be restricted to select Specialty Distributors and Specialty Pharmacies. These distribution partners must be capable of (1) properly storing and distributing CAM2038 (in compliance with applicable Schedule III Drug local, state, and federal regulations); (2) providing shipment tracking data to the Sponsor; and (3) providing adequate support to healthcare providers and patients choosing treatment with CAM2038. Included in their support of healthcare providers, distribution partners must ensure that (1) the healthcare provider ordering CAM2038 for their patients is DATA 2000 waived; (2) the provider is compliant with Title, 21, CFR Section 1301.71(a) of the Federal Code of Regulations for storage and disposal of controlled substances; (3) that the provider and patient have access to the Important Safety Information related to CAM2038.

Only healthcare providers with a Drug Addiction Treatment Act of 2000 ("DATA2000") waiver can order CAM2038 for their patients. There are currently 39,211 DATA2000 waived prescribers in three categories: 30 Patient Certified (69%), 100 Patient Certified (22.5%), and 275 Patient Certified (8.5%). Every day, SAMHSA tracks the number of physician waivers held throughout the country and monitors the progress of the program as a whole to evaluate its effectiveness. The standard operating procedure for our distribution partners will include verification of the DATA2000 waiver eligibility of all healthcare providers intending to order CAM2038 for their patients.

Absent an act of diversion in the distribution chain (mitigated by the Limited Distribution System), **patients will not have possession of CAM2038**. Any expired, damaged, or unused patient-specific product must be disposed of in compliance with facility procedures for a Schedule III drug product and per applicable local, state and federal regulations governing the disposal of pharmaceutical biohazardous waste.

11. BENEFIT-RISK PROFILE AND RISK MANAGEMENT

11.1. Introduction

Opioid use disorder (OUD) and opioid-related overdose deaths are escalating global health problems (Hedegaard, 2017; Rudd, 2016). OUD can be effectively managed with approved pharmacotherapies, including SL BPN, a partial μ-opioid receptor agonist on the World Health Organization's essential medications list (Mattick, 2014; Schuckit, 2016). Despite BPN's efficacy, currently approved daily SL and buccal BPN formulations have limitations. These include suboptimal treatment retention, nonadherence, diversion and misuse, and the potential for unintentional pediatric exposures. Further, the burden of daily medication use can contribute to negative perceptions, stigma, and barriers to treatment for patients with OUD.

CAM2038 was designed to optimize the efficacy of BPN, provide more convenient treatment and reduce the risks of misuse and diversion. The development program takes advantage of the extensive clinical experience with BPN in the treatment of OUD, referencing the products Subutex and Suboxone in the 505(b)(2) NDA. CAM2038 is a long-acting BPN injection designed for either once-weekly or once-monthly injection. CAM2038 is indicated for initiation, stabilization, and maintenance treatment of OUD. The product is supplied as a unit pack containing less than 1 mL prefilled glass syringe with a plunger stopper with needle and needle shield. The pre-filled syringe is assembled in a safety device for post-injection needle stick prevention and is labeled only for administration by a medical professional. Each syringe is prefilled with the appropriate volume for injection for both the weekly and monthly formulations and reconstitution is thus not required.

CAM2038 will provide the benefits of the sustained release of BPN to treat OUD while minimizing the risks of misuse, abuse, diversion, and accidental pediatric exposure associated with intraoral formulations of other approved BPN products.

11.2. Demonstration of Clinical Benefit

CAM2038 was non-inferior to SL BPN/NX for the primary endpoint of responder rate based on percentage of urine samples that were negative for illicit opioids. Further, superiority of CAM2038 versus SL BPN/NX on the CDF confirmed opioid-negative urine samples for Treatment Weeks 4 – 24 demonstrating that it is effective for the treatment of OUD. In subjects new to BPN treatment, CAM2038 rapidly reduced withdrawal and opioid craving and increased the proportion of urine samples negative for opioids. Among patients previously treated with SL BPN, transition to CAM2038 maintained the efficacy of the prior BPN treatment. Importantly, CAM2038 achieved efficacy comparable to the reference drug SL BPN with lower overall BPN dose requirements based on the weekly or monthly CAM2038 dosing interval.

11.3. Reduction in Risk of Misuse, Abuse, and Accidental Exposure

Currently available transmucosal BPN products for opioid addiction have a number of associated risks. These risks are enabled in part by dispensing directly to patients. Patients may not adhere to the prescribed treatment regimen, irregular use, using doses higher than prescribed or

unplanned drug holidays can lead to relapse or overdose. BPN products are also susceptible to being diverted, either for illicit resale, or misused by others. In addition, accidental pediatric ingestion continues to be a concern when the drugs are stored in patients' homes. These serious risks have prompted FDA to require a Risk Evaluation and Mitigation Strategy (REMS) for the presently approved BPN products (Subutex and Suboxone REMS, 2016).

As discussed in Section 10.2, the inherent characteristics of CAM2038 and the proposed Limited Distribution Plan is expected to minimize the risks of abuse, misuse, diversion and accidental exposure. Since CAM2038 can only be ordered by DATA 2000-waived physicians directly from Specialty Distributors or Specialty Pharmacies, and will only be shipped to HCPs for administration to a patient, the risks of abuse, misuse, diversion and accidental pediatric exposure are expected to be minimized. Absent an act of diversion, patients will not have access to CAM2038 and will only receive their injection by an HCP.

