CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210136Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	210136
Priority or Standard	Priority
Submit Date	June 26, 2018
Received Date	June 26, 2018
PDUFA Goal Date	December 26, 2018 (December 21, 2018 early action)
Division/Office	DAAAP
Reviewer Name(s)	Gioia M. Guerrieri, DO, FAPA
Review Completion Date	11/30/2018
Established/Proper Name	buprenorphine extended-release injection (CAM2038)
(Proposed) Trade Name	BRIXADI
Applicant	Braeburn Pharmaceuticals, Inc
Dosage Form(s)	Weekly Formulation: 8mg, 16mg, 24mg, 32mg Monthly Formulation: 64mg, 96mg, 128mg
Applicant Proposed Dosing Regimen(s)	New Adult Entrants to treatment: titrate to (b) (4) Weekly in the first week then dose adjust. Adults currently taking a buprenorphine product: transfer to appropriate Weekly or Monthly formulation.
Applicant Proposed Indication/Population	"CAM2038 is indicated for the treatment of moderate to severe OUD (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	For the treatment of moderate to severe opioid use disorder in patients who have tolerated at least a test dose of a 4 mg transmucosal buprenorphine product.

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BPN	buprenorphine
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DB	double-blind
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OL	open label
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OUD	Opioid Use Disorder
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RCT	randomized controlled trial
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGE	special government employee
SL	sublingual
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

CAM2038 is an extended-release formulation of buprenorphine (BPN) in a novel Fluid Crystal (FC) technology designed for administration by subcutaneous (not intramuscular) injection to be provided ready-for-use in a prefilled syringe (a drug-device combination) for the treatment of moderate to severe opiate use disorder (OUD) in adults who are new to BPN treatment or transferring from other forms of BPN treatment. The drug's proposed proprietary name is *Brixadi*, with a non-proprietary name of *buprenorphine extended-release injection.* For purposes of review, this product will be referred to as CAM2038, the name given to the drug during clinical development. The FC technology has not been used in other FDA approved drug products and, therefore, no comparisons are available.

The CAM2038 clinical program was initially and previously submitted as a 505(b)(2)[1] application on July 19, 2017 and represented a new formulation of an existing product. The application was given a priority review; and at the time of submission, no extended-release, injectable BPN product was on the market to treat this condition. On January 19, 2018, NDA 210136 was given a Complete Response. This review focuses on the resubmitted materials.

CAM2038 is available in a Weekly and Monthly formulation, each of which contains different doses, excipients, and volumes (Table 1). The Applicant-recommended starting dose of CAM2038 in BPN-naïve patients is 16 mg CAM2038 Weekly, followed by a single 8 mg CAM Weekly dose within the first week of treatment for a total dose of 24 mg CAM2038 Weekly in the first week of treatment (not to exceed to 32 mg). Initiating treatment with CAM2038 Weekly is done after tolerability to BPN is established with a single transmucosal dose of SL BPN, 4 mg, thus negating the need for a lead-in period of transmucosal BPN.

[1] Relying on the Agency's previous findings for Subutex, buprenorphine hydrochloride sublingual tablets [Indivior (Reckitt Benckiser) NDA 020732] and Suboxone, buprenorphine hydrochloride/naloxone hydrochloride sublingual tablets [Indivior (Reckitt Benckiser) NDA 020733]:
https://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf

Table 1: Proposed Doses of CAM2038 Weekly and CAM2038 Monthly Formulations

BPN Fluid crystal SC injection depot*			
CAM2038 Weekly		CAM2038 Monthly	
Dose (mg)	Volume (mL)	Dose (mg)	Volume (mL)
8	0.16	64	0.18
16	0.32	96†	0.27
24†	0.48	128	0.36
32	0.64		
Weekly injection product contents:		Monthly injection product contents:	
BPN, soybean phosphatidylcholine, glycerol dioleate, ethanol		BPN, soybean phosphatidylcholine, glycerol dioleate, N-methyl-2-pyrrolidone	
* The estimated depot size for the weekly formulation is (b) (4) cm in diameter and for the Monthly formulation is (b) (4) cm in diameter (*provided by Applicant on 8/2/2017 in response to FDA information request*).			
†Per the Applicant, 24 mg Weekly and 96 mg Monthly doses correspond to "12-16 mg/day" of SL BPN. For comparison, an average daily dose of SL BPN is 16 mg.			

Source: Reviewer

As with the previous submission, the Applicant proposes that subcutaneous delivery of CAM2038 will be administered only by a qualified health care provider (HCP) in a clinical setting. Several sites of administration have been proposed (Error! Reference source not found.)[2] based on the injection sites used during the clinical program. For the Weekly formulation, injection sites should be rotated weekly (the same site should not be injected more than once in an 8-week period). For the Monthly formulation, injections should also be rotated per the same guidelines. Upon injection, CAM2038 forms a small ball-like mass. The Applicant reported this mass to be palpable only in regions where subcutaneous tissue is thin (e.g., upper arm) and that, in general, it is poorly palpable in the subcutaneous space and diffuses into the surrounding tissue over time, leaving no mass behind. This product is not intended to be self-administered.

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[2] The upper arm injection site was ultimately found to yield reasonable exposures, although not strictly bioequivalent, (it was rejected as an injection site in the previous submission) after review of additional data. See the Clinical Pharmacology section for a review of this resolution.

Figure 1: CAM2038 Injection Sites Used in the Clinical Studies
Source: page 27, Applicant's Manual of Procedures

In patients transferring (or switching) from existing forms of BPN treatment to CAM2038 Weekly or Monthly formulations, the initial dosing of CAM2038 will be determined by the prescribing physician using a product conversion chart (Table 2) supplied by the Applicant and made available in the proposed product label.

Table 2: Proposed dosing for Patients Switching to CAM2038 from Current SL BPN

Daily dose of sublingual buprenorphine	Weekly dose BRIXADI	Monthly dose BRIXADI
≤ 6 mg	8 mg	--
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg

Source: Derived from Applicant-provided proposed label

If approved, CAM2038 would represent the second extended-release, injectable BPN product on the market to treat moderate to severe OUD. However, it would be the first to be available in a formulation for weekly administration.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Data supporting the efficacy of CAM2038 was submitted by the Applicant during the first review cycle, from a Phase 3, pivotal, non-inferiority Study (HS-11-421) of outpatient adult males and females with OUD; supported by the results of blockade Study HS-14-478. No new data was submitted for this review. In summary, the primary efficacy study design included the use of an active comparator, sublingual (SL) BPN/NX (Suboxone), and the recruitment of patients with moderate-to-severe OUD who met the Applicant's criteria for "new entry" to treatment (those not having received BPN treatment within 60 days of study initiation). The study was also conducted in two phases with two unique formulations of the CAM2038 product: a weekly formulation phase *('phase 1'*) followed by the monthly formulation *('phase 2'*), with each phase lasting 12 weeks. The Applicant's primary objective, to demonstrate non-inferiority of CAM2038 over the active comparator, was met ($p = 0.001$; with a non-inferiority margin of 10%) but data issues identified during the first review cycle prevented definitive conclusions about efficacy. New to this application was a review of the Applicant-provided third party Quality Control analyses of Study 421, summary of discrepancy resolution and root cause analyses, resubmitted datasets and post hoc analyses of dose/response and dose/adverse events. The overall efficacy and safety of CAM2038, as a suite of products, appears adequate based on the resubmitted data and responses to the Division's information requests.

1.3. Benefit-Risk Assessment

See below for the integrated assessment of benefit-risk for this application.

Benefit-Risk Integrated Assessment

CAM2038 (buprenorphine (BPN) extended release) for subcutaneous injection is proposed for the treatment of moderate to severe opioid use disorder in patients who have tolerated at least a 4 mg test dose of a transmucosal BPN-containing product. I recommend approval of this application. BPN is a partial agonist at the mu-opioid receptor and, as mentioned, has been demonstrated as an effective treatment for OUD. CAM2038 is an extended-release BPN product that can be dosed weekly or monthly. With the exception of injection-site adverse events (AEs), the safety profile observed with CAM2038 appeared consistent with the known systemic safety profile of BPN. No unexpected AEs were observed that would preclude approval of CAM2038.

CAM2038 is a modified-release formulation of BPN in a novel Fluid Crystal technology designed for administration by subcutaneous (not intramuscular) injection to be provided as a ready-for-use, prefilled syringe for the treatment of moderate to severe opiate use disorder (OUD) in adults. OUD, particularly if classified as moderate or severe, is a serious and life-threatening condition and contributes to increased rates of morbidity and mortality, as well as to social and economic costs to society.

Current OUD treatment options include non-drug (behavioral) treatment, as well as medication-assisted treatment (MAT) with antagonists (naltrexone), agonists (methadone) or partial agonists (buprenorphine). Methadone is available only at federally-registered opioid treatment programs (OTPs), and patients must visit the clinic daily for in-person dosing until they meet criteria for receiving gradually-increasing numbers of take-home doses. Although drug regimens are key in OUD treatment, most of these regimens require daily dosing and are subject to diversion, misuse, and abuse. Moreover, a risk for unintentional pediatric exposure exists if the current treatments are misused or diverted. Thus, there is an important need for well-tolerated, less burdensome treatments; with reduced liability for abuse, misuse, and overdose. As such, CAM2038 shares some common qualities with a 2017 Agency-approved, buprenorphine extended release product for subcutaneous injection, Sublocade, which can be used in patients who have completed a seven-day run-in on transmucosal buprenorphine.

No major safety issues related specifically to CAM2038 were identified in this review. Although BPN is associated with common side effects and serious risks, those side effects and risks did not appear to be exacerbated by the extended-release formulation or mode of delivery (injection) of CAM2038.

CAM2038 is to be administered only by Health Care Provider (HCP) and not intended for self-administration. This product was not tested outside of a controlled clinical environment. A REMS to ensure that the product will be administered by HCPs and not distributed to patients will be required to mitigate the risk of intravenous injection. The goal of the REMS is to mitigate the risk of serious harm or death with intravenous self-administration by ensuring healthcare settings and pharmacies are certified and only dispense CAM2038 directly to a HCP for administration by a HCP. The following materials were proposed to be part of the CAM2038 REMS:

- Healthcare Setting and Pharmacy Enrollment Form
- Dear Healthcare Provider REMS Letter
- Fact Sheet
- REMS Program Website

The efficacy and safety of CAM2038 were acceptably demonstrated during this review cycle. For OUD patients seeking treatment, the CAM2038 regimen has the potential to provide several advantages, including less frequent dosing to achieve target dosing of BPN, flexible dosing regimens (Weekly and Monthly), dosing options within each regimen, and the ability to receive BPN without take-home medications; all of which may contribute to better treatment adherence.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• OUD is a chronic, relapsing disease characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and physical consequences. Moderate to severe OUD corresponds, roughly, to the DSM-IV diagnosis "opioid dependence," and to the widely-used term, "addiction." Mild OUD corresponds to the DSM-IV diagnosis "opioid abuse." • In 2016, the National Survey on Drug Use and Health determined that more than 2.1 million Americans aged 12 and over met criteria for opioid abuse or dependence. • Goals of treatment vary for individual patients, but typically involves a substantial change in illicit drug use behavior sufficient to translate to clinical benefit. • For many patients, discontinuation of treatment leads to relapse; therefore, treatment may be required chronically.	OUD, particularly if classified as moderate or severe, is a serious and life-threatening condition and contributes to increased rates of morbidity and mortality. Further, OUD has a significant impact on the social and economic costs to society.
Current Treatment Options	• Current treatment options include non-drug (behavioral) treatment and medication-assisted treatment (MAT) with antagonists (naltrexone), agonists (methadone) or partial agonists (buprenorphine). Behavioral treatment alone (individual or group counseling, self-help groups) is not effective for many patients. • The BPN extended release product for subcutaneous injection, SUBLOCADE, was FDA approved for moderate to severe OUD, November, 2017. Based on trial design, labeling requires a seven-day run-in period on transmucosal BPN. • Methadone is available only at federally-registered opioid treatment programs (OTPs), and patients must visit the clinic daily for in-person dosing until they meet criteria for take-home doses of the drug. Methadone has been associated with fatal overdoses in patients and in their household contacts, including children. • The subdermal implant (PROBUPHINE) is suitable only for patients clinically stable on low-moderate dose of transmucosal buprenorphine (≤ 8 mg buprenorphine), requires surgical insertion and removal, and carries a risk of implant migration (with potentially serious consequences) or expulsion. • Oral naltrexone (REVIA) and depot naltrexone (VIVITROL) cannot be initiated until patients are fully detoxified; and might not be suitable or acceptable for all patients. Severe, and potentially serious, precipitated withdrawal can occur when naltrexone treatment is initiated. Serious injection site reactions requiring surgical intervention have been reported with VIVITROL. • Oral transmucosal buprenorphine and BPN/naloxone products and oral naltrexone products are intended to be self-administered by the patient daily. Limitations of daily use products include poor adherence, fluctuating plasma concentrations, intentional 'drug holidays', and patient convenience issues. Daily use agonist and partial agonist MAT products are subject to diversion, misuse, abuse and accidental pediatric exposure.	CAM 2038 reduces potential for diversion, misuse, abuse and accidental pediatric exposure. Further, no surgical procedure is required and dosing is flexible.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Based on the dataset analyzed in the first review cycle, Study 478 (the opioid blockade study) demonstrated that CAM2038 Weekly injections blocked the subjective effects of both 6 mg and 18 mg doses of hydromorphone in 47 non-treatment-seeking patients with moderate to severe OUD. • Based on the dataset analyzed in the first review cycle and amendments submitted with this application cycle, Study 421 (the pivotal Phase 3 trial; NCT02357901) demonstrated that patients (N=213) treated with CAM2038 (both Weekly and Monthly formulations) achieved a rate of response non-inferior to an active comparator (SL BPN/NX), with a non-inferiority margin of 10%. • CAM2038 would be administered by a health care provider subcutaneously every week or month and provides advantages over daily dose MAT products in terms of patient adherence, patient convenience, and risks of abuse, misuse, and accidental exposure.	This product is designed for (b) (4) Further, the multidisciplinary review findings determined that the previous discrepancies and deficiencies have been resolved and that the data are reliable for product approval, with a favorable risk-benefit ratio.
Risk and Risk Management	• The active ingredient, buprenorphine, has been marketed since 1981 and has been approved for opioid dependence treatment since 2002. The systemic safety profile of CAM2038 is consistent with the established safety profiles of transmucosal BPN products used for treatment of OUD, on face, but data is limited. • Safety concerns related to BPN include hepatic effects, cardiac conduction effects, allergy/anaphylaxis, and general effects of the opioid class (e.g. respiratory depression, CNS depression, etc.) • In the safety database of 440 opioid-dependent patients, systemic effects of BPN associated with CAM2038 (≥ 2% occurrence) included headache, nausea, constipation, vomiting, elevated liver enzymes, sedation and somnolence • Common injection site reactions included injection site pain, pruritus and erythema. • Treatment-emergent adverse events leading to drug discontinuation were reported in ≤5% of subjects in all treatment groups • No Hy's law cases were identified in the clinical development program • One death occurred in the CAM2038 group due to motor vehicle accident.	Although the flexible study design made it difficult to determine the AE profile by sequential CAM2038 dose and formulation, the overall safety profile (and lack of any dose/AE patterns) in the development program (with exposures up to 48 weeks), favored benefit over risk.

1.4. Patient Experience Data

No changes were made to the Patient Experience Data from the previous submission. Patient experience including patient-, observer-, and clinician-reported outcomes[3], was adequately incorporated into the submission of CAM2038 application.

2. Therapeutic Context

2.1. Analysis of Condition

Opioid use disorder (OUD) is a serious medical condition that results in significant morbidity and possibly death. OUD is characterized by misusing prescribed opioids or obtaining opioids illegally; and includes symptoms of tolerance, withdrawal, and interpersonal and occupational impairment, which are the defining features of addiction.

OUD is formally and currently diagnosed by a medical professional using the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5)[4]. To meet clinical criteria for OUD of any severity, the patient must report a problematic pattern of opioid use leading to clinically significant impairment or distress within a 12-month period in addition to scoring positive on an additional set of symptoms. Severity is categorized as mild (2-3 symptoms), moderate (4-5 symptoms), or severe (≥ six symptoms). The additional DSM-5 symptoms for OUD include: overusing opioids; unsuccessful effort (or desire) to decrease opioid use; significant time spent obtaining opioids; strong desire to use; important activities are sacrificed for opioids; recurrent opioid use in hazardous situations; continued use despite consequences; tolerance; and withdrawal.

In 2015, 12.5 million people were identified as having misused prescription opioids, 33,091 people died from opioid drug overdoses, and (b) (4) million adults were identified as having prescription OUD[5]. These data reflect the growing health concern of the opioid crisis and the national rise of cases of opioid abuse and misuse, both with prescribed opioid drugs and

[3] Patient reported outcomes included measures of opioid craving (Visual Analogue Scales of "Desire to Use" and "Need to Use") and withdrawal (Subjective Opiate Withdrawal Scale). Observer and Clinician reported outcomes were measured with the Clinical Opiate Withdrawal Scale.
[4] American Psychiatric Association (2013), Diagnostic and Statistical Manual of Mental Disorders (5th ed.), Arlington: American Psychiatric Publishing, pp. 540–546
[5] 2015 National Survey on Drug Use and Health (SAMHSA); Monthly Morbidity Weekly Report (MMWR), 2016; 65(50-51);1445–1452 [Center for Disease Control (CDC)]

illicit opioid use[6]. Additionally, there is a growing public health concern about abuse, misuse, and accidental pediatric exposure associated with currently marketed transmucosal buprenorphine (BPN) products. That, in combination with the growing interest in the design of buprenorphine products that can block endogenous opioids and accomplish extinction of illicit opioid drug abuse, in addition to individual patient (people who are receiving treatment for OUD) concerns related to the inconvenience, privacy, and security issues of daily dosing of BPN, have spurred the development of long-acting depot formulations of buprenorphine.

2.2. Analysis of Current Treatment Options

Current treatment options for OUD include non-drug (behavioral) treatment, as well as medication-assisted treatment (MAT) with antagonists (naltrexone), agonists (methadone) or partial agonists (buprenorphine); including an extended release, Monthly, buprenorphine injectable product, Sublocade, that was approved for commercial use November, 2017. A summary of currently marketed FDA-approved drugs for OUD is provided in Table 3.

Table 3: Summary of currently available FDA-approved drugs for opioid use disorder

Immediate-Release Products			
Generic Name	Trade Name	Applicant	Dosage forms
Buprenorphine/naloxone	Suboxone* (generics only)	Indivior	sublingual tablet
	Suboxone (and generics)	Indivior	sublingual film
	Bunavail (and generics)	Biodelivery Sci Intl	buccal film
	Zubsolv (and generics)	Orexo AB	sublingual tablet
Buprenorphine	Subutex** (generics only)	Indivior	sublingual tablet
Methadone HCl	Methadose (and generics)	Mallinckrodt	oral solution; bulk powder; tablet dispersible tablet
Methadone HCl	Dolophine (and generics)	Roxane	tablet; oral concentrate; oral solution
Naltrexone HCl	ReVia (and generics)	Duramed	tablet
Extended-Release Products			
Generic/Chemical Name	Trade Name	Applicant	Dosage forms
Naltrexone HCl	Vivitrol	Alkermes	injectable suspension
Buprenorphine	Probuphine***	Braeburn	subdermal implant
Buprenorphine	Sublocade	Indivior	injectable suspension

*NDA 020733; discontinued in US Market
**NDA 020732; discontinued in US market in 2011
***suitable only for patients clinically stable on low-moderate dose of transmucosal buprenorphine (≤ 8 mg), requires surgical insertion and removal, and carries a risk of implant migration or expulsion.

[6] In 2015, 828,000 people used heroin [2015 National Survey on Drug Use and Health (SAMHSA)] with 12,989 deaths attributed to heroin overdoses alone [Heroin Overdose Data; Center for Disease Control (CDC)]

Methadone is available only at federally-registered opioid treatment programs (OTPs) and patients must visit the clinic daily for in-person dosing until they meet criteria for receiving gradually-increasing numbers of take-home doses. Additionally, methadone has been associated with fatal overdoses in patients and in their household contacts, including children. Oral naltrexone (Revia) and depot naltrexone (Vivitrol) cannot be initiated until patients are fully detoxified; and may not be suitable or acceptable for all patients. Severe, and potentially serious, precipitated withdrawal can occur when naltrexone treatment is initiated. Serious injection site reactions requiring surgical intervention have been reported with Vivitrol. Further, currently available oral-transmucosal buprenorphine and buprenorphine/naloxone products and oral naltrexone products are intended to be self-administered by the patient daily. Approved long-acting buprenorphine products for OUD include Probuphine, a six-month implant requiring surgical insertion and removal, and carrying risks common to drug implants inserted in the arm; and Sublocade, a monthly subcutaneous depot injection which is labeled for use after at least a seven-day run-in period on transmucosal buprenorphine.

Buprenorphine (BPN) is a partial agonist at the μ-opiate receptor and was developed as a treatment for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the μ-opioid receptor. Like methadone, BPN's activity at the μ-receptor was expected to relieve patients' urge to use illicit opioids, and like methadone, the long duration of action would allow patients to achieve a steady state with daily dosing, without the alternating highs and lows associated with opioid abuse that impair daily functioning. At sufficiently high doses, buprenorphine blocks full opioid agonists from achieving their full effects, deterring abuse of these substances for BPN-maintained patients. However, compared to methadone, BPN is less likely to cause life-threatening respiratory depression and was therefore expected to be more suitable for take-home use.

A parenteral formulation of BPN was approved in 1981 for the treatment of pain, and two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence[7]. Three other transmucosal formulations have subsequently been approved for opioid dependence, as well as two transdermal products and one transmucosal product for pain. Moreover, an implantable buprenorphine product delivering a low to moderate dose of buprenorphine was approved in 2015 for stable patients for whom the dose is adequate. In November, 2017, a subcutaneous extended-release injectable suspension, Sublocade, was approved for the treatment of moderate to severe OUD following a period of at least 7 days' treatment with SL BPN.

[7] Subutex, buprenorphine sublingual tablets (Reckitt Benckiser NDA 20732) and Suboxone, buprenorphine/naloxone sublingual tablets (Reckitt Benckiser NDA 20733). Naloxone is intended to further deter abuse by the intravenous route by precipitating withdrawal if the product is injected by persons dependent on full agonists.

The current labeled recommended dose of SL BPN ranges from 12 mg to 16 mg daily. Limitations of daily use products include poor adherence, fluctuating plasma concentrations, intentional "drug holidays," as well as patient convenience issues. Daily use of agonist and partial agonist MAT products are subject to diversion, misuse, abuse, and accidental pediatric

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

CAM2038 has been developed for the (b) (4) treatment of moderate to severe OUD and is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

NDA 210136 was given a Complete Response (CR) on January 19, 2018 after a thorough, multidisciplinary, review revealed several deficiencies that would preclude its approval before the PDUFA deadline. These included significant manufacturing issues which are detailed in the CMC review of this product. The clinical deficiencies included the following summarized items communicated to the Applicant in the CR letter:

- Provide additional data (b) (4)
- The submitted clinical datasets were found to include a number of discrepancies and errors, which you have determined were likely caused by limited QC/edit function checks. For each of the data errors identified in prior information requests, and for any further errors identified in the corrected datasets, provide an explanation with relevant documentation as to how these errors occurred and were corrected. between the IVR database and the clinical database.
- Provide a revised Summary of Clinical Safety and Summary of Clinical Efficacy that includes analysis and discussion of the dose-response relationships and how they inform the overall balance of risk and benefit.
- For the safety datasets (i.e., ADSL and ADAE) specifically, ensure that the following variables are included: ORALDAY; ORALDOSE; INJECTIONDAY; INJECTIONDOSE; INJECTION FORM; LASTFULL EXPOSURE. Create a flag that indicates if a patient received a supplemental dose of CAM2038. Note that, as discrepancies or missing data are identified in the patient populations, narratives describing the nature of these findings should be generated and submitted.
- Provide descriptions of the steps taken to minimize bias of the site investigators who received any large honoraria for Studies HS-11-421, HS-13-478, and HS-14-499.

On May 2, 2018, a Type A, post action, meeting was convened in response to the Applicant's

March, 2018 request to discuss a limited number of questions from the CR letter and the resubmission of priority NDA 210136 for May 2018. During that meeting the Division re-emphasized key areas of concern and reiterated comments from the CR letter, in addition to the first review cycle information requests. Although no clinical questions were posed, we requested that the following issues be addressed before the resubmission:

- resubmitting data that incorporates the datasets, variables, and flags
- providing a revised summary of Clinical Safety and Summary of Clinical Efficacy that included:
  - analyses and a discussion of dose/response and risk/benefit evidence that the entire clinical database has been audited
  - supporting safety data (b) (4) (b) (4)
  - description of the steps taken to minimize bias in the clinical studies procedures to ensure that all facility issues are resolved and that these facilities are inspection ready during the second review cycle.

Further, the Division identified a SAE involving CAM2038 (b) (4) This event occurred after the data lock for NDA 210136 but before NDA submission on July 19, 2017 and is detailed in section 8.4.2 of this review. The Applicant was notified of this as an example of the barriers to the clinical review of CAM2038. See section 8.3.1 for a discussion of the data quality issues and steps taken by the Applicant to resolve them.

On May 23, 2018, the Applicant resubmitted NDA 210136. The clinical components of the resubmission included the results of the Data Quality Control and Remediation Report, tables and figures, a study report, injection site listings, Reviewer's guide, ISS, and resubmitted datasets. The review team determined that the resubmission was an Incomplete Response to the previously identified deficiencies. On June 26, 2018, the Applicant resubmitted the NDA, after having addressed the IR. The submission was accepted by the Division and the review commenced. Please refer to my clinical review dated 12/26/2018 for the summary of presubmission and submission regulatory activity with the first application cycle. For reference, Table 4 lists the studies that comprised the clinical development program.

Table 4: Studies included in the CAM2038 clinical development program

Study/ Type	Design	Duration (weeks)	Population (N) [completed]
HS-07-307 PK/BA*	Phase 1/2, single-center, single-blind, single dose-escalation, first in human. 4 doses of CAM2038 Weekly.	7	OUD patients: on SL BPN ≥6 months; 41 enrolled [one was treated in 2 groups (groups B and D)]
HS-11-421 Pivotal	Phase 3 multi-center study, randomized controlled trial, multicenter	24	Mod-severe OUD patients. 428 enrolled [247 completed].
HS-11-426 PK/BA	P1, RCT, OL (open label), single dose study of 3 CAM2038 weekly doses (8, 16, 32 mg). Control: IV Temgesic, SL Subutex (8,16,24mg)	1	Healthy volunteers on naltrexone blockade. 60 enrolled [54]
HS-13-478 PK	P2, RCT, DB, multicenter, repeat dose. Control: IM Hydromorphone, IR morphine sulfate Tablets	7	Mod-severe OUD patients. 47 enrolled [46]
HS-13-487 PK/BA	P1, RCT, OL, single and repeated monthly and weekly dose. Control: I.V. Temgesic, SL Subutex	4	Healthy volunteers on naltrexone blockade. 87enrolled [75]
HS-14-499 Safety	P3, Open Label (OL), multicenter study (29 sites). Uncontrolled.	48	Mod-severe OUD patients 227 enrolled, 156 completed.
HS-15-549 PK	P2, OL, partially randomized, multicenter, CAM2038 weekly /monthly at different injection Sites. Three groups (Grp) Control: 24 mg SL BPN/NX.	Grp 1:7-13 Grp 2:16-22 Grp 3: 17	Mod-severe OUD patients. Enrolled (completed): Grp 1=28 (23); Grp 2-20(16); Grp 3= 18(12).

Source: Reviewer
*PK=Pharmacokinetics/BA=bioavailability
**RCT=Randomized controlled trial, DB=double blind, DD=double dummy

3.3. Foreign Regulatory Actions and Marketing History

On November 22, 2018, the company Camurus (Lund, Sweden) announced that the European Commission (EC) approved CAM2038 WEEKLY and MONTHLY, as Buvidal® (prolonged release buprenorphine), for the treatment of opioid dependence in adults and adolescents, ages 16 years and older. This drug is marketed as the first long-acting treatment approved for OUD in the European Union (EU). Additionally, Camurus received approval to market the product in Australia on November 29, 2018.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

During the previous review cycle and specific to data integrity, the clinical review team worked in collaboration with the Office of Computational Science (OCS) and the Office of Scientific Investigations (OSI) to review sites that enrolled patients in Study 421, the pivotal efficacy trial. OSI's inspection of the Applicant (Braeburn Pharmaceuticals Inc.) and four clinical investigators revealed deviations in the database[8]. On December 14, 2017, the Applicant agreed to conduct a database quality control (QC), the results of which were the subject of this review cycle. The Applicant had identified discrepancies between the IVR database and the clinical database that were caused by limited QC/edit function checks between the two systems and submitted protocol amendments along with the QC report, May, 23, 2018.

4.2. Product Quality

Outstanding facilities and biopharmaceutical issues with source data and manufacturing were identified during the first application cycle and were a review issue with this submission. The issues identified by Office of Process and Facilities (OPF) during the previous review cycle were not resolved, which led the chemistry, manufacturing, and controls (CMC) review team to conclude that the data could not be relied upon to support drug approval during the first review cycle[9]. The Pharmaceutics International Incorported (Pii)[10] manufacturing sites under review for the follow-up of the preapproval inspections (PAI) were:

- (b) (4) Hunt Valley, MD (FEI 1000513101)
- (b) (4) Cockeysville, MD (FEI 3006503102)

[8] Examples of the deviations included the failure to prepare or maintain accurate case histories at two of the inspected sites; and the investigational drug disposition records at one site were not adequate with respect to dates and use by subjects.

[9] Results of the pre-approval inspection from 2017 revealed (b) (4)

[10] (b) (4)

As of November, 15, 2018, the PAI/CGMP inspections for sites (b) (4) (FEI 1000513101) and (b) (4) (FEI 3006503102) were complete. The inspection for site (b) (4) was classified VAI (voluntary action indicated) and the clinically relevant aspect of the inspection covered (b) (4) (b) (4) and the following clinical observations were cited and conveyed to the Applicant for correction:

(b) (4)

The inspection for site (b) (4) was also classified VAI. However, the single VAI observation related to NDA 210136 was Observation (b) (4)

Therefore, the Office of Regulatory Affairs (ORA) indicated that there were no other pending enforcement actions that would impact that decision. Subsequently, the Overall Manufacturing Inspection Recommendation (OMIR) and the Facility Review task are complete and the decision was made to recommend approval of NDA 210136.

4.3. Clinical Microbiology

Non-applicable.

4.4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology (PTOX) review team identified several issues during the previous application cycle. Outstanding issues at the conclusion of the last cycle were:

- The lack of adequate safety justification for N-methyl pyrrolidone (NMP)
- Lack of adequate safety justification for glycerol-3-dodecaethylene glycol (GDO)

[11] Observation (b) (4)

- Lack of human exposure margins (measured by area under the curve at steady state ($AUC_{12\text{-}36\ hour}$)) compared with animal exposure margins (data to support labeling).

Those deficiencies were relayed to the Applicant and the submission of additional leachable data were agreed to be submitted by the Applicant, which were the foci of the nonclinical review for this application cycle. At the time of this review, the Applicant-provided data was still under review by the PTOX team and final decision had not been made.

4.5. Clinical Pharmacology

The Division communicated to the Applicant in the CR (*deficiency #27, prescribing information*), that the recommended injection sites should be limited to the abdomen, buttock, and thigh because the arm site did not yield the expected PK and bioequivalence results (Table 5). In response to the CR, the Applicant did not provide new PK data (other than PK results of injection-site effect study HS-15-549 submitted during the first application cycle and reviewed by Dr. Naraharisetti) but did conduct post hoc analyses on the efficacy and safety data from the pivotal Phase 3 Study 421. These post hoc analyses were not ideal to characterize the PK at each injection site because, in Study 421 (as with each of the Applicant's multiple dosing studies), injection sites were rotated and the data from one injection site might be confounded by the injection data from other sites. However, a thorough review of the Applicant-provided analyses was conducted and specific consideration was given to the use of the upper arm injection site in the context of the 8-week injection rotation schedule necessitated by the dosing of the CAM2038 Weekly formulation (posited by the Applicant).

Table 5: CAM2038 PK Parameters and BA at Proposed Injection Sites.

Table 1.3.6a: Injection site effect: PK parameters of buprenorphine after repeated weekly SC 32 mg CAM2038 q1w, in the buttock, abdomen, thigh and upper arm in study HS-15-549.

Product Dose	Dose No.	Injection site	Parameter [geometric mean (CV%)]				
			Css,max (ng/mL)	Tss,max[a] (h)	Css,trough[b] (ng/mL)	AUCss [c] (ng*h/mL)	Css,av (ng/mL)
CAM2038 q1w 32 mg	4-7[d] (n=21)	Buttock	6.87 (37)	24.0 (0-72)	2.63 (39)	700 (27)	4.17 (27)
	4-7[d] (n=21)	Abdomen	6.56 (30)	24.0 (0-168)	2.68 (36)	657 (27)	3.91 (27)
	4-7[d] (n=21)	Thigh	5.37 (44)	24.0 (10-120)	2.70 (48)	613 (37)	3.65 (37)
	4-7[d] (n=21)	Upper arm	5.69 (43)	24.0 (4-48)	2.37 (37)	591 (34)	3.52 (34)

Median (min-max); [b]C168h; [c]AUC between 0 and 168 hours for CAM2038 q1w; AUCss: AUC over the dosing interval at steady-state; Css,av: average concentration during the dosing interval at steady-state; 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; Tss,max: time corresponding to occurrence of Css,max

Table 1.3.6b: The bioequivalence assessment between different injection sites using buttocks as a reference.

Site	Geometric mean ratio and 90% CI (lower, upper)			
	Css,max	AUCss	AUClast	Ctrough
Abdomen Vs. Buttock	96 (82, 112)	94 (84, 104)	94 (84, 104)	102 (88, 117)
Thigh Vs. Buttock	79 (68, 92)	88 (79, 97)	87 (79, 97)	103 (89, 118)
Upper Arm Vs. Buttock	83 (71, 97)	85 (77, 95)	85 (76, 95)	90 (78, 104)

Source: Dr. Naraharisetti's 12/21/2017 Clinical Pharmacology review of NDA 210136.

This table of pharmacokinetic (PK) and bioequivalence (BA) at each of the proposed injection sites, demonstrates the clinical pharmacologic concern of the proposed upper arm injection site. Based on the study results submitted from the first application cycle, the upper arm site showed lower buprenorphine trough levels compared with the other site and buttock. Further, the trough levels of upper arm site failed the bioequivalence criteria for the lower end of bioequivalence compared with buttock site. As noted in 2017 clinical pharmacology review by Dr. Naraharisetti, "although Cmax and AUC between different injection sites are important for CAM2038, the trough levels are considered more important for the efficacy of this product." Thus, the Division recommended against the use of the upper arm as an injection site during the first application cycle.

Findings from this secondary review included 1) that the steady-state trough levels of the upper arm site (2.37 ng/mL) marginally failed to meet bioequivalence parameters (meaning it was a low-sided failure) compared with the buttock site (2. 63 ng/mL); 2) that these values remain higher when compared to the steady-state of the currently marketed approved SL BPN 24 mg (1.24-1.61 ng/mL) by cross-study comparison; and 3) that the Applicant did not identify any therapeutic failures in their post hoc analyses of injection sites and efficacy in Study 421. Thus, since the upper arm site steady-state trough levels are 'only marginally' failed compared to the buttock site, and that these levels are higher than the steady-state SL BPN products, the Clinical Pharmacology team concluded that it is reasonable to allow the Applicant to use the upper arm site for CAM2038 injections.

Reviewer's Note: From a clinical perspective, it would seem prudent to avoid the arm site during initial dosing periods in patients new to treatment, who might be more vulnerable to relapse due to the potentially lower trough plasma levels. At the time of this review, the Division is considering labeling that would suggest deferring rotating to the upper arm injection site until several doses of CAM2038 have been administered.

For reference, I have included the comparative bioavailability of CAM2038 Weekly and CAM2038 Monthly, which were compared to Subutex using steady-state(ss) PK parameters; Area Under the Curve steady states (AUC,ss); and maximum concentration at steady state (Cmax,ss) across studies HS-11-426, HS-13-487 and HS-15-549 (Table 6) that were reviewed during the first application cycle. Because the CAM2038 formulations have different dosing intervals, AUC,ss was represented by average concentrations (Cavg,ss = AUCss,τ /dosing interval,τ). Refer to the detailed 2017 Clinical Pharmacology review by Dr. Narahansetti for additional details.

Table 6: Comparative Bioavailability and Steady-State Exposure of CAM2038

Drug Product	Dose (mg) (Study)	Dose No.	Population	Cmax,ss (ng/mL)	Tmax (h) [a]	Ctrough[b] (ng/mL)	AUCτ (ng*h/mL)	Cav,ss (ng/mL)
CAM2038 Weekly	16 (HS-13-487)	4	HV (n=15)	4.30 (44)	23.2	0.842 (22)	350 (24)	2.09 (24)
	32 (HS-15-549)	4-7	Pt (n=21)	6.87 (37)	24.0	2.63 (39)	700 (27)	**4.17 (27)**
CAM2038 Monthly	128(HS-15-549)	4	Pt (n=16)	**11.1 (54)**	10.0	2.09 (55)	2610 (42)	**3.89 (42)**
	160(HS-15-549)	4	Pt (n=12)	**15.4 (52)**	24.0	2.66 (61)	3540 (26)	**5.27 (26)**
SL BPN	24 (HS-11-426)	7	HV (n=16)	**7.78 (37)**	1.01	1.24 (44)	56.3 (29)	**2.34 (29)**
	24 (HS-13-487)	7	HV (n=16)	**8.45 (54)**	1.04	1.61 (40)	63.9 (34)	**2.66 (34)**

Source: Dr. Narahansetti's 2017 Clinical Pharmacology review
This table is a summary of the comparative BA for select steady state doses of CAM2038 compared with 24 mg SL BPN (the current maximum recommended daily dosing of SL BPN). Compared to Subutex 24 mg (SL BPBN), CAM2038 Monthly 128 mg and 160 mg demonstrate higher steady state Cmax; and, with the same comparator, (b) (4) 32 mg Weekly and 160 mg Monthly (highlighted in red) shows higher steady state, Cavg: dosing that exceeds the maximum recommended label dosing for Subutex. The Applicant used mathematical PK modeling to predict the parameters of the 24 mg weekly and the 96 mg monthly doses.

4.6. Devices and Companion Diagnostic Issues

The Agency's Center for Devices and Radiological Health (CDRH) reviewed the delivery device/CAM2038 combination product during the previous cycle's product development and did not identify any deficiencies in the product/delivery system.

Further, the Division of Medication Error Prevention and Analysis (DMEPA) concluded their review of the human factors risk analysis and validation protocol under IND 114802 (referencing this application) during the previous application cycle and deficiencies were

identified[12] that were later resolved by the Applicant. The Applicant worked with DMEPA during this review cycle to clarify labeling and product packaging.

4.7. Consumer Study Reviews

Non-applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The sources of clinical data reviewed for this submission include the resubmitted datasets for studies HS-11-421 (the pivotal, Phase-3 study) and HS-14-499 (the supportive Open label study), and the Integrated Summary of Safety (Clinical Summary). No new clinical trial data was provided for this review, nor were new supportive studies conducted. For reference, Table 7 lists the studies that comprised the clinical program and were submitted to the Agency during the first review cycle for NDA 210136.