11.4. Safety

Except for mild to moderate injection site reactions, CAM2038 has a safety profile comparable to the well-established BPN safety profile.

The most frequent AEs involved injection site reactions. These events were mild and moderate with a single exception. Other than these events that were specific to the SC administration route for CAM2038, no meaningful differences from the safety profile of SL BPN were identified. Importantly, ECG data from the CAM2038 clinical development program showed no apparent excess of QTc prolongation as compared to SL BPN. Indeed, only 1 subject in each treatment group had QTc >500 msec at any time during the pivotal study HS-11-421. These findings are reassuring, given the slightly higher BPN exposure achieved with the highest CAM2038 doses as compared with 24 mg SL BPN.

Taking into consideration the entire development program, findings for CAM2038 support reference to the safety labeling for Subutex, with the addition of appropriate information regarding injection site events.

11.5. Benefits and Risks Conclusions

The clinical and published data presented in this application provide strong evidence that CAM2038 provides clinical benefit in the treatment of OUD that is comparable to, or better than, that provided by SL BPN. The safety profile is manageable, as has been demonstrated for other BPN products and other injectable agents. The risk of injection reactions, which represents the only identified risk not shared by SL BPN, is far outweighed by the benefits provided by reduced abuse potential, convenient dosing regimen, and a depot formulation that ensures consistent exposure to BPN.

Consistent with US Clinical Practice Guidelines, CAM2038 will allow treating physicians the ability to individualize treatment based on patients' evolving needs, from treatment initiation through maintenance. As a flexible weekly or monthly injectable dose regimen, CAM2038 provides the sustained efficacy of BPN, while ensuring compliance and minimizing the risks of diversion, misuse, and pediatric accidental exposure.

12. REFERENCES

1. Abrahamsson T, Berge J, Öjehagen A, Håkansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment - a nation-wide register-based open cohort study. Drug Alcohol Depend. 2017;174:58-64.
2. Alhaddad H, Cisternino S, Salvatore, Decleves X et al. Respiratory toxicity of buprenorphine results from the blockage of P-glycoprotein – mediated efflux of norbuprenorphine at the blood-brain barrier in mice. 2012; 40:3215-3223
3. Alho H, Sinclair D, Vuori E, Holopainen A. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. *Drug Alcohol Depend*. 2007;88(1):75-78. Medline:17055191
4. AmBisome liposome for injection. Gilead Sciences, Inc. Revised March 2012
5. Anderson J.M, Rodriguez A, Chang D.T. Foreign body reaction to biomaterials. Sem Immunol. 2008; 20:86-100.
6. Böger RH. Renal impairment: a challenge for opioid treatment? The role of buprenorphine. Palliative Medicine. 2006;20:s17-s23.
7. Centers for Disease Control and Prevention (CDC). Buprenorphine prescribing practices and exposures reported to a poison center: Utah, 2002-2011. *MMWR Morb Mortal Wkly Rep*. 2012;61(49):997-1001. 23235296
8. Comer SD, Collins ED. Self-administration of intravenous buprenorphine and the buprenorphine/naloxone combination by recently detoxified heroin abusers. *J Pharmacol Exp Ther*. 2002;303(2):695-703. Medline:12388653
9. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anesthes 2006;96(5): 627-32.
10. Dijkstra BA, Krabbe PF, Riezebos TG, van der Staak CP, De Jong CA. Psychometric evaluation of the Dutch version of the Subjective Opiate Withdrawal Scale (SOWS). Eur Addict Res. 2007;13:81-88.
11. FDA Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, 2014
12. Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. N Engl J Med 2006;355:365-74.
13. Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug Alcohol Depend. 2014;144:1–11.
14. Hedegaard, H., Warner, M., and Miniño, A. M. Drug overdose deaths in the United States, 1999-2015. 2017.
15. Heel RC, Brogden RN, Speight TM, Avery GS. Buprenorphine: A review of its pharmacological properties and therapeutic efficacy. Drugs. 1979;17:81-110.
16. Hser YI, Huang D, Saxon AJ, et al. Distinctive trajectories of opioid use over an extended follow-up of patients in a multisite trial on buprenorphine + naloxone and methadone. J Addict Med 2017;11:63-9.

17. International Narcotics Control Board. Narcotic Drugs: Report 2016 Estimated World Requirements for 2017 - Statistics for 2015. United Nations Publication Sales No. T.17.XI.2. ISBN 978-92-1-060062-0. ISSN 1013-3453.
18. Intralipid 20% Fat Emulsion Label. Instructions for use, Johanna Erlksson, 018644046.
19. Isenberg D, Wong SC, Curtis JA. Serotonin syndrome triggered by a single dose of suboxone. Am J Emerg Med. 2008;26(7):840.e3-5.
20. Jones JD, Mogali S, Comer SD. Polydrug abuse: A review of opioid and benzodiazepine combination use Drug Alcohol Depend . 2012;125(1-2):8–18.
21. Kahan M, Srivastava A, Ordean A, Cirone S. Buprenorphine: new treatment of opioid addiction in primary care. Can Fam Physician. 2011; 57(3):281-9.
22. Kao, David P, Haigney, Mark C.P, Mehler, Philip S et al. Arrhythmia associated with buprenorphine and methadone reported to the food and drug administration. Addiction. 2015; 110: 1468-1475.
23. Katchman AN, et al. Influence of opioid agonists on cardiac human ether-a-go-go-related gene K(+) currents. J Pharmacol Exp Ther. 2002; 303(2):688-94.
24. Lintzeris N, Nielsen S. Benzodiazepines, methadone and buprenorphine: interactions and clinical management.Am J Addict. 2010;19(1):59-72.
25. Lee J, Frank V, David A. Unobserved home induction onto buprenorphine. *J Addict Med*. 2014;8(5)
26. Lofwall MR, Walsh SL. A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world. *J Addict Med*. 2014;8(5):315-326. Medline:25221984
27. Lovegrove MC, Mathew J, Hampp C, Governale L, Wysowski DK, Budnitz DS. Emergency hospitalizations for unsupervised prescription medication ingestions by young children. *Pediatrics*. 2014;134(4):e1009-e1016. Medline:25225137
28. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2014;CD002207.
29. Mattson ME and Lynch S. Medication prescribing and behavioral treatment for substance use disorders in physician office settings. The Center for Bahavioral Health Statistics and Quality Report. 2015,1.
30. Middleton LS, Nuzzo PA, Lofwall MR, Moody DE, Walsh SL. The pharmacodynamic and pharmacokinetic profile of intranasal crushed buprenorphine and buprenorphine/naloxone tablets in opioid abusers. Addiction. 2011;106(8):1460-1473. Medline:21395892
31. Nasser AF, Heidbreder C, Liu Y, Fudala PJ. Pharmacokinetics of Sublingual Buprenorphine and Naloxone in Subjects with Mild to Severe Hepatic Impairment (Child-Pugh Classes A, B, and C), in Hepatitis C Virus-Seropositive Subjects, and in Healthy Volunteers. Clin Pharmacokinet. 2015 Aug;54(8):837-49.
32. Nolan S, Klimas J, Wood E. Alcohol use in opioid agonist treatment. Addict Sci Clin Pract. 2016;11(1):17.
33. Rudd RA, Seth P, David F, Scholl L. Increases in drug and opioid-involved overdose deaths - United States, 2010-2015. MMWR Morb Mortal Wkly Rep 2016;65:1445-52.

34. Schwartz RP, McKenzie M, Rich JD. Opioid addiction and incarceration: an overview. Med Health R I 2007;90:157-8.

35. Scientific Committee on Consumer Safety (SCCS). 2011. Opinion on N-methyl-2-pyrrolidone. Report SCCS/1413/11.

36. Schuckit MA. Treatment of opioid-use disorders. N Engl J Med 2016;375:357-68.

37. Stallvik M, Nordstrand B, Kristensen O et al. Corrected QT interval during treatment with methadone and buprenorphine: Relation to doses and serum concentrations. Drug and alcohol dependence. 2013; 129: 88-93

38. Strathdee SA, Beyrer C. Threading the needle - how to stop the HIV outbreak in rural Indiana. N Engl J Med 2015;373:397-9.

39. Suryaprasad AG, White JZ, Xu F, et al. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006-2012. Clin Infect Dis 2014;59:1411-9.

40. Soyka M. Alcohol use disorders in opioid maintenance therapy: prevalence, clinical correlates and treatment. Eur Addict Res. 2015;21(2):78-87.

41. Tiberg F, Johnsson M, Nistor C, Joabsson F. Self- assembling liquid formulations. In: Wright JC, Burgess DJ, eds. *Long-Acting Injections and Implants*. New York, NY: Springer; 2012:315-334.

42. Tompkins DA, Bigelow GE, Harrison JA, Johnson RE, Fudala PJ, Strain EC. Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument. Drug Alcohol Depend. 2009;105:154-159.

43. US Subutex Label, Product Information SUBUTEX (buprenorphine) sublingual tablet for sublingual administration December 2016, Indivior Inc

44. US Suboxone Film Label, Product Information SUBOXONE (buprenorphine and naloxone) sublingual film, February 2017, Indivior Inc.

45. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies - tackling the opioid-overdose epidemic. N Engl J Med 2014;370:2063-6

46. Walley A, Alperen K, Cheng M. etal. Office based management of opioid dependence with buprenorphine: clinical practices and barriers. J Gen Intern Med 2008; 23(9):1393–8

47. Walsh SL, Preston KL, Bigelow GE, Stitzer ML. Acute administration of buprenorphine in humans: partial agonist and blockade effects. *J Pharmacol Exp Ther*. 1995;274(1):361-372. Medline:7542336

48. Walsh SL, Preston KL, Stitzer ML. et al. Clinical Pharmacology of Buprenorphine: Ceiling Effects at High Doses. 1994; 569-580

49. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med. 2007; 167(22):2469-75.

50. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Arch Gen Psychiatry 2011;68:1238-46

51. World Health Organization (WHO). 2001. N-Methyl-2-Pyrrolidone. Concise International Chemical Assessment (CICAD) Document 35. Geneva, Switzerland.

52. Winstock AR, Lea T, Sheridan J. Prevalence of diversion and injection of methadone and buprenorphine among clients receiving opioid treatment at community pharmacies in New South Wales, Australia. *Int J Drug Policy*. 2008;19(6):450-458. Medline:18359216

53. Baker J, Rainey PM, Moody DE, Morse GD, Ma Q, McCance-Katz EF. Interactions between buprenorphine and antiretrovirals: nucleos(t)ide reverse transcriptase inhibitors (NRTI) didanosine, lamivudine, and tenofovir. Am J Addict. 2010;19(1):17-29.