[12] The deficiencies focused on potential confusion (b) (4)

Table 7: Listing of clinical trials specific to the 2017 review of NDA 210136

Trial Identity	NCT no.	Trial Design	Regimen/ schedule	Treatment Duration (Follow Up)	No. patients enrolled	Study Population	No. of Centers/ Countries
Controlled Studies to Support Efficacy and Safety							
HS-11-421	02651584	Pivotal, Phase 3, Randomized control trial, double-blind, double-dummy, active-controlled, parallel group, multi-center study, designed to evaluate the non-inferiority of CAM2038 compared to existing standard of care*	Weekly CAM2038 dosing (12 weeks) then to Monthly CAM2038 dosing (12 weeks). Active control arm received 16-32 mg BPN/NX oral tablet dose daily with placebo injections throughout study	24 weeks (4weeks)	428	Treatment seeking Adults with OUD: New entrants to treatment (no BPN treatment within 60 days)	USA: 34 sites
Studies to Support Safety							
HS-14-499	02672111	Open Label, Phase 3, multisite study to evaluate the long-term safety of CAM2038 in both the Weekly and Monthly formulations.	Participants could be started on the CAM2038 Weekly or Monthly formulation with flexible dosing	48 weeks	227	Treatment seeking Adults with OUD who were a) transitioning from current BPN treatment or b) New entrants to BPN treatment	USA: 10 sites Europe: 16 sites
Other studies pertinent to the review of efficacy or safety							
HS-13-478	02611752	Phase 2, RCT, DB, multicenter, repeat dose. Control: IM Hydromorphone, IR Morphine Tablets	Opioid blockade study in adults who are opioid-tolerant. Three groups of patients received 2 doses of CAM2038 Weekly (24 or 32 mg) or two doses of placebo; each dose followed by drug-liking challenge.	7 weeks	47	Non-treatment seeking adults with OUD	USA: 4 sites
HS-15-549	02710526	P2, OL, partially randomized, multicenter, CAM 2038 weekly /monthly at different injection Sites. Control: 24 mg SL BPN/NX	Three groups of patients received CAM2038 Weekly or Monthly injections at different sites; each group of exposures lasted 7-22 weeks.	7 – 22 weeks	62	Adults with OUD	USA: 3 sites
307	None**	Phase 1/2, single-center, single-blind, single dose-escalation, first in human; no control.	Study conducted on four groups of patients who were opioid tolerant. Four doses of CAM2038 Weekly over the course of 4-weeks.	7 weeks	41	Adults with OUD who had been on SL BPN treatment at least 6 months before study start	Europe: Germany, single site

Source: Reviewer *sublingual buprenorphine (SL BPN) / naloxone (NX)
** Study completed by Camurus in 2011 at a single site in Germany. This study does not have an NCT number

5.2. Review Strategy

The clinical review, for this second application cycle, focused on the resubmitted efficacy and safety data provided by the Applicant, which was Study 421 (HS-11-421), the pivotal efficacy trial in OUD patients who had not received medication treatment for moderate-severe OUD for at least 60 days prior to study start.

A re-evaluation of Study 499 (HS-14-499), the 48-week, open-label study, intended to provide safety information about the longer-term use of the CAM2038 product, was also conducted. However, the Applicant did not re-analyze/resubmit data related to Study 499 because the Applicant determined that it was not subject to the quality control issues that were present with Study 421. Additionally, Study 499, was not a supporting efficacy study because it was open-label and had no comparator arm.

The efficacy review was primarily conducted by FDA Biometrics reviewer, Dr. James Travis, who worked collaboratively with the clinical team in identifying the efficacy of the proposed drug for this population. Key efficacy findings from his review of Study 421 are referenced in this review and key issues related to this review are highlighted section 6.2.

The safety review, as in the previous cycle, focused on deaths, non-fatal serious adverse events, common adverse events, ECG monitoring, vital signs, laboratory results and dropouts due to adverse events from the pivotal efficacy study (421) and the open label safety study (499). Previously reviewed material from Studies 307, 478, and 549 were included in the analysis of deaths and SAEs and no new information was submitted for this review. Additional materials and communications examined during the clinical review of this application are listed in their respective sections.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study HS-13-478 (Study 478): Blockade Study

Title: *A Multiple Dose Opioid Challenge Study to Assess Blockade of Subjective Opioid Effects of CAM2038 q1w (Buprenorphine FluidCrystal® Subcutaneous Injection Depots) in Adults with Opioid Use Disorder* (conducted: October 09, 2015 – April 29, 2016).

The primary review of the blockade study was performed during the first (2017) NDA review cycle by CSS Medical Officer, Dr. Alan Trachtenberg, and Biostatistics Reviewer, Wei Liu; with consultation by Michael Bewernitz, Ph.D., Reviewer with the Division of Pharmacometrics. No new information was included with this submission but relevant attributes of the 2017 submission are included below. For a more detailed clinical review of this study, please refer to my December, 2017, clinical review of NDA 210136.

6.1.1. Study Design

Overview and Objective

Study HS-13-478 (Study 428) was a Phase 2, randomized (1:1) multiple-dose, within-patient comparison study of an opioid challenge, to assess the blockade of subjective opioid effects CAM2038 24 mg and 32 mg Weekly formulation, compared with placebo.

Trial Design

Forty-seven, non-treatment seeking patients were enrolled while physically dependent and self-reported a minimum of 21 days of IV or insufflated opioid-use in the 30-days preceding screening. Positive urine drug screens for opioids were provided at the time of screening. There were four "phases" to the study: Screening, Qualification, Treatment, and Follow-Up, as shown in Figure 2.

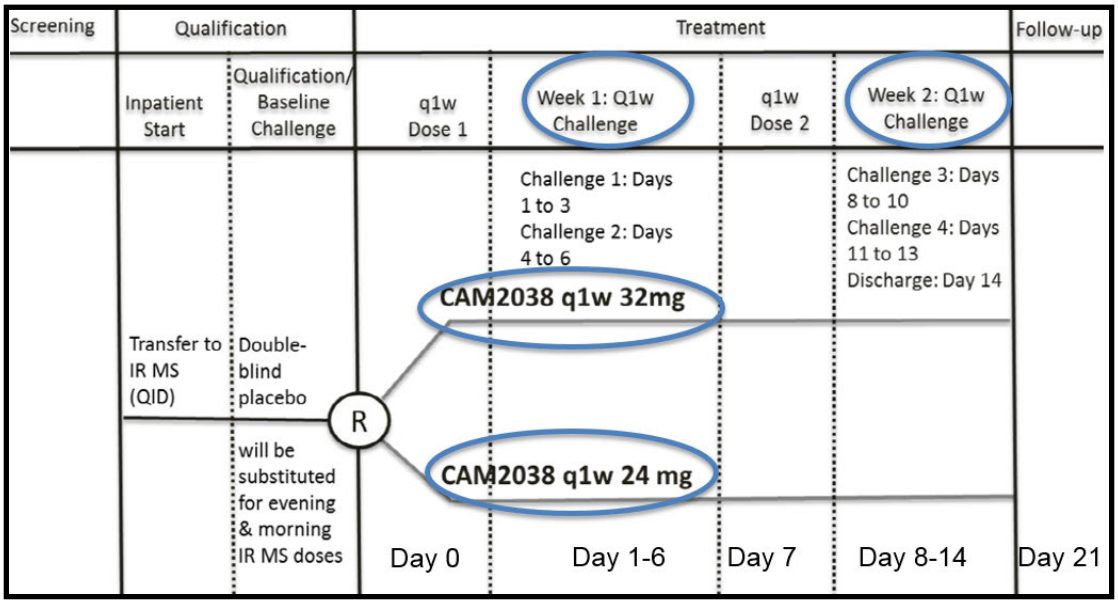

Figure 2: Design schematic for Study 478

Study Endpoints

The primary study endpoint was maximum effect (Emax) of Drug Liking (bipolar VAS) for hydromorphone. Additional pharmacokinetic endpoints (for BPN and norBPN) were collected and are presented in the primary Clinical Pharmacology review, dated 12/21/2017.

6.1.2. Study Results

Baseline characteristics are listed in Table 8, were comparable between groups and were similar to the patient characteristics presented in Study 421, reviewed in 6.2. Efficacy for opioid blockade at both CAM2038 Weekly doses (24 and 32 mg) were adequately demonstrated by the Applicant. Additionally, pharmacometric reviewer, Dr. Bewernitz, performed a placebo-corrected analysis and a PK/ PD analysis (which revealed a trend of reduced drug-liking with increasing buprenorphine exposure) of the submitted data (figures not shown in this review). Drug liking scores within a dosing interval generally corresponded with the buprenorphine concentration profile.

Table 8: Demographic Characteristics in Study 478

Demographic variables	24 mg CAM2038 Weekly (N=22)	32 mg CAM2038 Weekly (N=25)	Total CAM2038 Patients (N=47)
Age, years			
Mean (SD)	36.1 (9.3)	35.6 (9.1)	35.8 (9.1)
Min, Max	21, 53	18, 54	18, 54
Sex, N (%)			
Male	16 (72.7%)	19 (76.0%)	35 (74.5%)
Female	6 (27.3%)	6 (24.0%)	12 (25.5%)
Race, N (%)			
Black or African	9 (40.9%)	15 (60.0%)	24 (51.1%)
White	12 (54.5%)	10 (40.0%)	22 (46.8%)
Other	1 (4.5%)	0	1 (2.1%)
Ethnicity, N (%)			
Non-Hispanic or Latino	22 (100.0%)	24 (96.0%)	46 (97.9%)
Hispanic or Latino	0	1 (4.0%)	1 (2.1%)
BMI, kg/m^2			
Mean (SD)	25.2 (4.28)	24.4 (4.25)	24.8 (4.24)
Range	20, 34	17, 34	17, 34

Source: Applicant provided table from Study 478

A plot of patient drug-liking relative to plasma BPN levels following hydromorphone administration and illustrates the relationship between BPN exposure and drug liking after an 18 mg hydromorphone dosing challenge and is shown in Figure 3. In this figure, data from the CAM2038 Weekly 24 mg dosing arm was pooled with data from the CAM2038 Weekly 32 mg

dosing arm to show the relative drug liking effect (VAS) to plasma levels of BPN. The plot further demonstrates that the dispersion in drug-liking scores is wider at the lower BPN exposures compared with higher BPN exposures. Although it remains unclear what factors might be contributing to the variable drug-liking at the lower BPN plasma levels, this observation underscores the importance of adequate dosing of CAM2038 for efficacy (which contributed to the Division's concern with using the upper arm injection site, particularly early on in treatment).

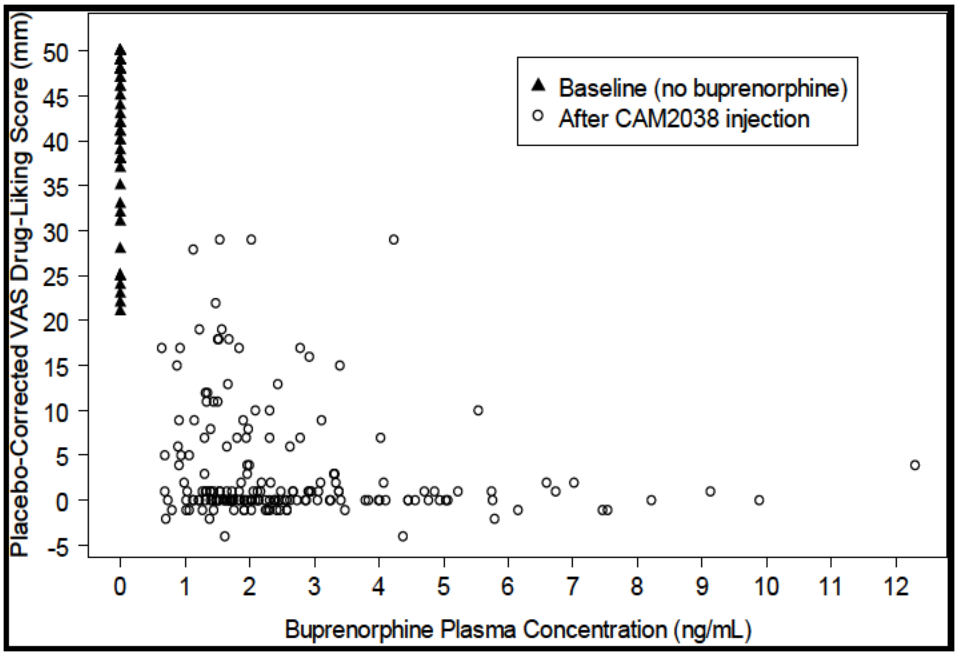

Figure 3: Drug-Liking Relative to Plasma BPN after Hydromorphone Challenge in Study 478

Source: Dr. Michael Bewernitz's 2017 pharmacometric review of NDA 210136

This figure shows the placebo-corrected Drug Liking VAS vs. Plasma Buprenorphine Concentration Following 18 mg Hydromorphone Challenges for the pooled CAM2038 24 mg and 32 mg dosing arms in Study 428.

The primary endpoint in Study 428 was the peak effect (Emax) on a 100-mm bipolar (i.e., 50=neutral response) "Drug Liking" VAS. The pre-defined upper bound of the 95% CI for complete blockade of drug liking was an 11-mm difference between VAS Emax scores obtained for HM doses compared with placebo.

During the qualification/baseline phase, mean Emax scores for placebo were neutral while intramuscular hydromorphone 6 and 18 mg produced dose-related increases in the scores. **Figure 4** and **Figure 5** show that, starting with the first injection of CAM2038 24 mg or 32 mg Weekly, no active intramuscular hydromorphone dose resulted in a mean drug liking VAS Emax score of 11 mm or greater when compared to placebo. Thus, based on mean scores, CAM2038 Weekly demonstrated complete blockade that was sustained throughout the first and second dosing intervals (shown in **Figure 4**). However, considerable inter-patient variability was

observed, with some patients reporting liking scores considerably above the cutoff that defined blockade. Individual patient scores for hydromorphone liking after CAM2038 Weekly dosing are shown in Figure 5.

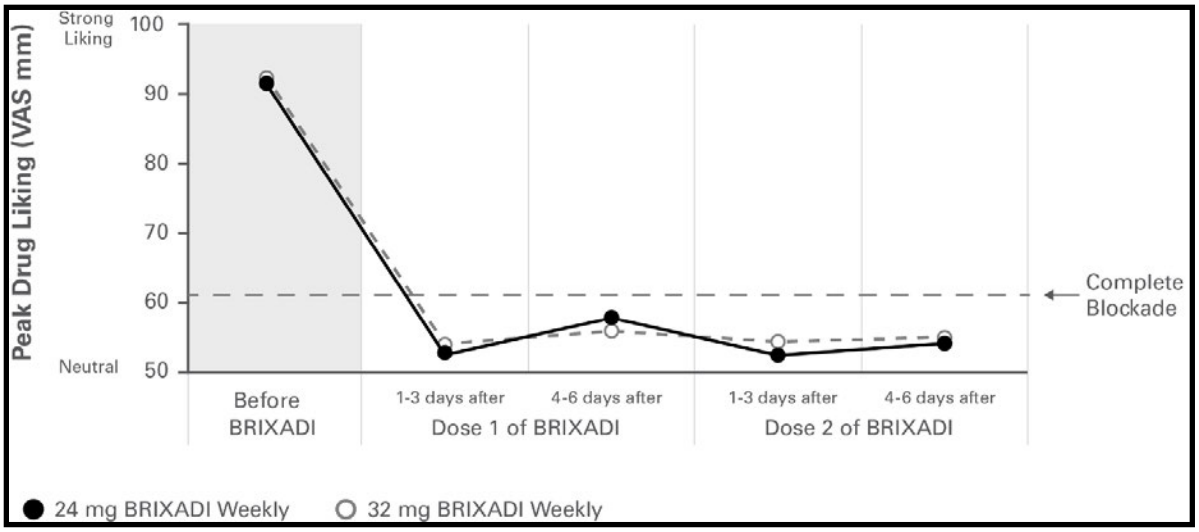

Figure 4: Mean Difference in Peak Drug Liking

Source: Applicant-provided graphical presentation of drug liking for NDA 210136 proposed labeling

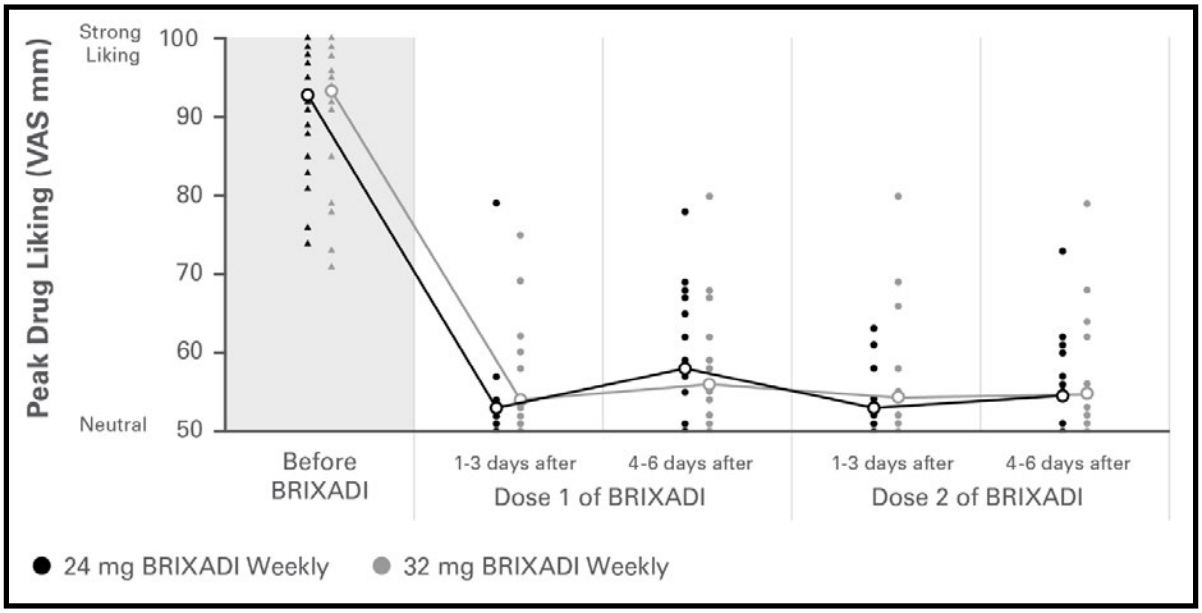

Figure 5: Mean Difference in Peak Drug Liking with Individual Scores

Source: Applicant-provided graphical presentation of drug liking results using individual patient scores for NDA 210136 proposed labeling

6.2. Study HS-11-421 (Study 421): Pivotal Efficacy Trial

Title: *A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel Group, Multi-center Trial Assessing the Efficacy and Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Treatment of Adult Outpatients with Opioid Use Disorder* (conducted: December 29, 2015 - October 19, 2016).

The primary review was performed during the first (2017) NDA review cycle by the statistical reviewer, James Travis, Ph.D., Division of Biometrics. The purpose of this review was to determine if the Applicant's responses were sufficient to address the deficiencies in the CR letter and support CAM2038 approval. The QC report stated that the primary root cause of the data issues were unreconciled differences between two study-data handling systems: the applicant's primary Electronic Data Capture (EDC) system and the Interactive Web Response/Interactive Voice Response systems (IWRS). The QC audit report stated, "1) discrepant data resided primarily in data fields that these two systems having in common, and 2) the data management group confirmed that there was limited cross checking between these two (2) systems."

The QC report also stated there were no data corrections that were expected to have a direct and material impact on the prior analyses performed and submitted to FDA. Although this was true for Dr. Travis' primary analysis, several of his supportive analyses (designed to provide understanding the conduct of the study) were impacted by the data corrections. However, Dr. Travis' conclusions did not change and his review supports approval. An overview of the key elements (that were unchanged from the previous applicant) of the pivotal study[13] and Dr. Travis' updated findings (based on the application resubmission[14]) are both presented in this review.

6.2.1. Study Design

Overview and Objective

Trial Design

For reference, Study 421 was a Phase 3, double-blind, double-dummy, active-controlled (non-inferiority trial[15]), parallel-group multicenter USA study, designed to evaluate CAM2038

[13] Location of the original submission: \\CDSESUB1\evsprod\NDA210136\0002\m5\datasets
[14] Location of the resubmitted documents for Dr. Travis' review: \\CDSESUB1\evsprod\NDA210136\0079\m5\datasets
[15] FDA. Guidance for Industry Non-Inferiority Clinical Trials, March 2010,: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugsgen/documents/document/ucm202140.pdf

compared to an existing standard of care (SL BPN/NX) in initiation and maintenance treatment of patients with OUD. The study involved four "phases": Screening, Phase 1, Phase 2, and the study follow-up (**Figure 6**).

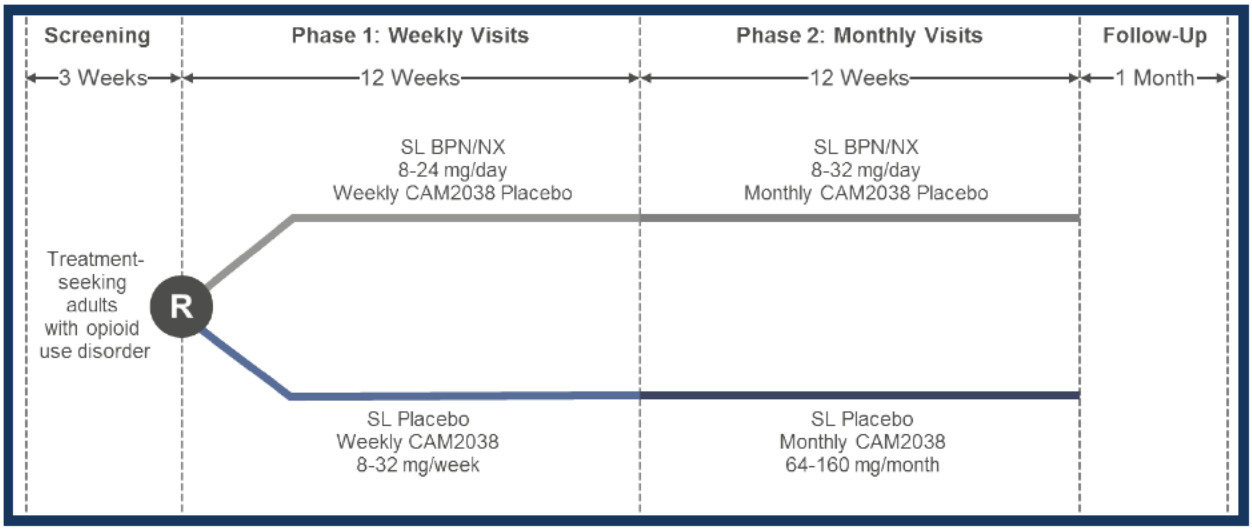

Figure 6: Schematic of Pivotal Trial, Study 421

No Changes to the study design were made and no new (only audited) data were submitted. For reference, the Inclusion and Exclusion criteria; Procedures and Schedule; Dose Selection, Subject Characteristics; and of use of concomitant medications are listed below and in my previous review of NDA 210136, and did not differ with this review.

Inclusion Criteria

- Males and females, ages 18-65 years
- Diagnosis of moderate or severe opioid use disorder, per DSM-5
- Treatment seeking for OUD
- No medication-assisted treatment for OUD within 60 days of study start
- Considered by the investigator to be a good candidate for BPN treatment
- Patients of childbearing potential were willing to use a reliable method of contraception during the entire study (Screening visit to Follow-up)

Exclusion Criteria

- Current diagnosis of Acquired Immune Deficiency Syndrome (AIDS)
- Current diagnosis of chronic pain requiring opioids for treatment
- DSM-5 diagnosis of moderate to severe substance use disorder on any other psychoactive substances other than opioids, caffeine, or nicotine (e.g., alcohol, cocaine, sedatives) and the non-opioid substance use disorder(s) were considered primary or co-primary, causing current (last 30 days) significant impairment and/or in the judgement of the investigator would interfere with the efficacy and safety

assessments

- Pregnant or lactating or planning to become pregnant during the study
- Hypersensitivity or allergy to BPN or other opioids, naloxone or other opioid antagonists, or excipients of CAM2038 or SL BPN
- Required use of agents that are strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) such as some azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., clarithromycin), or protease inhibitors (e.g., ritonavir, indinavir)
- Subjects with active signs or symptoms of hepatitis and requiring treatment.
- Recent history of or current evidence of suicidal ideation or active suicidal behavior based on the Columbia Suicide Severity Rating Scale ("Yes" to questions 4 or 5)
- Any pending legal action that could prohibit participation or compliance in the study
- Exposure to any investigational drug within the four weeks prior to Screening
- History of risk factors of Torsades de Pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome) or ECG demonstrating a Fridericia's corrected QT interval (QTcF) > 450 msec in males and QTcF > 470 in females at Screening
- AST levels > 3 × the upper limit of normal (ULN), alanine aminotransferase (ALT) levels > 3 × ULN, total bilirubin > 1.5 × ULN, or creatinine > 1.5 × ULN on the Screening lab assessments, or other clinically significant lab abnormalities, which the investigator decided that the patient could not safely participate in the study

Procedures and Schedule

The procedures and schedules of assessments for both phases of Study 421 are presented in Table 9 and Table 10. These procedures remained unchanged from the previous NDA 210136 application submission.

Table 9: Schedule of Assessments in Study 421, '*phase 1'*

Study Period/Phase:	Screeni	Phase 1 (Weekly Visits)							
Month:	-1	M1					M1-3		
Week:	-3 to	W1					W2-W11		W12
Day:	-21 to	D1[a]	D2	D	D4	D5-7	D8	Weekly[b]	
Informed Consent[c]	X								
Eligibility Criteria Review[d]	X	X							
Demographic Data and Psychosocial History	X								
Medical and Medication History/Substance Abuse and Treatment History (questionnaires)	X								
DSM-5	X								
Physical Examination[e]	X								
Weight, BMI	X	X							X
Height	X								
Vital Signs[f]	X	X[g]			X		X	Weekly	X
ECG	X	X[g]					X	Weekly	X
Biochemistry, Hematology, Urinalysis and Coagulation	X	X							X
Pregnancy Test[h]	X	X					X	Weekly	X
Hepatitis B/C, HIV[i]	X								
Injection Site Examination		X	X		X	(X)	X	Weekly	X
Dispense Treatment		X							
Urine Toxicology	X	X					X	Weekly	X
Illicit Drug Use Self-Report	X	X					X	Weekly	X
SOWS, COWS, VAS[j]	X	X	X		X	(X)	X	Weekly	X
C-SSRS[k]	X	X	X		X	(X)	X	Weekly	X
Measurement of Morning Desire to Use/Need to Use							X	Weekly	X
SL BPN/NX or SL placebo dispensing		X	X		X	(X)	X	Weekly	X
SL BPN/NX or SL placebo administration[l]		X	X	X	X	Daily	X	Daily	X
CAM2038 q1w or placebo SC		X			X	(X)	X	Weekly	X
Psychosocial Counseling		X					X	Weekly	X
Adverse Events[n]	X	X	X		X	(X)	X	Weekly	X
Concomitant Medications/Procedures	X	X	X		X	(X)	X	Weekly	X
On-Site Visits	X	X	X		X	(X)	X	Weekly	X

Abbreviations: BMI, body mass index; COWS: Clinical Opiate Withdrawal Scale; C-SSRS: Columbia Suicide Severity Rating Scale; EOT: end of treatment; SOWS: Subjective Opiate Withdrawal Scale; VAS: visual analogue scale

[a]Subjects were randomized to one of two treatment groups (SL BPN/NX or CAM2038) after confirmation of eligibility ≥ 1 hour following an

open-label 4 mg SL BPN/NX test dose. [b] A window of ± 2 days was allowed for weekly visits during Weeks 2 to 12, in addition to Week 13. [c] Subjects voluntarily provided written informed consent prior to any study-related procedures being performed. [d] Prior to randomization on Day 1, a review of the eligibility criteria was made. [e] A complete physical exam of all major body systems was performed at the Screening visit. [f] Included temperature, blood pressure, pulse rate, respiration rate. [g] Vital signs and ECG were measured at approximately 15 to 30 minutes before the test dose, approximately 15 to 30 minutes after the CAM2038/SL BPN/NX dose on Day 1 and approximately 15 to 30 minutes predose at the other visits as indicated in the table (or during the visit if no dose was given). [h] A serum pregnancy test was performed at Screening. An "in-office" urine pregnancy test was required on Day 1 PRIOR to randomization and test dose administration and weekly thereafter (for women of childbearing potential). [i] It was the investigator's responsibility to understand and comply with all laws and regulations that apply to HIV, Hepatitis B, and Hepatitis C and testing of blood. Hepatitis B/C and HIV testing was required unless a site's IRB prohibited such testing. [j] SOWS/COWS/VAS were completed each time the subject visited the clinic, as needed based on titration and dosage adjustment. On Day 1, COWS, SOWS, and VAS were completed before the test dose was administered (Baseline). COWS were completed after the test dose on Day 1 to evaluate tolerability, and on Day 2. [k]Screening version at Visit 1 (Screening), Since Last Visit version at all subsequent visits. [l] Not to exceed 24 mg SL BPN/NX (or placebo) per day, this administration was done at home. m Not to exceed 32 mg CAM2038 q1w (or placebo) per week. [n] Any spontaneously reported adverse event was recorded after the subject signed the informed consent form. In addition, adverse events were elicited using a non-leading question each time the subject visited the clinic. (X) indicates as needed based on the individual subject.

Table 10: Schedule of Assessments in Study 421, '*phase 2'*

Study Period/Phase:	Phase 2 (Monthly Visits)						Follow-up		
Month:	M4		M5		M6		M7		
Week: [a]	W13	W14-16	W17	W18-20	W21	W22-24	(EOT) W25	W26-28	W29
Weight and BMI	X		X		X		X		
Physical Examination							X		
Vital Signs[b,c]	X		X		X		X		
ECG[c]	X		X		X		X		
Biochemistry, Hematology, Urinalysis and Coagulation	X		X		X		X		
Pregnancy Test[d]	X		X		X		X		
Injection Site Examination	X		X		X		X		X
Urine Toxicology	X		X		X		X		
Illicit Drug Use Self-Report	X		X		X		X		
Random Urine Toxicology and Illicit Drug Use Self-Report[e]	3 x random urine toxicology								
SOWS, COWS, VAS	X		X		X		X		X
C-SSRS[f]	X		X		X		X		X
Measurement of Morning Desire to Use/Need to Use	X		X		X		X		X
SL BPN/NX or SL Placebo Dispensing	X		X		X				
SL BPN/NX or SL Placebo	X	Daily	X	Daily	X	Daily			
CAM2038 q4w or Placebo SC Injection[h]	X		X		X				
Transition to Standard Care							X		
Psychosocial Counseling	X		X		X		X		
Adverse Events[i]	X		X		X		X	X	X
Concomitant Medications/Procedures	X		X		X		X	X	X
Scheduled On-site Visit	X		X		X		X		X
Telephone Contact								Weekly	

Abbreviations: BMI, body mass index; COWS: Clinical Opiate Withdrawal Scale; C-SSRS: Columbia Suicide Severity Rating Scale; EOT: end of treatment; SOWS: Subjective Opiate Withdrawal Scale; VAS: visual analogue scale

[a] Treatment Visits were conducted within a window of ± 7 days for monthly visits (other than Week 13, which had a visit window of ± 2 days). If a subject missed a visit or completed a visit early or late, the original schedule was resumed at the subsequent visit such that the ensuing visits occurred as originally scheduled, relative to Day 1. [b] Included temperature, blood pressure, pulse rate, respiration rate. [c] Vital signs and ECG were measured approximately 15 to 30 minutes pre-dose and approximately 15 to 30 minutes post-dose at Week 13. At the other visits, ECG was measured approximately 15 to 30 minutes predose as indicated in the table (or during the visit if no dose is given). [d] A serum pregnancy test was performed at the End of Treatment visit (Week 25). An "in-office" urine pregnancy test was required at Weeks 13, 17 and 21 prior to injection being administered (for women of childbearing potential). [e] A total of three random urine toxicology visits during Month 4 to Month 6, preferably once a month. Illicit drug use self-reports were also completed by the subjects at these visits. [f] C-SSRS "Since Last Visit version" was used. [g] Not to exceed 32 mg/8 mg SL BPN/NX (or placebo) per day. [h] Subjects received the first CAM2038 q4w injection (active or placebo) at the beginning of Week 13 (± 2 days). Not to exceed 160 mg CAM2038 q4w (or placebo) per month. Subjects received their last CAM2038 q4w dose at Week 21. [i] Any spontaneously reported adverse events were recorded after the subject signed the informed consent form. In addition, adverse events were elicited using a non-leading question each time the subject visited the clinic and during the telephone contacts in the Follow-up period.

Assignment to treatment, Study treatments, Blinding

No changes were made from the previous review. All patients who met screening criteria and consented were given a unique number and were given one, 4 mg, test dose of SL BPN. If the test dose was tolerated, the patient was randomized in a 1:1 blinded fashion. A central randomization, through an Interactive Web Response System, managed by DSG, Inc., was used after patients were assigned a unique number. All study drugs were administered in a double-blind, double-dummy manner, such that patients received both SL tablets (active BPN/NX or placebo) and SC injections (active CAM2038 Weekly/Monthly or placebo) throughout the study (except for Days 2 and 3, when only SL BPN/NX or SL placebo tablets were given). Patients received treatment for up to 24 weeks during the study: 12 weeks during '*phase 1'* and 12 weeks during '*phase 2'*. To maintain the blind, CAM2038 and the active comparator were designed to look similar in terms of injections and tablets. However, they did not look identical. Thus, the injecting clinician did not collect patient outcomes data and the study staff did not engage the injecting clinician in patient study assignments.

CAM2038/placebo were injected in the buttocks, abdomen, thighs, and the upper arms and the injection sites were rotated such that no injections were administered into the same site (most the injection sites were gluteal). The following injection schedule was used:

- CAM2038 Weekly/placebo injections were not to be administered into a previously injected site for at least 8 weeks.
- CAM2038 Monthly/placebo injections were not to be administered in a sited previously injected with CAM2038 Monthly/placebo.

During '*phase 2'*, an 8mg dose of CAM2038 Weekly could be administered as a booster medication for symptomatic patients requiring additional treatment, per the investigator. This supplemental CAM2038 dosing occurred in both groups to maintain the treatment blinding.

Patients returned unused tablets (placebo or SL BPN/NX) to the clinic at each study visit. Unused tablets were counted and documented.

Dose Selection and Dose Adjustments

No changes were made from the previous review:

CAM 2038: Doses were selected to deliver similar exposure as the SL BPN/NX doses in clinical practice (approximating daily doses of 8-24 mg SL BPN/NX in '*phase 1'* and up to 32 mg SL BPN/NX in '*phase 2'*). The Applicant reported that, as in clinical practice, dose adjustments (increases in case of withdrawal effects or cravings or decreases for tolerability reasons) were allowed during the study at scheduled study visits during both *phase 1* and *phase 2*.

Active comparator: The study included a range of doses as used in clinical practice (8

mg to 24 mg SL BPN/NX per day in '*phase 1'* and up to 32 mg SL BPN/NX in '*phase 2'*), based on each patient's individual needs.

Primary endpoint

The primary endpoint for this study was the percentage of patients who were responders in '*phase 1'* and '*phase 2'*:

The responder definition for '*phase 1'* was as follows:

- No evidence of illicit opioid use during week 12 (evaluated during Week 13 visit).
- No more than one positive urinalysis in the six illicit opioid use assessments performed in weeks 10 to 12.

The responder definition for '*phase 2'* was as follows:

- No evidence of illicit opioid use during the week 25 visit (end of month 6).
- No more than one positive urinalysis in the six illicit opioid use assessments performed during '*phase 2'*.

6.2.2. Study Results

Patient Disposition

In study 421, 600 patients were screened and 434 patients received the SL BPN/NX test dose. Three patients did not tolerate the test dose and were not randomized. Another three subjects did not get randomized for other reasons (site logistics, withdrawal of consent after the test dose, or subject left the site after the test dose and was lost to follow-up before randomization). Therefore, 428 patients enrolled, were randomized, and received at least one dose of study drug (215 in the SL BPN/NX group; 213 in the CAM2038 group). Thus, all patients were included in the safety, ITT and PP populations by the Applicant and this data did not change from the previous submission.

As with the previous submission, per Applicant, 57.7% of the patients were identified as completers. Of the 181 (42.3%) who discontinued the study early, approximately half (n=90) were due to withdrawal by subject request (21.0% of total subjects). Eleven (2.6%) subjects withdrew from treatment but completed the study. Seven (1.6%) subjects (1 in the SL BPN/NX group and 6 in the CAM2038 group) discontinued due to an AE, which was a review issue and is elucidated in sections 8.3.1 and 8.4.3. There was one death in the CAM2038 group during the study (section 8.4.1), which was reviewed in the previous submission and remained unchanged with this submission. No new deaths were recorded from the previous application submission (Table 11).

Withdrawal by subject and lost to follow-up was reported in both groups. More subjects in the CAM2038 group withdrew due to adverse events.

Table 11: Patient disposition in Study 421

Category of Disposition Event	Subcategory of Disposition Event	Disposition Event	CAM2038		SL BPN (Control)	
			Subject Count	%	Subject Count	%
Protocol Milestone	Informed Consent	Informed Consent Obtained	213	100.0	215	100.0
	Randomization	Randomized	213	100.0	215	100.0
Disposition Event	Early Termination	Withdrawal By Subject	44	20.7	46	21.4
		Lost To Follow-Up	27	12.7	29	13.5
		Other	9	4.2	9	4.2
		Adverse Event	6	2.8	1	0.5
		Physician Decision	4	1.9	3	1.4
		Death	1	0.5	0	0.0
		Protocol Deviation	1	0.5	0	0.0
		Pregnancy	0	0.0	1	0.5
	Study Completion	Completed	121	56.8	126	58.6

Source: Applicant-provided disposition table from the 2017 NDA 210136 submission. A new disposition table was not provided with this application. This table is included for reference.

Protocol Violations/Deviations

The Applicant reported one protocol violation in Study 421 (Table 11) with the previous application submission. Examples of protocol violations with this applicant remained unchanged from the previous application and included violations of inclusion or exclusion criteria during the study and failure to adhere to the treatment schedule that were established before the database lock.

As a result of the data audit, the Applicant provided, on 5/23/18, a post hoc review of protocol deviations and violations after the datasets had been corrected. It was determined that five (not one) patients had major protocol violations related to drug exposure during the study; three patients in the CAM2038 group and two patients in the SL BPN/NX group:

CAM2038

- (b) (6) received placebo instead of 128 mg CAM2038 Monthly
- (b) (6) received a booster 8 mg dose while on CAM2038 160 mg Monthly
- (b) (6) received an extra CAM2038 Weekly dose at the start of Phase 2 (Week 13), due to delay in delivery of drug product, per Applicant, and then resumed with the CAM2038 Monthly dose at Week 14.

SL BPN/NX

- (b) (6) received an extra dose during 'phase 1', prior to first dosing in 'phase 2'

- (b) (6) received a booster dose of CAM2038 8 mg after a q4w 160 mg placebo dose.

Additional analyses with these subjects excluded (called the post hoc PP-1 population) were performed for the primary efficacy variables of RR and percentage of urine samples negative for illicit opioids, and results did not differ from the primary analysis (Section 11.4.1.1.1 and Section 11.4.1.1.2 of Study 421 report body, SDN 0079).

Reviewer's Note: Per the Applicant, the aforementioned patients did not experience SAEs or early discontinuations due to the reported violations. On review of the provided materials, I agree with the Applicant's assessment.

Further, the Applicant submitted a re-analysis of the protocol deviations in Study 421. The numbers of protocol deviations did not differ from the previous application cycle; and, as per the previous submission, those deviations did not appear to adversely affect the study outcomes. A total of 87 patients reported one or more protocol deviations, the most common of which were missed study visits (N=66) and one or more missing urine toxicology samples (N=44).

Table of Demographic Characteristics

Table 12 represents the baseline demographics at time of randomization. These values do not differ from the previous submission. All sites were located in the United States and no significant differences between baseline demographic characteristics were observed.