54. Bruce RD, Winkle P, Custodio JM, Wei LX, Rhee MS, Kearney BP, et al. The pharmacokinetic and pharmacodynamic interactions between buprenorphine/naloxone and elvitegravir/cobicistat in subjects receiving chronic buprenorphine/naloxone treatment. J Acquir Immune Defic Syndr. 2013b;63(4):480-4.

55. Bruce RD, Moody DE, Chodkowski D, Andrews L, Fang WB, Morrison J, Parsons TL, Friedland GH. Pharmacokinetic interactions between buprenorphine/naloxone and raltegravir in subjects receiving chronic buprenorphine/naloxone treatment. Am J Drug Alcohol Abuse. 2013c;39(2):80-5.

56. Bruce RD, Altice FL, Moody DE, Lin SN, Fang WB, Sabo JP, et al. Pharmacokinetic interactions between buprenorphine/naloxone and tipranavir/ritonavir in HIV-negative subjects chronically receiving buprenorphine/naloxone. Drug Alcohol Depend. 2009;105(3):234-9.

57. Bruce RD, Moody DE, Fang WB, Chodkowski D, Andrews L, Friedland GH. Tipranavir/ritonavir induction of buprenorphine glucuronide metabolism in HIV-negative subjects chronically receiving buprenorphine/naloxone. Am J Drug Alcohol Abuse. 2011;37(4):224-8.

58. Bruce RD, Altice FL, Moody DE, Morse GD, Andrews L, Lin SN, et al. Pharmacokinetic interactions between buprenorphine/naloxone and once-daily lopinavir/ritonavir. J Acquir Immune Defic Syndr. 2010;54(5):511-4.

59. Comer SD, Sullivan MA, Vosburg SK, Manubay J, Amass L, Cooper ZD, Saccone P, Kleber HD. Abuse liability of intravenous buprenorphine/naloxone and buprenorphine alone in buprenorphine-maintained intravenous heroin abusers. Addiction 2010; 105(4): 709-18.

60. Comer SD, Sullivan MA, Walker EA. Comparison of intravenous buprenorphine and methadone self-administration by recently detoxified heroin-dependent individuals. J Pharmacol Exp Ther 2005; 315(3): 1320-30.

61. Comer SD, Sullivan MA, Whittington RA, Vosburg SK, Kowalczyk WJ. Abuse liability of prescription opioids compared to heroin in morphine-maintained heroin abusers. Neuropsychopharmacology 2008; 33(5): 1179-91.

62. Center for Substance Abuse Research. One-Third of U.S. Treatment Applicants Report Buprenorphine/Naloxone Sold on Street; One-Fifth Report the Drug Is Used to Get High.

63. Tetrault JM, McCance-Katz EF, Moody DE, Fiellin DA, Lruie BS, DInh A, et al. The impact of recent cocaine use on plasma levels of methadone and buprenorphine in patients with and without HIV-infection. J Subst Abuse Treat. 2015;51:70-4.

64. McCance-Katz EF,Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. Am J Addict. 2010;19(1):4-16.

65. McCance-Katz EF. Drug interactions associated with methadone, buprenorphine, cocaine, and HIV medications: implications for pregnant women. Life Sci. 2011;88(21-22):953-8.

66. Moody DE, Chang Y, Huang W, McCance-Katz EF. The in vivo response of novel buprenorphine metabolites, M1 and M3, to antiretroviral inducers and inhibitors of buprenorphine metabolism. Basic Clin Pharmacol Toxicol. 2009;105(3):211-5.

67. McCance-Katz EF, Moody DE, Morse GD, Ma Q, DiFrancesco R, Friedland G, et al. Interaction between buprenorphine and atazanavir or atazanavir/ritonavir. Drug Alcohol Depend. 2007;91(2-3):269-78.

68. Gelston EA, Coller JK, Lopatko OV, James HM, Schmidt H, White JM, et al. Methadone inhibits CYP2D6 and UGT2B7/2B4 in vivo: a study using codeine in methadone- and buprenorphine-maintained subjects. Br J Clin Pharmacol. 2012;73(5):786-94.

69. King JR, Menon RM. Pharmacokinetic evaluation of once-weekly and once-monthly ombitasvir/paritaprevir/ritonavir and dasabuvir: drug interactions with antiretroviral agents and drugs for substance abuse. Clin Pharmacol Drug Dev. 2017;6(2):201-5.

70. Menon RM, Badri PS, Wang T, Polepally AR, Zha J, Khatri A, et al. Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir. J Hepatol. 2015;63(1):20-9.

71. Hulskotte EG, Bruce RD, Feng HP, Webster LR, Xuan F, Lin WH, et al. Pharmacokinetic interaction between HCV protease inhibitor boceprevir and methadone or buprenorphine in subjects on stable maintenance therapy. Eur J Clin Pharmacol. 2015;71(3):303-11.

72. Joseph D, Schobelock MJ, Riesenberg RR, Vince BD, Webster LR, Adeniji A, et al. Effect of steady-state faldaprevir on the pharmacokinetics of steady-state methadone and buprenorphine-naloxone in subjects receiving stable addiction management therapy. Antimicrob Agents Chemother. 2015;59(1):498-504.

73. Garimella T, Wang R, Luo WL, Wastall P, Kandoussi H, DeMicco M, et al. Assessment of drug-drug interactions between daclatasvir and methadone or buprenorphine-naloxone. Antimicrob Agents Chemother. 2015;59(9):5503-10.