Table 12: Patient Demographics in Study 421

Demographic Baseline Characteristics		CAM2038 (N=213)	SL BPN/NX (N=215)	Overall (N=428)
		N (%)	N (%)	N (%)
Sex	F	92 (43.2)	73 (34.0)	165 (38.6)
	M	121 (56.8)	142 (66.0)	263 (61.4)
Age	Mean years [SD]	38.7 [11.2]	38.0 [10.9]	38.4 [11.0]
	Median years	36	36	36
	Min, Max years	19, 65	18, 65	18, 65
Age Group	N(%) Age <65 yrs	212 (99.5)	214 (99.5)	426 (99.5)
	N(%) Age ≥ 65 yrs	1 (0.5)	1 (0.5)	2 (0.5)
Race	American Indian N(%)	2 (0.9)	1 (0.5)	3 (0.7)
	Asian N(%)	1 (0.5)	0	1 (0.2)
	Black N(%)	47 (22.1)	48 (22.3)	95 (22.2)
	Native Hawaiian/Pacific Islander N(%)	1 (0.5)	0	1 (0.2)
	White N(%)	159 (74.6)	164 (76.3)	323 (75.5)
	Other N(%)	3 (1.4)	2 (0.9)	5 (1.2)
Ethnicity	Hispanic N(%)	25 (11.7)	24 (11.2)	49 (11.4)
	Not Hispanic N(%)	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]
Diagnosis of Hepatitis C at study entry		49 (23.0%)	50 (23.3%)	99 (23.1%)

Source: Reviewer

Other Baseline Characteristics

Table 13 represents a summary of other baseline characteristics of patients in Study 421, which did not differ from the previous submission.

Table 13. Other Baseline characteristics of Patients in Study 421

Category	SL BPN/NX N=215	CAM2038 N=213
Employed full time or part time, n (%)	72 (33.5)	76 (35.7)
Education, n (%)		
Did not Complete High School	37 (17.2)	36 (16.9)
High School Diploma or GED	79 (36.7)	82 (38.5)
Some College or Certificate	69 (32.1)	77 (36.2)
College or University	24 (11.2)	16 (7.5)
Graduate Degree	5 (2.3)	2 (0.9)
Primary Opioid of Use at Baseline, n (%)		
Heroin	151 (70.2)	152 (71.4)
Prescription Opioid(s)	64 (29.8)	61 (28.6)
Urine Drug Screen Results, n (%)		
Positive for Any Opioid at Screening, n (%)	200 (93.0)	193 (90.6)
Fentanyl Positive at Baseline, n (%)	49 (22.8)	62 (29.1)
Most Common Non-opioid Drugs used at Screening, n (%)	149 (69.3)	155 (72.8)
Amphetamines	32 (14.9)	38 (18.0)
Benzodiazepine	35 (16.3)	30 (14.2)
Cocaine	53 (24.7)	53 (25.1)
Marijuana	64 (29.8)	57 (27.0)
Hepatitis C at Study Entry, n (%)	50 (23.3)	49 (23.0)
Medical History of Depression, n (%)	28 (13.0)	25 (11.7)
Medical History of Major Depression, n (%)	12 (5.6%)	2 (0.9)

Source: Applicant provided table of other baseline characteristics in Study 421, extracted from Section 2.7.3 of the Study 421 Report Body.

Treatment Compliance and Concomitant Medications

No changes were made from the previous applicant submission. Treatment compliance was measured through drug dispensing inventory management and drug accountability, per the Applicant-provided protocol. Many patients (67.1%) took at least one concomitant medication during the study (Table 14). Overall, the most common class of concomitant medications taken during the study was opioids (22.2%), followed by anti-inflammatory medications. The use of concomitant medications was comparable between the treatment groups. Thirty-five subjects

took CYP3A4 inhibitors during the study (after randomization). Of these, 11 were in the CAM2038 treatment group and 24 were in the SL BPN/NX treatment group.

Table 14: Use of Concomitant Medications in Study 421

Drug Classes*	CAM 2038 (N=213) N (%)	SL BPN/NX (N=215) N (%)	Total (N=428) N (%)
Patients taking at least 1 medication	145 (68.1)	142 (66)	287 (67.1)
Adrenergics/Inhalants	15 (7.0)	15 (7.0)	30 (7.0)
Antidepressants	29 (13.6)	30 (14.0)	59 (13.8)
Anti-inflammatory agents	33 (15.5)	29 (13.5)	62 (14.5)
Antipsychotics	14 (6.6)	12(5.6)	26(6.1)
Anxiolytics	17 (8.0)	21 (9.8)	38 (8.9)
Drugs for Constipation	11 (5.2)	15 (7.0)	26 (6.1)
Hypnotics and Sedatives	17 (8.0)	14 (6.5)	31 (7.2)
Opioids**	41 (19.2)	54 (25.1)	95 (22.2)
Other analgesics and antipyretics	4 (11.2)	30 (14.1)	54 (12.6)

Source: Reviewer-derived from Applicant-provided data in Clinical Study Report HS-11-421: Table 14.1.6.2.
*WHO drug ATC Class designations. This table represents most widely used drug classes by patients in the study.
** On 12/20/2017, the Applicant clarified that the use of opioids during the study included patients transferring back to SL BPN or requiring it for analgesia.

CAM2038 Dosing Patterns and Rescue Medication Use: "Booster" dosing

To better visualize how CAM2038 was dosed in Study 421, Dr. Travis plotted the administered dose of CAM2038 over time for each patient in the study. Figure 7 shows the plot for 'phase 1', which was comprised of CAM2038 Weekly doses. Figure 8 shows the plot for 'phase 2' which employed CAM2038 Monthly dosing. The 8 mg CAM2038 dose of the Weekly formulation was mostly used in the first week of Study 421 as a booster dose for patients who needed it. The 8 mg CAM2038 dose was also allowed as a booster dose for patients who required additional supplemental doses later in the study. In both uses, the 8 mg CAM2038 dose was added to the previously administered CAM2038 dose and is indicated by a red + symbol in both plots. Dose adjustments were permitted throughout the entire study, which was consistent with the Applicant's choice of study design.

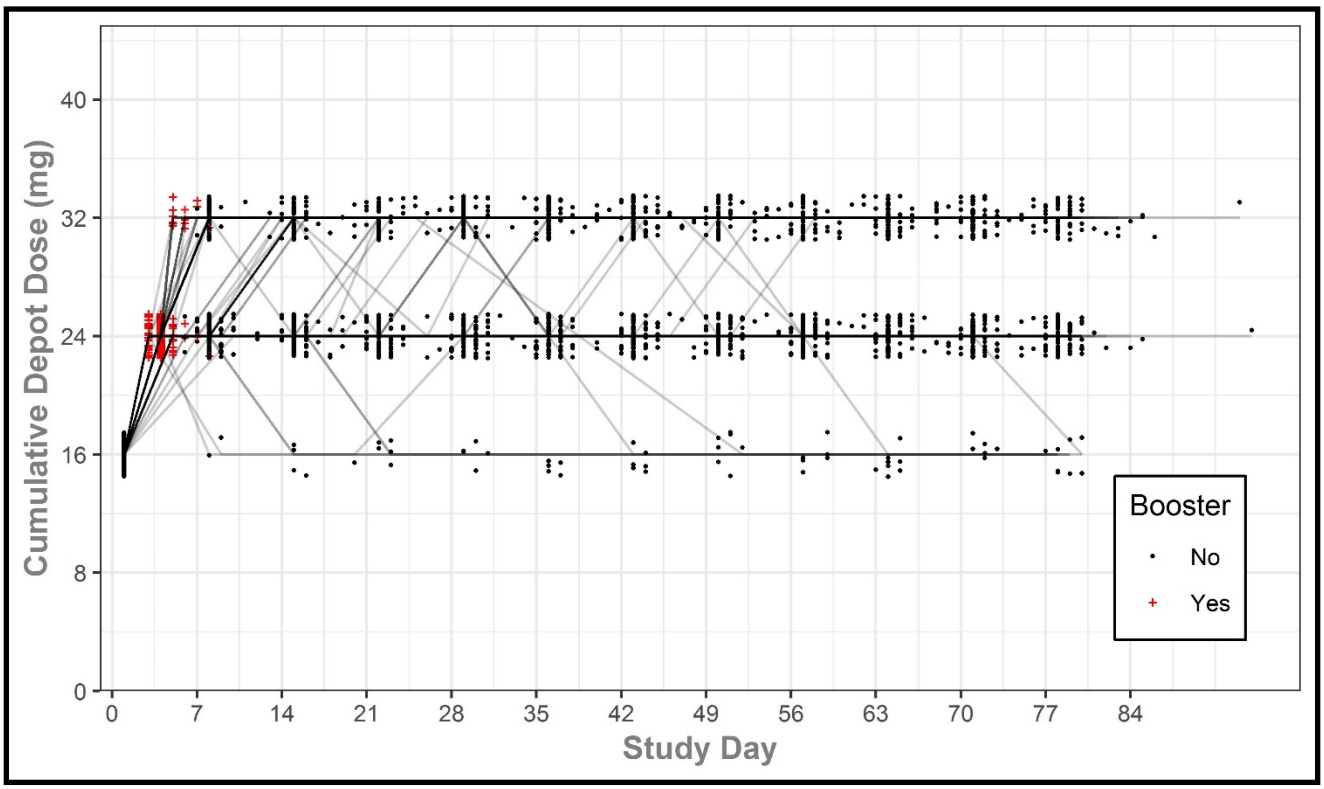

Figure 7: CAM2038 Dosing Patterns for 'phase 1' (Months 1-3) in Study 421
Source: Statistical reviewer, Dr. Travis

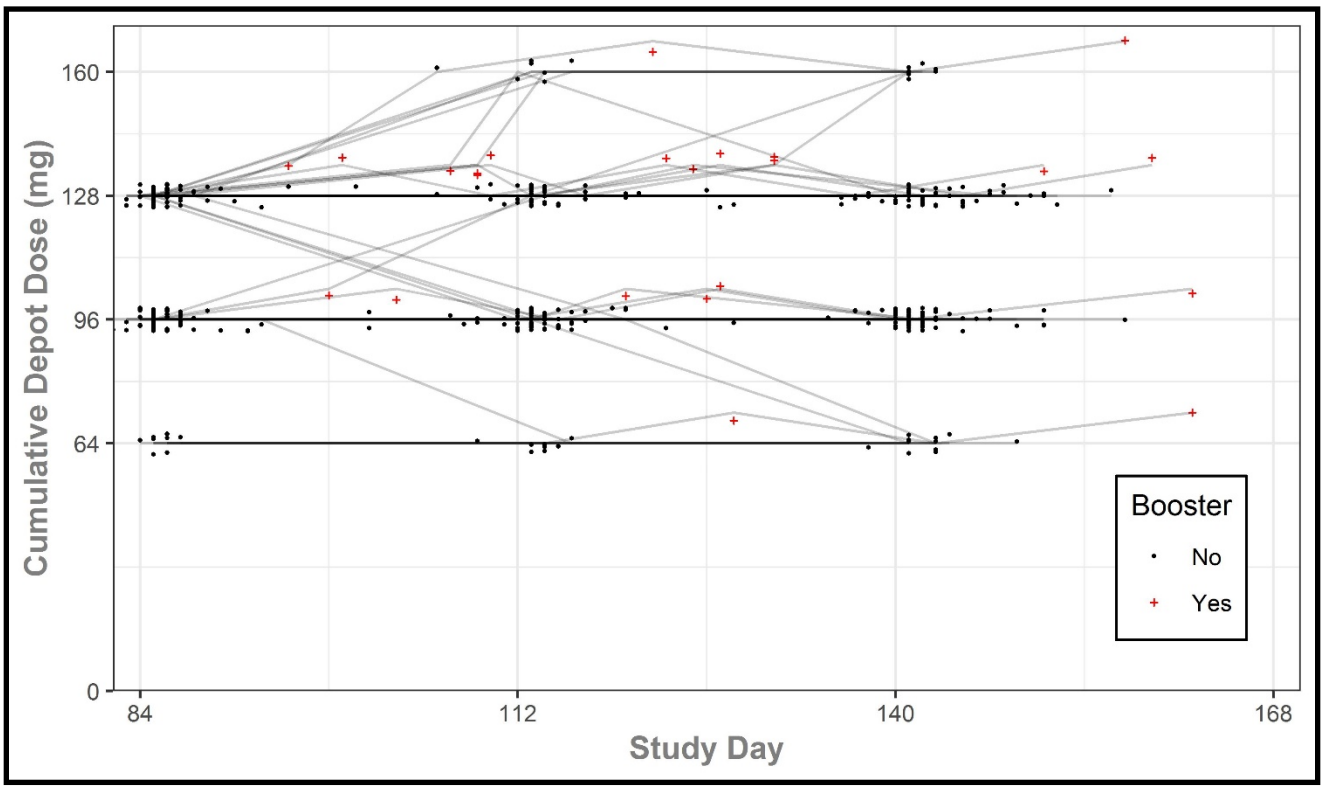

Figure 8: CAM2038 Dosing Patterns for 'phase 2' (Months 4-6) in Study 421
Source: Statistical reviewer, Dr. Travis

Efficacy Results – Primary Endpoint

This review of efficacy focused on the analyses that were impacted by the data quality issues identified during the first review cycle. The updated primary efficacy analysis is shown in Table 15. The results were unaffected by the changes made to the corrected data. And because the lower bound of the confidence interval (-3.9%) exceeds the 10% margin that was agreed upon with the Agency, it is evident that CAM2038 was non-inferior to SL BPN/NX. It should be noted that Dr. Travis' efficacy findings do not agree with the Applicant's results as there were two patients (HS-11-421-(b) (6) and HS-11-421-(b) (6)) incorrectly defined as responders by the Applicant. These patients failed to meet the responder definition due to positive urinalyses at their final visit and were classified as non-responders in Dr. Travis' analysis.

Table 15: FDA Statistical Reviewer Analysis of Responder Rate in Study 421

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)	Non-Inferiority P-value 2-sided
Responder, n (%)	36 (16.9%)	30 (13.9%)	2.9% (−3.9%, 9.8%)	< 0.001
Non-Responder, n (%)	177 (83.1%)	185 (86.0%)		

Source: Statistical reviewer, Dr. Travis
Abbreviations: CI, Confidence interval; SL BPN/NX, sublingual buprenorphine/naloxone

The applicant classified a urinalysis as indeterminant if at least one of the individual panels was classified as "unanalyzable". The Applicant considered these samples as negative in their analyses. In Dr. Travis' analysis, indeterminant samples were considered positive. Table 16 shows Dr. Travis' sensitivity analysis with indeterminate results characterized as positive. As a result, the number of responders in each treatment arm decreased slightly but the estimated treatment effect remains similar. Thus, the conclusion of non-inferiority does not change as the lower bound of the 95% confidence exceeds the pre-specified margin of 10%.

Table 16: FDA Statistical Reviewer Sensitivity Analysis of Responder Rate in Study 421

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)
Responder, n (%)	33 (15.5%)	27 (12.6%)	2.9% (−3.6%, 9.5%)
Non-Responder, n (%)	180 (84.5%)	188 (87.4%)	

Source: Statistical reviewer, Dr. Travis
Abbreviations: CI, Confidence interval; SL BPN/NX, sublingual buprenorphine/naloxone

Dr. Travis provided an additional responder rate analysis of 'phase 1' of Study 421, the phase that administered only the CAM2038 Weekly formulation to patients randomized to the treatment arm (Table 17). Although the Applicant did not design Study 421 to evaluate the CAM2038 Weekly or Monthly formulation independent of each other, the Division sought to determine if CAM2038 Weekly showed the same pattern of efficacy as the trials predetermined efficacy endpoints. Because the lower bound of the confidence intervals (-2.6%) exceeds the 10% margin that was agreed upon with the Agency, evidence suggests that CAM2038 Weekly, independent of CAM2038 Monthly, was also non-inferior to SL BPN/NX.

Table 17: FDA Statistical Reviewer Analysis of Responder Rate in 'phase 1' of Study 421

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)	Non-Inferiority P-value 2-sided
Responder, n (%)	65 (30.5%)	53 (24.7%)	5.9% (−2.6%, 14.3%)	< 0.001
Non-Responder, n (%)	148 (69.5%)	162 (75.3%)		

Source: Statistical reviewer, Dr. Travis
Abbreviations: CI, Confidence interval; SL BPN/NX, sublingual buprenorphine/naloxone

In addition to the responder analyses presented above, the Applicant presented analyses of the cumulative distribution function of the percentage of negative opioid use assessments over week 5-25. These results are shown are shown in Figure 9. A corresponding tabulation of that figure is shown in Table 18, listing the Cumulative Distribution Function (CDF) of percentage of urine samples negative for illicit opioids Supported by self-reported illicit opioid use in weeks 5-25 of Study 421. Numerically, a greater proportion of patients provided greater percentages of negative urine samples for patients receiving CAM2038 compared to SL BPN/NX. This was confirmed by the statistical hypothesis test shown in Table 19. These results are unchanged from the Applicant's original analyses. Further, Dr. Travis performed corresponding analyses of the CDF of the percentage of negative urine samples for the sensitivity analyses he performed (where indeterminate results were classified as positive). Please see Dr. Travis' review for a tabular listing of those results. His subsequent analyses and our conclusions are consistent with the previous analyses using the applicant's methodology.

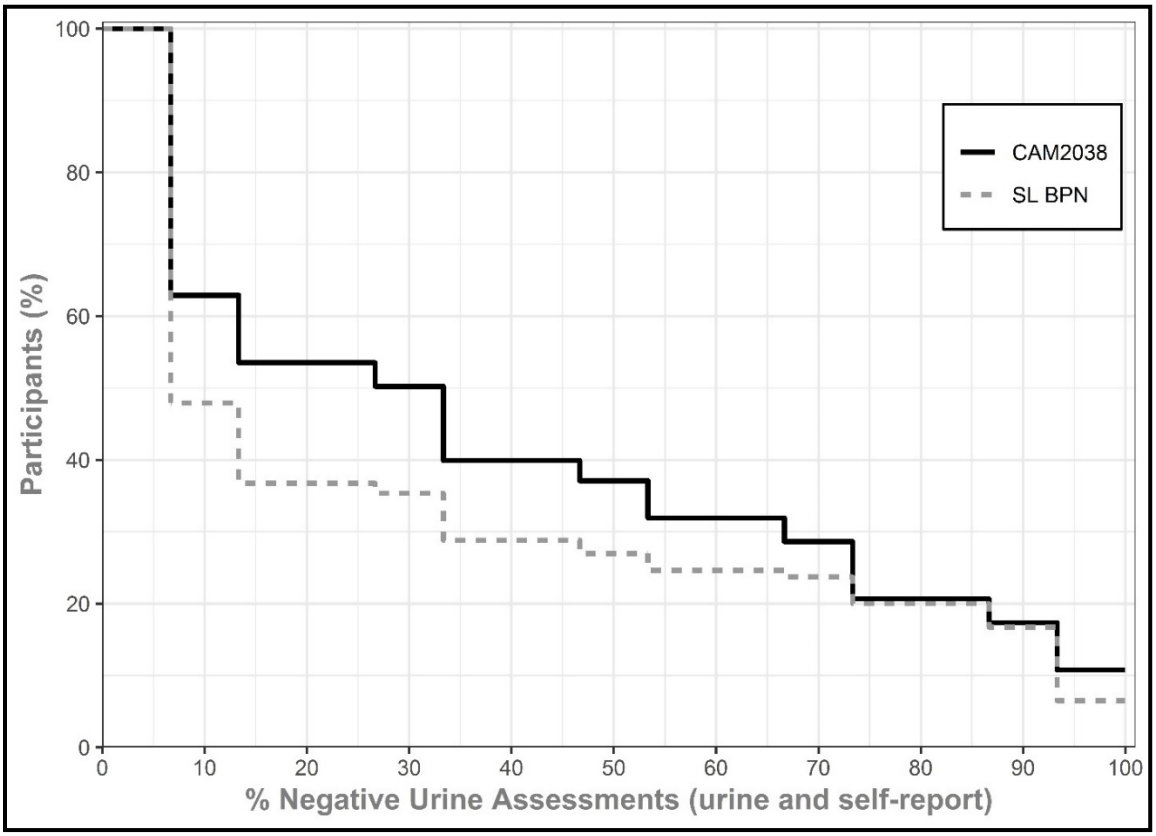

Figure 9: CDF of Percentage of Negative Opioid Use Assessments over Weeks 5-25

Source: Statistical reviewer, Dr. Travis

This Figure shows the Cumulative Distribution Function (CDF) of the percent of negative opioid use assessments over weeks 5-25 in Study 421.

Table 18: CDF for Illicit Opioids by Self-Report

% Self-Reports Negative for Illicit Opioid Use	Number (%) of Patients	
	CAM2038 N=213	SL BPN/NX N=215
≥ 0%	213 (100.0)	215 (100.0)
≥ 10%	121 (56.8)	87 (40.5)
≥ 20%	114 (53.5)	79 (36.7)
≥ 30%	95 (44.6)	67 (31.2)
≥ 40%	85 (39.9)	62 (28.8)
≥ 50%	74 (34.7)	56 (26.0)
≥ 60%	68 (31.9)	53 (24.7)
≥ 70%	51 (23.9)	49 (22.8)
≥ 80%	44 (20.7)	43 (20.0)
≥ 90%	28 (13.1)	27 (12.6)
≥ 100%	23 (10.8)	14 (6.5)

Source: Statistical reviewer, Dr. Travis
This table shows the Cumulative Distribution Function (CDF) for Illicit Opioids supported by self-reported illicit opioid use over weeks 5-25 in Study 421.

Table 19: CDF of Percentage of Urine Samples Negative for Illicit Opioids by Self-Report

Statistic	CAM2038 N=213	SL BPN/NX N=215
Mean (SD)	35.1 (37.17)	26.7 (37.15)
Median	26.7	0
Min, Max	0.0 – 100.0	0.0 – 100.0
Wilcoxon Rank Sum Test P-value	0.004	

Source: Table 14, Applicant's Study Report, 5/23/2018
Abbreviations: SD, standard deviation; SL BPN/NX, sublingual buprenorphine/naloxone.
This table shows the Cumulative Distribution Function (CDF) of negative urine samples for illicit opioid use supported by self-reported illicit opioid use over weeks 5-25 in Study 421.

Utilizing the corrected datasets provided by the Applicant, updated plots of the opioid use assessment results were made and are displayed in Figure 10. In this patient-level presentation, each test result for each individual patient is represented along the y-axis. On the x-axis are the time points during which opioid use assessments were completed.

From Dr. Travis' review, "In this study, opioid use assessments were completed weekly for the first twelve weeks, followed by monthly scheduled tests with three randomly scheduled assessments during the final twelve weeks. Light blue circular dots are used to represent opioid- negative assessments, while orange triangular dots are used to represent opioid-positive assessments. Ideally, a patient achieving treatment success would have many more

blue data points than red data points, particularly along the right-hand side of the x-axis which represents later periods of the study. The data points that appear as black '+' symbols denote missing samples. Black stars indicate patients who did not complete all three randomly scheduled assessments during the final three months. Patients who did not complete the full study are shown at the top of each display, ordered by the total time in the study. Opioid use assessments after discontinuation were assumed to be positive. Completers are shown in the bottom of each display, arranged by time to last positive opioid use assessment. In both treatment arms, there were several patients who did not complete the required follow-up after completion of the double-blind portion of the study but were considered responders."

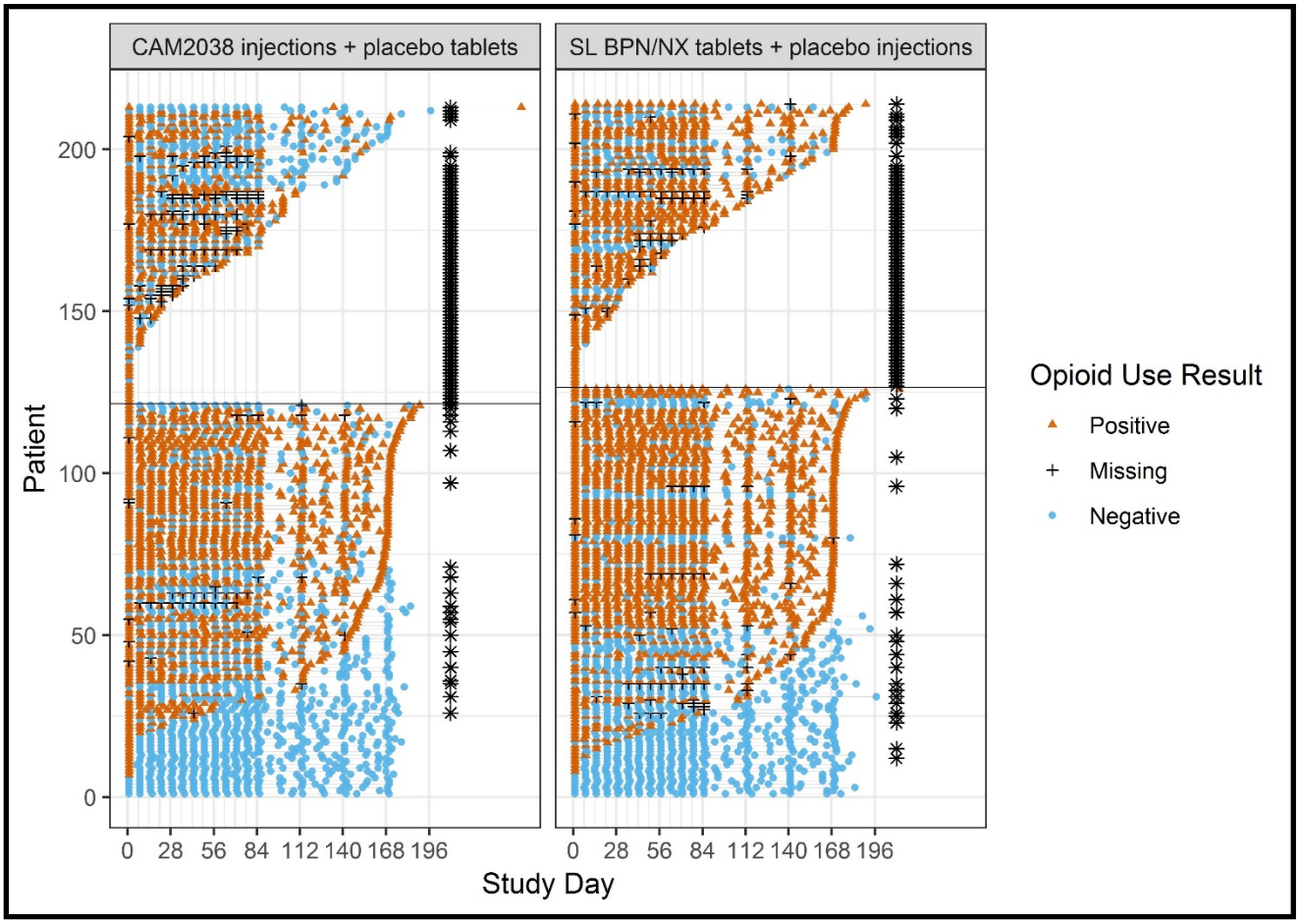

Figure 10: Plot of the Opioid Use Assessment Results

Source: Statistical reviewer, Dr. Travis

Note: Patients with missed random tests are indicated by a star on the right-hand side of the plot. Patients above the horizontal line did not complete the entire study and were classified as non-responders.

Figure 11 shows the urinalysis results for patients who were classified as responders in Study 421. These results used the same pattern of color-coded classification that was outlined above.

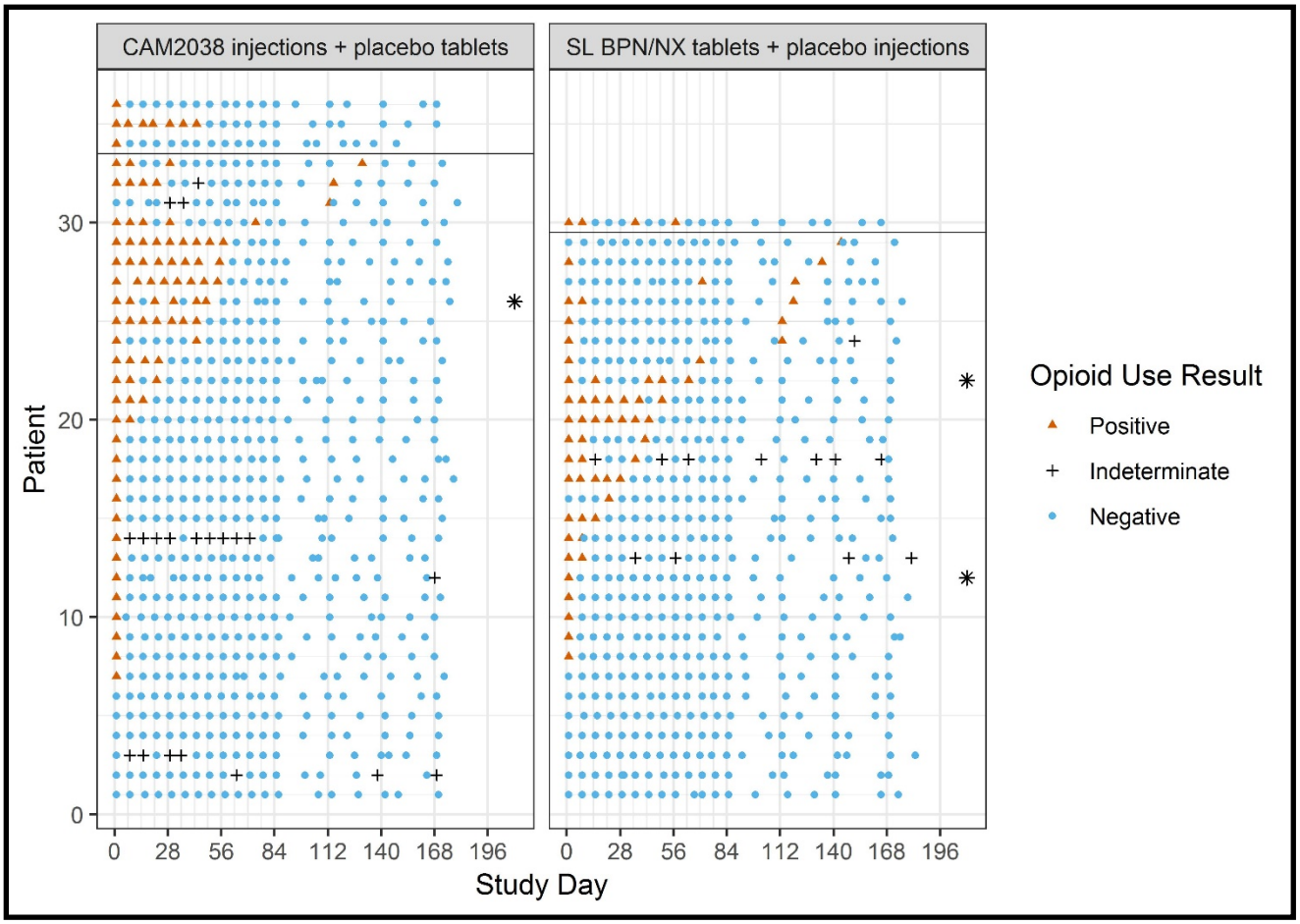

Figure 11: Plot of the Urinalysis results for Responders
Source: Statistical reviewer, Dr. Travis
Patients with missed random tests are indicated by a star on the right-hand side of the plot.

Data Quality and Integrity

In my previous review, I noted that there were numerous cases of uncorrected data errors that should have been detected and corrected in the applicant's original audit of the data which brought into question the overall quality and integrity of the submitted datasets. In response to these concerns the applicant conducted an additional audit which confirmed and corrected the noted data errors. It was therefore determined that the data quality issues noted in the original cycle were adequately addressed with this application submission.

Additional Analyses Conducted on the Individual Trial

Patient opioid use and route of use at time of study start

Analyses for two special subgroups (primary opioid of use at initiation and route of illicit opioid) are shown in Table 20. Patients reported primaryily as heroin users who received SL BPN/NX had a lower response rate (4.6%) than seen overall (13.9%) while those who received CAM2038 had a similar response rate (14.5%) to the overall CAM2038 response rate (16.9%). Patients who primarily used prescription opioid pain relievers had a higher response rate in both treatment groups compared to the overall rate. The same effect is seen for injection vs non-injection users in both treatment groups. This trend is reversed for patients who reported primarily prescription opioid pain reliever use at baseline with patients receiving SL BPN responding at a higher rate (35.9%) than patients who received CAM2038 (23.0%).

Table 20: Primary Analysis by Opioid Use History

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)
Primary opioid of use at initiation			
Heroin	22/152 (14.5%)	7/151 (4.6%)	9.8% (3.3%, 16.4%)
Prescription opioid pain reliever	14/61 (23.0%)	23/64 (35.9%)	-13.0% (-28.8%, 2.8%)
Route of illicit opioid			
Injection	17/113 (15.0%)	8/111 (7.2%)	7.8% (-0.3%, 16.0%)
Non-injection	19/100 (19.0%)	22/104 (21.2%)	-2.2% (-13.1%, 8.8%)

Source: Statistical reviewer, Dr. Travis

Although these results appear to be consistent with the expectation that patients with more severe opioid use disorder would be more likely to benefit from the enforced compliance of depot formulations, this analysis is post-hoc (b) (4) (b) (4) (It may also be noted that these post-hoc analyses suggest that CAM 2038 may not be as effective as sublingual buprenorphine for patients whose primary drug of choice is prescription analgesics.)

7. Integrated Review of Effectiveness

7.1. Considerations and Relevant Benefits of CAM2038

It is evident, in the context of the country's current opioid crisis and the results of the November 1, 2017, FDA Advisory Committee (AC) meeting, that a product with the features of CAM2038 holds clinical-meaningfulness to both patients and physicians and that the clinical

benefit of a product with multiple possible dosing regimens, could be desirable in a clinical setting. Thus, despite the review issues of this application from the previous cycle into this one, the availability of two formulations (Weekly and Monthly); adjustable dosing (four doses in the Weekly formulation and three in the Monthly formulation); and with the availability of a supplemental 8 mg Weekly dose to augment the patient's treatment regimen, are benefits of CAM2038 (noted in the panel's comments regarding the CAM2038 drug product during the 2017 AC meeting).

Reviewer's Comment: Because CAM2038 can be administered after a single test dose of transmucosal buprenorphine, this product has the potential to be used early on in MAT or, potentially, in emergency room settings where treatment can be initiated before the patient follows up with a provider upon discharge (however, this was not part of the clinical development program or studied by the Applicant and, therefore, the efficacy of this treatment paradigm is not known). Thus, CAM2038 could provide clinical benefits for the treatment of OUD.

8. Review of Safety

8.1. Safety Review Approach

The safety evaluation of this application did not include new studies and was based primarily on the pivotal efficacy study 421 and the supporting open-label study 499, like the evaluation of the previous review cycle. The emphasis of this review was to better understand the dose-adverse event relationship of CAM2038 based on resubmitted documentation from the Applicant, which was previously difficult to ascertain. This review also re-evaluated the treatment emergent adverse events, laboratory findings, vital signs, protocol violations, injection site reactions, and study discontinuations of the application. Further, this evaluation was compared with the previous submission and differential findings are noted as they are presented in the text below.

Several changes were made by the Applicant in response to the Quality Control review made on Study 421. These changes did not affect the safety conclusions of the review and represent differences in individual exposure counts or numbers of exposures to CAM2038. However, the changes did not lead to statistically meaningful differences that would preclude CAM2038 drug approval. (b) (4) In summary, this review revealed no new safety findings that would preclude approval of this application, or necessitate other regulatory action.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Across the seven studies in the clinical development of CAM2038 for OUD, 729 subjects (no change in the number of subjects previously reported) were exposed to at least one dose of the study drug (including healthy volunteers); which represented 8697 injections (from 8693 in the previous submission) of CAM2038 (of either formulation) and an average of 11.9 injections per subject. Across dosing regimens, 604 subjects received CAM2038 WEEKLY only and 408 subjects received CAM2038 Monthly only. Table 21 represents the safety analysis set, defined by the Applicant as all patients with OUD who took at least one dose of CAM2038 and had at least one post-baseline safety assessment (N = 594).

Table 21: Overall Patient Exposure to CAM2038 in the Clinical Program

Duration of Exposure	CAM2038 WEEKLY (N=531)	CAM2038 MONTHLY (N=346)	CAM2038 Total (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%)

Source: Extracted from the Applicant-provided Summary of Clinical Safety, 2017 (and 5/23/2018 resubmission)
The value in the CAM2038 column does not necessarily match the sum of the CAM2038 Weekly and CAM2038 Monthly columns. For example (and per Applicant), if a patient was treated for 3 weeks with 24 mg CAM2038 Weekly, 5 weeks with 32 mg CAM2038 Weekly and 40 weeks with 128 mg CAM2038 Monthly, the patient was not included as treated for at least 48 weeks with CAM2038 Weekly or CAM2038 Monthly but in the total column for CAM2038. Thus, the patient would appear as treated for at least 8 weeks with CAM2038 Weekly; at least 24 weeks with CAM2038 Weekly; and at least 48 weeks with CAM2038.

Most subjects received both formulations of CAM2038 because Study 421, per protocol, began all patients on the Weekly formulation and any patient still in the study at the end of Week 12 was switched to the Monthly formulation. In the open-label study, dosing was entirely at investigator's discretion and many participants were exposed to both formulations. This review focuses on the Phase 3 studies, of which 440 patient exposures (who received 7917 injections, with a mean of 18 injections per patient) to CAM2038 were reported in the clinical program.

Table 22 elucidates the number of patients exposed to the varying doses of the CAM2038 Weekly and Monthly formulations the pivotal Phase 3 Study (421) on review of the audited materials, which differs from the previous submission and is shown in Table 23. These changes did not affect the conclusions about the approvability of the CAM2038 drug product. I also included the active comparator arm for reference in both tables because patients taking SL BPN could also receive "booster" injections of the 8 mg CAM2038 product, if symptomatic. In total, thirteen patients in the CAM2038 group and 17 in the SL BPN group received booster injections in Study 421.

Table 22: Patients Exposed and Injections Administered in Study 421

CAM2038 Dose (mg)	CAM2038 Formulation	Number of Patients Exposed (*Number injections administered*)	
		CAM2038	SL BPN
8	Weekly	200 (*238*)	198 (*239*)
16	Weekly	213 (*277*)	215 (*257*)
24	Weekly	142 (*1045*)	153 (*1163*)
32	Weekly	85 (*729*)	90 (*714*)
64	Monthly	11 (*27*)	4 (*11*)
96	Monthly	88 (*224*)	85 (*233*)
128	Monthly	68 (*159*)	73 (*182*)
160	Monthly	9 (*14*)	9 (*15*)

Source: Reviewer

Table 23: Patients Exposed/Injections Administered in Study 421 from the 2017 Submission

CAM2038 Dose (mg)	CAM2038 Formulation	Number of Patients Exposed (*Number injections administered*)	
		CAM2038	SL BPN
8	Weekly	199 (*237*)	197 (*241*)
16	Weekly	211 (*278*)	212 (*262*)
24	Weekly	146 (*1058*)	156 (*1165*)
32	Weekly	84 (*721*)	89 (*709*)
64	Monthly	11 (*27*)	5 (*13*)
96	Monthly	89 (*224*)	84 (*228*)
128	Monthly	68 (*159*)	74 (*181*)
160	Monthly	9 (*14*)	9 (*15*)

Source: Reviewer

8.2.2. Relevant characteristics of the safety population

In general, the Phase-3 safety population did not differ from that of the efficacy population and was comprised of moderate to severe OUD subjects who were treatment seeking. Within the safety and efficacy and efficacy population were subjects who were "new entrants" to or those returning to BPN treatment. Study 499 included those subjects, in addition to subjects who were transferring to CAM2038 from another form BPN treatment. Despite a relatively small database of total exposures (~ N=700) to both CAM2038 formulations in the clinical program, the safety findings appeared to be representative of the target population; allowing for generalizability of the safety findings in this review. No changes to the relevant characteristics of the safety population were identified in this review.

Study 421

The study population was comprised of patients with OUD, approximately 50% of them were former intravenous drug abusers, and many of them had a history of hepatitis and elevated liver function tests. Please refer section 6.2 for the review of the patient population and baseline demographics for Study 421.

Study 499

Like Study 421, the population of Study 499 (N=227) had many of the same baseline characteristics (including patients with history of intravenous drug use and patients with a history of hepatitis C/elevated liver function tests) with few other demographic differences. No changes were made to tabulation of the baseline clinical characteristics of this study (Table 24) based on the data audit. Of the 227 subjects who enrolled in Study 499, 156 subjects were included in the safety population (128 who were receiving SL BPN at time of entry and 28 who were new to BPN treatment) because they completed a median duration of 48 weeks (range: 47-50 weeks) exposure to CAM2038. The Applicant referred to this as the "Full Exposure Safety Population".