74. Luo X, Trevejo J, van Heeswijk RP, Smith F, Garg V. Effect of telaprevir on the pharmacokinetics of buprenorphine in volunteers on stable buprenorphine/naloxone maintenance therapy. Antimicrob Agents Chemother. 2012;56(7):3641-7.

75. Gruber VA, Rainey PM, Moody DE, Morse GD, Ma Q, Prathikanti S, et al. Interactions between buprenorphine and the protease inhibitors darunavir-ritonavir and fosamprenavir-ritonavir. Clin Infect Dis. 2012;54(3):414-23.

76. Sekar V, Tomaka F, Lefebvre E, De Pauw M, Vangeneugden T, van den Brink W, et al. Pharmacokinetic interactions between darunavir/ritonavir and opioid maintenance therapy using methadone or buprenorphine/naloxone. J Clin Pharmacol. 2011;51(2):271-8.

77. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. Arch Gen Psychiatry 1978; 35(4): 501-16.

78. Vol. 21 (25) College Park, MD: Center for Substance Abuse Research; 2012. CESAR Fax Issues on Buprenorphine.

79. Suboxone Sublingual Tablets [package insert]. Richmond, VA: Reckitt Benckiser Pharmaceuticals Inc.; 2016.

80. Treatment improvement protocol (TIP) Series 40. Center for Substance Abuse Treatment. Clinical Guidelines for the use of buprenorphine in the treatment of opioid addiction. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance abuse and mental health services administration, 2004

81. Mégarbane B, Marie N, Pirnay S, Borron SW, Gueye PN, Risède P, Monier C, Noble F, Baud FJ. Buprenorphine is protective against the depressive effects of norbuprenorphine on ventilation. Toxicol Appl Pharmacol. 2006;212:256-67.

82. Rosenthal RN, Ling W, Casadonte P, et al. Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. Addiction 2013;108:2141-9.

83. Vergara-Rodriguez P, Tozzi MJ, Botsko M, Nandi V, Altice F, Egan JE, et al; BHIVES Collaborative. Hepatic safety and lack of antiretroviral interactions with buprenorphine/naloxone in HIV-infected opioid-dependent patients. J Acquir Immune Defic Syndr. 2011;56 Suppl 1:S62-7.

84. FDA approved REMS for Suboxone (buprenorphine and naloxone) and Subutex (buprenorphine) (modified July 2016), available at www.accessdata.fda.gov/drugsatfda_docs/rems/Suboxone_Subutex_2016_07-07_Full.pdf

APPENDIX A. PHARMACOKINETIC PARAMETERS

Appendix A- 1: Summary of PK parameters of BPN based on NCA after SC buttock injections of CAM2038 q1w and CAM2038 q4w and SL administration of Subutex and Suboxone film (studies HS-11-426, HS-13-487, HS-07-307, HS-15-549 and HS-13-478)

Product	Dose (mg) (Study)	Dose No.	Population	C_{max} (ng/mL)	T_{max}[a] (h)	C_{trough}[b] (ng/mL)	AUC_{τ} (ng*h/mL)	AUC_{inf} (ng*h/mL)	C_{av} (ng/mL)	$t_{½}$ (h)	% Fluctuation	R_{ac} (AUC_{τ})
CAM2038 q1w	7.5 (HS-07-307)	1	Patient (n=6)	1.58 (38)	18.0	NC	NC	161 (17)	NA	70.2	NA	NA
	8 (HS-11-426)	1	HV (n=18)	1.71 (36)	23.0	0.304 (26)	131 (24)	166 (20)	NA	70.7 (28)	NA	NA
	15 (HS-07-307)	1	Patient (n=6)	2.75 (18)	24.0	NC	NC	349 (14)	NA	107	NA	NA
	16 (HS-11-426)	1	HV (n=15)	3.08 (49)	23.1	0.611 (25)	241 (28)	335 (13)	NA	96.4 (44)	NA	NA
	16 (HS-13-487)	1	HV (n=15)	3.05 (46)	23.6	0.580 (25)	243 (30)	NC	NA	NC	NA	NA
	16 (HS-13-487)	4[c]	HV (n=15))	4.30 (44)	23.2	0.842 (22)	350 (24)	NA	2.09 (24)	126 (44)	160 (36)	1.44 (25)
	22.5 (HS-07-307)	1	Patient (n=8)	3.67 (34)	24.0	NC	NC	420 (18)	NA	80.5	NA	NA
	24 (HS-13-478)	1	Patient (n=22)	3.64 (39)	24.0	0.822 (25)	304 (30)	NA	NA	NC	NA	NA
	30 (HS-07-307)	1	Patient (n=6)	4.92 (28)	24.0	NC	NC	529 (15)	NA	87.8	NA	NA
	32 (HS-11-426)	1	HV (n=16)	5.27 (45)	22.9	1.13 (24)	431 (25)	638 (12)	NA	112 (45)	NA	NA
	32 (HS-13-478)	1	Patient (n=24)	4.39 (43)	24.0	0.993 (32)	376 (31)	NA	NA	NC	NA	NA
	32 (HS-15-549)	4-7[c]	Patient (n=21)	6.87 (37)	24.0	2.63 (39)	700 (27)	NA	4.17 (27)	NC	95.3 (39)	NA
CAM2038 q4w	64 (HS-13-487)	1	HV (n=17)	3.81 (60)	10.0	0.449 (57)	955 (33)	1360 (33)	NA	447 (52)	NA	NA
	96 (HS-13-487)	1	HV (n=14)	5.47 (56)	10.0	0.538 (28)	1170 (29)	1830 (26)	NA	555 (34)	NA	NA
	128 (HS-13-487)	1	HV (n=16)	6.59 (68)	6.1	0.934 (33)	1580 (44)	2550 (26)	NA	502 (52)	NA	NA
	128 (HS-15-549)	4[c]	Patient (n=16)	11.1 (54)	10.0	2.09 (55)	2610 (42)	NA	3.89 (42)	NC	220 (44)	NC
	160 (HS-15-	4[c]	Patient	15.4 (52)	24.0	2.66 (61)	3540 (26)	NA	5.27 (26)	NC	237 (80)	NC