The primary differences between patients in Study 499 compared with Study 421 were:

- Subject selection criteria: Although there were no differences in the inclusion and DSM-5 criteria for OUD, Study 499 included new entrants to treatment AND subjects transferring from current BPN treatment; compared with Study 421, which was comprised of only new entrants to treatment and subjects who had not been on a buprenorphine product for at least 60-days before study start.
- CAM2038 dosing regimen: Study 499 employed flexible dosing throughout the 48-week open-label treatment period, which makes pooling study data by Dose/AE data difficult

Table 24: Demographics and Baseline Clinical Characteristics of Patients in Study 499

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

Abbreviations: BMI, body mass index; BPN, buprenorphine; SD, standard deviation; SL BPN, sublingual buprenorphine; US, United States.
Source: Table 14.1.2.1 and Table 14.1.3.1.

Source: Applicant-provided Study 499 Demographics table from 2017 and the 5/23/2018 application resubmission.

8.2.3. Adequacy of the safety database

In general, the common systemic adverse events associated with CAM2038 treatment were similar to those seen with sublingual buprenorphine treatment and no new findings were identified in this review. The review of the hepatic effects and effects on cardiac conduction, were also consistent with buprenorphine's expected effects. The most notable aspects of the safety database were:

- The large number of discontinuations and 'withdraw by consent' in the CAM2038 program (which did not differ significantly from the active control group and might reflect the population characteristics of the recruited patients in the clinical trials)

- the safety database of numbers of exposures to doses of CAM2038 greater than 24 mg Weekly and 90 mg Monthly were small, which made it difficult to generalize safety information for a specific dose. Further, because patients transitioned between weekly and monthly formulations, I was not able to evaluate safety specifically by formulation or dose.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Prior the conclusion of the previous application cycle on January 19, 2018, it was agreed upon that the Applicant would conduct a quality control (QC) analysis of the data, focusing on Study 421, to evaluate the root cause of the clinical discrepancies identified in the first review cycle. The Applicant hired (b) (4) associates to perform the QC analyses of the data, which was reviewed. The preliminary results of those findings were submitted to the Agency December, 2017, and the final report was made available on May 23, 2018.

Thus, the strategy for this submission included a thorough review of the resubmitted Study 421 and ISS ADAE datasets, including, but not limited to, the following documents:

- 12/21/2017: The Applicant submitted the protocol deviation plan that was not included with previous submission.
- 12/22/2017: QC analysis of data
- 1/04/2018: resubmitted data
- 4/04/2018: Summary of changes, injection site listings by site, post hoc and updated tables and figures for Study 421
- 5/23/18: Resubmission of NDA 210136 with clinical data; Complete QC report for Study 421 (Prepared (b) (4) on March, 7, 2018); and summaries of changes in PDF format, REMS, labeling, and a Safety Update not included with the previous submission (*summarized in Section 8.4.2 of this review*). The resubmission also included several post hoc tables (SAS outputs) of Applicant-provided Study 421 and ISS analyses.
- 6/26/2018: Class II resubmission, with dataset corrections, resubmitted STDM and ADAM datasets (ISS, Study 421, Study 499), annotated CRF, and Study 499 reviewer's guide.
- 7/03/2018: Response to clinical Information Request, Incomplete Response letter submitted by Agency 6/22/2018, and Study 421 clarification of OUD subject classification by symptoms severity. Specifically, this documentation summarized changes between the previous 2017 NDA submission in terms of the ISS and Study 499 datasets as a result of the QC audit. Although the raw data did not change, the programming rule used to derive adverse event by dose was corrected. Those corrections resulted in 28 occurrences (records) with dose-change assignments. The corrections did not change the findings of the study. Thus, the ADAE and Study 499

ADEFF datasets were updated to reflect the QC corrections.

- 7/12/2018: resubmitted ISS dataset (ADAE) with data definition guide, which included EXLOC, VISIT, dose volume, and supplemental use flag. Changes affected derived, but not raw, data in Studies 421 and 499. These changes appeared related to the timing of AE in the context of dosing and did not affect the conclusions about the overall safety profile of CAM2038.
  Reviewer's note: *This was the dataset used to generate my analyses and comparisons with the Applicant-provided data for this review and did not reveal issues that would preclude NDA 210136 approval.*
- 9/13/2018: Response to clinical Information Request for clarification of discontinuations in Studies 421 and 499.

Audit of resubmitted materials
As with the previous submission, the case report forms (CRFs) provided adequate summaries for each patient. Further, I audited CRFs to evaluate the consistency of adverse event information reported across the CRF, the narrative summary, and the individual trial adverse event tabulations (ADAE dataset) for each of the subjects in Study 421 who were listed as having experienced a non-fatal SAE. My analysis of the resubmitted data utilized the ADaM datasets.

The adverse event information was found to be consistent across documents. However, in-text Tables of Study Report 421 still presented numeric differences in the presentation of the "Serious TEAEs"; "SAEs"; "Nonfatal SAEs". For example, there were several instances where the text report (in the Study Report Body for Study 421) of an adverse event did not align with the SAS line items or the text/table reports did not match the symptom severity as defined in the protocol (e.g., "requiring hospitalization" meets criteria for an SAE but several hospitalization events were listed as non-serious AEs). After review of the available data, I believe they are adequately characterized in section 8.4.2.

Another example of organizational inconsistency was the designation of subject (b) (6) as having had a "Moderate TEAE" when he was hospitalized for a seizure with dehydration, hypokalemia, hyperglycemia, and illicit substance withdrawal symptoms. A similar example included subject (b) (6) a 31-year-old female who was randomized to 32 mg CAM2038 when an SAE was reported. On review of the CRF, she experienced nonfatal SAEs of sacral fracture and injury with hospitalization, in the context of a motor vehicle accident (MVA) and positive urine toxicology screen, but the SAEs was marked as *mild* or *moderate intensity* and *not treatment emergent* in the safety database. No changes to the aforementioned events were made between application submissions and those events remained consistent with this application review. However, and despite my lack of concurrence with the Applicant's reporting, my findings (even upon recategorization of those events for consistency) did not compromise the safety review or my conclusions of the overall safety profile of the CAM2038 product.

A revised Study 499 and Integrated Summary of Safety (Clinical Summary of Safety by the Applicant) written report was not provided with this resubmission. However, the Applicant did provide a Summary of Clinical Safety for the clinical development program with a Summary of Changes addendum (text clarifications). Additionally, the Applicant resubmitted the ISS dataset (SDN 0081 dated July 12, 2018) with updated variables (including EXLOC and PREDOS/PREREG, which were missing from the SDTM data sets) to facilitate identification of injection site reactions and adverse event by dose, which were independently reviewed.

8.3.2. Categorization of Adverse Events

Adverse Events (AE)
As with the previous review, an AE was defined as any new untoward medical occurrence or worsening of a preexisting medical condition regardless of causal relationship with treatment. Each reported AE required a complete and thorough description on the AE case report form (CRF). An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or increase in severity of a preexisting abnormality, temporally associated with the use of a medicinal (investigational) product, whether considered related to the medicinal (investigational) product or not.

Treatment Emergent Adverse Events (TEAE)
A TEAE was defined as any AE with an onset date on or after date of randomization, or any ongoing event on the date of first dose that worsened in severity after date of randomization. Per the Applicant, only TEAEs with an onset date prior to date of last dose + 30 days were tabulated in summary tables. TEAEs considered by the investigator to be 'possibly', 'probably', or 'definitely' related to study drug were classified as study drug-related events.

Reviewer's note: On review, I identified TEAE's not coded as treatment emergent that met criteria for treatment emergent. Specifically, this included injection site reactions. My findings did not change the interpretation of the Applicant's results.

Serious Adverse Events (SAE)
A SAE was any untoward medical occurrence at any dose that, per the Applicant, resulted in any of the following outcomes or actions:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization (not including treatment for a previous condition or elective procedure)
- Persistent or significant disability or incapacity
- A congenital anomaly or birth defect (in an offspring)

- An important medical event that did not result in death, was not life threatening, or did not require hospitalization, but jeopardized the subject and required medical intervention to prevent one of the outcomes listed in this definition.

An AE that did not meet any of the criteria for seriousness listed above was regarded as a non-serious AE by the Applicant. Deaths, non-fatal SAEs, and AEs leading to discontinuation were also examined from Studies 421 and 499 and are described in sections 8.4.

Coding and Auditing
Adverse event investigator terms were coded to Preferred Terms using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0, terminology, per the Applicant. The categories of adverse event preferred terms of interest included 'Hepatic', 'Suicide', 'Mood', 'Cardiovascular', and, 'Overdose, Abuse, Depression, and Dependence'. I assessed the accuracy of the Applicant's coding process by examining several variables, including: AEBODYSYS, AEHLGT (reported term) and AEDECOD (Preferred Term) in the adverse event dataset (ADAE) using JMP, version 12.2.0, and MAED, version 1.9 (for a MedDRA summary). Coding was judged to be reasonably accurate.

In addition, I audited an approximate 10% sample of reported adverse events from the ISS dataset ADAE.XPT, in Studies 421 and 499, to compare the reported (verbatim) term (AEDECOD) with the coded (or preferred) term. I identified no deficiencies in adverse event coding from this audit. However, as with my previous review of the safety data, I noticed instances where multiple coded terms could represent very similar adverse events (e.g., supraventricular tachycardia and tachycardia). For purposes of this review, all preferred terms reflective of one condition, (e.g., increased heart rate) were carefully evaluated. Those findings did not change the conclusions about the safety profile of CAM2038 or affect my assessment of the Applicant's findings/reports.

8.3.3. Routine Clinical Tests

No new data was submitted and no changes were made from the previous submission. As with the previous submission, no significant differences or abnormalities between groups were identified in routine clinical tests. Additionally, the identified QC issues did not affect the raw or derived laboratory data.

8.4. Safety Results

8.4.1. Deaths

No new deaths were reported for the clinical studies submitted with this application.

Study 421

One, previously reported, death occurred in a subject randomized to CAM2038. This subject was described in my previous review: a 41-year-old female with no other reported medical history and no concomitant medications reported within 30 days of the start of the event. On Day 147 (b) (6) at approximately 1:30 am, she attempted to cross a 4-lane street when she was hit by a car and died instantly (motor vehicle accident). Per the Applicant, there was no evidence of suicidal ideation during the study or at the last visit. She denied using substances since her last visit; however, urine drug screen was positive for marijuana and benzoylecgonine. The urine toxicology labs were negative for opiates. After reviewing the case, I concurred that the death was not likely related to CAM2038.

Study 499: No deaths were reported for OL Study 499.

Supportive studies: No deaths were reported in Studies 307 or 549.

8.4.2. Serious Adverse Events (SAEs)

Non-fatal SAEs in the clinical program

The pattern of SAEs did not identify novel systemic findings inconsistent with the known safety profile of buprenorphine. No SAEs were related to injection site injury, per the Applicant, and this was confirmed. Narratives of SAE's did not appear misleading. As with the previous submission, the Applicant reported a total of 20 events in 17 subjects (2.3%) across all 729 subjects (including healthy volunteers) in the CAM2038 clinical program supporting this application. Table 25 shows the nonfatal SAE's reported in the clinical program. These values did not differ from that of the previous submission.

Table 25: Summary of Applicant-provided SAE's in the CAM2038 Clinical Program

Category	Severity	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%)

Source: Reviewer, derived from Applicant-provided summary of safety, Table 37, SDN 0075, Module 2.1.3, 5/23/18.
Abbreviations: SAE = serious adverse event
Table represents Applicant-provided AE by severity in the entire clinical program (including Healthy Volunteers).

Reviewer's note: The pattern of SAEs did not identify novel systemic findings inconsistent with the known safety profile of buprenorphine and the narratives of SAE's did not appear misleading. Of note, I disagree with the Applicant's report of symptom severity but this did not adversely affect my review of the CAM2038 product.

New to this submission is a SAE that was identified in the CAM2038 program involving chronic pain patients requiring buprenorphine treatment. In a communication dated 5/23/2018, the Applicant reported that a SAE occurred in a subject who was exposed to CAM2038 in IND (b) (4) (not the supporting IND 114082 for this application) after the 2017 database lock and before NDA 210136 was submitted. The related SAE and MedWatch Safety report was submitted to IND (b) (4) on 6/29/2017 but not disclosed with the previous NDA 210136 application. At the time the event occurred, the Applicant determined that the event was not related to the CAM2038 although the individual investigator did consider CAM2038 to be a contributing factor. The SAE occurred in a morbidly obese female subject with type II diabetes, obstructive sleep apnea, and history of cardiovascular disease who presented to the emergency department with acute onset altered mental status, rhabdomyolysis, acute renal failure, and markedly elevated liver transaminases leading to acute liver failure. She presented to the emergency department one day after receiving the first depot injection of 8 mg after and was medically managed in intensive care, after which the episode resolved and she was discharged to home and discontinued from study participation. Follow-up to the initial report was also made. The patient recovered completely from the SAE. The Applicant maintains that the event

was not likely related to the study drug. On review of the case and the follow-up, it cannot be ruled-out that CAM2038 was a contributing factor to the events that led to the patient requiring hospitalization. Buprenorphine has been associated with hepatic toxicity, as noted in labeling for sublingual buprenorphine products. However, several comorbid contributing factors made it difficult to assign causation.

Study 421

As with the previous submission, the Applicant reported five (2.3%) subjects with non-fatal SAEs in the CAM2038 group compared with 13 (6.0%) in the SL BPN group in Study 421; and fifteen subjects (3 in the CAM2038 group and 12 in the SL BPN group, respectively) were hospitalized in Study 421. These numbers did not differ from the previous submission but the non-fatal SAEs identified in the CAM2038 group are listed in Table 26. This table does include one SAE (subject 113-006) that was not reported as an SAE in the Clinical Study Report because the event was considered not to be treatment emergent by the Applicant. Because of the timeline of events (the patient had taken one dose of CAM2038), the event is characterized by me as a treatment-emergent SAE. However, I do not think that SAE appears to be related to CAM2038. Similarly, most of the reported SAE's do not appear to be causally linked to CAM2038. Two events for which a relationship to CAM2038 seems possible are highlighted in gray below.

Table 26: Non-fatal SAEs Reported in the CAM2038 Group in Pivotal Study 421

Subject	Sex	Age (yrs)	Event	CAM2038 dose at time of SAE reporting
(b) (6)	F	24	Pregnancy that led to brief hospitalization and elective abortion in an African American female. This event did not appear related to CAM2038.	64 mg Monthly
	M	23	Suicidal ideation in Caucasian male, who continued in the study, he was admitted to the hospital on day 141 of the study due to agitation and suicidal ideations in the context of intoxication (cocaine, cannabis, and benzodiazepines). He was released from the hospital on quetiapine after his mood improved and he continued in the study. This event did not appear related to CAM2038.	128 mg Monthly
	M	51	Non-cardiac chest pain in a Caucasian male on day 21 of CAM2038 treatment (previous dose was 16 mg Weekly). He had a history of gastric ulcers, atrial fibrillation and coronary artery disease and went to the hospital after substernal burning pain did not resolve with nitroglycerin. Concomitant medications included diltiazem, duloxetine, baclofen, amitriptyline, pregabalin, and tizanidine. Hospitalization did not reveal cardiac origin of pain (including serial negative troponins, echocardiogram, ECG, and cardiac stress test). The Applicant reported that the event was not due to the study medication. Upon review of the case, it was difficult to determine causality but CAM2038 could have been a contributing factor.	32 mg Weekly
	F	31	MVA that led to sacral fracture and hospitalization in a Native Hawaiian female after she fell asleep at the wheel of her vehicle while driving, during study participation. Urine toxicology was positive for illicit substances but she denied intoxication or substance use. The accident was listed as serious but the events were marked as mild or moderate in the safety database and not treatment emergent. Upon review of the case, it was difficult to determine causality but CAM2038 could have been a contributing factor.	32 mg Weekly
	M	54	African American male was admitted to hospital shortly after study start with sepsis secondary to a bacterial infection (cellulitis) after self-report of cut on rusty tail pipe. Participant stopped study. This SAE was considered by the Applicant to be a non-treatment emergent event and thus, was not included in reports of SAEs related to the CAM2038 product. Upon review of the case, it was difficult to determine causality but CAM2038 did not appear to be a contributing factor.	16 mg Weekly
	M	47	On day four of CAM2038, a Caucasian male, with a history of gastroesophageal reflux disease, esophageal tears, and self-induced vomiting, experienced nausea and vomiting leading to hospitalization. He discontinued the Study. The Applicant had reported that the event did appear related to CAM2038. Upon review of the timeline, CAM2038 did appear to be a contributing factor.	16 mg Weekly

Source: Reviewer

SAEs in the active comparator group (SL BPN/NX) included one seizure in a patient with a known history of epilepsy who was identified as having abused benzodiazepines; accidental

overdose (N=4); intentional overdose (with suicidal ideations status post intoxication (N=1); elevated liver enzymes (N=5); cellulitis (N=2, not related to injection site reactions); tooth abscess (N=1); arthralgia (N=1); backpain (N=1); decreased libido (N=1). Of note, no accidental or intentional overdoses were reported for subjects treated with CAM2038; compared with the five reported overdoses in the SL BPN/NX group [four accidental (three with heroin, one with clonazepam) and one intentional overdose during a suicide attempt]. None were fatal.

Study 499

The summary of SAEs in OL Study 499 is provided in Table 27 and did not differ from the previous submission. 17 SAE's in 14 subjects were identified in study 499 in the overall safety population (N=227). In the identified safety population (N=156), the Applicant reported that 15 of them were treatment emergent. On review of the safety dataset, three of the SAEs in Study 499 occurred in patients taking CAM2038 Monthly[16]; in one of which, the patient who experienced ventricular tachycardia, CAM2038 could have had a contributory role (cases possible related to CAM2038 are shaded in the table). Six patients experienced SAEs on CAM2038 Weekly[17]; in none of which CAM2038 appeared to have a contributory role.

Table 27: Summary of Serious AEs in Study 499

Subject	Sex	Age (yrs)	Event	CAM2038 formulation at time of SAE reporting
(b) (6)	M	37	Presented to ER with unspecified convulsion and paranoia. Admitted benzodiazepine abuse and was admitted to psychiatric unit. After admission, urine was found positive for amphetamines, THC, buprenorphine, benzodiazepines, and oxycodone. Upon review of the timeline, CAM2038 did not appear to be a contributing factor.	128 mg Monthly
	M	47	Duodenitis. Patient was hospitalized and treated. Upon review of the timeline, CAM2038 did not appear to be a contributing factor.	96 mg Monthly
	M	42	Follicular Thyroid carcinoma. With postoperative cellulitis requiring treatment. Upon review of the timeline, CAM2038 did not appear to be a contributing factor.	32 mg Weekly
	F	32	Substance induced psychosis: patient admitted 6-weeks of methamphetamine use and was sent to hospital via ambulance from the study site with auditory hallucinations and suicidal ideations. Upon review of the timeline, CAM2038 did not appear to be a contributing factor.	96 mg Monthly
	M	44	Drug withdrawal syndrome due to abrupt antidepressant discontinuation: Patient was sent to the hospital by his mother for disorientation, diarrhea, anxiety, diaphoresis. He was treated in the hospital returned to medications and discharged. Upon review of the timeline, CAM2038 did not appear to be	160 mg Monthly

[16] Subjects (b) (6) (ventricular tachycardia), (b) (6) (disc degeneration), and (b) (6) (UTI)
[17] Cellulitis (not related to injection site reaction), Thyroid Carcinoma, Pneumonia, recurrence of mental disorder

(b) (6)

		a contributing factor.	
F	41	Intervertebral disc degeneration at L5-S1 with back pain and UTI. Patient hospitalized and treated for infection. The Applicant did not consider this event to be related to CAM2038. Upon review of the timeline, CAM2038 did not appear to be a contributing factor.	64 mg Monthly
M	46	Patient was hospitalized for community acquired pneumonia and treated with antibiotics. The Applicant did not consider this event to be related to CAM2038. Upon review of the timeline, CAM2038 did not appear to be a contributing factor.	24 mg Weekly
M	53	Patient was treated for malignant melanoma of the skin (which was biopsied and resolved). The Applicant did not consider this event to be related to CAM2038. Upon review of the timeline, CAM2038 did not appear to be a contributing factor.	128 Mg Monthly
M	38	Patient presented to ER with acute intoxication and was admitted for drug detoxification. Urinalysis revealed benzodiazepine, cocaine, and pregabalin. The Applicant did not consider this event to be related to CAM2038. Upon review of the timeline, CAM2038 did not appear to be a contributing factor. *The Applicant did not consider this event to be treatment emergent.*	16 mg Weekly
F	34	Patient had surgical removal of gallbladder for acute on chronic cholecystitis. The Applicant did not consider this event to be related to CAM2038. Upon review of the timeline, CAM2038 did not appear to be a contributing factor.	64 mg Monthly
M	47	MVA with facial fracture, intervertebral disc injury, multiple injuries, throat trauma, R leg fracture requiring surgery (11 procedures) and wheelchair, after rear-ending another vehicle. The SAE was considered not related to the study drug, per Applicant. It is unclear if CAM2038 was a contributory factor in the MVA and cannot be ruled out.	32 mg Weekly
F	56	Ventricular tachycardia occurred in a patient after drinking five Red Bull energy drinks in succession. Patient was treated at a hospital and received defibrillation. An implantable defibrillator was placed. The Applicant did not consider this event to be related to CAM2038. It is unclear if CAM2038 was a contributory factor in the event but on review of the case, although unlikely, I can't rule out a contributory role of CAM2038.	64 mg Monthly
M	24	Patient was taken to hospital by sister after suffering seizure. Attributed to abrupt benzodiazepine withdrawal. Patient had been taking 2 mg alprazolam daily for 6-months. The Applicant did not consider this event to be related to CAM2038. On review of this case, CAM2038 does not appear to be a contributing factor.	64 mg Monthly
F	34	Reported case of Neonatal Abstinence Syndrome (NAS). Patient was not on CAM 2038 at the time of the event: her baby was born with NAS. Patient had stayed in the study after she found out she was pregnant but was taking Subutex at time of delivery. Baby was treated with morphine sulfate. No birth anomalies. The Applicant did not consider this event to be related to CAM2038. CAM2038 did not appear to be a contributing factor but patient is listed as having had a 128 mg Monthly injection during treatment. Thus, it is not possible to rule out CAM2038 (or other buprenorphine product).	---

Source: Reviewer

Supportive Studies: No SAE's were reported or identified for studies 307, 478, or 549.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In general, the number of patients and healthy volunteers exposed to CAM2038 and discontinued from any study in the entire clinical development program was 226 (31.0%). However, the number of participants who were reported as discontinued due to an AE in the clinical development program was lower [12 (1.6%) out of the 729 exposures, which included healthy volunteers]. Reasons for discontinuation included physician decision, lack of efficacy, lost to follow-up, withdrawal by subject, and other and are highlighted in Table 28. The reported values of discontinuations between application cycles did not change but the Applicant provided a reanalysis of these discontinuations, which is described below.

Table 28: Applicant-Provided Discontinuations in the Clinical Development Program

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

Source: Applicant-provided summary of clinical safety, Table 37, SDN 0075, Module 2.1.3, 5/23/18

Per the Applicant, the following protocol specified criteria were used to determine if a subject was listed as discontinued from the study:

- Discretion of the study investigator or sponsor
- in the event of an adverse event
- if the patient was lost to follow-up

- If a patient withdrew themselves from the study

The following criteria were used to determine subject study discontinuation by the investigator or Applicant:

- Patient refused or was unable to adhere to the study protocol
- Major protocol violation (e.g., violation of inclusion or exclusion criteria during the study, failure to adhere to the treatment schedule)
- Pregnancy
- Physician's discretion

Narratives were provided of discontinuations that were attributed to AE. These narratives themselves did not appear misleading but the Applicant's categorization of reason for discontinuation was a focus of review because some of the discontinuations for other reasons may have been more accurately attributed to AEs. In the pooled studies 421 and 499, 123 patients were listed as 'withdrawal by subject', 17 patients were discontinued by 'Physician Decision', and 16 were discontinued by 'other'. Per the Division's IR, the Applicant reanalyzed these data and contacted the Sites that reported discontinuations in these studies. The Applicant submitted this reanalysis on 9/13/2018[18], in the form of text narratives and Excel formatted listings of patients who discontinued for any reason (for the pooled Studies 421 and 499); and included whether the discontinuation was affiliated, at any time point, with an AE, whether or not the Applicant considered the discontinuation to be related to an AE. I audited the materials and determined that the subsequent findings did not change the overall safety profile of CAM2038 or the total number of discontinuations in these studies. However, the reanalysis did reveal differences in the reasons for patient discontinuation, namely discontinuations due to AEs, and are outlined below.

Study 421

For discontinuations due to any reason, Table 29 shows the Applicant-reported tabulation of all discontinuations, including AEs that led to patient discontinuation, in Study 421 for this application cycle. Thus, per the Applicant, six patients in the CAM2038 group (2.8%) discontinued due to an AE and one ((0.5%) discontinued in the SL BPN/NX arm, for a total of seven reported discontinuations. These numbers were consistent with the previous application cycle.

[18] SDN 88: \\CDSESUB1\evsprod\NDA210136\0088

Table 29: Applicant-reported Discontinuations in Study 421

Discontinuations	CAM2038 N= 213	SL BPN/NX N=215	TOTAL (N=428)
Discontinuation for any reason	92 (43.2%)	89 (41.4%)	181 (42.3%)
Discontinuation due AE*	6 (2.8%)	1 (0.5%)	7 (1.6%)
Discontinuation due to Withdrawal by Subject	44 (20.7%)	46 (21.4%)	90 (21.0%)
Discontinuation due to Physician Decision	8 (3.8%)	4 (1.9%)	12 (2.8%)
Discontinuation due to Lost to Follow-up	27 (12.7%)	29 (13.5%)	56 (13.1%)
Discontinuation due to Other	6 (2.8%)	8 (3.7%)	14 (3.3%)
Discontinuation due to Death	1 (0.5%)	0 (0.0%)	1 (0.2%)
Discontinuation due to Pregnancy	0 (0.0%)	1 (0.5%)	1 (0.2%)

Source: Reviewer. Derived from Applicant Table 14.1.1.2, Study 421 - Section 14 tables resubmitted 5/23/2018 (page 7 of 395)
*This is Applicant-provided data but inconsistent with the Applicant provided numbers for total subjects who discontinued Study 421 due to a treatment adverse event. In text, and upon, line listing verification, the total number of Applicant provided discontinuations as of 5/23/2018, was ten: seven subjects in the CAM2038 and 3 subjects in the SL BPN/NX groups.

However, upon further review, (and in reference to the Applicant provided Study 421 report body text 12.3.1.3 (page 122) and Applicant-provided table of narratives of discontinuations and SAEs in section 14.3.3 of the study report), the Applicant stated that a total of ten patients, in Study 421, discontinued due to an adverse event (seven patients in the CAM2038 and 3 patients in the SL BPN/NX groups) before the requested reanalysis was performed and submitted to the Agency September, 13, 2018. Those subject numbers are listed in Table 30.

Table 30: Reviewer-reported Discontinuations in Study 421 before 2018 Reanalysis

CAM2038	SL BPN/NX
(b) (6)	

Source: Reviewer. Extracted from Applicant-provided table of narratives of discontinuations and SAEs in section 14.3.3 of the Study 421 report body.
Numbers listed are the individual subject numbers of patients who were discontinued due to an adverse event before the Applicant submitted data related to Study 421 discontinuations.

Further, upon the September 2018 reanalysis of Study 421 discontinuations, the Applicant corrected the total number of discontinuations due to AE's to be twelve: eight patients (3.8%) in the CAM2038 group and four (1.9%) in the SL BPN/NX group discontinued due to an AE.

However, my subsequent review of those data yielded different findings than that of the

Applicant but did not preclude approval of the CAM2038 product. My review of the of discontinuation report yielded the following subject numbers of patients who discontinued due to AEs:

- (b) (6) Previously coded as withdrawal by subject. Moderate AE (possibly related) of liver function test abnormal. Five days later, a positive hepatitis C test was revealed, classified as a moderate AE (not related). The patient discontinued from the study two months later (SL BPN/NX)
- (b) (6) Previously coded as physician decision and discontinued due to "moderate AE of hepatic enzyme increased that was not considered to be related to study drug" Patient was referred to gastroenterologist (CAM2038)
- (b) (6) Discontinued due to injection site ulcer. Previously coded as withdrawal by subject (SL BPN/NX)
- (b) (6) Discontinued due to injection site ulcer. Previously coded as withdrawal by subject (CAM2038)
- (b) (6) Previously coded as physician decision and discontinued due to "mild AEs" of anxiety and depression (CAM2038)

Therefore, I identified a total of 15 discontinuations due to AEs (10 in the CAM2038 group and five in the SL BPN/NX group) that were formerly tabulated as discontinuations due to other causes (Table 31). Section 13.2 shows the subjects numbers that I identified as having discontinued from Study 421 compared with what the Applicant reported as a discontinuation due to an AE.

Table 31: Reviewer-reported Discontinuations in Study 421 after 2018 Reanalysis

Discontinuations	CAM2038 N= 213	SL BPN/NX N=215	TOTAL (N=428)
Discontinuation for any reason	92 (43.2%)	89 (41.4%)	181 (42.3%)
Discontinuation due AE	10 (4.7%)	5 (2.3%)	15 (3.5%)
Discontinuation due to Withdrawal by Subject	43 (20.2%)	44 (20.5%)	87 (20.3%)
Discontinuation due to Physician Decision	6 (2.8%)	4 (1.9%)	10 (2.3%)
Discontinuation due to Lost to Follow-up	27 (12.7%)	29 (13.5%)	56 (13.1%)
Discontinuation due to Other	6 (2.8%)	8 (3.7%)	14 (3.3%)
Discontinuation due to Death	1 (0.5%)	0	1 (0.2%)
Discontinuation due to Pregnancy	0	1 (0.5%)	1 (0.2%)

Source: Reviewer. Derived from Applicant Table 14.1.1.2, Study 421 - Section 14 tables resubmitted 5/23/2018 and Clinical Information amendment SDN 088, 9/2018.
This table reflects my enumerations of discontinuations in Study 421 after the Applicant-provided additional analyses and narratives of patient discontinuations.

Study 499

No new tabulations were provided for OL Study 499 and the Applicant reported that three patients withdrew (1.3%) due to an AE in the overall safety population (n=227), which was comprised of all patients enrolled in Study 499. Two of them discontinued due to injection site TEAE's (0.9%)[19] and one discontinued to several TEAEs (due to a road traffic accident)[20]. However, on review and in the Study Report, the Applicant identified two other discontinuations due to "pain in extremity" (in a patient new to BPN treatment)[21] and an abnormal ECG[22] (in a patient who was transferred from SL BPN/NX). Therefore, before the reanalysis, five patients had discontinued due to an AE (2.2%).

Of the 70 patients (30.8%) who discontinued the study for reasons not related to an AE, approximately half (n=33) were due to withdrawal by subject request (14.5% of total subjects). Thirteen patients (5.7%) were lost to follow-up, and 12 (5.3%) discontinued due to lack of efficacy. Per the study report, four patients who completed 48 weeks of treatment were subsequently lost to follow-up. Line listings were provided by the Applicant; a tabulation was not provided. The most common type of event leading to discontinuation in all studies was "lost to follow-up".

Upon reanalysis of the data, in response to our IR, the Applicant identified three patients who discontinued in Study 499 and were not included in the original study report: (b) (6) was previously coded "physician decision" and discontinued due to an EEG abnormality that did not require treatment, Patient (b) (6) discontinued due to Injection site reaction, and patient (b) (6) discontinued due to fatigue and myalgia. Thus, the total number of discontinuations due to AEs in Study 499 was 4.0%. Table 32 shows the discontinuations reported in Study 499 (within the overall safety population) before and after the data audit. Section 13.2 shows the subject numbers of patients that I identified as having discontinued from a TEAE Study 499.

[19] Patients (b) (6) (ISR of pain, tenderness and erythema) and (b) (6) (ISRs of erythema, pruritus, swelling)
[20] Patient (b) (6) (multiple injuries reported with SAE).
[21] Patient (b) (6)
[22] Patient (b) (6)

Table 32: Discontinuations Reported in Study 499 before and after Data Audit

Discontinuations	TOTAL Provided with submission (N=227)	TOTAL Provided by Clinical Reviewer after data audit (N=227)
Discontinuation for any reason	70 (30.8%)	70 (30.8%)
Discontinuation due AE	4 (1.8%)	9 (4.0%)
Discontinuation due to Withdrawal by Subject	33 (14.5%)	30 (13.2%)
Discontinuation due to lack of efficacy	12 (5.3%)	12 (5.3%)
Discontinuation due to Physician Decision	5 (2.2%)	4 (1.8%)
Discontinuation due to Lost to Follow-up	13 (5.7%)	13 (5.7%)
Discontinuation due to Other	2 (0.9%)	2 (0.9%)
Discontinuation due to Death	0	0
Discontinuation due to Pregnancy	1 (0.4%)	1 (0.4%)

Source: Reviewer. Derived from Applicant Table 14.1.1.2, Study 421 - Section 14 tables resubmitted 5/23/2018
This table reflects my enumerations of discontinuations in Study 421 after the Applicant-provided additional analyses and narratives of patient discontinuations.

8.5. Significant Adverse Events

Cardiovascular effects, hepatic effects, and injection site reactions are of concern among opioids and injectables. In addition, the AE profile of SL BPN has been characterized in the safety databases for buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets. marketed, approved products. Each of the event types of notable concern to this drug product are reviewed below in their representative sections. This section will focus on non-fatal significant adverse events. Further discussion of events of concern is also found in section 8.8 (Submission-specific safety concerns).

8.5.1. Treatment Emergent Adverse Events and Adverse Reactions

Table 33 illustrates the most common treatment emergent adverse events (TEAEs) in the pooled Phase 3 studies in the CAM2038 development program. TEAEs are grouped by High Level Group Term (HGLT) and Preferred Term (PT). Specific findings for Studies 421 and 499 are outlined below. Common AEs included administration site reactions, infection, gastrointestinal symptoms, and nervous system disorders (headache). This table also reflects all injection site reactions: the Applicant did not flag all injection site reactions as treatment emergent.

Table 33: TEAEs by HGLT in CAM2038 in the Pooled Phase 3 Studies

Adverse Events (**≥2%)** by HGLT in Pooled Phase 3 Studies HS-11-421 and HS-13-499	
System Organ Class (SOC) High Level Group Term (HLGT)[a] Preferred Term (PT)	CAM2038 Total[b] (N=440) N (%)
Cardiac disorders	
Cardiac arrhythmias	10 (2.3%)
Tachycardia	8 (<2.0%)
Gastrointestinal disorders	
Dental and gingival conditions	12 (2.7%)
Toothache	11 (2.5%)
Gastrointestinal motility and defaecation conditions	37 (8.4%)
Constipation	22 (5.0%)
Diarrhea	15 (3.4%)
Gastrointestinal signs and symptoms	50 (11.4%)
Nausea	31 (7.0%)
Vomiting	21 (4.8%)
General disorders and administration site conditions	
Administration site reactions	87 (19.8%)
Injection site pain	56 (12.7%)
Injection site swelling	38 (8.6%)
Injection site erythema	35 (8.0%)
Injection site pruritus	19 (4.3%)
Injection site reaction	9 (2.0%)
General system disorders NEC	29 (6.6%)
Fatigue	13 (3%)
Infections and infestations	
Bacterial infections disorders	9 (2.0%)
Cellulitis	4 (<2%)
Injection site cellulitis	3 (<2%)
Infections - pathogen unspecified	100 (22.7%)
Urinary tract infection	23 (5.2%)
Nasopharyngitis	22 (5.0%)
Upper respiratory tract infection	15 (3.4%)
Viral infectious disorders	23 (5.2%)
Influenza	9 (2.0%)
Viral infection	7 (<2%)
Injury, poisoning and procedural complications	
Injuries NEC	37 (8.4%)

Laceration Road traffic accident	6 (<2%) 6 (<2%)
Musculoskeletal and connective tissue disorders	
Joint disorders	17 (3.9%)
Arthralgia	11 (2.5%)
Muscle disorders	9 (2.0%)
Muscle spasm	5 (<2%)
Musculoskeletal and connective tissue disorders NEC	26 (5.9%)
Pain in extremity Back pain	13 (3.0%) 11 (2.5%)
Nervous system disorders	
Headaches	40 (9.1%)
Headache	34 (7.7%)
Migraine	9 (2%)
Neurological disorders NEC	23 (5.2%)
Hypoaesthesia Dizziness	7 (<2%) 6 (<2%)
Psychiatric disorders	
Anxiety disorders and symptoms	15 (3.4%)
Anxiety	13 (3.0%)
Depressed mood disorders and disturbances	16 (3.6%)
Depression Depressed mood	12 (2.7%) 4 (<2%)
Sleep disorders and disturbances	18 (4.1%)
Insomnia	17 (3.9%)
Respiratory, thoracic and mediastinal disorders	
Respiratory disorders NEC	9 (2.0%)
Cough Rhinorrhea	5 (<2%) 2 (<2%)
Skin and subcutaneous tissue disorders	
Epidermal and dermal conditions	18 (4.1%)
Rash Erythema	5 (<2%) 3 (<2%)

Source: Reviewer
a = Report of adverse events that occurred in ≥ 2% of patients exposed to CAM2038 Weekly and/or CAM2038 Monthly in the Phase 3 Trials HS-11-421 and HS-13-499. Patients are represented once per HLGT and are organized by SOC. Tabulation included all events coded as treatment emergent and all injection site reactions, regardless of treatment emergent flags.
b = This group includes all subjects exposed to varying doses of both the CAM2038 WEEKLY and MONTHLY formulations.

Study 421

Common adverse events in Study 421 are listed in Table 34, and include all injection site reactions, regardless of treatment emergent flag. Common TEAEs in CAM2038, compared with

the active comparator group, include administration site reactions, gastrointestinal disorders, infections, injuries, and nervous system disorders (headache); which mirrors the observed AE profile of the pooled Phase 3 CAM2038 data and does not differ from the known effects of buprenorphine.

Table 34: Common TEAEs in Study 421

Adverse Events (**≥5%** in CAM2038 exposures) by HGLT and treatment group in Study HS-11-421		
System Organ Class (SOC) High Level Group Term (HLGT)[a] Preferred Term (PT)	CAM2038 Total[b] (N=213) n(%)	SL BPN/NX[c] (N=215) n(%)
Cardiac disorders		
Cardiac Arrhythmia	6 (2.8%)	9 (4.2%)
Tachycardia	5 (2.3)	5 (2.3)
Gastrointestinal disorders		
Gastrointestinal signs and symptoms	25 (11.7%)	21 (9.8%)
Nausea	15 (7.0%)	17 (7.9%)
Vomiting	9 (4.2%)	8 (3.7%)
General disorders and administration site conditions		
Administration site reactions	41 (19.2%)	48 (22.3%)
Injection site pain	21 (9.8%)	17 (7.9%)
Injection site erythema	14 (6.6%)	12 (5.6%)
Injection site pruritis	13 (6.1%)	13 (6.0%)
Injection site swelling	10 (4.7%)	7 (3.3%)
Injection site reaction	9 (4.2%)	7 (3.3%)
Injection site induration	4 (1.9%)	6 (2.3%)
Infections and infestations		
Infections - pathogen unspecified	34 (16%)	40 (18.6%)
Urinary tract infection	11 (5.2%)	10 (4.6%)
Upper respiratory tract infection	9 (4.2%)	9 (4.2%)
Nasopharyngitis	4 (1.9%)	2 (<1%)
Injury, poisoning and procedural complications		
Injuries NEC	16 (7.5%)	12 (5.6%)
Laceration	4 (1.9%)	3 (<1%)
Contusion	2 (<1%)	1 (<1%)
Road traffic accident	2 (<1%)	1 (<1%)
Nervous system disorders		
Headaches	17 (7.9%)	18 (8.4%)
Headache	16 (7.5%)	17 (7.9%)
Neurological disorders NEC	13 (6.1%)	10 (4.6%)
Hypoaesthesia	4 (1.9%)	0 (<1%)
Dizziness	3 (1.4%)	2 (<1%)
Paraesthesia	2 (<1%)	2 (<1%)

Sedation Somnolence	2 (<1%) 2 (<1%)	1 (<1%) 2(<1%)
Psychiatric disorders		
Anxiety disorders and symptoms	6 (2.8%)	7 (3.3%)
Anxiety	6 (2.8%)	7 (3.3%)
Sleep disorders and disturbances	12 (5.6%)	7 (3.3%)
Insomnia	12 (5.6%)	6 (2.3%)

Source: Reviewer

a = report of adverse events that occurred in > 5% of the CAM2038 population in Study 421. = Subjects are represented once per HLGT. Tabulation included all events coded as treatment emergent and all injection site reactions, regardless of treatment emergent flags. All subjects received a single test dose of 4mg SL BPN/NX before randomization into either arm.
b = This group includes all subjects exposed to varying doses of both the CAM2038 WEEKLY and MONTHLY formulations.
c = SL BPN/NX denotes the active comparator: subjects assigned to daily buprenorphine with sham (placebo) injections. Subjects randomized to this group could also receive a 'booster' injection of CAM2038, per protocol.