Product	Dose (mg) (Study)	Dose No.	Population	C_{max} (ng/mL)	T_{max}[a] (h)	C_{trough}[b] (ng/mL)	AUC_{τ} (ng*h/mL)	AUC_{inf} (ng*h/mL)	C_{av} (ng/mL)	$t_{½}$ (h)	% Fluctuation	R_{ac} (AUC_{τ})
	549)		(n=12)									
	192 (HS-13-487)	1	HV (n=13)	7.54 (58)	4.0	1.26 (36)	1790 (34)	3260 (31)	NA	611 (28)	NA	NA
Subutex	8 (HS-11-426)	1	HV (n=18)	4.32 (32)	1.49	0.249 (38)	17.5 (29)	NC	NA	NC	NA	NA
		7[c]	HV (n=18)	4.74 (29)	1.25	0.606 (46)	27.2 (34)	NA	1.13 (34)	35.8 (35)	373 (16)	NC
	8 (HS-13-487)	1	HV (n=17)	4.35 (41)	1.03	0.259 (35)	18.5 (30)	NC	NA	NC	NA	NA
		7[c]	HV (n=17)	4.74 (36)	1.48	0.677 (52)	29.8 (33)	NA	1.24 (33)	42.5 (34)	338 (30)	1.61 (23)
	16 (HS-11-426)	1	HV (n=15)	6.71 (62)	1.03	0.381 (36)	25.4 (45)	NC	NA	NC	NA	NA
		7[c]	HV (n=15)	6.25 (49)	1.48	0.794 (58)	38.5 (37)	NA	1.60 (37)	38.7 (28)	347 (33)	NC
	16 (HS-13-487)	1	HV (n=15)	5.88 (31)	1.00	0.374 (44)	26.5 (34)	NC	NA	NC	NA	NA
		7[c]	HV (n=15)	6.72 (47)	1.02	1.05 (46)	45.7 (33)	NA	1.90 (33)	42.8 (16)	308 (35)	1.73 (28)
	24 (HS-11-426)	1	HV (n=16)	7.08 (19)	1.03	0.490 (39)	33.1 (25)	NC	NA	NC	NA	NA
		7[c]	HV (n=16)	7.78 (37)	1.01	1.24 (44)	56.3 (29)	NA	2.34 (29)	39.0 (23)	282 (34)	NC
	24 (HS-13-487)	1	HV (n=16)	8.23 (60)	0.83	0.544 (44)	34.8 (34)	NC	NA	NC	NA	NA
		7[c]	HV (n=16)	8.45 (54)	1.04	1.61 (40)	63.9 (34)	NA	2.66 (34)	38.3 (33)	272 (27)	1.84 (28)
Suboxone	8 (HS-15-549)[d]	19[c]	Patient (n=16)	11.1 (61)	1.69	NC	NC	NC	NC	NC	NC	NC

Values are geometric mean (geometric CV%); [a] Median; [b] C_{168h} for CAM2038 q1w, C_{28d} for CAM2038 q4w and C_{24h} for Subutex; [c] Steady-state PK parameters; [d] three times/day
AUC_{inf}: AUC extrapolated to infinity; AUC_{τ}: AUC over the dosing interval; BPN: buprenorphine; C_{av}: average concentration during the dosing interval; C_{max}: maximum observed plasma concentration; C_{trough}: observed concentration before the next actual or intended dose; CV%: coefficient of variation percentage; %Fluctuation: percentage fluctuation of concentration from average concentration; HV: healthy volunteer; NA; not applicable; NC: not calculated; NCA: non-compartmental analysis; R_{ac}: accumulation ratio; SC: subcutaneous; SL: sublingual; $t_{½}$: half-life; T_{max}: time corresponding to occurrence of C_{max}
Source: Extracted from summary of clinical pharmacology, Table 19

Appendix A- 2: Summary of PK parameters of norBPN based on NCA after SC buttock injections of CAM2038 q1w and CAM2038 q4w and SL administration of Subutex and Suboxone film (studies HS-11-426, HS-13-487, HS-15-549 and HS-13-478)