The Applicant also performed post hoc analyses of AEs by dose using data from the HS-11-421 study (*Module 2.7.4/ Section 2.1.1.5*). They reported the incidence of subjects with at least 1 AE increasing with increasing dose of CAM2038 Weekly in 'phase 1' (the weekly dosing). The Applicant identified a similar dose-response pattern in the active control group (SL BPN/NX). In contrast, no dose-response pattern was observed for CAM2038 q4w or the corresponding SL BPN/NX group in 'phase 2' (the phase with Monthly CAM2038 dosing). The observed increase in AEs with increasing CAM2038 q1w dose could be attributed to subjects being new to BPN treatment or because there were more exposures to the CAM2038 Weekly product compared with the Monthly product, or because the population exposed to the Monthly product had already tolerated the Weekly product. Because of the study design, any patient not completing the first 12 weeks of treatment was not exposed to the Monthly product. Limitations to interpretation exist due to the study design.

Study 499

Common adverse events in Study 499 are listed in the Applicant-provided Table 35. No new TEAEs were identified and no new analyses were provided by the Applicant. Common TEAEs included administration site reactions, gastrointestinal disorders, and nervous system disorders (headache); which does not differ greatly from the known side effects of buprenorphine.

Table 35: Applicant-provided TEAEs in Study 499

System Organ Class/Preferred Term	Overall Safety Population in Study 499		
	Currently Receiving SL BPN/NX N=190 n (%)	New to BPN N=37 n (%)	Total CAM2038 N=227 n (%)
Patients 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)
Diarrhoea	8 (4.2)	1 (2.7)	9 (4.0)
Nervous system disorders	32 (16.8)	1 (2.7)	33 (14.5)
Headache	18 (9.5)	0	18 (7.9)
Migraine	8 (4.2)	0	8 (3.5)
Musculoskeletal and connective tissue disorders	32 (16.8)	3 (8.1)	35 (15.4)
Pain in extremity	8 (4.2)	1 (2.7)	9 (4.0)
Vascular disorders	9 (4.7)	1(2.7)	10 (4.4)
Hypertension	7 (3.7)	1(2.7)	8 (3.5)

Source: Reviewer adapted from Applicant Table 22, page 91, from 499 Study Report Body, SDN 002, 2017

8.5.2. Laboratory Findings

No changes were made to laboratory data from the first application cycle to this one and the QC analyses did not indicate, to the Applicant, that additional analyses were warranted. As with the previous submission, mean laboratory findings[23] were not summarized in tables by the

[23] Basophils, eosinophils, hemoglobin, hematocrit, leukocytes, monocytes, neutrophils, platelets, amylase, lipase, albumin; liver function tests (AST, ALT, alkaline phosphatase, bilirubin); and electrolytes.

Applicant in the 421 Study report but were available for review in the provided SAS table outputs (by week of treatment) and in the datasets. Further, laboratory findings were not presented by dose, only by treatment arm (CAM2038 compared with SL BPN/NX). Inspection of reported laboratory data (specifically change from baseline at week 25/end-of-treatment) revealed no remarkable findings or differences between groups. It was not possible to ascertain laboratory changes by CAM2038 dose. Of note, laboratory reference ranges were not submitted with the application but the data were presented in such a way that the review could be conducted. No safety signals were identified in my review of the dataset.

Table 36: Laboratory Means in Study 421

Laboratory value	CAM2038 N= 213 (mean)	SL BPN/NX N=215 (mean)
Alanine Aminotransferase [ALT] (U/L) *		
Baseline	24.8	27.0
Week 25/End of treatment	24.5	26.4
Alkaline Phosphatase (U/L)		
Baseline	70.8	70.9
Week 25/End of treatment	73.0	72.7
Aspartate Aminotransferase [AST] (U/L) **		
Baseline	22.6	23.5
Week 25/End of treatment	25.5	24.6
Bilirubin (umol/L)		
Baseline	7.99	7.74
Week 25/End of treatment	8.43	7.55
Creatine Kinase [CK] (U/L) ***		
Baseline	127	151
Week 25/End of treatment	205	179
Gamma Glutamyl Transferase (U/L)		
Baseline	34.2	36.0
Week 25/End of treatment	33.3	36.4

Source: Reviewer. Derived from Applicant-provided Section 14.4.2.1 'FDA tables referenced but not included' in the study report body submitted 5/23/2018

* The number of patients who had a shift from normal ALT at Baseline to high post-Baseline in ALT (normal range: 6-41 U/L) was higher in the CAM2038 group than the SL BPN/NX group throughout the study. The greatest difference was observed at Week 17 (not shown), where 11.9% of CAM2038-treated patients experienced ALT elevations compared with 3.5% in the SL BPN/NX group. However, at Week 25/End of treatment (EOT), the percent of patients who had a shift from normal at Baseline to high post-Baseline in ALT was 6.4% in the CAM2038 group and 4.0% in the SL BPN/NX group, respectively.

** The greatest difference in plasma measures was observed at Week 17 (not shown), where 15.4% of CAM2038-treated patients experienced an AST increase compared with 2.1% in the SL BPN/NX group. At Week 25/EOT, the percent of patients who had a shift from normal at Baseline to high post-Baseline in AST was 11.3% in the CAM2038 group and 6.0% in the SL BPN/NX group.

*** The greatest difference in plasma measures was observed at Week 17 (not shown), where 11.9% of CAM2038-treated patients had elevated levels of CK compared with 4.2% in the SL BPN/NX group. At Week 25/EOT, the percent of patients who had a shift from normal at Baseline to high post-Baseline in CK was 13.5% in the CAM2038 group and 9.3% in the SL BPN/NX group. No SAEs or discontinuations were related to this lab value.

Laboratory value abnormalities

In Study 421, the Applicant reported that exposure to CAM2038 did not reveal significant differences in lab abnormalities compared with SL BPN/NX and the submitted cases of lab abnormalities did not exceed what is reported with buprenorphine products. Most of the TEAEs related to laboratory values were with liver enzymes (**Table 37** and section **8.6.2**).

Table 37: Laboratory-related TEAEs in Study 421

Preferred Term	SL BPN/NX N=215 n (%)	CAM2038 N=213 n (%)	Total N=428 n (%)
Alanine aminotransferase increased	4 (1.9)	4 (1.9)	8 (1.9)
Aspartate aminotransferase increased	4 (1.9)	4 (1.9)	8 (1.9)
Gamma-glutamyltransferase increased	3 (1.4)	2 (0.9)	5 (1.2)
Blood glucose increased[a]	3 (1.4)	1 (0.5)	4 (0.9)
Hepatic enzyme increased	2 (0.9)	2 (0.9)	4 (0.9)
Haematocrit decreased	2 (0.9)	0	2 (0.5)
Haemoglobin decreased	2 (0.9)	0	2 (0.5)
Lipase increased	0	2 (0.9)	2 (0.5)
Liver function test abnormal	2 (0.9)	0	2 (0.5)
White blood cell count increased[a]	2 (0.9)	0	2 (0.5)
Blood creatine phosphokinase increased	0	1 (0.5)	1 (0.2)
Blood glucose decreased	0	1 (0.5)	1 (0.2)
Blood potassium increased	1 (0.5)	0	1 (0.2)
Blood urine present	0	1 (0.5)	1 (0.2)
Mean cell haemoglobin concentration (low)	1 (0.5)	0	1 (0.2)
Mean cell haemoglobin decreased	1 (0.5)	0	1 (0.2)
Red blood cell count decreased	1 (0.5)	0	1 (0.2)

[a] One of the 2 cases of white blood cell count increased occurred in the context of infection (Subject (b) (6)); 1 of the 4 cases of blood glucose increased occurred in a subject with diabetes type 2 (Subject (b) (6) CAM2038).
Abbreviations: SL BPN/NX, sublingual buprenorphine /naloxone; TEAE, treatment-emergent adverse event
Note: TEAEs are ordered by decreasing incidence in the Total column and then alphabetically for terms with like incidence.
Denominators for percentages were N, the total number of subjects overall. At each level of subject summarization, a subject was counted only once if the subject reported 1 or more events.
Only events that started on or after first dose date and within 30 days of last dose date were summarized.
Source: Table 14.3.5.1; Listing 16.2.7.1

Source: Applicant provided from the Study 421 Report body

Similarly, in Study 499, the Applicant reported very few (6) laboratory-related TEAEs in the Safety population (N=156; **Table 38**) and no new data was submitted. Patients who had multiple abnormal events were counted once and only events that started on or after the first dose date and within 30-days of the last dose were summarized. From the data provided, it appears that CAM2038 does not pose a specific laboratory abnormality risk compared with commercially available BPN products, and the overall findings did not differ significantly from

that which was reported for Study 421.

Table 38: Laboratory-related TEAEs in the Safety population of Study 499

	Overall Safety Population			Full Exposure Safety Population		
Preferred Term	Currently Receiving SL BPN/NX N=190 n (%)	New to BPN Treatment N=37 n (%)	Total CAM2038 N=227 n (%)	Currently Receiving SL BPN/NX N=128 n (%)	New to BPN Treatment N=28 n (%)	Total CAM2038 N=156 n (%)
Blood creatine phosphokinase increased	1 (0.5)	1 (2.7)	2 (0.9)	1 (0.8)	1 (3.6)	2 (1.3)
Blood creatinine increased	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Blood lactic acid increased	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Blood urea increased	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Liver function test abnormal	0	1 (2.7)	1 (0.4)	0	1 (3.6)	1 (0.6)

Source: Applicant provided Table 14.3.2.1

8.5.3. Vital Signs

No changes were made to vital sign data from the first application cycle and the QC analyses did not indicate, to the Applicant, that additional analyses were warranted; nor were safety signals were identified in my review of the datasets. Mean vital signs were not summarized in tables by the Applicant in the 421 Study Report but were available for review in the provided SAS table outputs (by week of treatment) and dataset. Further, vital sign findings were not presented by dose, only by treatment arm (CAM2038 compared with SL BPN/NX). Inspection of reported vital signs (specifically change from baseline at week 25/end-of-treatment) revealed no remarkable findings and no changes from baseline that were remarkable. It was not possible to ascertain vital signs by CAM2038 dose given the study design. Vital sign means from baseline to study week 25/End of treatment are presented in Table 39.

Table 39: Vital Sign Means in Study 421

Laboratory value	CAM2038 N= 213 (mean)	SL BPN/NX N=215 (mean)
Systolic Blood Pressure (mm/Hg)		
Baseline	126.6	125.3
Week 25/End of treatment	124.4	123.9
Diastolic Blood Pressure (mm/Hg)		
Baseline	79.2	80
Week 25/End of treatment	78.2	78.4
Temperature (Celsius)		
Baseline	36.7	36.8
Week 25/End of treatment	36.7	36.7
Heart Rate (beats/min)		
Baseline	77.6	78.6
Week 25/End of treatment	75.5	77.4
Respiratory Rate (breaths/min)		
Baseline	16.6	16.6
Week 25/End of treatment	16.2	15.9
BMI (kg/m^2)		
Baseline	25.6	26.2
Week 25/End of treatment	25.5	26.2

Source: Reviewer.
Derived from Applicant-provided Section 14.4.7 'FDA tables referenced but not included' in the study report body, submitted 5/23/2018

Vital Sign abnormalities

In Study 421, vital-sign[24] related TEAEs, did not appear to exceed vital sign changes observed with known BPN products, affected 5.8% of the patient population (N=428), and the TEAEs were evenly distributed between groups. No new data was submitted. One of the preferred terms were reported as an SAE and only one was attributed to the study drug (weight decreased), per Applicant. The Applicant reported that the vital sign related TEAEs were of mild-moderate intensity and did not lead to discontinuation, which appeared, on face, to be accurate (Table 40) and consistent with the previous submission.

[24] Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), temperature (Celsius), respiratory rate (breaths/min), weight (kg), height (cm), BMI (kg/m^2), ECGs.

Table 40: Vital-sign related TEAEs in Study 421

Preferred Term	SL BPN/NX N=215 n (%)	CAM2038 N=213 n (%)	Total N=428 n (%)
Tachycardia	5 (2.3)	5 (2.3)	10 (2.3)
Pyrexia	3 (1.4)	3 (1.4)	6 (1.4)
Weight decreased	3 (1.4)	3 (1.4)	6 (1.4)
Hypertension	2 (0.9)	0	2 (0.5)
Bradycardia	1 (0.5)	0	1 (0.2)

Source: Applicant provided table 14.3.5.1
A patient was counted only once for a vital sign related TEAE if they experienced more than one TEAE. Events that started on or after the first dose and within 30 days of the last dose were included.

Similarly, in Study 499, vital-sign related TEAEs did not appear to exceed the type of vital sign changes observed with known BPN products. Vital sign TEAEs affected 9.3% of the overall safety population (N=227). None of the preferred terms were reported as SAEs (Table 41) and no new data was submitted.

Table 41: Vital-sign related TEAEs in Study 499

	Overall Safety Population			Full Exposure Safety Population		
Preferred Term	Currently Receiving SL BPN/NX N=190 n (%)	New to BPN Treatment N=37 n (%)	Total CAM2038 N=227 n (%)	Currently Receiving SL BPN/NX N=128 n (%)	New to BPN Treatment N=28 n (%)	Total CAM2038 N=156 n (%)
Hypertension	7 (3.7)	1 (2.7)	8 (3.5)	7 (5.5)	1 (3.6)	8 (5.1)
Abnormal loss of weight	3 (1.6)	0	3 (1.3)	2 (1.6)	0	2 (1.3)
Pyrexia	3 (1.6)	0	3 (1.3)	3 (2.3)	0	3 (1.9)
Tachycardia	3 (1.6)	0	3 (1.3)	2 (1.6)	0	2 (1.3)
Dyspnoea exertional	1 (0.5)	0	1 (0.4)	0	0	0
Heart rate irregular	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Underweight	1 (0.5)	0	1 (0.4)	0	0	0
Weight increased	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)

Source: Applicant provided Table 14.3.2.1; and Table 14.3.2.2

8.5.4. Electrocardiograms (ECGs)

A signal for QT prolongation has been identified in a study of transdermal buprenorphine used for analgesia. The extent of prolongation noted was considered to meet the threshold for regulatory concern, a value which is used to determine whether the effect of a drug on the QT/QTc interval in target patient populations should be studied intensively during later stages of drug development. Electrocardiogram (ECG) parameters were evaluated from the Applicant-provided data for the pooled Phase 3 studies, and elevations above baseline have been noted. The data confirm that QT prolongation may be seen in patients treated with buprenorphine. In study 421, more ECG related TEAE's reported in the SL BPN arm than the group randomized to CAM2038 (seven versus three, respectively), which is supportive for the concept that ECG irregularities are related to buprenorphine and not to the specific formulation.

Study 421

Table 42 and Table 43 present the percent of patients who had an ECG-related TEAE, per Applicant, in Study 421. Within both groups, ECG-related events were few and they affected less than 1% of the safety population. The events were considered mild to moderate and did not lead to discontinuation of CAM2038 or SL BPN/NX. Narratives were provided and in my review of them, they did not appear misleading. This is consistent with the previous applicant submission and the high-level summary of from the Interdisciplinary Review Team for QT Studies.

Table 42: ECG-related TEAEs in Study 421

Preferred Term	**SL BPN/NX N=215 n (%)**	**CAM2038 N=213 n (%)**	**Total N=428 n (%)**
Electrocardiogram abnormal	2 (0.9)	1 (0.5)	3 (0.7)
Atrial fibrillation	0	1 (0.5)	1 (0.2)
Defect conduction intraventricular	1 (0.5)	0	1 (0.2)
Electrocardiogram QT prolonged	1 (0.5)	0	1 (0.2)
Electrocardiogram ST segment elevation	0	1 (0.5)	1 (0.2)
Electrocardiogram T wave amplitude decreased	1 (0.5)	0	1 (0.2)
Myocardial infarction	1 (0.5)	0	1 (0.2)
Sinus tachycardia	1 (0.5)	0	1 (0.2)

Source: Applicant-provided summary of clinical safety, Table 49, SDN 0075, Module 2.1.3, 5/23/18

Table 43: Summary of QTcF Intervals in Study 421

Timepoint/Category	SL BPN/NX N=215 n (%)	CAM2038 N=213 n (%)	Total N=428 n (%)
Baseline			
<450 ms	212 (99.5)	209 (98.1)	421 (98.8)
≥450 to <480 ms	1 (0.5)	4 (1.9)	5 (1.2)
≥480 to <500 ms	0	0	0
≥500 ms	0	0	0
Any Post-Baseline Visit			
<450 ms	181 (89.6)	170 (86.3)	351 (88.0)
≥450 to <480 ms	17 (8.4)	26 (13.2)	43 (10.8)
≥480 to <500 ms	3 (1.5)	0	3 (0.8)
≥500 ms	1 (0.5)	1 (0.5)	2 (0.5)
EOS Visit			
<450 ms	210 (98.1)	210 (98.6)	420 (98.1)
≥450 to <480 ms	4 (1.9)	2 (0.9)	6 (1.4)
≥480 to <500 ms	0	0	0
≥500 ms	0	1 (0.5)	1 (0.2)
Increase from Baseline at any Post-Baseline Visit			
<30 ms	151 (74.8)	136 (69.0)	287 (71.9)
≥30 to <60 ms	42 (20.8)	55 (27.9)	97 (24.3)
≥60 ms	9 (4.5)	6 (3.0)	15 (3.8)
Increase from Baseline to EOS Visit			
<30 ms	199 (93.0))	201 (94.4)	400 (93.4)
≥30 to <60 ms	12 (5.6)	10 (4.7)	22 (5.1)
≥60 ms	3 (1.4)	2 (0.9)	5 (1.2)

Source: Applicant-provided summary of clinical safety, Table 48, SDN 0075, Module 2.1.3, 5/23/18

Study 499

In the safety population of Study 499 (N=156), two patients (1.3%) had at least 1 ECG-related TEAE, which included myocardial ischemia and tachycardia (Table 44). No new data was submitted. A female[25] was reported with myocardial ischemia on day 337 of treatment (transfer to CAM2038), completed the study and the event was considered a TEAE of mild intensity and not related to the study drug. No narrative was provided for this case and the Applicant reported the issue as resolved with no interruption in treatment. Another female[26] (also a transfer to CAM2038) experienced a serious TEAE of tachycardia on day 313, which resulted in hospitalization. CAM2038 was not discontinued and the Applicant did report it as related to CAM2038. The patient had reported 3-5 highly caffeinated energy drinks prior to the episode and became unresponsive while driving. Concomitant medications included buspirone, citalopram, Lisinopril, and omeprazole. ECG revealed atrial flutter. The patient was provided an implantable defibrillator and continued the study. Per the Applicant, the hospitalist attributed the event to the caffeine drink. This appeared to be a reasonable assessment with

[25] Subject (b) (6)
[26] Subject (b) (6)

the provided information.

Table 44: ECG-related TEAEs in Study 499

	Overall Safety Population			Full Exposure Safety Population		
Preferred Term	Currently Receiving SL BPN/NX N=190 n (%)	New to BPN Treatment N=37 n (%)	Total CAM2038 N=227 n (%)	Currently Receiving SL BPN/NX N=128 n (%)	New to BPN Treatment N=28 n (%)	Total CAM2038 N=156 n (%)
Electrocardiogram QT prolonged	1 (0.5)	0	1 (0.4)	0	0	0
Electrocardiogram QRS complex abnormal	1 (0.5)	0	1 (0.4)	0	0	0
Myocardial ischaemia	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Ventricular tachycardia	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)

Source: Applicant provided Tables 14.3.2.1 and 14.3.2.2 from SDN 002, 2017

A formal review by the Interdisciplinary Review Team for QT Studies (QT-IRT) was performed during the first review cycle (refer to the 11/27/2017 review; reference ID: 4185454). The materials submitted with this application (as with the previous one because the data had not changed) supported an absence of large mean increases (i.e., 20 ms) in the QTc interval for CAM2038 at the time of expected maximum BPN exposure for CAM2038 compared to a baseline where patients had been taking BPN (with low systemic exposure). These results did not reveal a specific concern for CAM2038. The data used for the QT-IRT assessment was obtained from Studies 307, 426, 487, 421, 499, and 599, respectively. The Applicant also provided an evaluation of the QTc effects by BPN concentration with this submission. The evaluation demonstrated no concentration-dependent effects on QTc following administration of CAM2038 (Module 2.7.2/ Section 3.3.2) and appeared reasonable.

8.5.5. Immunogenicity

Non-applicable

8.6. Analysis of Submission-Specific Safety Issues

8.6.1. Injection Site Reactions (ISRs)

Study 421

The Applicant reported no SAEs related to ISRS in Study 421. With this submission, the Applicant provided a post hoc analyses of the percent of injections associated with an AE by injection location. Per the Applicant, the percent of injections associated with an AE ranged from 11.0% in the thigh in the CAM2038 group (15.5% in the SL BPN/NX group) to 26.2% in the buttock in the SL BPN/NX group (23.9% in the CAM2038 group). Although this information is

helpful in determining the safety of the injections, the data were confounded by the fact that the injections sites were rotated during the Study, per protocol. The analysis attributed any AE to the last injection prior to the report. Thus, delayed injection site reactions would be confounded by the nature of the rotating injection schedule. The Applicant further noted that 78 patients (N=42 in SL BPN/NX; N=36 in CAM2038) had at least one clinically significant sign or symptom reported on the injection site form across all time points; some of these were also recorded as AEs, as per investigator judgement during the clinical trials. The most commonly reported reaction was erythema, followed by tenderness and pain. It is possible that the frequency of AEs in the context of ISRs could be related more to injection volume than to buprenorphine dose, as illustrated in Table 45. No subject in either treatment group had any injection site reactions of severe intensity, as rated by the investigator at the time of the study, but some patients did discontinue the clinical program due to injection site reactions (please refer to 8.4.3. for discontinuations due to an injection site reaction).

Table 45: Injection site-related AEs in Study 421

	SC CAM2038			SL BPN/NX			
BPN (mg)	**Injection vol. SC CAM2038 (mL)**	**N**	**n (%)**	**SL BPN/NX (mg)**	**Injection vol. SC placebo (mL)**	**N**	**n (%)**
16	0.32	213	5 (2.3)	8	0.32	215	4 (1.9)
24	0.48	142	16 (11.3)	16	0.48	153	17 (11.1)
32	0.64	85	17 (20.0)	24	0.64	90	19 (21.1)
q1w[a]		**213**	**35 (16.4)**	**Phase 1[a]**		**215**	**39 (18.1)**
64	0.18	11	0 (0.0)	8	0.16	4	0 (0.0)
96	0.27	88	4 (4.5)	16	0.32	85	5 (5.9)
128	0.36	67	6 (9.0)	24	0.32	74	8 (10.8)
160	0.45	9	1 (11.1)	32	0.48	9	0 (0.0)
q4w		**158**	**9 (5.7)**	**Phase 2**		**159**	**13 (8.2)**

AE:adverse event; BPN:buprenorphine; BPN/NX:buprenorphine/naloxone; No.:number; q1w:once-weekly injection of CAM2038; q4w:once-monthly injection of CAM2038; SC:subcutaneous; SL:sublingual; vol:volume
[a] Including AEs reported during the titration week
Note: All patients in the CAM2038 treatment group also received SL placebo tablets q.d. (not shown in the table)
Source: Extracted from NS Table 7.2 and NS Table 7.2.1

Source: Applicant provided Table 19 No. of subjects with at least one injection-site-related AE by treatment group and dose inHS-11-421 (safety population) from page 71 of the resubmitted Summary of Clinical Safety

Table 46 represents all injection site reactions identified from the resubmitted datasets for Study 421, regardless of treatment emergent flag (which was missing for several ISRs in both treatment arms).

Table 46: Injection site reactions by HGLT and PT in Study 421

Injection site reactions in the Double-Blind Phase 3 Study HS-11-421		
Preferred Term (PT)[a]	CAM2038 Total[b] (N=213) N(%)	SL BPN/NX[c] (N=215) N(%)
Any injection site reaction by HLGT[d]	44 (20.7%)	49 (22.8%)
Injection site pain	21 (9.8%)	17 (7.9%)
Injection site erythema	14 (6.6%)	12 (5.6%)
Injection site pruritus	13 (6.1%)	13 (6.0%)
Injection site swelling	10 (4.7%)	7 (3.3%)
Injection site reaction	9 (4.2%)	7 (3.3%)
Injection site induration	4 (1.9%)	6 (2.3%)
Injection site cellulitis	3 (<2%)	1 (<1%)
Injection site mass	3 (<2%)	1 (<1%)
Injection site inflammation	2 (<1%)	9 (4.2%)
Injection site ulcer	2 (<1%)	3 (<1%)
Injection site bruising	1 (<1%)	4 (<2%)
Injection site urticaria	1 (<1%)	0
Injection site haemorrhage	0	2 (<1%)
Injection site discomfort	0	1 (<1%)
Injection site erosion	0	1 (<1%)
Injection site irritation	0	1 (<1%)
Injection site rash	0	1 (<1%)
Injection site warmth	0	1 (<1%)

Source: Reviewer

a = Report of all Injection site reactions (ISR) that occurred in the controlled trial, HS-11-421. ISRs are presented as MedDRA preferred terms (PTs), regardless of treatment emergent flag and presented from greatest to least in the CAM2038 group.
b = This group includes all subjects exposed to varying doses of both the CAM2038 WEEKLY and MONTHLY formulations.
c = SL BPN/NX denotes the active comparator: subjects assigned to daily buprenorphine with sham (placebo) injections. Subjects randomized to this group could also receive a 'booster' injection of CAM2038, per protocol.
d = injection site reactions were identified under two HLGTs: Administration site reactions and Bacterial infectious disorders (of which, there were three injection site related cellulitis reactions in the CAM2038 group and one in the SL BPN/NX group, respectively). Tabulation included all events coded as treatment emergent *and* injection site reactions, regardless of treatment emergent flags.

Pooled Phase 3 Studies

The injection site reaction data presented here by preferred term for CAM2038 is from the pooled Phase 3 studies (421 and 499) presented in the Summary of Clinical Safety from the first application cycle. Injection site reactions are presented by formulation (Weekly versus

Monthly) and by dose in Table 47 and Table 48. Of note, injection site reactions in the CAM2038 group of the controlled Phase 3 study, HS-11-421, were comparable to the SL BPN injection site reactions reported by patients exposed to placebo injections, in terms of type of reaction (pain, erythema, swelling, and pruritus) and percent of injection site reactions reported [n=40 (18.8 %) and n=48 (22.3%) in the CAM2038 and active comparator groups, respectively]. This suggests that buprenorphine, itself, is not responsible for tissue reactions over and above those of vehicle. An apparent effect of dose (or volume) is seen for the Weekly formulation; this relationship is less clear for the Monthly.

Table 47: CAM2038 Weekly injection site reactions by dose in the Phase 3 Studies

	8 mg	16 mg	24 mg	32 mg
	n (%)	n (%)	n (%)	n (%)
Patients with at least 1 AE	10(2.7%)	15 (4.2%)	34 (11.9%)	42 (18.3%)
Treatment related AE's	10	32	122	106
AE's per injection	0.011	0.03	0.05	0.06

Number (n) and percent (%) of injection site reactions in the Applicant-provided Safety Population for the CAM Weekly formulation.
Source: Reviewer, from applicant provided data from the 2017 submission

Table 48: CAM2038 Monthly injection site reactions by dose in the Phase 3 Studies

	64 mg	96 mg	128 mg	160 mg
	n (%)	n (%)	n (%)	n (%)
Patients with at least 1 AE	4(4.5%)	18 (9.4%)	11 (6.8%)	7 (11.1%)
Treatment related AE's	12	59	21	9
AE's per injection	0.03	0.08	0.04	0.04

Number (n) and percent (%) of injection site reactions in the Applicant provided Safety Population for the CAM Monthly formulation.
Source: Reviewer, from applicant provided data from the 2017 submission

Study 499

The Applicant provided additional ISR analyses for Study 499 with this submission. Forty-six (20.3%) patients had at least one injection site AE. The most common ISRs, per the Applicant, were injection site pain (15.4%), injection site swelling (11.9%) injection site erythema (9.3%). Most AEs were mild or moderate in intensity, although, by convention, I found discrepancies in my audit of any AE by intensity in the ISS dataset (but this did not affect the overall safety profile of CAM2038). One patient had a severe injection site AE (injection site pain). That event occurred on Day one of the study and resolved the same day with no change in study drug. Two patients had a single occurrence of injection site ulcer and those events were reported as mild or moderate in intensity and resolved. Both patients completed the study. This is consistent with my review of the data.

8.6.1. Drug Withdrawal

Before randomization to either treatment arm in Study 421, patients were given a 4 mg test dose of SL BPN/NX and observed for several hours. If tolerated, the patient was randomized to receive either placebo or CAM2038 injections. The Applicant reported that no patient experienced precipitated withdrawal due to CAM2038.

During the study, drug withdrawal syndrome was reported by three patients (0.7%) receiving CAM2038 and three patients (1.4%) receiving SL BPN/NX in Study 421. The Applicant reported that two of the three CAM2038 AEs of drug withdrawal syndrome included 'benzodiazepine withdrawal' and 'antidepressant discontinuation symptom'. The withdrawal was not related to CAM2038, nor did withdrawal syndrome occur after initiation of CAM2038 treatment. One patient, randomized to SL BPN/NX, discontinued treatment due to a drug withdrawal.

No serious AEs or discontinuations were due to CAM2038 drug withdrawal in Study 499.

8.6.2. Hepatic Function

Buprenorphine has been associated with hepatitis, abnormal liver function tests (LFTs), and other hepatic events. The Warnings and precautions section of current labeling for sublingual buprenorphine (as Suboxone) includes safety labeling regarding hepatitis and hepatic events (found in product labeling). The Applicant reported no "Hy's Law"[27,28] cases in the clinical

[27] Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)

development program, which are considered indicative of potential drug-induced liver injury. On review, the provided data appears consistent with these reports, although several patients experienced asymptomatic elevations in liver function tests that resolved. The CAM2038 safety database revealed no new hepatic safety concerns beyond those previously identified. Additionally, no new data was submitted with this application cycle but the Applicant did perform post hoc analyses which were reviewed.

Study 421

As with the previous application cycle, no subject was missing baseline hepatic function tests but several patients in each group were missing post-baseline liver function tests (N=36 (16.9%)) in the CAM2038 group and N= 41 (19.1%) in the control group, respectively). No subject was identified as having experienced laboratory values meeting criteria for Hy's law, although one subject in the SL BPN/NX group experienced a flare of his underlying Hepatitis C, which is reflected in the significant abnormalities seen in Table 49. These findings were consistent with the previous submission. A shift from normal-to-high in LFT's was observed in alanine aminotransferase (ALT), with 5.6% of the CAM2038 patients compared with 4.2% of the control group. Similarly, the same normal-to-high shift was observed with aspartate aminotransferase (AST) and bilirubin (6.0% and 1.3% in the CAM2038 group and 4.2% and 0.5% in the SL BPN/NX group, respectively). Although there were no statistical differences between these labs, I would have anticipated a trend in the opposite direction for the CAM2038 group, given that it is presumed that an injectable form of BPN would bypass first pass metabolism.

3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

[28] Excerpt from Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

Table 49: Evaluation of hepatic tests on patients in Study 421

Liver Lab Test	CAM2038 N = 213			SL BPN /NX N = 215		
ALT ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	49	17	7.98	47	21	9.77
3x ULN	14	9	4.23	25	9	4.19
5x ULN	4	3	1.41	18	7	3.26
10x ULN	0	0	0.00	5	3	1.40
20x ULN	0	0	0.00	3	2	0.93
AST ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	60	22	10.33	43	19	8.84
3x ULN	13	6	2.82	20	10	4.65
5x ULN	1	1	0.47	9	4	1.86
10x ULN	0	0	0.00	5	3	1.40
20x ULN	0	0	0.00	1	1	0.47
ALP ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	0	0	0.00	2	1	0.47
3x ULN	0	0	0.00	1	1	0.47
5x ULN	0	0	0.00	0	0	0.00
10x ULN	0	0	0.00	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00
TB ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
1.5x ULN	4	2	0.94	1	1	0.47
2x ULN	0	0	0.00	1	1	0.47
3x ULN	0	0	0.00	0	0	0.00

Source: Reviewer
All scores are post-baseline. Subject scores may be counted more than once in that they will be counted in all conditions (e.g., 2x, 3x, 5x) that apply. ALT= alanine aminotransferase; AST= aspartate aminotransferase; ALP= alkaline phosphatase; TB= total bilirubin

Additionally, the Applicant performed post hoc analyses of shifts in liver function test (LFT) test results (including aspartate aminotransferase, alanine aminotransferase, bilirubin and gamma-glutamyltransferase) based on CAM2038 Weekly and Monthly formulation dosing administered before the laboratory sample collection (or based on the cumulative dose received prior to the laboratory sample collection) in Study 421 (*Module 2.7.4/ Section 3.2 dated 5/23/18*). The analyses demonstrated no apparent relationship between increasing CAM2038 dose and results for any of the individual LFT parameters. However, given the flexible dosing design of the Study, the findings are reassuring but not definitive.

Study 499

No subject was missing baseline hepatic function tests but several patients in each group were missing post-baseline liver function tests. Twenty-four (12.6%) in the transfer to treatment group and nine (24.3%) in the new entrants to treatment group, were missing post-baseline liver lab tests. No subject was identified as having experienced laboratory values meeting criteria for Hy's law (Table 50).

Table 50: Evaluation of hepatic tests on patients in Study 499

Liver Lab Test	Currently Receiving N = 190			NEW TO BPN Treatment N = 37		
ALT ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	4	4	2.11	1	1	2.70
3x ULN	0	0	0.00	1	1	2.70
5x ULN	0	0	0.00	1	1	2.70
10x ULN	0	0	0.00	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00
AST ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	2	1	0.53	1	1	2.70
3x ULN	0	0	0.00	1	1	2.70
5x ULN	0	0	0.00	1	1	2.70
10x ULN	0	0	0.00	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00
ALP ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	0	0	0.00	0	0	0.00
3x ULN	0	0	0.00	0	0	0.00
5x ULN	0	0	0.00	0	0	0.00
10x ULN	0	0	0.00	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00
TB ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
1.5x ULN	0	0	0.00	0	0	0.00
2x ULN	0	0	0.00	0	0	0.00
3x ULN	0	0	0.00	0	0	0.00

Source: Reviewer

All scores are post-baseline. Subject scores may be counted more than once in that they will be counted in all conditions (e.g., 2x, 3x, 5xthat apply). ALT= alanine aminotransferase; AST= aspartate aminotransferase; ALP= alkaline phosphatase; TB= total bilirubin

8.6.3. Dosing Patterns and Enumeration of AEs by Dose in the Phase 3 Studies

The Applicant chose to use a 'flexible dosing' strategy for Studies 421 and 499.

Study 421

In Study 421, this flexible dosing strategy occurred in both 'phases', although no patient was exposed to CAM2038 Monthly before day 84 of the study. A visual representation of this drug dosing in Study 421 is shown in Figure 12 (CAM2038 dosing patterns in Study 421).

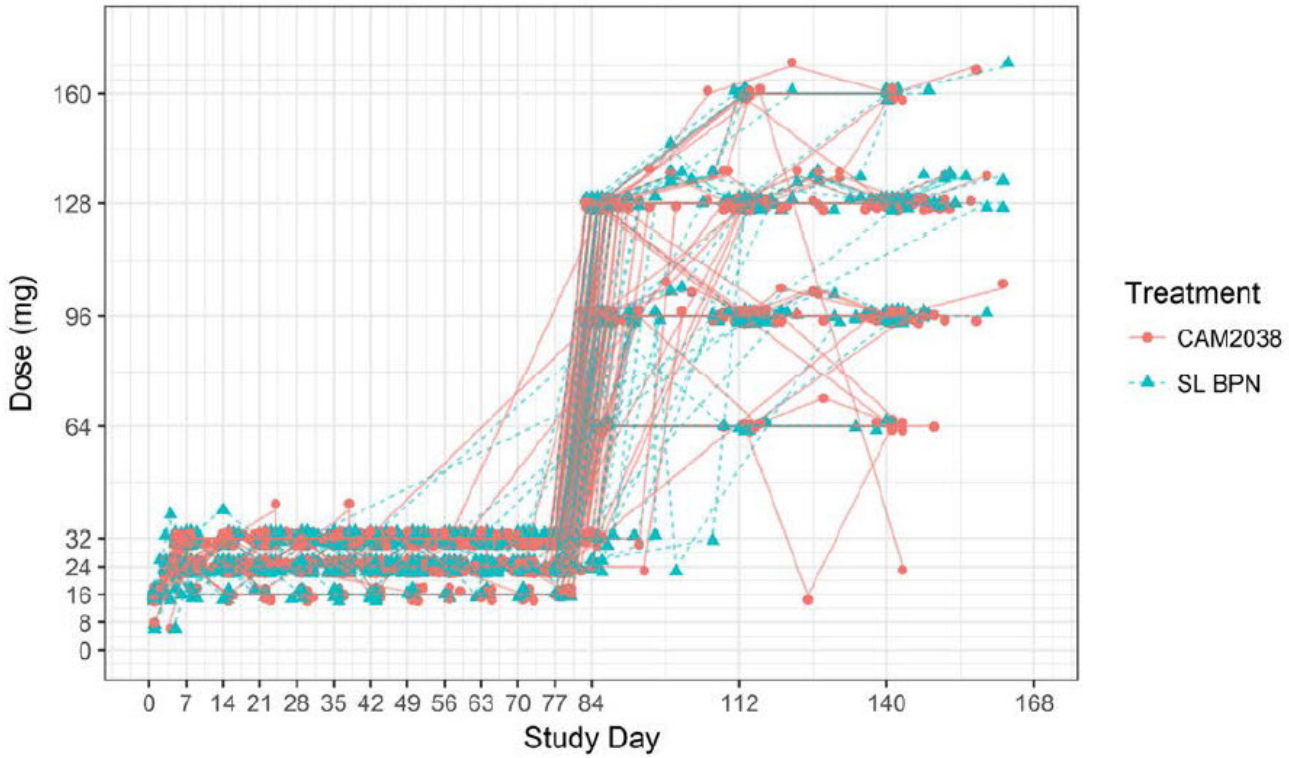

Figure 12: CAM2038 Injection Dosing patterns in Study 421
Source: Statistical reviewer James Travis from the 2017 review cycle.

Because of the flexible dosing within each CAM2038 formulation (Weekly and Monthly) and because Study 421 included patients exposed to both formulations, it was difficult to enumerate AEs specifically by a formulation or dose. Therefore, the Applicant provided several post hoc analyses of the Study 421 safety dataset and presented them as tertiles.[29]

[29] Tertiles were defined by the Applicant as patients exposed to cumulative CAM2038 or SL BPN/NX doses:

- < 33% ('phase 1': N= 69, CAM2038; N=67, SL BPN/NX); ('phase 2': N= 35, CAM2038; N=27, SL BPN/NX)
- 33%-67% ('phase 1': N= 02, CAM2038; N=76, SL BPN/NX); ('phase 2': N= 70, CAM2038; N=74, SL BPN/NX)

The tertile analyses[30] were presented in several tables; most of them including > 2% patients who experienced an adverse event by PT, HGLT in each 'phase' of Study 421. On review, these analyses did not reveal any patterns of AEs that differed from the known effects of buprenorphine products or from my previous analyses; or from what was previously reported by the Applicant. It remained difficult to determine an AE by a specific dose but no specific AE or patterns of AEs by dose or formulation were identified.

Study 499

In Study 499, a similar but different dosing pattern was employed. For patients transferring to CAM2038, they could be started on the Weekly or Monthly formulation (most patients were started on the Monthly formulation), which is shown in **Figure 13.** In the 37 patients who were new entrants to treatment (patients who met the same criteria as Study 421), each of them were started on CAM2038 Weekly. Of those, eight transferred to CAM2038 Monthly and of those, three remained on CAM2038 monthly and the other five went back to the Weekly formulation (**Figure 14**). These figures illustrate the difficulty of characterizing the "dose" received by any given patient. Moreover, doses were not determined on a randomized basis, making comparisons by dose inherently difficult to interpret.

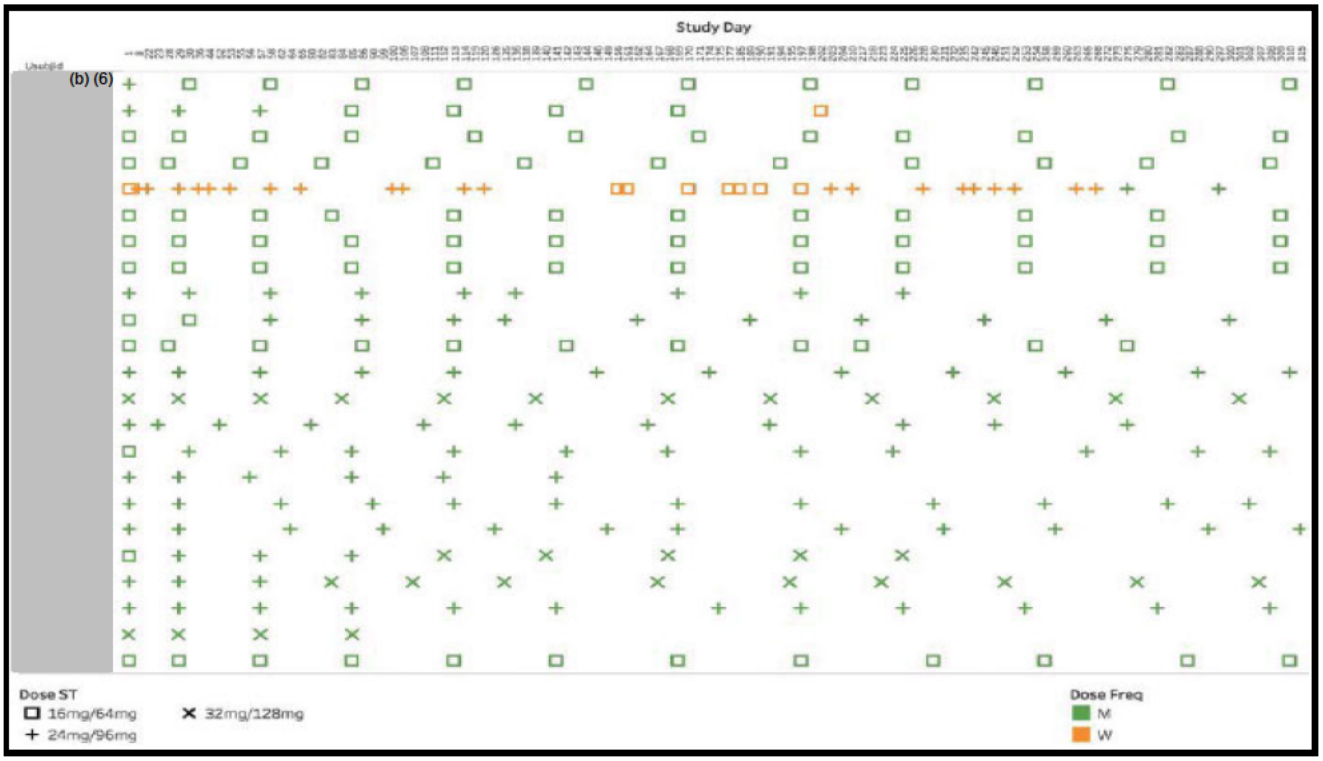

Figure 13: Dosing pattern of CAM2038 in" Transfers" to treatment in Study 499

- > 67% ('phase 1': N= 142, CAM2038; N=72, SL BPN/NX); ('phase 2': N= 53 in CAM2038; N=59, SL BPN/NX)

[30]SDN 0079: Applicant provided HS-11-421-NS-Tables 9.1, 9.2, 10.1, 10.2,

This Applicant-provided figure from the 2017 review cycle shows the dosing pattern in transfers to CAM2038 from patients who were receiving SL BPN treatment. Specifically, this group shows the dosing pattern without supplemental CAM2038 use.

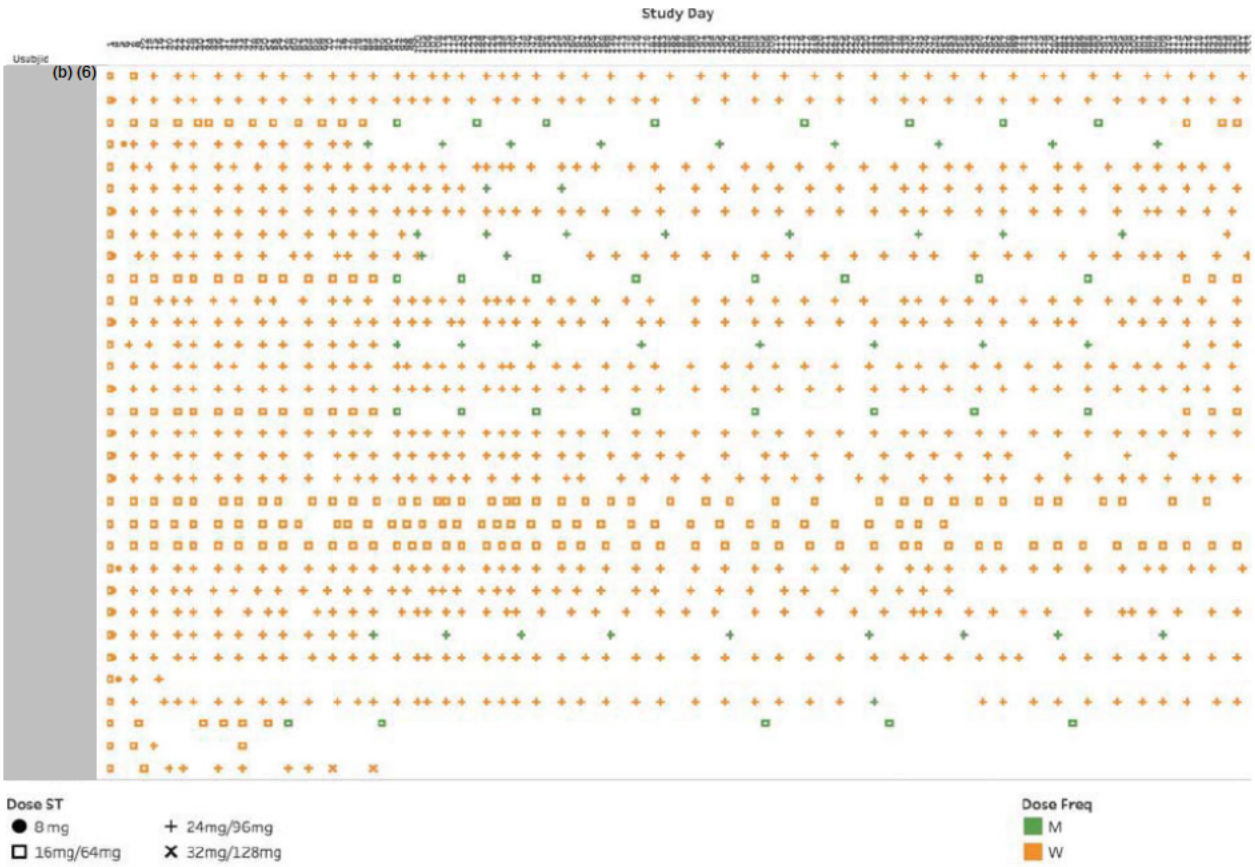

Figure 14: Dosing pattern of CAM2038 in "New Entrants" to treatment in Study 499
This Applicant-provided figure from the 2017 review cycle shows the dosing pattern in patient who were new entrants to CAM2038 treatment and had not been receiving any SL BPN treatment before starting the study. Specifically, this group shows the dosing pattern without supplemental CAM2038 use, which occurred in 5 patients who were new entrants to treatment.

A review challenge of this application, as was the case with the first review cycle, was in evaluating specific AEs by dose in both Phase 3 studies. Although no safety signals emerged in the review of the CAM2038 program, which would preclude approval or that differed from the expected AE profile of the referenced buprenorphine products; and was reassuring for the safety of the CAM2038 product, it was difficult to ascertain a relationship between a reported adverse event and the timing of that event in the context of a specific CAM2038 dose or formulation. The aforementioned dosing patterns show the challenge of determining AEs by dose, given the flexible dosing designs of the studies. **Table 51** shows the AEs in the Pooled Phase 3 Studies (421 and 499) by CAM2038 dose and formulation. In this table, reported

events were attributed to the dose/formulation that had been received at the visit prior to the report. Reassuringly, the profile of AEs is consistent with that of known BPN products. Although it is difficult to interpret the results of the presented AEs (because it is probable that each patient was exposed to differing doses and formulations of CAM2038), there is a trend of AEs with increasing doses of CAM2038 Weekly formulation, which might be explained by the fact that more patients were exposed to the Weekly than the Monthly formulation, and that AEs were assessed more frequently during weekly dosing than during monthly dosing.

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Table 51: AEs in the Pooled Phase 3 Studies by dose and Formulation.

Adverse Events (**≥2%)** in CAM2038 exposures by HGLT and last dose administered in Pooled Phase 3 Studies HS-11-421 and HS-13-499									
System Organ Class (SOC) High Level Group Term (HLGT)[a]	CAM2038[b] N=440	CAM2038 Weekly dose (mg)				CAM2038 Monthly dose (mg)			
		8	16	24	32	64	96	128	160
	Total N(%)								
Cardiac disorders									
Cardiac arrhythmias	10 (2.3%)	0	2	4	2	1	1	0	0
Gastrointestinal disorders									
Gastrointestinal signs and symptoms	57 (13%)	4	14	15	7	5	6	3	3
Gastrointestinal motility and defaecation conditions	39 (8.9%)	3	5	10	11	1	3	5	1
Dental and gingival conditions	13 (3%)	1	1	4	5	1	0	1	0
General disorders and administration site conditions									
Administration site reactions	110 (25%)	5	13	29	26	6	15	12	4
General system disorders NEC	30 (6.8%)	1	2	13	6	3	1	3	1
Infections and infestations									
Infections - pathogen unspecified	117 (27%)	12	11	24	21	14	12	19	4
Viral infectious disorders	23 (5.2%)	2	3	5	6	1	3	2	1
Bacterial infectious disorders	10 (2.3%)	0	0	3	2	0	2	2	1
Injury, poisoning and procedural complications									
Injuries NEC	39 (8.9%)	2	2	3	10	6	9	7	0
Bone and joint injuries	9 (2%)	0	1	1	2	1	0	4	0
Musculoskeletal and connective tissue disorders									
Musculoskeletal and connective tissue disorders NEC	27 (6.1%)	1	5	5	6	3	2	3	2
Joint disorders	17 (3.9%)	0	1	4	6	1	4	1	0
Muscle disorders	10 (2.3%)	2	1	3	2	0	0	2	0
Nervous system disorders									
Headaches	46 (10.4%)	7	10	10	6	0	8	3	2
Neurological disorders NEC	25 (5.7%)	4	1	5	8	1	3	1	2
Psychiatric disorders									
Sleep disorders and disturbances	19 (4.3%)	2	9	1	6	0	1	0	0
Depressed mood disorders and disturbances	16 (3.6%)	0	1	5	4	1	1	2	2
Anxiety disorders and symptoms	15 (3.4%)	0	3	3	3	2	1	3	0
Respiratory, thoracic and mediastinal disorders									
Respiratory disorders NEC	9 (2%)	0	1	3	1	1	1	0	2
Skin and subcutaneous tissue disorders									
Epidermal and dermal conditions	19 (4.3%)	0	1	3	8	2	2	3	0

Source: Reviewer

a = report of adverse events that occurred in ≥2% of patients exposed to CAM2038 in the Phase 3 trials HS-11-421 and HS-13-499. Subjects are represented once per HLGT at the dose where the AE was reported. Tabulation included all events coded as treatment emergent and all injection site reactions, regardless of treatment emergent flags.
b = This group includes all patients exposed to varying doses of both the CAM2038 WEEKLY and MONTHLY formulations. More patients were exposed to the weekly formulation than the monthly formulation, and more AEs were reported with the weekly formulation than the monthly formulation.

8.7. Safety Analyses by Demographic Subgroups

In general, there were no differences between demographic subgroups that warranted further analysis at the time of this review. The main identified demographic subgroup difference was with patient-reported sex (Male (M)/Female (F)); where more males than females were randomized to the Phase 3 studies. Table 52 and Table 53 show the numbers of Males and Females randomized to each treatment group in Studies 421 and 499, respectively.

Table 52: Demographic baseline by Sex in Study 421

Sex	CAM2038 SC injections + SL placebo tablets N=213		SL BPN tablets + placebo subcutaneous (SC) injections N=215		Overall N=428	
	Count	%	Count	%	Count	%
F	92	43.2	73	34.0	165	38.6
M	121	56.8	142	66.0	263	61.4

Source: Reviewer, from the 2017 application review

Table 53: Demographic baseline by Sex in Study 499

Sex	Currently Receiving N=190		NEW TO BPN Treatment N=37		Overall N=227	
	Count	%	Count	%	Count	%
F	71	37.4	13	35.1	84	37.0
M	119	62.6	24	64.9	143	63.0

Source: Reviewer, from the 2017 application review

The Applicant-provided baseline demographic data from Study 421 (Table 54) and Study 499 (Table 55) is listed below. In general, the disposition of discontinuations between Males and Females was unremarkable. I did an additional subanalysis of numbers of AEs by sex for Study 421. In general, Women reported more AEs than Men and more individual AEs were reported (not numbers of patients) in the CAM2038 group compared with the SL BPN/NX group. The exception was with Headaches and Migraines in the SOC Nervous System disorders: In the CAM2038 group, Men (N= 22 AEs) reported more Headaches than women (N=9 AES) and Women (N=10 AEs) reported more migraines than Men (N=2). In the SL BPN/NX group, more

Men (N=11 AEs) reported more Headaches or Migraines compared with Women (N=9 AEs). No additional analyses were performed.

Table 54: Disposition by Sex in Study 421

Standard Disposition Term	Sex	CAM2038 SC injections + SL placebo tablets N=213	SL BPN tablets + placebo subcutaneous (SC) injections N=215
		Count	Count
Adverse Events (SOC)*			
General disorders and administration site conditions	F	137	82
	M	117	93
Gastrointestinal disorders	F	63	41
	M	40	37
Infections and infestations	F	80	42
	M	42	37
Nervous system disorders	F	34	14
	M	40	22
Death	F M	1 0	1 0
Discontinuations**			
Lost to Follow-Up	M F	19 8	39 17
Other	F M	5 4	8 10
Physician Decision	M F	3 1	6 1
Pregnancy	F M	0 0	1 0
Protocol Deviation	F M	1 0	1 0
Withdrawal By Subject	 M F	 27 17	 57 33

Source: Reviewer, from the previous application cycle (please refer to text descriptions of the Applicant's audit of discontinuations due to 'physician decision' and 'withdrawal by subject').

*Reported by number of PTs in most common System Organ Classes (SOC), not all AE's. Does not represent individual patients in each SOC. In general, Women reported more AEs than Men and more individual AEs were reported (not numbers of patients) in the CAM2038 group compared with the SL BPN/NX group. The exception was with Headaches and Migraines in the SOC Nervous System disorders: In the CAM2038 group, Men (N= 22 AEs) reported more Headaches than women (N=9 AES) and Women (N=10 AEs) reported more migraines than Men (N=2). In the SL BPN/NX group, more Men (N=11 AEs) reported more Headaches or Migraines compared with Women (N=9 AEs).

**Based on Applicant-reported data before response to IR was received and discontinuation reanalysis was made.

Table 55: Disposition by Sex in Study 499

Disposition Term	Sex	Currently Receiving N=190		NEW TO BPN Treatment N=37		Overall N=227	
		Count	%	Count	%	Count	%
Adverse Event	M	2	1.7	1	4.2	3	2.1
	F	1	1.4	0	0.0	1	1.2
Completed	F	51	71.8	9	69.2	60	71.4
	M	81	68.1	16	66.7	97	67.8
Lack Of Efficacy	M	8	6.7	0	0.0	8	5.6
	F	4	5.6	0	0.0	4	4.8
Lost To Follow-Up	F	2	2.8	4	30.8	6	7.1
	M	2	1.7	5	20.8	7	4.9
Other	F	1	1.4	0	0.0	1	1.2
	M	1	0.8	0	0.0	1	0.7
Physician Decision	M	4	3.4	0	0.0	4	2.8
	F	1	1.4	0	0.0	1	1.2
Pregnancy	F	1	1.4	0	0.0	1	1.2
	M	0	0.0	0	0.0	0	0.0
Withdrawal By Subject	M	21	17.6	2	8.3	23	16.1
	F	10	14.1	0	0.0	10	11.9

Source: Reviewer, from the 2017 application review
The Count column shows the count of subjects in each demographic group per arm whose last disposition event is the disposition term shown. The % column shows the proportion of the demographic group in each arm that the count represents.

8.8. Specific Safety Studies/Clinical Trials

No additional safety studies were conducted, as a specific safety signal was not identified during the course of this review. This was consistent with the previous application cycle.

8.9. Additional Safety Explorations

8.9.1. Human Carcinogenicity or Tumor Development

No formal assessments of human carcinogenicity were performed by the Applicant during this review cycle or the last; and no tumors or malignancies were identified during the course of the review. Thus, there was no indication that neoplastic investigations of the CAM2038 product would need to be conducted.

8.9.2. Human Reproduction and Pregnancy

No new findings were identified in my review. As with the previous submission, two pregnancies were reported in the Pooled Phase 3 studies of the CAM2038 Clinical program. One of those pregnancies (in a female exposed to CAM038) resulted in an early spontaneous abortion (reported as a SAE above because the event resulted in a brief hospitalization) and the patient continued in the study. No additional pregnancy information was provided and no data on lactating women was obtained. The Division of Pediatric and Maternal Health (SPMH) was not consulted to review the application materials but was consulted to review the proposed label and PLLR section of the draft label.

8.9.3. Pediatrics and Assessment of Effects on Growth

The Applicant received a full waiver (with an agreed iPSP) for the proposed indication of "(b) (4)[31]." The CAM2038 product triggered the Pediatric Research Equity Act (PREA) as a new dosage form, new dosing regimen and new route of administration. The PREA population is generally defined as up to age 16. The Division noted that despite a growing issue with opioid use disorder, the use and addiction of opioids in younger teens does not appear to be increasing. The use of this product for the proposed indication is most likely to occur in older teens 17 to 19 years of age, not the PREA-defined pediatric population. The Pediatric Review Committee (PeRC) subsequently agreed with the division to grant a full waiver in all pediatric patients for the following reason:

> *Studies are impossible or highly impractical because there are too few patients who will require medically assisted treatment (MAT).*

8.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Buprenorphine is controlled as Schedule III of the Controlled Substances Act. Abuse liability and language for the corresponding sections of labeling were reviewed by the CMC and CSS reviewers.

[31] This oddly-worded indication appears to be (b) (4) (b) (4) not applicable to CAM 2038.

8.10. Safety in the Postmarket Setting

8.10.1. Safety Concerns Identified Through Postmarket Experience

No postmarketing studies have been conducted on this product. It is not yet approved for use.

8.10.2. Expectations on Safety in the Postmarket Setting

During product development, CAM2038 was administered by a health care provider in a clinical setting. No data was provided on the take-home use or self-administration of CAM2038 by product by patients and that is not how the studies were conducted. No extraction studies (of the CAM2038 product after administration) were performed, nor was there a request to do so during this application cycle.

A risk exists that patients, many of whom have a history of intravenous drug abuse and drug misuse, could improperly self-administer CAM2038 if they were to have access to the product. Thus, the potential exists whereby a life-threatening situation could develop or have untoward consequences.

Because of these concerns, the Agency worked closely with the Applicant, during this review cycle and the previous one, to develop a risk evaluation and mitigation strategy (REMS) that would result in safe use in the postmarketing setting.

8.10.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified in the course of this review; or that were associated with the development of a risk evaluation and mitigation strategy.

8.11. Integrated Assessment of Safety

Overall, no new safety signals were identified in the review of the CAM2038 program that differentiate the overall safety profile from that established for other buprenorphine products; or that differed from the previous review cycle. The overall safety database of CAM2038 appeared to be consistent with the known safety profile of buprenorphine. Further, despite the lack of any comparable products with the fluid crystal technology, no serious injection site reactions (ISRs) were identified and relatively few ISRs led to study discontinuation, per review of the Applicant-provided materials.

The Applicant adequately addressed the clinical deficiencies identified in the last review cycle; albeit indirectly in some ways and with datasets that resulted in a less-than-ideal review environment (due in part to the use of a flexible study design with two CAM2038 product

formulations and multiple dosing options within each formulation). The Applicant also adequately verified the integrity of the source data through QC analyses.

9. Advisory Committee (AC) Meeting and Other External Consultations

9.1. AC Meeting

No new AC meeting was held for this resubmission. Please refer to my 2017 clinical review for a summary of the PDAC meeting held on November, 1, 2017. The AC voted in favor of approving the Brixadi Weekly and Monthly formulations, 17:3, at the conclusion of the meeting.

9.2. Exclusivity

During the CAM2038 application review, the CDER Exclusivity Board regularly met to address whether the unexpired 3-year exclusivity for Sublocade[32] or Probuphine[33] would block the approval of both formulations of Brixadi or block the approval of the Monthly formulation of Brixadi (or neither). At the time of this review, the Exclusivity Board's decision was that unexpired exclusivity for Sublocade precluded the approval of the Monthly formulation of Brixadi. A Tentative Approval could be issued if the application is otherwise ready for approval.

The Division concluded that the data could support marketing of the Weekly formulation by itself until the period of exclusivity preventing the marketing of the Monthly formulation expires. However, at this writing it is not clear whether the Applicant would be receptive to this approach.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

At the time of this review, the final label is in development. The proposed labeling was submitted in PLR (Physician's Labeling Rule) and PLLR (Pregnancy and Lactation Labeling Rule) formats. The foundation for the approved labeling was the Subutex drug label (See Appendix) and buprenorphine drug class labeling considerations, with relevant information of the new formulation and related clinical trials included.

[32] A Monthly, subcutaneous buprenorphine ER injectable drug product (NDA 209819) that was granted exclusivity on November 30, 2017 and expires on November 30, 2020.
[33] A six-month, buprenorphine implant for subdermal administration (NDA 204442) that was granted exclusivity on May 26, 2016 and expires on May 26, 2019.

Several changes were made to the INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, and CLINICAL TRIALS EXPERIENCE sections of the drug labeling. At the time of this review, the proposed label changes had not been finalized and the Applicant had not received the proposed changes. Further, the Division held a telephone conference with the Applicant on 11/19/2018 to discuss the potential of the Applicant submitting separate labels for BRIXADI (Weekly) and BRIXADI (Monthly); and (although the Trade Name, BRIXADI, was approved by DMEPA for both formulations) to consider the submission of independent Trade Names for the Weekly and Monthly CAM2038 formulations.

At the time of this review, it appears that the Monthly formulation of CAM2038 (BRIXADI) cannot be approved due to unexpired exclusivity for the currently marketed, approved drug, Sublocade. Therefore, to support potential marketing of the Weekly product alone, the Division has developed a label in which reference to the use of the Monthly formulation will be removed from the dosing and administration directions, and the clinical trials and safety sections will be amended to note that the data include a formulation that is not commercially marketed.

Assuming no other issues preclude approval in this cycle, The MONTHLY CAM2038 product [BRIXADI (monthly)] will receive Tentative Approval and a corresponding label describing the use of both formulations is being drafted that would become final when the full approval is issued.

Key clinical changes to the proposed labeling included:

- Clarification of INDICATIONS and USAGE
- In the DOSING and ADMINISTRATION section, the instructions for initiating CAM2038 weekly were revised to align with the way the product was administered in the controlled clinical trial, including:
    - Clarification that BRIXADI has two formulations.
    - BRIXADI (weekly) cannot be combined to equal a monthly dose
    - Recommendation that dosing in new entrants to treatment begin after a 4 mg test dose of SL BPN, not 8 mg, as was written in the proposed label. 4 mg test doses were used in the clinical trials.
    - Recommended dosing amended to reflect how dosing was achieved in Study 421: a 16 mg CAM2038 Weekly dose, followed by an 8 mg dose, titrated to achieve the recommended weekly doses of 24 mg CAM2038 for the first week.
    - Addition of a PATIENT SELECTION section, with a description of the patient populations to be treated with each formulation (for instance, new entrants to treatment, in both Phase 3 studies, were only started on CAM2038 Weekly. No new entrant to treatment was started on CAM2038 Monthly).
    - Instructions for use of the supplemental 8 mg, CAM2038 Weekly, formulation
- Injection instructions including details of injection site selection
- Rotation of the Injection Site for the CAM2038 Monthly product

- In CLINICAL TRIALS EXPERIENCE, Adverse reactions leading to study discontinuation were updated to include the correct values of discontinuations in Study 421, as previously mentioned. Additionally, tables representing Adverse Drug Events were utilized from Section 8 of my review. The Applicant's presentation of Adverse events were submitted in a format with PTs listed by dose with each of the CAM2038 formulations in comparison with the active control arm (SL BPN), also listed by dose of tablets, administered in Study 421. This representation minimizes the representation of AEs experienced throughout the study. Additionally, this representation does not characterize the patient population because patients were not randomized to specific dose arms of CAM2038. Instead, they were flexibly dosed during the study, such that, it is not known if a reported AE at a CAM2038 Weekly dose of 24 mg actually represents an AE at the 24 mg dose or if the AE better represented a dose that they were on previous to that dose change.
- In CLINICAL TRIALS EXPERIENCE, tables representing Injection Site Reactions were utilized from Section 8 of my review, because we included all injection site reactions as treatment emergent, regardless of the Applicant's assignment of a treatment emergent flag to an injection site reaction.

10.2. Nonprescription Drug Labeling

Non-applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

The Division of Risk Management (DRISK) evaluated the Applicant's proposed risk evaluation and mitigation strategy (REMS) for Brixadi. The REMS was developed during the previous review cycle (the Applicant had not initially submitted a REMS) and the Applicant continued to work with DRISK to provide appropriate REMS materials. The development of this REMS program was in keeping with the Agency's Guidance[34] for prescription drug products.

The following summary is extracted from Dr. Somya Dunn's (medical officer with DRISK) review of the 2017 and 2018 NDA 210136 application submissions:

> *"DRISK determined, based on feedback from the REMS Oversight Committee and the Brixadi Advisory Committee, that a REMS with elements to assure safe use (ETASU) is needed to ensure the benefits of Brixadi outweigh its risks. The ETASU will consist of a one-time certification of healthcare settings and pharmacies that order and dispense*

[34] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

Brixadi to ensure that it is administered by healthcare providers and not dispensed directly to patients. The original submission in May 2017 did not contain a REMS. The REMS proposed in the May 23, 2018 submission consists of elements to assure safe use (i.e., healthcare setting and pharmacies that dispense Brixadi must be certified)."

Thus, in negotiations with the Agency the Applicant had accepted DRISK's recommendations for the REMS and submitted the following, required, amended documents to comply with those recommendations:

- *Brixadi REMS Document*
- *Brixadi REMS Supporting Document*
- *Brixadi REMS Program Healthcare Setting and Pharmacy Enrollment Form*
- *Brixadi REMS Program Letter for Healthcare Settings and Pharmacies*
- *Brixadi REMS Program Fact Sheet: How to Obtain Brixadi*
- *Brixadi REMS Program Website Home Page Screenshots*

12. Postmarketing Requirements and Commitments

Results from the pivotal, Phase 3, study demonstrated that, after a single test dose of SL BPN/NX, CAM2038 Weekly can be administered and *titrated* to the recommended CAM2038 weekly dose (which is the 24 mg dose shown to block opioids in Study 478) within the first week of use (receiving an initial 16mg CAM2038 Weekly dose, with an 8 mg dose administered within three days), which is how CAM2038 was dosed in Study 421. The Applicant updated these dosing recommendations in the clinical overview (b) (4) of this application submission, to reflect the dosing schedule that was used in Study 421[35]. This differed from the first NDA submission (July, 2017), when the Applicant had proposed, (b) (4) (b) (4)

Because, the Applicant did not study single-dosing of Weekly CAM2038 to new entrants to treatment (and did not study dosing of CAM2038 Monthly at all in patients who were new entrants to treatment), additional studies would need to be conducted to market CAM2038, single dosing, upon treatment initiation.

(b) (4)

[35] \\CDSESUB1\evsprod\NDA210136\0079\m2\25-clin-over

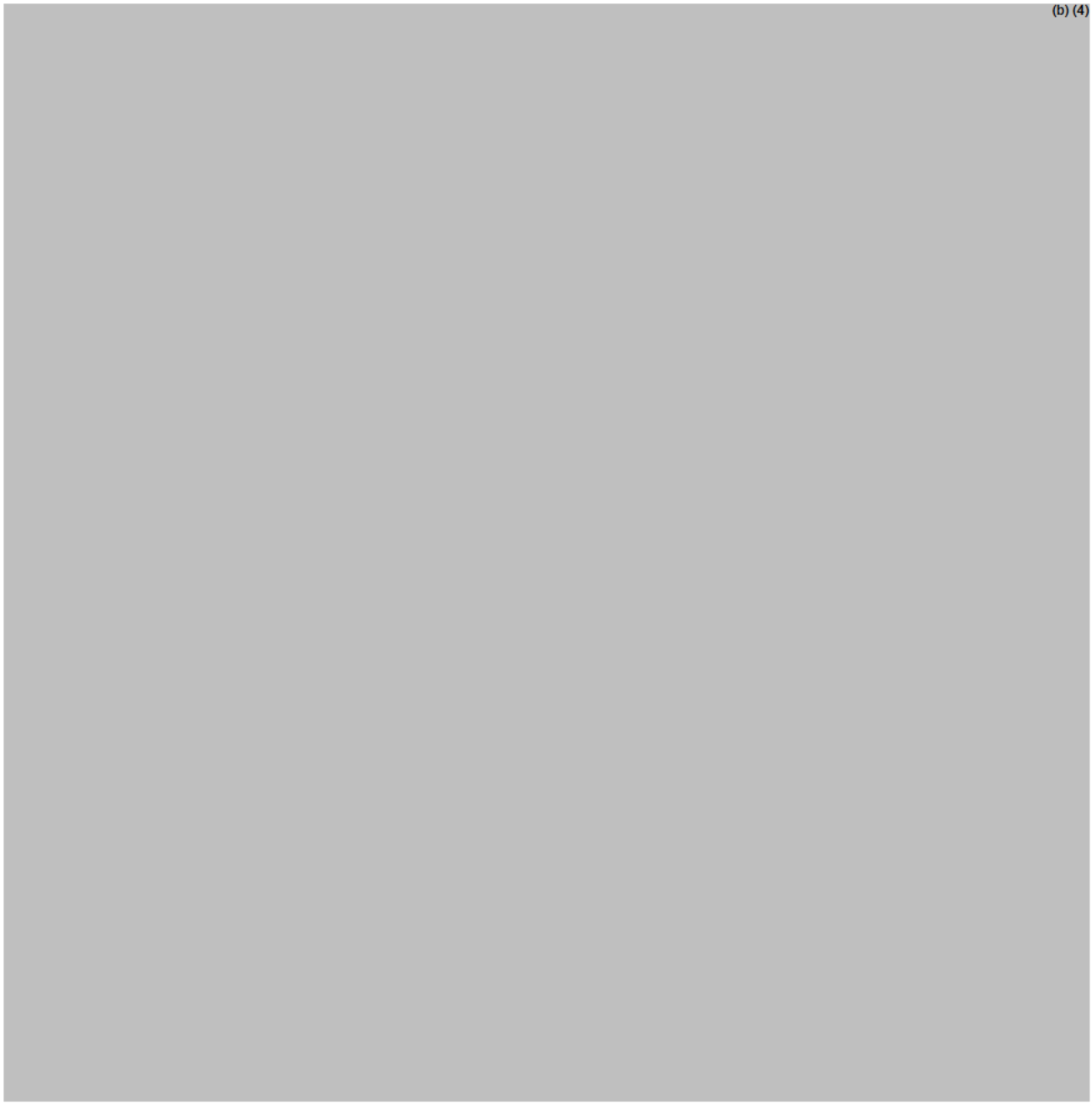
Pharm Tox and CMC Postmarketing requirements (PMRs) are being discussed.

13. Appendices

13.1. References

Applicable references for this review were included in-text or as footnotes.

13.1. Subutex Drug Product Label



Reference ID: 4149688

13.2. Tabulation of Recoded Discontinuations due to AEs in Studies 421 and 499

The table below represents the Applicant-reported recoded discontinuations and the clinical Reviewer-recoded discontinuations due to AEs in Studies 421 and 499.

Table 56: Discontinuations due to AEs from Applicant-provided Response to IR

Study	Subject number	Reason for discontinuation	Treatment arm
421	(b) (4)	Previously coded as withdrawal by subject. Moderate AE (possibly related) of liver function test abnormal. Five days later, a positive hepatitis C test was revealed, classified as a moderate AE (not related). The patient discontinued from the study 2 months later.	SL BPN/NX
421		Previously coded as physician decision and discontinued due to "moderate AE of hepatic enzyme increased that was not considered to be related to study drug" Patient was referred to gastroenterologist.	CAM2038
421		Discontinued due to injection site ulcer. Previously coded as withdrawal by subject.	SL BPN/NX
421		Discontinued due to injection site ulcer. Previously coded as withdrawal by subject.	CAM2038
421		Previously coded as physician decision and discontinued due to "mild AEs" of anxiety and depression.	CAM2038
499		discontinued due to fatigue and myalgia. Previously coded as withdrawal by subject.	CAM2038
499		discontinued due to Injection site reaction. Previously coded as withdrawal by subject.	CAM2038
499		Previously coded as withdrawal by subject. Moderate AE of depression occurred 2 days after the most recent dose of CAM2038, was ongoing at the time of discontinuation, and was not considered to be related to study drug. No action was taken with respect to the AE. The patient left the study and did not provide reason for discontinuation.	CAM2038
499		Patient was previously coded "physician decision" and discontinued due to an EEG abnormality that did not require treatment but the Applicant agreed that the event should be reclassified as an AE.	CAM2038

Source: Reviewer. Table derived from Applicant provided response to Division's IR and includes tabulations of all discontinuations in Studies 421 and 499. EDR location: \\CDSESUB1\evsprod\NDA210136\0088\m1\us
*Represents subject numbers (n=5) that the Applicant agreed were study discontinuations due to AEs. The Applicant did not agree with the numbers of TEAE's leading to discontinuation that I identified.

13.3. Financial Disclosure

As requested, the Applicant provided a description of the steps taken to minimize potential

bias in Studies 421, 499, and 478, respectively, which was not included in the original application. The provided information was found adequate and no financial disclosure issues were identified (Table 57).

Table 57: Financial Disclosures of Covered Clinical Studies 421, 499, 478

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list)
Total number of investigators across studies identified: 251		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: Three received honoraria or compensation for consultations Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigators: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GIOIA M GUERRIERI
12/19/2018

CELIA J WINCHELL
12/20/2018

CLINICAL REVIEW

Application Type	NDA
Application Number	210136
Priority or Standard	Priority
Submit Date	July 19, 2017
Received Date	July 19, 2017
PDUFA Goal Date	January 19, 2018
Division/Office	DAAAP
Reviewer Name	Gioia M. Guerrieri, DO, FAPA
Review Completion Date	December 26, 2017
Established/Proper Name	buprenorphine extended-release injection (CAM2038)
Proposed Trade Name	Brixadi
Applicant	Braeburn Pharmaceuticals, Inc
Dosage Forms	Weekly Formulation: 8mg, 16mg, 24mg, 32mg Monthly Formulation: 64mg, 96mg, 128mg (b) (4)
Applicant Proposed Dosing Regimen	New Entrants to treatment: titrate to (b) (4) Weekly in the first week then dose adjust. Adults stabilized on current buprenorphine product: transfer to appropriate Weekly or Monthly formulation.
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population	N/A

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BPN	buprenorphine
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DB	double-blind
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OL	open label
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OUD	Opioid Use Disorder
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RCT	randomized controlled trial
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGE	special government employee
SL	sublingual
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

CAM2038 is an extended-release formulation of buprenorphine (BPN) in a novel Fluid Crystal (FC) technology designed for administration by subcutaneous (not intramuscular) injection to be provided ready-for-use in a prefilled syringe (a drug-device combination) for the treatment of moderate to severe opiate use disorder (OUD) in adults. It was submitted as a 505(b)(2)[1] application and represents a new formulation of an existing product. The drug's proposed proprietary name is *Brixadi*, with a non-proprietary name of *buprenorphine extended-release injection.* For purposes of this review, this product will be referred to as CAM2038, the name given to the drug during clinical development.

CAM2038 is available in a Weekly and Monthly formulation, each of which contains different doses and excipients (Table 1). The Applicant-recommended (b) (4) CAM2038 (b) (4) (b) (4) FC technology has not been used in other FDA approved drug products and, therefore, no comparisons are available.

The Applicant is also seeking approval for CAM2038 (b) (4)

[1] Relying on the Agency's previous findings for Subutex, buprenorphine hydrochloride sublingual tablets [Indivior (Reckitt Benckiser) NDA 20732] https://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf

Table 1: Proposed Dosing and Volume of CAM2038 Weekly and Monthly Formulations

BPN Fluid crystal SC injection depot			
CAM2038 Weekly		CAM2038 Monthly	
Dose (mg)	Volume (mL)	Dose (mg)	Volume (mL)
8	0.16	64	0.18
16	0.32	96†	0.27
24†	0.48	128	0.36
32	0.64	(b) (4)	
Weekly injection product contents:		**Monthly injection product contents:**	
BPN, soybean phosphatidylcholine, glycerol dioleate, ethanol		BPN, soybean phosphatidylcholine, glycerol dioleate, N-methyl-2-pyrrolidone	

The buprenorphine content of the Weekly and Monthly product formulations contains 50mg/mL and 356mg/mL, respectively. †Per the Applicant, these doses correspond to "12-16 mg/day" of sublingual buprenorphine. Typical daily dosing of sublingual buprenorphine (from existing product labeling) is 16 mg/day.

The Applicant proposes that subcutaneous delivery of CAM2038 will be administered only by a qualified health care provider (HCP) in a clinical setting. Several sites of administration have been proposed (Figure 1)[2]. For the Weekly formulation, injection sites should be rotated weekly (the same site should not be injected more than once in an 8-week period). For the Monthly formulation, injections should also be rotated per the same guidelines. Upon injection, CAM2038 forms a small ball-like mass. The Applicant reported this mass to be palpable only in regions where subcutaneous tissue is thin (e.g., upper arm) and that, in general, it is poorly palpable in the subcutaneous space and diffuses into the surrounding tissue over time, leaving no mass behind. This product is not intended to be self-administered.

[2] The upper arm site was ultimately found to yield non-bioequivalent exposures and will not be recommended by the Clinical Pharmacology review team.

Source: page 27, Applicant's Manual of Procedures
Figure 1: Proposed CAM2038 injection site locations

1.2. Conclusions on the Substantial Evidence of Effectiveness

Data supporting the efficacy of CAM2038 was submitted by the Applicant from a Phase 3, pivotal, non-inferiority study (HS-11-421) of 428 outpatient adult males and females with moderate-to-severe OUD, supported by the results of blockade study HS-14-478. Unique to the pivotal study design was the choice of an active comparator (Suboxone[3]) and the recruitment of patients with OUD who met the Applicant's criteria for "new entry" to treatment (not receiving BPN treatment within 60 days of study initiation). The study was conducted in two phases: a weekly formulation phase (*phase 1*) followed by the monthly formulation (*phase 2*), with each phase lasting 12 weeks. The Applicant's primary objective, to demonstrate non-inferiority of CAM2038 over the active comparator, was established (p = 0.001; with a non-inferiority margin of 10%). However, due to the design of the pivotal study (two drug formulations with four dosing options in each formulation), it was difficult to distinguish the safety and efficacy of each formulation and dose, independent from the overall findings of CAM2038 compared to the active comparator.