Product	Dose (mg) (Study)	Dose No.	Population	C_{max} (ng/mL)	T_{max}[a] (h)	C_{trough}[b] (ng/mL)	AUC_{τ} (ng*h/mL)	AUC_{inf} (ng*h/mL)	C_{av} (ng/mL)	$t_{½}$ (h)	R_{ac} (AUC_{τ})	Metab ratio C_{max}	Metab ratio AUC_{τ}
CAM2038 q1w	8 (HS-11-426)	1	HV (n=18)	0.359 (51)	84.6	0.147 (54)	39.2 (52)	67.5 (41)	NA	83.6 (34)	NA	NC	NC
	16 (HS-11-426)	1	HV (n=15)	0.649 (51)	71.6	0.309 (45)	71.3 (46)	113 (38)	NA	85.2 (41)	NA	NC	NC
	16 (HS-13-487)	1	HV (n=15)	0.763 (44)	70.7	0.286 (43)	75.9 (57)	NC	NA	NC	NA	NC	NC
	16 (HS-13-487)	4[c]	HV (n=15)	0.921 (55)	72.6	0.416 (41)	108 (49)	NA	0.643 (49)	132 (64)	1.52 (46)	0.242 (41)	0.348 (34)
	24 (HS-13-478)	1	Patient (n=22)	0.770 (51)	72.0	0.454 (45)	88.6 (50)	NC	NA	NC	NC	NC	NC
	32 (HS-11-426)	1	HV (n=16)	0.938 (58)	71.3	0.418 (96)	96.3 (56)	165 (57)	NA	97.1 (33)	NA	NC	NC
	32 (HS-13-478)	1	Patient (n=24)	0.865 (52)	72.0	0.547 (43)	102 (50)	NC	NA	NC	NC	NC	NC
	32 (HS-15-549)	4-7[c]	Patient (n=21)	1.85 (75)	72.0	1.08 (85)	204 (64)	NA	1.22 (64)	NC	NC	0.305 (59)	0.354 (57)
CAM2038 q4w	64 (HS-13-487)	1	HV (n=17)	0.792 (41)	74.6	0.136 (65)	256 (35)	359 (32)	NA	346 (56)	NA	0.235 (58)	NC
	96 (HS-13-487)	1	HV (n=14)	1.10 (71)	95.9	0.146 (83)	305 (68)	443 (64)	NA	394 (54)	NA	0.227 (46)	NC
	128 (HS-13-487)	1	HV (n=16)	1.36 (84)	108	0.266 (78)	439 (69)	653 (53)	NA	386 (47)	NA	0.233 (50)	NC
	128 (HS-15-549)	4[c]	Patient (n=16)	2.14 (123)	84.1	0.835 (201)	795 (131)	NA	1.18 (131)	NC	NC	0.219 (79)	0.344 (79)
	160 (HS-15-549)	4[c]	Patient (n=12)	4.61 (55)	121	1.78 (159)	1590 (55)	NA	2.37 (55)	NC	NC	0.339 (73)	0.532 (50)
	192 (HS-13-487)	1	HV (n=13)	1.62 (58)	73.7	0.390 (54)	555 (55)	895 (47)	NA	432 (34)	NA	0.243 (54)	NC
Subutex	8 (HS-11-426)	1	HV (n=18)	1.61 (37)	1.50	0.578 (34)	15.3 (34)	NC	NA	NC	NA	NC	NC
		7[c]	HV (n=18)	3.35 (36)	1.49	1.81 (47)	47.0 (42)	NA	1.96 (42)	34.8 (23)	NC	NC	NC
	8 (HS-13-487)	1	HV (n=17)	1.46 (59)	1.50	0.515 (46)	14.3 (42)	NC	NA	NC	NA	NC	NC

Product	Dose (mg) (Study)	Dose No.	Population	C_{max} (ng/mL)	T_{max}[a] (h)	C_{trough}[b] (ng/mL)	AUC_{τ} (ng*h/mL)	AUC_{inf} (ng*h/mL)	C_{av} (ng/mL)	$t_{½}$ (h)	R_{ac} (AUC_{τ})	Metab ratio C_{max}	Metab ratio AUC_{τ}
		7[c]	HV (n=17)	3.03 (34)	1.50	1.52 (47)	42.6 (35)	NA	1.77 (35)	35.7 (38)	2.97 (27)	0.721 (39)	1.62 (39)
	16 (HS-11-426)	1	HV (n=15)	3.90 (41)	0.72	1.10 (45)	31.1 (38)	NC	NA	NC	NA	NC	NC
		7[c]	HV (n=15)	5.41 (80)	1.45	2.90 (80)	74.3 (77)	NA	3.10 (77)	35.4 (35)	NC	NC	NC
	16 (HS-13-487)	1	HV (n=15)	3.96 (49)	1.00	1.10 (63)	34.1 (38)	NC	NA	NC	NA	NC	NC
		7[c]	HV (n=15)	7.04 (66)	0.70	3.81 (54)	105 (51)	NA	4.36 (51)	33.5 (21)	3.07 (38)	1.19 (34)	2.59 (35)
	24 (HS-11-426)	1	HV (n=16)	4.26 (40)	1.24	1.46 (32)	39.9 (30)	NC	NA	NC	NA	NC	NC
		7[c]	HV (n=16)	8.02 (43)	1.08	3.82 (53)	106 (49)	NA	4.43 (49)	35.1 (31)	NC	NC	NC
	24 (HS-13-487)	1	HV (n=16)	4.96 (55)	0.67	1.47 (43)	42.3 (47)	NC	NA	NC	NA	NC	NC
		7[c]	HV (n=16)	9.29 (48)	1.48	4.11 (156)	139 (47)	NA	5.81 (47)	33.5 (33)	3.29 (32)	1.24 (48)	2.46 (45)
Suboxone	8 (HS-15-549)[d]	19[c]	Patient (n=16)	7.92 (76)	1.78	NC	NC	NC	NC	NC	NC	NC	NC

Values are geometric mean (geometric CV%); [a] Median; [b] C_{168h} for CAM2038 q1w, C_{28d} for CAM2038 q4w and C_{24h} for Subutex; [c] Steady-state PK parameters [d] three times a day
AUC_{inf}: AUC extrapolated to infinity; AUC_{τ}: AUC over the dosing interval; C_{av}: average concentration during the dosing interval; C_{max}: maximum observed plasma concentration; C_{trough}: observed concentration before the next actual or intended dose; CV%: coefficient of variation percentage; HV: healthy volunteer; NA; not applicable; NC: not calculated; NCA: non-compartmental analysis; norBPN: norbuprenorphine; R_{ac}: accumulation ratio; SC: subcutaneous; SL: sublingual; $t_{½}$: half-life; T_{max}: time corresponding to C_{max}

Source: Extracted from summary of clinical pharmacology, Table 20

APPENDIX B. SAFETY TABLES

Appendix B- 1 ECG Parameters in Phase 3 Study HS-11-421

Table 36 Summary of QTcB and QTcF Intervals (Safety Population)

Parameter/Timepoint/Category	SL BPN/NX N=215 n (%)	CAM2038 N=213 n (%)	Total N=428 n (%)
QTcB Interval			
Baseline			
<450 msec	200 (93.9)	194 (91.1)	394 (92.5)
≥450 to <480 msec	12 (5.6)	19 (8.9)	31 (7.3)
≥480 to <500 msec	1 (0.5)	0	1 (0.2)
≥500 msec	0	0	0
Any Post-Baseline Visit			
<450 msec	137 (67.8)	124 (62.9)	261 (65.4)
≥450 to <480 msec	55 (27.2)	64 (32.5)	119 (29.8)
≥480 to <500 msec	5 (2.5)	8 (4.1)	13 (3.3)
≥500 msec	5 (2.5)	1 (0.5)	6 (1.5)
Increase from Baseline at any Post-Baseline Visit			
<30 msec	125 (61.9)	130 (66.0)	255 (63.9)
≥30 to <60 msec	63 (31.2)	57 (28.9)	120 (30.1)
≥60 msec	14 (6.9)	10 (5.1)	24 (6.0)
QTcF Interval			
Baseline			
<450 msec	212 (99.5)	209 (98.1)	421 (98.8)
≥450 to <480 msec	1 (0.5)	4 (1.9)	5 (1.2)
≥480 to <500 msec	0	0	0
≥500 msec	0	0	0
Any Post-Baseline Visit			
<450 msec	181 (89.6)	170 (86.3)	351 (88.0)
≥450 to <480 msec	17 (8.4)	26 (13.2)	43 (10.8)
≥480 to <500 msec	3 (1.5)	0	3 (0.8)
≥500 msec	1 (0.5)	1 (0.5)	2 (0.5)
Increase from Baseline at any Post-Baseline Visit			
<30 msec	151 (74.8)	136 (69.0)	287 (71.9)
≥30 to <60 msec	42 (20.8)	55 (27.9)	97 (24.3)
≥60 msec	9 (4.5)	6 (3.0)	15 (3.8)

Abbreviations: SL BPN/NX, sublingual buprenorphine /naloxone
Source: Table 14.4.8.3

Appendix B- 2 ECG Shift Table Across all Studies in Subjects with Opioid Use Disorder

			BASELINE			
	STUDY	RESULT	NORMAL	ABN, NCS	ABN, CS	TOTAL
END OF STUDY	HS-11-421	NORMAL	99 (46.5%)	32 (15.0%)	0 (0.0%)	131
		ABNORMAL, NCS	36 (16.9%)	46 (21.6%)	0 (0.0%)	82
		ABNORMAL, CS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
		TOTAL	135	78	0	213
	HS-13-478	NORMAL	29 (61.7%)	9 (19.1%)	0 (0.0%)	38
		ABNORMAL, NCS	2 (4.3%)	7 (14.9%)	0 (0.0%)	9
		ABNORMAL, CS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
		TOTAL	31	16	0	47
	HS-14-499	NORMAL	137 (62.3%)	26 (11.8%)	0 (0.0%)	163
		ABNORMAL, NCS	25 (11.4%)	29 (13.2%)	0 (0.0%)	54
		ABNORMAL, CS	1 (0.5%)	2 (0.9%)	0 (0.0%)	3
		TOTAL	163	57	0	220
	HS-15-549	NORMAL	20 (31.3%)	8 (12.5%)	0 (0.0%)	28
		ABNORMAL, NCS	13 (20.3%)	23 (35.9%)	0 (0.0%)	36
		ABNORMAL, CS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
		TOTAL	33	31	0	64
	TOTAL	NORMAL	285 (52.4%)	75 (13.8%)	0 (0.0%)	360
		ABNORMAL, NCS	76 (14.0%)	105 (19.3%)	0 (0.0%)	181
		ABNORMAL, CS	1 (0.2%)	2 (0.4%)	0 (0.0%)	3
		TOTAL	362	182	0	544

ABN, NCS = ABNORMAL, NON CLINICAL SIGNIFICANT; ABN, CS = ABNORMAL, CLINICAL SIGNIFICANT.

Source: ADEG; Table: T100302A.LIS; Run: 29JUN2017 07:52
Program: P:\ADMINISTRATION\WORK\BRAEBURN\CAM2038\ISS\PGM\TABLES\T100302.SAS
Sponsor: Braeburn/Camurus, Table 10.3.2, FINAL