In addition, and ideally, CAM2038 dosing for the pivotal study would have been chosen based on the findings of the blockade study (HS-13-478), which was conducted to identify the dose required to block exogenous opioids using hydromorphone challenge tests. Although the doses of CAM2038 Weekly chosen for the Blockade study (24 mg and 32 mg, respectively), were

[3] Suboxone, buprenorphine hydrochloride and naloxone hydrochloride (SL BPN/NX)

found to be an effective blockade to the hydromorphone challenge and were both used in the pivotal study, the pivotal study was initiated before the blockade study was completed, and doses were included in the pivotal study that were lower than those shown to provide a blocking plasma level per study (HS-13-478).

Despite these observations, the overall efficacy and safety of CAM2038 as a suite of products, appears adequate based on the submitted data, but problems with the dataset and manufacturing issues were identified during review. Many information requests were sent to the Applicant to obtain clarifying information by dose/responses and adverse events/dose of CAM2038. The Applicant complied and the responses to these requests are incorporated in this clinical review. Ultimately, because of discrepancies between the dataset submitted and the source data, conclusions about safety and efficacy could not be definitively drawn.

1.3. Benefit-Risk Assessment

See below for the integrated assessment of benefit-risk for this application.

Benefit-Risk Integrated Assessment

CAM2038 (buprenorphine (BPN) extended release) for subcutaneous injection is proposed for the treatment of moderate to severe opioid use disorder in patients who have tolerated at least a 4 mg test dose of a transmucosal buprenorphine-containing product. I recommend a complete response for this application.

CAM2038 is a modified-release formulation of BPN in a novel Fluid Crystal technology designed for administration by subcutaneous (not intramuscular) injection to be provided as a ready-for-use, prefilled syringe for the treatment of moderate to severe opiate use disorder (OUD) in adults. OUD, particularly if classified as moderate or severe, is a serious and life-threatening condition and contributes to increased rates of morbidity and mortality, as well as to social and economic costs to society

Current OUD treatment options include non-drug (behavioral) treatment, as well as medication-assisted treatment (MAT) with antagonists (naltrexone), agonists (methadone) or partial agonists (buprenorphine). Methadone is available only at federally-registered opioid treatment programs (OTPs), and patients must visit the clinic daily for in-person dosing until they meet criteria for receiving gradually-increasing numbers of take-home doses. Although drug regimens are key in OUD treatment, most of these regimens require daily dosing and are subject to diversion, misuse, and abuse. Moreover, a risk for unintentional pediatric exposure exists if the current treatments are misused or diverted. Thus, there is an important need for well-tolerated, less burdensome treatments, with reduced liability for abuse, misuse, and overdose. As such, CAM2038 shares some common qualities with a recent Agency-approved, the buprenorphine extended release product for subcutaneous injection, Sublocade, which may be used in patients who have completed a seven-day run-in on transmucosal buprenorphine.

BPN is a partial agonist at the mu-opioid receptor and, as mentioned, has been demonstrated as an effective treatment for OUD. CAM2038 is an extended-release BPN product that can be dosed weekly or monthly and can be used early on in treatment for OUD. This product was granted fast-track designation[4] because preliminary evidence suggested that CAM2038 would provide a reduced abuse liability over available therapies for moderate to severe OUD in adults.

The efficacy and safety of CAM2038 could not be concluded in this review cycle due to uncertainties about the quality of the manufacturing data, as well as discrepancies in the clinical data set.

[4] Fast track designation: Guidance for Industry *Expedited Programs for Serious Conditions – Drugs and Biologics* https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

The discrepancies in the clinical data may potentially be resolved by the Applicant through an audit of the source data. Analysis of the initially-submitted data concluded that the combined CAM2038 dosing regimens and formulations did achieve non-inferiority to the referenced comparator BPN product for the treatment of moderate to severe OUD (as demonstrated by a non-inferiority margin of 10%) in clinical Study 421, but this remains to be confirmed in re-submitted data. For OUD patients seeking treatment, the CAM2038 regimen has the potential to provide several advantages, including less frequent dosing to achieve target dosing of BPN; flexible dosing regimens; and the ability to receive BPN without take-home medications, all of which may contribute to better treatment adherence. However, there was an insufficient evidence to determine the drug's efficacy by specific dose (b) (4)

No major safety issues related specifically to CAM2038 were identified in this review. Although BPN is associated with common side effects and serious risks and did not appear to be exacerbated by the extended-release formulation or mode of delivery (injection) of CAM2038, issues with data reliability during the review process preclude a definitive conclusion on the datasets reviewed with this application.

CAM2038 is to be administered only by Health Care Provider (HCP) and not intended for self-administration. This product was not tested outside of a controlled clinical environment. A REMS to ensure that the product will be administered by HCPs and not distributed to patients will be required to mitigate the risk of intravenous injection. The goal of the REMS is to mitigate the risk of serious harm or death with intravenous self-administration by ensuring healthcare settings and pharmacies are certified and only dispense CAM2038 directly to a HCP for administration by a HCP. The following materials were proposed to be part of the CAM2038 REMS**:**

- Healthcare Setting and Pharmacy Enrollment Form
- Dear Healthcare Provider REMS Letter
- Fact Sheet
- REMS Program Website

Because of data quality issues in the clinical and manufacturing data, approval of CAM2038 for use in the treatment of adult patients with moderate to severe OUD cannot be recommended at this time. Although CAM2038 would be the first BPN-containing drug with a weekly and monthly formulation for OUD and represents an alternative to the currently available treatment armamentarium, the application, as initially submitted, does not have adequate efficacy and safety findings for approval.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• OUD is a chronic, relapsing disease characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and physical consequences. Moderate to severe OUD corresponds, roughly, to the DSM-IV diagnosis "opioid dependence," and to the widely-used term, "addiction." Mild OUD corresponds to the DSM-IV diagnosis "opioid abuse." • In 2016, the National Survey on Drug Use and Health determined that more than 2.1 million Americans aged 12 and over met criteria for opioid abuse or dependence. • Goals of treatment vary for individual patients, but typically involves a substantial change in illicit drug use behavior sufficient to translate to clinical benefit. • For many patients, discontinuation of treatment leads to relapse; therefore, treatment may be required chronically.	• Opioid use disorder, particularly if classified as moderate or severe, is a serious and life-threatening condition and contributes to increased rates of morbidity and mortality, as well as to social and economic costs to society.
Current Treatment Options	• Current treatment options include non-drug (behavioral) treatment, as well as medication-assisted treatment (MAT) with antagonists (naltrexone), agonists (methadone) or partial agonists (buprenorphine) and behavioral treatment alone (individual or group counseling, self-help groups) is not effective for many patients. • The buprenorphine extended release product for subcutaneous injection, SUBLOCADE, was FDA approved for moderate to severe OUD, November, 2017. Based on trial design, labeling requires at least a seven-day run-in period on transmucosal buprenorphine. • Methadone is available only at federally-registered opioid treatment programs (OTPs), and patients must visit the clinic daily for in-person dosing until they meet criteria for receiving gradually-increasing numbers of take-home doses. Methadone has been associated with fatal	• Reduces potential for diversion, misuse, abuse and accidental pediatric exposure • No surgical procedure needed

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	overdoses in patients and in their household contacts, including children. • The subdermal implant (PROBUPHINE) is suitable only for patients clinically stable on low-moderate dose of transmucosal buprenorphine (≤ 8 mg buprenorphine), requires surgical insertion and removal, and carries a risk of implant migration (with potentially serious consequences) or expulsion. • Oral naltrexone (REVIA) and depot naltrexone (VIVITROL) cannot be initiated until patients are fully detoxified, and may not be suitable or acceptable for all patients. Severe, and potentially serious, precipitated withdrawal can occur when naltrexone treatment is initiated. Serious injection site reactions requiring surgical intervention have been reported with VIVITROL. • Oral transmucosal buprenorphine and buprenorphine/naloxone products and oral naltrexone products are intended to be self-administered by the patient daily. Limitations of daily use products include poor adherence, fluctuating plasma concentrations, intentional "drug holidays," as well as patient convenience issues. Daily use agonist and partial agonist MAT products are subject to diversion, misuse, abuse and accidental pediatric exposure. •	
Benefit	• Based on the dataset analyzed, the opioid blockade Study (478) demonstrated that CAM2038 Weekly injections blocked subjective effects of both 6 mg and 18 mg doses of hydromorphone were blocked in 47 non-treatment-seeking subjects with moderated to severe OUD. • Based on the dataset analyzed, the pivotal efficacy trial (Study 421), NCT02357901 (N=428) demonstrated that patients treated with CAM2038 (Weekly and Monthly formulations) achieved a rate of response non-inferior to an active comparator (SL BPN/NX) with a non-	• (b) (4) • The number of discrepancies and multidisciplinary review findings suggest that the data are not reliable to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	inferiority margin of 10%. CAM2038 would be administered by a health care provider subcutaneously every week or month and provides advantages over daily dose MAT products in terms of patient adherence, patient convenience, and risks of abuse, misuse, and accidental exposure.	determine that the approval of this product, at this time, has a favorable risk-benefit ratio.
Risk and Risk Management	• The active ingredient, buprenorphine, has been marketed since 1981 and has been approved for opioid dependence treatment since 2002. The systemic safety profile of CAM2038 is consistent with the established safety profiles of transmucosal buprenorphine products used for treatment of OUD, on face, but data is limited. • Safety concerns related to buprenorphine include hepatic effects, cardiac conduction effects, allergy/anaphylaxis, and general effects of the opioid class (e.g. respiratory depression, CNS depression, etc.) • In a safety database of 440 opioid-dependent patients, systemic effects of buprenorphine associated with CAM2038 (≥ 2% occurrence) included headache, nausea, constipation, vomiting, elevated liver enzymes, sedation and somnolence • Common injection site reactions included injection site pain, pruritus and erythema. • Treatment-emergent adverse events leading to drug discontinuation were reported in ≤5% of subjects in all treatment groups • No Hy's law cases were identified in the clinical development program • One death occurred in the CAM2038 group due to motor vehicle accident.	• (b) (4) • Long-term safety data for exposures greater than 12 weeks are lacking. In addition, efficacy and safety measures were not evaluated sequentially by formulation or dose.

1.4. Patient Experience Data

Patient experience was incorporated into the submission of CAM2038 application. Relevant material included the results of patient-reported and clinician-reported outcomes assessments that were incorporated in the submitted clinical studies and is reflected in Table 2.

Table 2. Patient Experience Data Related to the CAM2038 Application

Patient experience data submitted as part of the application		Section where discussed
Clinical outcome assessment (COA) data:		Sections 6.1.1 and 6.2.1 Study Endpoints
□	Patient reported outcome (PRO)	Opioid desire/withdrawal[1] and self-reported illicit drug use.
□	Observer reported outcome (ObsRO)	Measures of opioid withdrawal[2]
□	Clinician reported outcome (ClinRO)	Measures of opioid withdrawal

[1]Patient reported outcomes included measures of opioid craving (Visual Analogue Scales of "Desire to Use" and "Need to Use") and withdrawal (Subjective Opiate Withdrawal Scale).
[2]Observer and Clinician reported outcomes were measured with the Clinical Opiate Withdrawal Scale.

2. Therapeutic Context

2.1. Analysis of Condition

Opioid use disorder (OUD) is a serious medical condition that results in significant morbidity and possibly death. OUD is characterized by misusing prescribed opioids or obtaining opioids illegally; and includes symptoms of tolerance, withdrawal, and interpersonal and occupational impairment, which are the defining features of addiction.

OUD is formally and currently diagnosed by a medical professional using the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5)[5]. To meet clinical criteria for

[5] American Psychiatric Association (2013), Diagnostic and Statistical Manual of Mental Disorders (5th ed.), Arlington: American Psychiatric Publishing, pp. 540–546

OUD of any severity, the patient must report a problematic pattern of opioid use leading to clinically significant impairment or distress within a 12-month period in addition to scoring positive on an additional set of symptoms. Severity is categorized as mild (2-3 symptoms), moderate (4-5 symptoms), or severe (≥ six symptoms).

The additional DSM-5 symptoms for OUD include: overusing opioids; unsuccessful effort (or desire) to decrease opioid use; significant time spent obtaining opioids; strong desire to use; important activities are sacrificed for opioids; recurrent opioid use in hazardous situations; continued use despite consequences; tolerance; and withdrawal.

In 2015, 12.5 million people were identified as having misused prescription opioids, 33,091 people died from opioid drug overdoses, and (b) (4) million adults were identified as having prescription OUD[6]. These data reflect the growing health concern of the opioid crisis and the national rise of cases of opioid abuse and misuse, both with prescribed opioid drugs and illicit opioid use[7]. Additionally, there is a growing public health concern about abuse, misuse, and accidental pediatric exposure associated with currently marketed transmucosal buprenorphine (BPN) products. That, in combination with the growing interest in the design of buprenorphine products that can block endogenous opioids and accomplish extinction of illicit opioid drug abuse, in addition to individual patient (people who are receiving treatment for OUD) concerns related to the inconvenience, privacy, and security issues of daily dosing of BPN, have spurred the development of long-acting depot formulations of buprenorphine.

2.2. Analysis of Current Treatment Options

[6] 2015 National Survey on Drug Use and Health (SAMHSA); Monthly Morbidity Weekly Report (MMWR), 2016; 65(50-51);1445–1452 [Center for Disease Control (CDC)]
[7] In 2015, 828,000 people used heroin [2015 National Survey on Drug Use and Health (SAMHSA)] with 12,989 deaths attributed to heroin overdoses alone [Heroin Overdose Data; Center for Disease Control (CDC)]

Current treatment options for OUD include non-drug (behavioral) treatment, as well as medication-assisted treatment (MAT) with antagonists (naltrexone), agonists (methadone) or partial agonists (buprenorphine). A summary of currently marketed FDA-approved drugs for OUD is provided in

Table **3**.

Table 3: Summary of currently available FDA-approved drugs for opioid use disorder

Immediate-Release Products			
Generic Name	**Trade Name**	**Applicant**	**Dosage forms**
Buprenorphine/naloxone	Suboxone* (generics only)	Indivior	sublingual tablet
	Suboxone (and generics)	Indivior	sublingual film
	Bunavail (and generics)	Biodelivery Sci Intl	buccal film
	Zubsolv (and generics)	Orexo AB	sublingual tablet
Buprenorphine	Subutex** (generics only)	Indivior	sublingual tablet
Methadone HCl	Methadose (and generics)	Mallinckrodt	oral solution; bulk powder; tablet dispersible tablet
Methadone HCl	Dolophine (and generics)	Roxane	tablet; oral concentrate; oral solution
Naltrexone HCl	ReVia (and generics)	Duramed	tablet
Extended-Release Products			
Generic/Chemical Name	**Trade Name**	**Applicant**	**Dosage forms**
Naltrexone HCl	Vivitrol	Alkermes	injectable suspension
Buprenorphine	Probuphine***	Braeburn	subdermal implant
Buprenorphine	Sublocade	Indivior	injectable suspension

*NDA 020733; discontinued in US Market
**NDA 020732; discontinued in US market in 2011
***suitable only for patients clinically stable on low-moderate dose of transmucosal buprenorphine (≤ 8 mg), requires surgical insertion and removal, and carries a risk of implant migration or expulsion.

Methadone is available only at federally-registered opioid treatment programs (OTPs) and patients must visit the clinic daily for in-person dosing until they meet criteria for receiving gradually-increasing numbers of take-home doses. Additionally, methadone has been associated with fatal overdoses in patients and in their household contacts, including children. Oral naltrexone (Revia) and depot naltrexone (Vivitrol) cannot be initiated until patients are fully detoxified; and may not be suitable or acceptable for all patients. Severe, and potentially serious, precipitated withdrawal can occur when naltrexone treatment is initiated. Serious injection site reactions requiring surgical intervention have been reported with Vivitrol.

Further, currently available oral-transmucosal buprenorphine and buprenorphine/naloxone products and oral naltrexone products are intended to be self-administered by the patient daily. Approved long-acting buprenorphine products for OUD include Probuphine, a six-month implant requiring surgical insertion and removal, and carrying risks common to drug implants inserted in the arm; and Sublocade, a monthly subcutaneous depot injection which is labeled for use after at least a seven-day run-in period on transmucosal buprenorphine.

Buprenorphine (BPN) is a partial agonist at the μ-opiate receptor and was developed as a treatment for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the μ-opioid receptor. Like methadone, BPN's activity at the μ-receptor was expected to relieve patients' urge to use illicit opioids, and like methadone, the long duration of action would allow patients to achieve a steady state with daily dosing, without the alternating highs and lows associated with opioid abuse that impair daily functioning. At sufficiently high doses, buprenorphine blocks full opioid agonists from achieving their full effects, deterring abuse of these substances for BPN-maintained patients. However, compared to methadone, BPN is less likely to cause life-threatening respiratory depression and was therefore expected to be more suitable for take-home use.

A parenteral formulation of BPN was approved in 1981 for the treatment of pain, and two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence[8]. Three other transmucosal formulations have subsequently been approved for opioid dependence, as well as two transdermal products and one transmucosal product for pain. Moreover, an implantable buprenorphine product delivering a low to moderate dose of buprenorphine was approved in 2015 for stable patients for whom the dose is adequate. In November, 2017, a subcutaneous extended-release injectable suspension, Sublocade, was approved for the treatment of moderate to severe OUD following a period of at least 7 days' treatment with SL BPN.

The current labeled recommended dose of SL BPN ranges from 12 mg to 16 mg daily. Limitations of daily use products include poor adherence, fluctuating plasma concentrations, intentional "drug holidays," as well as patient convenience issues. Daily use of agonist and partial agonist MAT products are subject to diversion, misuse, abuse, and accidental pediatric exposure.

[8] Subutex, buprenorphine sublingual tablets (Reckitt Benckiser NDA 20732) and Suboxone, buprenorphine/naloxone sublingual tablets (Reckitt Benckiser NDA 20733). Naloxone is intended to further deter abuse by the intravenous route by precipitating withdrawal if the product is injected by persons dependent on full agonists.

Due to its partial agonist properties, the euphorigenic effects of BPN are understood to reach a "ceiling" at moderate doses, beyond which increasing doses of the drug do not produce the increased effect that would result from full opioid agonists. This was expected to limit its attractiveness as a drug of abuse, an additional feature permitting take-home use.
In addition, when a partial agonist displaces a full agonist at the receptor, the relative reduction in receptor activation can produce withdrawal effects. Individuals dependent on full agonists may therefore experience sudden and severe symptoms of withdrawal if they use BPN; predicted to serve as a further deterrent to abuse. Despite these features, BPN sublingual products have been increasingly identified in the illicit drug market, and it is known that they are diverted, abused, and misused. Additionally, they have been implicated in several cases of accidental poisonings in children. Therefore, a depot injection or an implantable product which would be difficult to divert or abuse, and would be less likely to be accidentally ingested by children, offers potential advantages. In addition, if a depot or implantable product provided a sufficient plasma level of buprenorphine to block the effects of exogenous opioids, the nature of the product would enforce compliance so that patients could not periodically discontinue use to allow the blocking effect to dissipate, so that they could experience the effects of their opioids of choice.

Approximately (b) (4) million prescriptions from outpatient retail pharmacies were dispensed and approximately (b) (4) million patients received a dispensed prescription for buprenorphine tablets or films during 2016[9] and these numbers continue to increase. Primary care physicians accounted for 39% of dispensed prescriptions, followed by psychiatrists (21%), osteopaths (14%), emergency physicians (4%) and anesthesiologists (4%)[10]. Recently, the authority to prescribe buprenorphine for office-based treatment of OUD was expanded to include Nurse Practitioners and Physician's Assistants, so the distribution of specialties may be expected to change in the future. Thus, it is important to have formulations of BPN for OUD treatment that can be safely monitored in primary care settings, reduce potential for misuse, and improve patient outcomes.

3. Regulatory Background

[9] Quintiles IMS, Total Patient Tracker (TPT); Data Extracted August 2017
[10] IMS Health, National Prescription Audit (NPA); Data Extracted August 2017

3.1. U.S. Regulatory Actions and Marketing History

CAM2038 has been developed for the (b) (4) treatment of moderate to severe OUD and is not currently marketed in the U.S. At the time of application submission, no extended-release buprenorphine injectable products were FDA approved.

3.2. Summary of Presubmission/Submission Regulatory Activity

The CAM2038 clinical program was undertaken with advice from the Division. A description of general Agency advice for MAT program development, presubmission and submission activities are outlined below.

General Division Recommendations for MAT Phase 3 Study Development

Under Division guidance, several features were incorporated into this program to address the difficulties of retaining patients in treatment and to address the concern that patients may be clinically successful despite occasional lapses in abstinence. These recommendations included:

- Use of less frequent urine testing
- A responder definition that allows a few missing or positive samples
- The incorporation of a "grace period"
- The use of a "continuous responder" analysis

Infrequent urine sampling inherently allows patients who are not fully abstinent to be adjudicated as successful, even if the definition of response is 100% negative samples, because some use will not be detected. The Division accepts this for reasons of feasibility. In studies of treatments that are not administered under supervision daily, or treatments that are not inherently reinforcing, it has been challenging to ensure complete collection of thrice-weekly samples (a historic standard). Thus, there has been concern that a study design with frequent sampling, along with an analytic strategy of imputing positive results to missing samples, creates an unrealistic situation in which even some clinically successful patients would be adjudicated as unsuccessful.

The use of a responder definition that does not require all samples to be present and negative, particularly during a study with an infrequent sampling schedule introduces additional flexibility. Because the Applicant sought to establish efficacy of the weekly product (used for the first 12 weeks of the pivotal Phase 3 study) as well as the monthly product (used for the second 12 weeks of the pivotal Phase 3 study) it was necessary to construct a responder

definition that required demonstration of response during both phases of treatment. The number or percent of allowable missing or positive samples was chosen taking into consideration the total number of samples to be collected. For example, "80% of samples negative" would be more compelling in a six-month study with thrice-weekly samples (58 negative samples) than in a study with once-monthly samples (4 negative samples).

Incorporating a "grace period" (assessments at the beginning of treatment which are not considered in the analysis) was considered reasonable by the Division because patients may not respond immediately to drug treatment. In the Applicant's proposed Phase 3, pivotal study, a grace period of 1 or 4-weeks was considered with some analyses, while the responder definition included a grace period at the beginning of each "phase" of treatment.

One compromise approach that the Division proposed is to perform an analysis that considers the full range of responder definitions, from complete abstinence to no abstinence, but to emphasize the effect of the drug on promoting abstinence or near-abstinence. This is called a "continuous responder" analysis. This approach, the continuous responder curve, or the cumulative distribution function (CDF) of drug use assessments, was employed by the Applicant. The CDF curve gives an overall picture of the drug's effect on drug use behavior. Augmenting this analysis with a responder rate comparison ensures that the effect is of a magnitude that has clinical meaningfulness. In the Applicant's pivotal, Phase 3, clinical study, there were two 'phases' of urine sample collections, each corresponding with the CAM2038 dosing formulation (Weekly or Monthly). Urine samples in the first 'phase' were scheduled to be collected over 12 weeks. The Applicant performed analyses incorporating either a 1-week or a 4-week grace period because patients may not respond immediately to treatment. In 'phase' two, urine samples were scheduled every four weeks (3 samples) over 12 weeks, augmented by three additional random samples, to yield a total of six samples for each patient to be included in the analysis in the second 'phase'.

A CDF of patient responses could not be employed as the primary endpoint, because the primary endpoint needed to encompass demonstration of response to both 'phases' of the treatment. Thus, a responder analysis requiring response to both formulations was deemed the primary endpoint, and the secondary endpoint was the CDF. In endeavoring to develop an appropriate responder definition for a study that involved one product formulation in Weeks 1-12 and another product formulation for Weeks 13-24, the Division referred to an example from literature[11]. The Division proposed that a responder be defined in such a way that the sample collected in the final week of each treatment would be negative, along with three of four of the

[11] 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(12):1238-1246

previous samples in that phase. As a practical matter, this yielded a responder definition with a long grace period in both 'phases' of treatment, but for the CDF analysis, grace periods of 1 and 4 weeks were applied. Such responders may have several undetected occasions of drug use. However, the ability to attend study visits and provide negative urine samples over a 24-week period is nevertheless an indicator of some degree of clinical stability.

Pre-Submission Communications

Many meetings, Advice Letters, and Information requests comprised the pre-submission aspect of the program development. A timeline of key dates is highlighted in Table 4. The entire program was placed on hold while the Applicant responded to deficiencies identified in the early stages of protocol development. The Applicant addressed the deficiencies and continued the program in an expedited manner. Key advice relayed to the Applicant during the pre-NDA meeting included the recommendation against a fixed time-point in the pivotal Phase 3 trial; that an ideal open label study would expose 100 subjects to the CAM2038 Weekly and 100 subjects to the CAM2038 Monthly products independent of each other; (b) (4) and to submit injection site reaction data by subject and by time.

The Applicant was advised to first conduct a study to target a plasma buprenorphine level that completely blocked the effects of exogenous opioids at clinically-relevant doses (blockade study). A single study showing this effect, with compelling results of the product to treat patients with opioid dependence, could be considered as substantial evidence of efficacy and supportive for submission.

Regarding the pivotal Phase 3 randomized controlled trial (RCT), the Applicant was also advised that it would be challenging to evaluate both the weekly and monthly formulations in a single study. The weekly formulation was envisioned as suitable for less -stable patients (potentially early in treatment) requiring weekly visits, while the monthly product was envisioned for patients ready to transition to a lower intensity of treatment. A study involving both formulations, with patients transitioned based on pre-specified stability criteria, could potentially provide support for such a regimen.

Table 4: Timeline of Key Regulatory Pre-Submission Activities in the Clinical Program

Date	Key Pre-submission activity*
3/13/2012	PIND Meeting (Camurus AB)
4/09/2015	IND 114082 submitted (Braeburn) 3/31/15
2/24/2015	End of Phase 2 Meeting

5/12/2015	(inactivating and reactivating IND)
7/09/2015	IND place on Full clinical hold
7/10/2015	Fast Track Designation granted
9/04/2015	Hold Removal with imposition of partial holds*
3/17/2017	PreNDA meeting
3/28/2017	Pediatric Study Plan: Pediatric Waiver Request (children < (b) (4) years) (b) (4)
9/15/2017	Priority Review granted

***** Does not include Advice Letters and Information Requests
**proposed studies HS-13-478, HS-11-421, HS-14-499 could not proceed until each deficiency was met

Application Submission

At the time of submission, the CAM2038clinical development program comprised several studies that encompassed clinical trials in healthy volunteers and in patients with OUD and included two Phase 2 studies (the dose finding/blockade study HS-13-478 and the multi injection site study HS-15-549, respectively) and two Phase 3 studies (the pivotal randomized controlled trial (RCT) HS-11-421 for efficacy; and the open-label, uncontrolled, 48 week study HS-14-499 in OUD patients, respectively). The early studies in the program (307 and 487) were conducted by the Swedish company Camurus, manufacturer of the CAM2038 product, prior to opening the IND. Camurus then partnered with Braeburn to develop and market the product. Braeburn served as the Sponsor of the IND and is the Applicant. Refer to **Table 5** for the complete list of clinical studies in the CAM2038 development program.

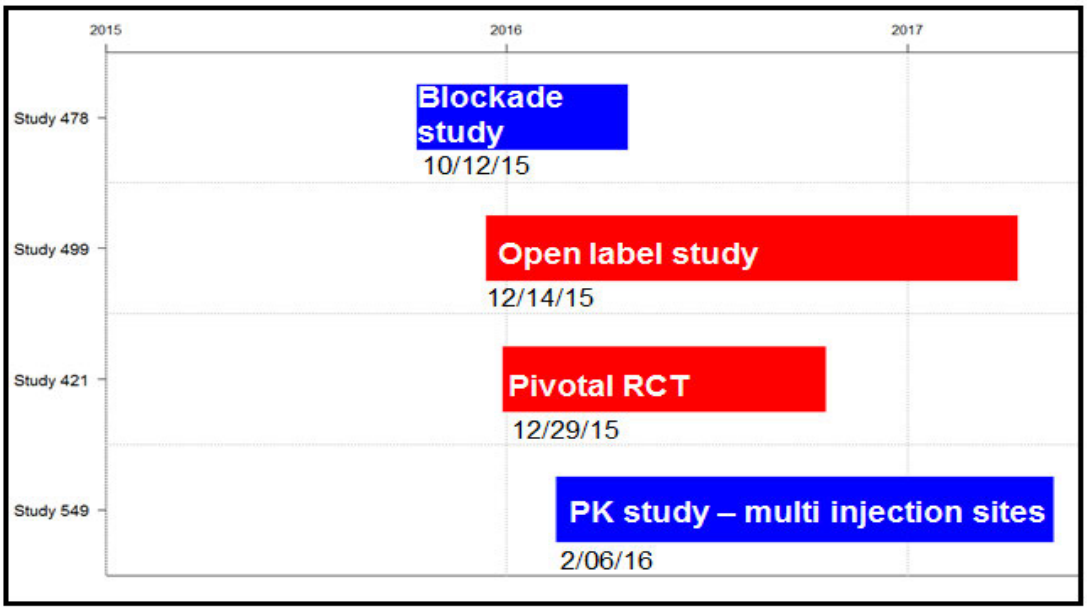
Table 5: Studies included in the CAM2038 clinical development program

Study/ Type	Design	Duration (weeks)	Population (N) [completed]
HS-07-307 PK/BA*	Phase 1/2, single-center, single-blind, single dose-escalation, first in human. 4 doses of CAM2038 Weekly.	7	OUD patients: on SL BPN ≥6 months; 41 enrolled [one was treated in 2 groups (groups B and D)]
HS-11-421 Pivotal	Phase 3 multi-center study, randomized controlled trial, multicenter	24	Mod-severe OUD patients. 428 enrolled [247 completed].
HS-11-426 PK/BA	P1, RCT, OL (open label), single dose study of 3 CAM2038 weekly doses (8, 16, 32 mg). Control: IV Temgesic, SL Subutex (8,16,24mg)	1	Healthy volunteers on naltrexone blockade. 60 enrolled [54]
HS-13-478 PK	P2, RCT, DB, multicenter, repeat dose. Control: IM Hydromorphone, IR morphine sulfate Tablets	7	Mod-severe OUD patients. 47 enrolled [46]
HS-13-487 PK/BA	P1, RCT, OL, single and repeated monthly and weekly dose. Control: I.V. Temgesic, SL Subutex	4	Healthy volunteers on naltrexone blockade. 87enrolled [75]
HS-14-499 Safety	P3, Open Label (OL), multicenter study (29 sites). Uncontrolled.	48	Mod-severe OUD patients 227 enrolled, 156 completed.
HS-15-549 PK	P2, OL, partially randomized, multicenter, CAM2038 weekly /monthly at different injection Sites. Three groups (Grp) Control: 24 mg SL BPN/NX.	Grp 1:7-13 Grp 2:16-22 Grp 3: 17	Mod-severe OUD patients. Enrolled (completed): Grp 1=28 (23); Grp 2-20(16); Grp 3= 18(12).

*PK=Pharmacokinetics/BA=bioavailability
**RCT=Randomized controlled trial, DB=double blind, DD=double dummy

However, the Applicant elected not to conduct the key studies for this application sequentially, as was recommended, and instead submitted the protocols for the key studies simultaneously and initiated them in an overlapping fashion. Thus, starting doses in the pivotal RCT that were not evaluated in the blockade study were included in the clinical study. And, although the design and analysis of the blockade study were agreed to with the Division and the Controlled Substances Staff prior to the study, only two doses within one formulation (the Weekly formulation) were evaluated in the Blockade study. Further, the OL study was initiated before the pivotal RCT began (and during the blockade study), which is typically a design to be conducted following the completion of an RCT.

Figure 2: Timeline of key studies in the CAM2038 clinical development program



*Study HS-13-478 was a 7-week, Phase 2, multicenter, blinded, active control, repeat dose RCT to determine effective blockade of CAM2038 in 47 patients with moderate to severe OUD. The control was intramuscular hydromorphone and immediate release morphine sulfate tablets. Study HS-15-549 was a Phase 2, multicenter, open-label, partially randomized, 7-22 weeks (3 groups) study of CAM2038 weekly and monthly at different injection sites. Sixty-two patients with moderate to severe OUD were enrolled. The control was 24 mg SL BPN/NX, dosed daily.

3.3. Foreign Regulatory Actions and Marketing History

CAM2038 is not currently marketed in foreign countries.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Specific to data integrity, the clinical review team worked in collaboration with the Office of Computational Science (OCS) and the Office of Scientific Investigations (OSI) to review sites that enrolled patients in Study 421, the pivotal efficacy trial. OSI conducted inspection of the Applicant (Braeburn Pharmaceuticals Inc.) and four clinical investigators. These inspections were performed as a routine data audit for this application and the preliminary inspectional findings at the time of this review are summarized in Table 6.

Table 6: Clinical Investigator Sites audited for the review of NDA 210136

Site	Subjects (N)	Protocol #	Clinical Investigator	Location	Inspection dates (2017)	Preliminary Compliance classification*
101	42	HS-13-478	Dr. Debra Kelsh	Overland Park, KS	November 13-21	NAI
107	12	HS-11-421	Dr. John Bernard	Belvidere, NJ	October 12-16	NAI
124	12	HS-11-421	Dr. Jason Anderson	Orem, UT	November 13-17	VAI
138	33	HS-11-421	Dr. Otto Dueno	Dayton, OH	November 01-15	VAI
Applicant, Braeburn Pharmaceuticals, Inc		HS-11-421 HS-13-478			November 17-27	NAI

*NAI = No Action Indicated; VAI = Voluntary Action Indicated

Based on preliminary inspection reports, the Applicant site and Drs. Kelsh (site 101) and Bernard (site 107) sites appeared to be in compliance with Good Clinical Practice (GCP). No FDA 483 form (Inspectional Observations) was issued to Drs. Kelsh, Bernard, or the Applicant.

However, the preliminary inspection reports of Drs. Anderson (site 124) and Dueno (site 138) revealed deviations from GCP. Inspection of Dr. Anderson's site (site 124) revealed deviations such as failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. The inspection at Dr. Dueno's site (site 138) revealed failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Additionally, the investigational drug disposition records at site 138 were not adequate with respect to dates and use by subjects. Overall, Drs. Anderson's (site 124) and Dueno's (site 138) executions of the protocol were found to be compliant with GCP, per OSI, and the inspection of both sites revealed no significant deficiencies.

Furthermore, after the OSI completion of the Applicant site inspection, November 30, 2017, the Division met with OSI to discuss their preliminary findings and share our concerns related to the quality of the datasets we received with application. The Division, in collaboration with OSI,

then discussed these quality issues with the Applicant on December 14, 2017, and the sponsor agreed to conduct a database quality control (QC). The Applicant acknowledged the timelines and the criticality of resolving the data concerns. Thus, the Applicant proposed to deliver corrected datasets within a week of the teleconference with a clear and concise QC strategy that would allow the Division to fully understand the QC approach, what corrections were made, and how.

On December 19, 2017, the Applicant responded to the Division with an update on the QC review of the clinical database. The Applicant's vendor identified what appeared to be the root cause of the data errors. As of this review, the Applicant identified discrepancies between the IVR database and the clinical database that were caused by limited QC/edit function checks between the two systems. The Applicant anticipated re-sending corrected datasets by close of business on December 22, 2017. These issues suggest the reviewed data could not be relied on to support approval of this application. However, due to issues noted below, the resubmitted data will not be reviewed in this review cycle.

4.2. Product Quality

Outstanding facilities and biopharmaceutical issues with source data and manufacturing were identified and were being evaluated at the time of this review. Significant issues were identified during the inspection of the testing facility, per the Office of Process and Facilities (OPF). These issues led the chemistry, manufacturing, and controls (CMC) review team to conclude that the data could not be relied upon to support approval. Results of the pre-approval inspection revealed (b) (4) Please see Dr. Abraham's review for details.

These issues are not readily resolved and will preclude approval in this review cycle.

4.3. Clinical Microbiology

Non-applicable.

4.4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology (PTOX) review team identified several issues that suggested the provided data might not be adequate to support an approval recommendation of the application with the specific concerns summarized as follows:

- The extraction study conditions to characterize the safety of the container closure were inadequate with this application as submitted
- The leachable data were also inadequate with this application as submitted

Additional outstanding issues included:

- The lack of adequate safety justification for N-methyl pyrrolidone (NMP)
- Lack of adequate safety justification for glycerol-3-dodecaethylene glycol (GDO)
- Lack of human exposure margins (measured by area under the curve at steady state ($AUC_{12\text{-}36\ hour}$)) compared with animal exposure margins (data to support labeling).

During the review process, three new extraction studies were proposed by the PTOX and CMC review teams to be completed within this review cycle. As of December 14, 2017, one of the studies (an extraction study (b) (4)) was submitted by the Applicant but not reviewed in detail by the PTOX team. The remaining two proposed extraction studies (b) (4) were outstanding at the time of this review.

Additional leachable data were to be submitted by the Applicant with December 14, 2017 and February, 2018 deadlines to provide 24-month (for each formulation) and interim timepoint data for each formulation, respectively.

The outstanding extraction and leachable study information preclude approval for the application for this review cycle.

4.5. Clinical Pharmacology

The comparative bioavailability of CAM2038 Weekly and CAM2038 Monthly was compared to Subutex using steady-state (ss) PK parameters, Area Under the Curve steady state (AUC,ss) and maximum concentration at steady state (Cmax,ss) across studies (HS-11-426, HS-13-487 and HS-15-549) (Table 7). Because the CAM2038 formulations have different dosing intervals,

AUC,ss was represented by average concentrations (Cavg,ss = AUCss,τ /dosing interval,τ). Refer to the detailed Clinical Pharmacology review by Dr. Narahansetti for details.

The Clinical Pharmacology review team did not find deficiencies in the submission that would preclude approval. However, from a data quality perspective, it would have been ideal if the comparative Bioavailability (BA) studies were conducted before the Pivotal and Open-Label Phase 3 clinical trials. Although the BA studies HS-13-487 and HS-11-426 were conducted before the other studies in the clinical program, comparative BA Study HS-15-549, was a multiple injection site conducted after the Phase 3 studies had started (Figure 2). Furthermore, several cross-study comparisons were required to achieve a full picture of how the various weekly and monthly doses compared to one another and to the sublingual product. The Applicant presented some comparisons based on modeling, but the clinical pharmacology team also noted that the values for the observed data were not aligned with the modeled data, and recommended that the observed data be considered definitive.

Table 7: Summary of the comparative bioavailability and steady-state exposure of CAM2038

Drug Product	Dose (mg) (Study)	Dose No.	Population	Cmax,ss (ng/mL)	Tmax (h) [a]	Ctrough[b] (ng/mL)	AUCτ (ng*h/mL)	Cav,ss (ng/mL)
CAM2038 Weekly	16 (HS-13-487)	4	HV (n=15)	4.30 (44)	23.2	0.842 (22)	350 (24)	2.09 (24)
	32 (HS-15-549)	4-7	Pt (n=21)	6.87 (37)	24.0	2.63 (39)	700 (27)	**4.17 (27)**
CAM2038 Monthly	128(HS-15-549)	4	Pt (n=16)	**11.1 (54)**	10.0	2.09 (55)	2610 (42)	**3.89 (42)**
	160(HS-15-549)	4	Pt (n=12)	**15.4 (52)**	24.0	2.66 (61)	3540 (26)	**5.27 (26)**
SL BPN	24 (HS-11-426)	7	HV (n=16)	**7.78 (37)**	1.01	1.24 (44)	56.3 (29)	**2.34 (29)**
	24 (HS-13-487)	7	HV (n=16)	**8.45 (54)**	1.04	1.61 (40)	63.9 (34)	**2.66 (34)**

Summary of the comparative BA for select steady state doses of CAM2038 compared with 24 mg SL BPN (the current maximum recommended daily dosing of SL BPN). Compared to Subutex 24 mg (SL BPBN), CAM2038 Monthly 128 mg and 160 mg demonstrate higher steady state Cmax; and, with the same comparator, [redacted] (b) (4) 32 mg Weekly and 160 mg Monthly (highlighted in red) shows higher steady state, Cavg: dosing that exceeds the maximum recommended label dosing for Subutex. The Applicant used mathematical PK modeling to predict the parameters of the 24 mg weekly and the 96 mg monthly doses.

In summary, [redacted] (b) (4) 32 mg Weekly and 160 mg Monthly, showed higher exposure (AUCss, represented by Cavg) compared with the highest recommended sublingual dose of Subutex at 24 mg daily:

- After single dose injection, dose-proportional increase in BPN AUC was demonstrated for both CAM2038 Weekly and CAM2038 Monthly. Cmax increased in a dose-proportional manner for CAM2038 Weekly and in a less than dose proportional manner for CAM2038 Monthly.

- After multiple dose injections, (b) (4) 32 mg CAM2038 Weekly and 160 mg CAM2038 Monthly showed higher steady state exposure (Cavg,ss) by 57-78% and 82-98%, respectively, compared with the SL BPN at 24 mg.
- The norBPN to BPN AUCss ratio ranges 0.35 to 0.53 for SC injection of CAM2038, but much higher for SL Subutex (with a range of 1.6 to 2.5 ng/mL). This observation confirms that BPN, after SC injection of CAM2038, results in *lesser* metabolism to norBPN compared to a SL BPN product due to lack of first-pass effect.
- Due to lack of first-pass effect for CAM2038, the magnitude of drug interaction with a 3A4 inhibitor or inducer is expected to be less for CAM2038 in comparison to SL BPN products.
- No dedicated CAM2038 pharmacokinetic studies were conducted in hepatic or renal patients. Due to lack of first-pass effect, the effect on hepatic impairment on pharmacokinetics of CAM2038 would be expected to be less than that of SL BPN drug products because BPN undergoes hepatic extraction and metabolism and BPN systemic clearance is not significantly related to renal function.

4.6. Devices and Companion Diagnostic Issues

The Agency's Center for Devices and Radiological Health (CDRH) reviewed the delivery device/CAM 2038 combination product during product development and did not identify any deficiencies in the product/delivery system.

The Division of Medication Error Prevention and Analysis (DMEPA) concluded their review of the human factors risk analysis and validation protocol under IND 114802 (referencing this application) on October, 18, 2017. DMEPA identified several deficiencies and provided recommendations to the Application for resolution of those deficiencies. As of August, 31, 2017, the Applicant had implemented DMEPA's recommendations.

Specific concerns included the potential for confusion of the weekly and monthly formulations, (b) (4) and for clinicians to assume that combinations of the weekly formulation could yield the monthly formulation (e.g., 2 x 16 mg weekly substituted for 32 mg monthly). Changes to labeling and carton and container were made to address these concerns but potential for medication errors remains a concern.

4.7. Consumer Study Reviews

Non-applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Several clinical studies were conducted as part of the CAM2038 development program. These studies encompassed Phase 1, Phase 2, and Phase 3 trials evaluating PK/PD, biovailability, efficacy and safety of the CAM2038 product. These studies were conducted in healthy adult volunteers and in treatment seeking and non-treatment seeking adults with moderate to severe OUD (Table 5). The studies specific for this review focused on efficacy and safety and included key Phase 2 and Phase 3 trials (Table 8). Pediatric studies were not conducted.

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Table 8: Listing of clinical trials specific to the review of NDA 210136

Trial Identity	NCT no.	Trial Design	Regimen/ schedule	Treatment Duration (Follow Up)	No. of patients enrolled	Study Population	No. of Centers/ Countries
Controlled Studies to Support Efficacy and Safety							
HS-11-421	**02651584**	Pivotal, Phase 3, Randomized control trial, double-blind, double-dummy, active-controlled, parallel group, multi-center study, designed to evaluate the non-inferiority of CAM2038 compared to existing standard of care*	Weekly CAM2038 dosing (12 weeks) then to Monthly CAM2038 dosing (12 weeks). Active control arm received 16-32 mg BPN/NX oral tablet dose daily with placebo injections throughout study	24 weeks (4weeks)	428	Treatment seeking Adults with OUD: New entrants to treatment (no BPN treatment within 60 days)	USA: 34 sites
Studies to Support Safety							
HS-14-499	**02672111**	Open Label, Phase 3, multisite study to evaluate the long-term safety of CAM2038 in both the Weekly and Monthly formulations.	Participants could be started on the CAM2038 Weekly or Monthly formulation with flexible dosing	48 weeks	227	Treatment seeking Adults with OUD who were a) transitioning from current BPN treatment or b) New entrants to BPN treatment	USA: 10 sites Europe: 16 sites
Other studies pertinent to the review of efficacy or safety							
HS-13-478	**02611752**	Phase 2, RCT, DB, multicenter, repeat dose. Control: IM Hydromorphone, IR Morphine Tablets	Opioid blockade study in adults who are opioid-tolerant. Three groups of patients received 2 doses of CAM2038 Weekly (24 or 32 mg) or two doses of placebo; each dose followed by drug-liking challenge.	7 weeks	47	Non-treatment seeking adults with OUD	USA: 4 sites
HS-15-549	**02710526**	P2, OL, partially randomized, multicenter, CAM 2038 weekly /monthly at different injection Sites. Control: 24 mg SL BPN/NX	Three groups of patients received CAM2038 Weekly or Monthly injections at different sites; each group of exposures lasted 7-22 weeks.	7 – 22 weeks	62	Adults with OUD	USA: 3 sites

307	**None****	Phase 1/2, single-center, single-blind, single dose-escalation, first in human; no control.	Study conducted on four groups of patients who were opioid tolerant. Four doses of CAM2038 Weekly over the course of 4-weeks.	7 weeks	41	Adults with OUD who had been on SL BPN treatment at least 6 months before study start	Europe: (Germany) single site

*sublingual buprenorphine (SL BPN) / naloxone (NX)
** Study completed by Camurus in 2011 at a single site in Germany. This study does not have an NCT number.
¥ Sweden, Germany, Denmark, Hungary, Great Britain, Austria

5.2. Review Strategy

The clinical review focused on the pivotal efficacy and safety data provided by the Applicant and included Studies 478, 421, and 499, respectively. Study 478 was a hydromorphone blockade study in OUD patients to determine the appropriate dose of CAM2038 for treatment of OUD. Study 421 was the pivotal efficacy trial in OUD patients who had not received medication treatment for OUD for at least 60 days prior to the study starting. Last, Study 499 was a 48-week, open-label study that was intended to provide safety information about the longer-term use of the CAM2038 product. Although the Applicant did collect efficacy outcome measures in Study 499, it was not reviewed as a supporting efficacy study because it was open-label and had no comparator arm. Two additional studies (307 and 549) were included for pooling aspects of the safety review (e.g., injection site reactions) but were not considered key studies for this review.

The efficacy review was primarily conducted by FDA Biometrics reviewer, Dr. James Travis, who worked collaboratively with the clinical team in identifying the efficacy of the proposed drug for this population. Key efficacy findings from his review of Study 421 are referenced in this review and key issues related to this review (namely determining adequate efficacy by dose and by formulation) are highlighted.

The safety review focused on deaths, non-fatal serious adverse events, common adverse events, ECG monitoring, vital signs, laboratory results and dropouts due to adverse events from the pivotal efficacy study (421); the open label safety study (499); as well as the studies 307 and 549 for pooling safety data. A detailed review of QT, focusing in Study 549, was also incorporated into the safety review and was performed by the Interdisciplinary Review Team for QT Studies (the QT-IRT team). A high-level summary of their review is included in this report.

The safety review was limited for several reasons:

1) No comparisons to placebo were included in the main clinical trials. The design of study 499 was open-label, and the design of Study 421 was active-controlled, thereby making the results of the safety data less interpretable;
2) Because subjects from Study 421 were not followed longitudinally (i.e., not included in an open-label extension design) the number of patients exposed to CAM2038 on any formulation or dose for > 48 weeks was limited to the number of patients who enrolled in the OL study, which was performed simultaneously to the pivotal study; and
3) it was difficult to effectively review specific safety differences of the weekly versus the monthly CAM2038 formulations because studies of each formulation were not performed independent of each other,

4) the submitted study reports and datasets made no attempt to break out the safety experience by dose or formulation, and when this information was provided, it appeared that frequent dose changes were made throughout the study so that an individual patient's dosing was difficult to characterize.

No sections of the review template were omitted from this review. Additional materials and communications examined during the clinical review of this application are listed in Table 9 and include several responses to information requests.

Table 9: Materials and communications reviewed for NDA 210136

Submission Date	eCTD Sequence Number	Contents
07/19/2017	0002	Original Supplement
07/19/2017	0002	Financial Disclosure Information
07/19/2017	0002	Draft Labeling
07/31/2017	0003	Response to Information Request: Medical consequences of CAM2038 intravenous injection
08/01/2017	0005	Response to Information Request: Size range of CAM2038 in vivo bolus
08/09/2017	0006	Response to Information Request: Inclusion of variables for efficacy and safety datasets for Studies 421, 478, and 499
09/05/2017	0011	Response to Information Request: Subject level data listings by site
09/08/2017	0012	Response to Information Request: Clarification of urinalyses reports; Study 421 dataset and define file resubmission; explanation of subject listings with scheduled and unscheduled visits on same day
09/11/2017	0013	Response to Information Request: Analyses of primary endpoint by demographic subgroup (age, sex, and race)
09/11/2017	0014	Response to Information Request: ITT analysis dataset with SAS code
09/15/2017	0016	Response to Information Request: Dataset that lists whether the kit contained placebo or active buprenorphine tablets, and the corresponding dose strength.
09/18/2017	0017	Response to Information Request: Sensitivity analysis of urinalysis classifications in Study 421 and kit numbers for SL BPN tablets
09/28/2017	0019	Responses to Information Request from Filing Communication Review Issues: NCT numbers, explanation of role of Study 549 in ISS; cumulative exposure of doses by duration in weeks; and clarification of urinalyses
10/10/2017	0024	Response to Information Request: Proposed REMS with appendices (Medication Guide, Communication Letters, Closed Distribution Diagram)

10/13/2017	0026	Response to Information Request from Filing Communication Review Issues: Proposal of trade dress and labeling language to mitigate confusion between the CAM2038 formulations (b) (4)
10/13/2017	0027	Response to Information Request for clarification of screen failures, randomized subjects, inclusion of baseline opioid free subjects, and disposition coding
10/20/2017	0022	Responses to Information Request from Filing Communication Review Issues: timing and discontinuation of dosing; dose responses, supplemental dosing (included new graphics)
10/25/2017	0034	Responses to Information Request: clarification of protocol violations/deviations; clarification of discontinuations; clarification of starting dosing and actual doses used in clinical studies (421, 499, and 478)
11/21/2017	0049	Responses to Information Request related to AC meeting, briefing package errata, and efficacy data: clarification of SC properties of injected product and ability of surgical removal; proposed labeling content; injection sites for Study 499; multiple explanations for subject specific dosing and dose duplications
11/28/2017	0051	Responses to Information Request from Filing Communication Review Issues, Question 6e: subgroup safety analysis for Study 421.
11/30/2017	0050	Responses to Information Request for graphical displays of liver function tests; total doses administered in *phase 1* and doses of Monthly formulation before week 17; tertile reports of drug exposure and AE's in Study 421.
12/08/2017	0062	Responses to Information Request for subject-level and SDTM dataset clarification of identified errors
12/08/2017	0063	Responses to Information Request to provide clarification of supplemental injection dosing and classification of non-responders in Study 421; dataset of total doses administered in study 421; recalculation of tercile tables previously requested
12/11/2017	0064	Response to sequence number 0049: total number and location of injections administered in Study 421.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. HS-13-478 (Study 478): Blockade Study

6.1.1. 478 Study Design

Overview and Objective

Title: *A Multiple Dose Opioid Challenge Study to Assess Blockade of Subjective Opioid Effects of CAM2038 q1w (Buprenorphine Fluid Crystal® Subcutaneous Injection Depots) in Adults with Opioid Use Disorder* (conducted: October 09, 2015 – April 29, 2016).

Study HS-13-478 (Study 428) was a Phase 2, randomized (1:1) multiple-dose, within-patient comparison study of an opioid challenge, to assess the blockade of subjective opioid effects CAM2038 24 mg and 32 mg Weekly formulation, compared with placebo.

The CAM2038 Monthly formulation was not evaluated in this Study. Further, Study 478 was initiated 8-weeks before Study 499 (the Open-Label, Phase 3 trial) started; and 10-weeks before Study 421, the pivotal, Phase 3, clinical trial was started. Although neither of these two issues precluded the review of Study 478, an opioid blockade study is ideally designed to provide dose-finding information for subsequent Phase 3 studies. In this case, Study 478 completed patient enrollment when Study 499 had been underway for 4-months and Study 421 was more than 50% complete. Thus, despite the determination of effective opioid blockade at doses of 24 mg and 32 mg CAM2038 Weekly, respectively, which did correlate with weekly doses used in Studies 421 and 499, those doses did not *inform* the dosing aspect of the design of either of the Phase 3 studies in the CAM2038 clinical program and the study did not provide information about monthly doses.

Review Strategy

The Applicant-provided data were reviewed by the Controlled Substances Staff (CSS) and the Pharmacometrics Review Team. A high-level summary of their findings is outlined below and can be found in their reviews. In summary, the primary outcome analysis of the Emax "Drug liking" VAS demonstrated a full opioid blockade, based on the lack of significant difference between placebo and active IM hydromorphone in 6 mg or 18 mg doses. This finding confirmed that, under the opioid blockade of weekly subcutaneous CAM2038 in doses of either 24 mg (n=22) or 32 mg (n=24), IM injections of hydromorphone doses up to 18 mg failed to demonstrate opioid subjective effects. Pharmacometrics Reviewer, Dr. Bewernitz, also completed an independent review of the data. Additionally, the descriptive analyses of the primary and secondary endpoints were verified by FDA's Office of Biostatistics. The reviewer confirmed the Applicant's results about the opioid blocking effects of weekly CAM2038 following administration of IM hydromorphone (6 mg and 18 mg) compared with placebo, as

measured by the primary endpoint, peak "Drug Liking" VAS, based on the non-inferiority margin of 11 points that was pre-determined by the Applicant[12].

The results of these findings revealed that, if the Applicant-provided data is reliable, there are no review issues with Study 478, as submitted.

Study 478 Objectives

The primary endpoint and outcome measure for Study 478 was "Drug Liking" as measured by a bipolar visual analog scale (VAS)[13]. This study design is like that of a human abuse potential (HAP) study and should be understood as a multi-dose HAP study for IM hydromorphone, with the independent variable being the efficacy of CAM2038 to block the subjective effects of hydromorphone, which are well known and were not in question with this review. Secondary objectives included the evaluation of opioid-blocking effects of weekly CAM2038 as a function of plasma BPN concentration at measured timepoints following injection and challenged with IM hydromorphone.

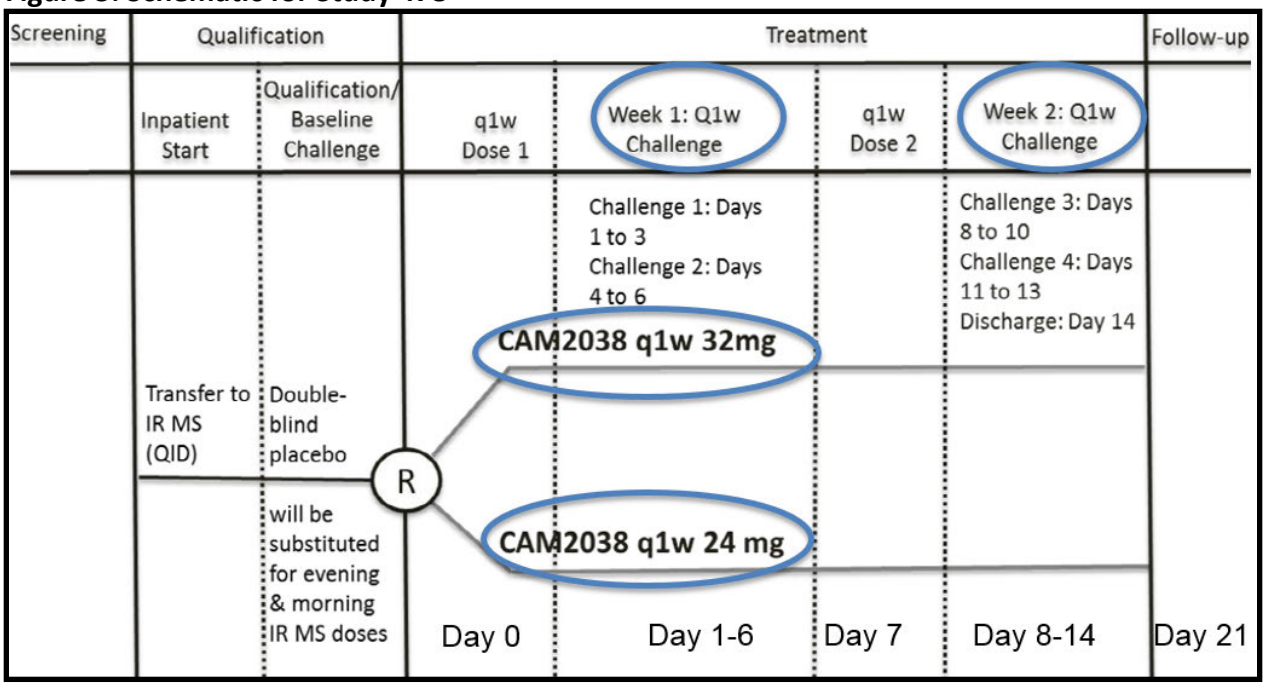
Trial Design

[12] This non-inferiority margin is based on a CSS meta-analysis of human abuse liability studies and is employed in the interpretation of such studies.

[13] VAS scores utilized a 100mm bipolar scale (where 0 = dislike; 50=neutral response; 100 = like)

Forty-seven, non-treatment seeking patients were enrolled while physically dependent and self-reported a minimum of 21 days of IV or insufflated opioid-use in the 30-days preceding screening. Positive urine drug screens for opioids were provided at the time of screening. There were 4 "phases" to the study: Screening, Qualification, Treatment, and Follow-Up (
Figure 3). Patients were admitted to a clinical research unit and stabilized with a short-acting oral opioid (30 mg immediate-release [IR] morphine) 4 times daily for 3-7 days. After stabilization, all subjects were qualified in the 3-day qualification/baseline period by challenge with 3 IM treatments of 0, 6 and 18 mg hydromorphone, administered once daily on Days -3, -2 and -1 in a double-blind, randomized crossover pattern. Only subjects meeting a minimum criterion for response to hydromorphone, and whose responses distinguished the 6 mg from the 18 mg dose, were eligible to continue. Including screening and follow-up, the duration of Study 478 was 7 weeks. The testing portion of the study was 2 weeks.

Figure 3: Schematic for Study 478



Following Qualification, eligible subjects were randomized in a 1:1 ratio to receive SC injections of either 24 or 32 mg of CAM2038, on Days 0 and 7. Four hydromorphone challenge periods, consisting of 3 consecutive days each, were conducted on Days 1-3, 4-6, 8-10, and 11-13 during the Treatment phase (study schematic
Figure 3)

- **Key inclusion criteria**: Non-treatment seeking adult male and female patients ages 18 to 55 years, with a primary diagnosis of moderate or severe OUD using DSM-5 and positive urine drug test for opioids during screening. Concomitant medications were allowed on a case-by-case basis and monitored closely (61.7% of the population was on at least one concomitant medication).
- **Key exclusion criteria**: other substance use disorder; any condition requiring opioids (e.g., chronic pain); active hepatic, neurologic, or cardiac conditions; strong inhibitors or inducers of cytochrome P450-3A4; and recent history or current suicidal ideations or behavior.

Study Endpoints

Primary endpoint: maximum effect (Emax) of Drug Liking (bipolar VAS) for hydromorphone.

Secondary endpoints:

- E_{max} of High VAS
- E_{max} of Good Drug Effects VAS
- E_{max} of Bad Drug Effects VAS
- Minimum effect (E_{min}) of Alertness/Drowsiness VAS
- E_{max} of Any Drug Effects VAS
- E_{max} of Desire to Use VAS

Pharmacokinetic endpoints were also obtained for BPN and norBPN and were reviewed and are presented in the Clinical Pharmacology review.

6.1.2. Study 478 Results

Protocol Violations/Deviations

The Applicant did not report protocol violations or deviations in Study 478.

Table of Demographic Characteristics

Baseline characteristics are listed in

Table 10 and were comparable between groups. Baseline characteristics were also similar in content to the patient characteristics of Study 421, reviewed in section 6.2.

Table 10: Demographic Information for Study 478

Demographic variables	24 mg CAM2038 Weekly (N=22)	32 mg CAM2038 Weekly (N=25)	Total CAM2038 Patients (N=47)
Age, years			
Mean (SD)	36.1 (9.3)	35.6 (9.1)	35.8 (9.1)
Min, Max	21, 53	18, 54	18, 54
Sex, N (%)			
Male	16 (72.7%)	19 (76.0%)	35 (74.5%)
Female	6 (27.3%)	6 (24.0%)	12 (25.5%)
Race, N (%)			
Black or African	9 (40.9%)	15 (60.0%)	24 (51.1%)
White	12 (54.5%)	10 (40.0%)	22 (46.8%)
Other	1 (4.5%)	0	1 (2.1%)
Ethnicity, N (%)			
Non-Hispanic or Latino	22 (100.0%)	24 (96.0%)	46 (97.9%)
Hispanic or Latino	0	1 (4.0%)	1 (2.1%)
BMI, kg/m^2			
Mean (SD)	25.2 (4.28)	24.4 (4.25)	24.8 (4.24)
Range	20, 34	17, 34	17, 34

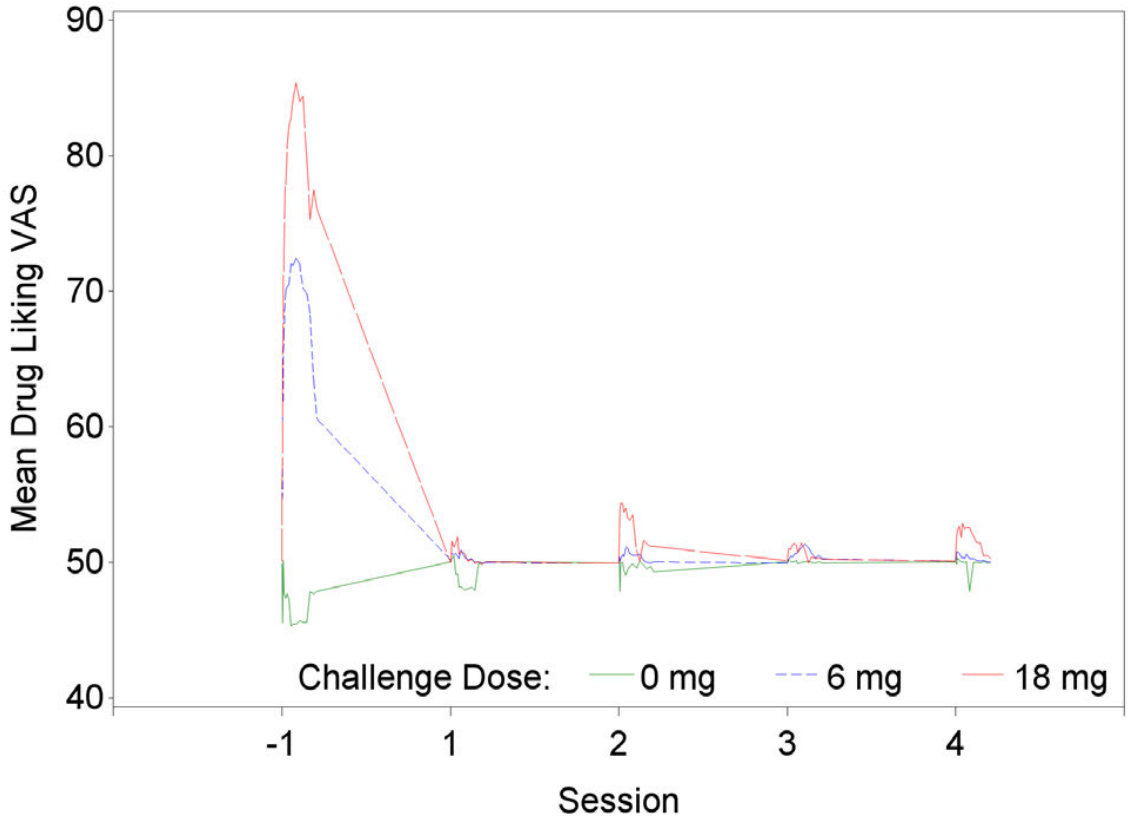
Source: Applicant provided Table 14.1.2, Listing 16.2.4.1 (Safety Population). BMI = body mass index; Max = maximum; Min = minimum; SD = standard deviation.

Efficacy Results – Primary Endpoint

The results of the Applicant's primary analysis are shown in Figure 4 and
Figure 5 and indicate efficacy for opioid blockade at both CAM2038 Weekly doses.

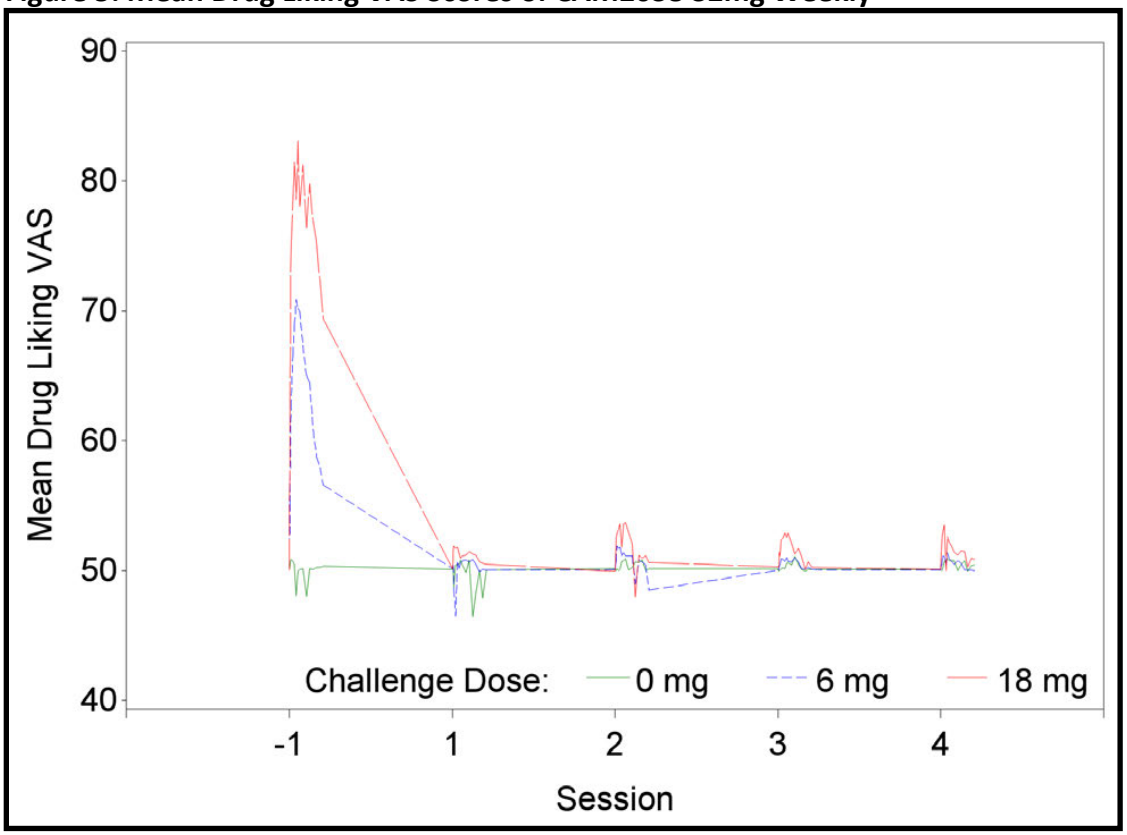
Figure 4
Figure 5

Figure 4: Mean Drug Liking VAS Scores of CAM2038 24mg Weekly



Source: Figure 4 in Applicant's HS-13-478-report-body-1.pdf
the Drug Liking visual analog scale (VAS) item was presented to the patient as: "At this moment, my liking of this drug is," where values can range from 0 ("Strong disliking") to 100 ("Strong liking") and 50 is the neutral point. Graph represents drug liking at each testing session and after each of the three hydromorphone challenge doses (0mg, 6mg, or 18 mg)

Figure 5: Mean Drug Liking VAS Scores of CAM2038 32mg Weekly



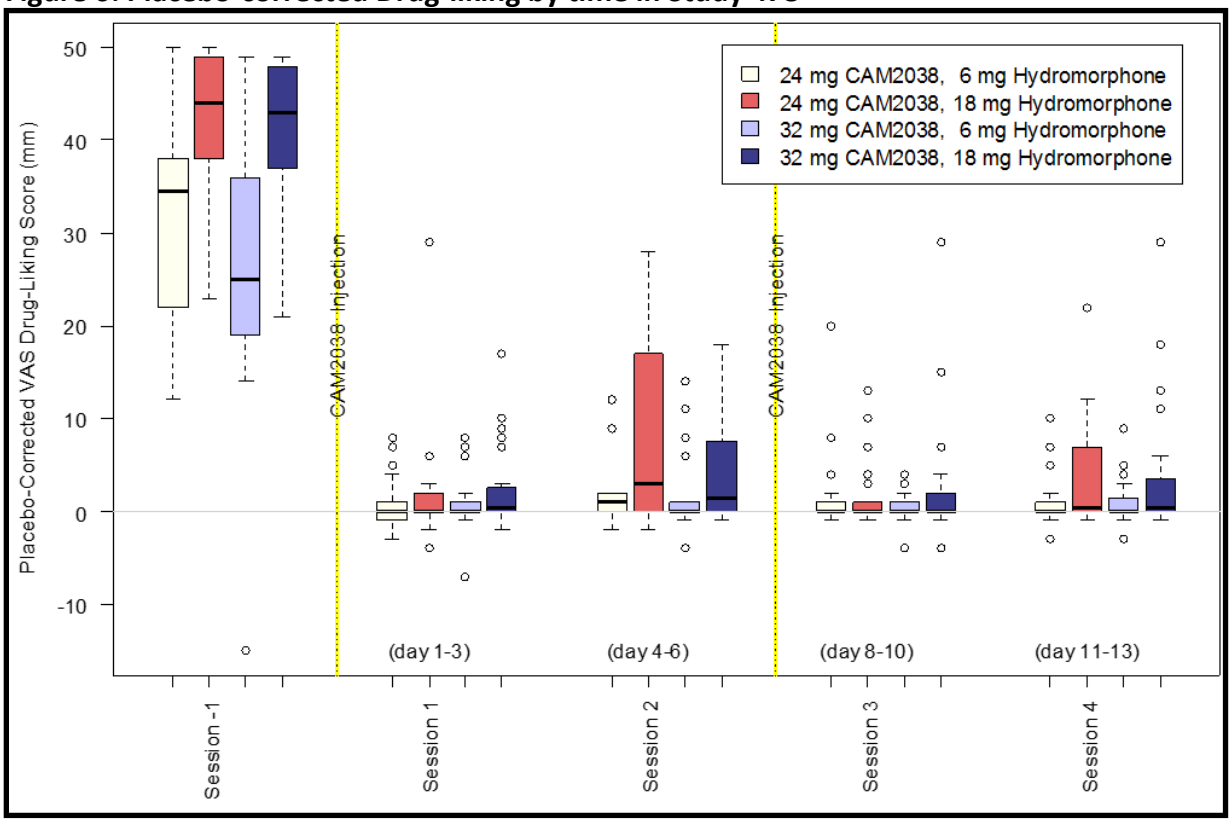
Source: Figure 4 in Applicant's HS-13-478-report-body-1.pdf
the Drug Liking visual analog scale (VAS) item was presented to the patient as: "At this moment, my liking of this drug is," where values can range from 0 ("Strong disliking") to 100 ("Strong liking") and 50 is the neutral point. Graph represents drug liking at each testing session and after each of the three hydromorphone challenge doses (0mg, 6mg, or 18 mg)

Efficacy Results – FDA Analyses

Pharmacometric reviewer, Dr. Bewernitz, performed a placebo-corrected analysis (Figure 6) and a PK/ PD analysis (

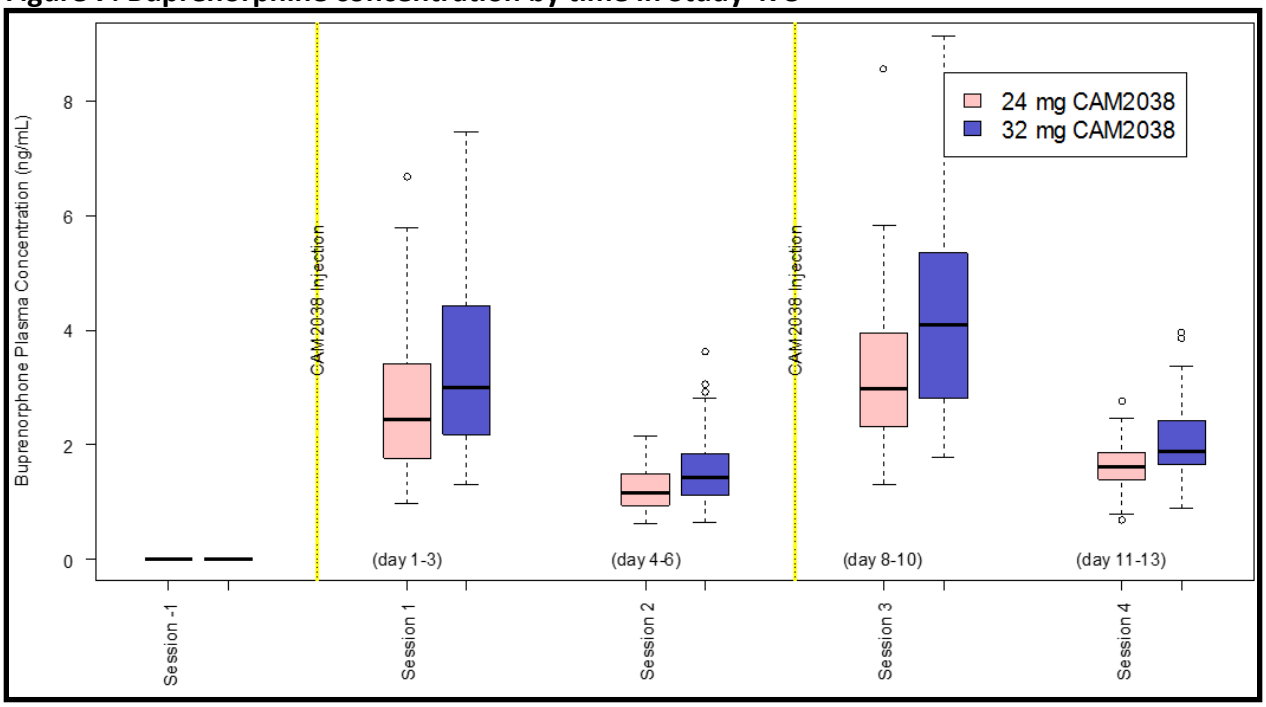
Figure 7) of the submitted data. Drug liking scores within a dosing interval generally corresponded with the buprenorphine concentration profile. However, in a subset of subjects, drug-liking scores did not correlate as well with buprenorphine concentrations. This observation might likely to be other unknown factors contributing to drug-liking scores. In addition, the PK/PD analyses revealed a trend of reduced drug-liking with increasing buprenorphine exposure. A higher buprenorphine concentration was required to counter drug-liking for higher hydromorphone dose level (18 mg vs 6 mg).

Figure 6: Placebo-corrected Drug-liking by time in Study 478



Source: Pharmacometrics Reviewer
This figure shows the placebo-corrected drug-liking scores by time at each session and by each dose (24 mg and 32 mg) of the CAM2038 Weekly formulation.

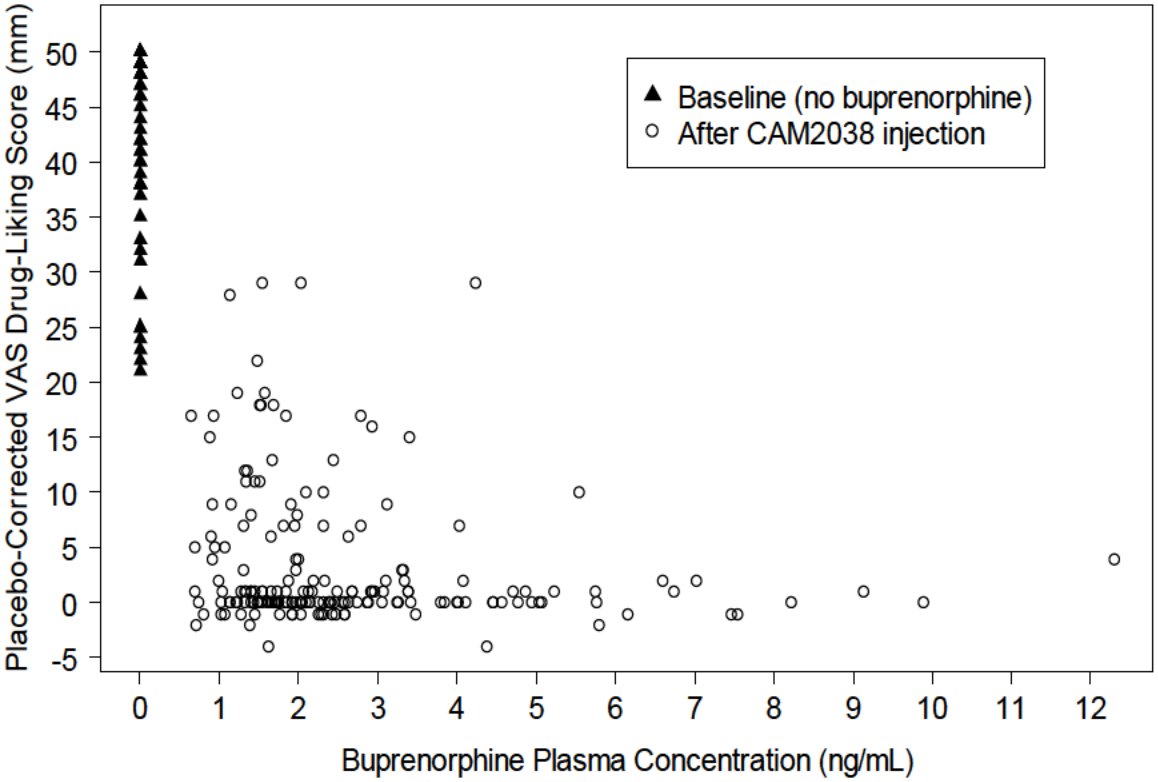
Figure 7: Buprenorphine concentration by time in Study 478



Source: Pharmacometrics Reviewer
This figure shows the plasma concentration of BPN after two sessions of both CAM2038 Weekly formulations used in this study (24mg and 32 mg).

Figure 8 illustrates the relationship between buprenorphine plasma level and drug liking after an 18 mg hydromorphone dosing challenge. In this Figure, data from the CAM2038 Weekly 24 mg dosing arm is pooled with data from the CAM2038 Weekly 32 mg dosing arm to show the relative drug liking effect (VAS) to plasma levels of BPN.

Figure 8: Plot of Drug-liking relative to plasma BPN levels after a hydromorphone challenge in Study 478



Source: Pharmacometrics Reviewer

This figure shows the placebo-corrected Drug Liking VAS vs. Plasma Buprenorphine Concentration Following 18 mg Hydromorphone Challenges for the pooled CAM2038 24 mg and 32 mg dosing arms in Study 428.

6.2. HS-11-421 (Study 421): Pivotal Efficacy Trial

6.2.1. 421 Study Design

Overview and Objective

Title: *A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel Group, Multi-center Trial Assessing the Efficacy and Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Treatment of Adult Outpatients with Opioid Use Disorder*

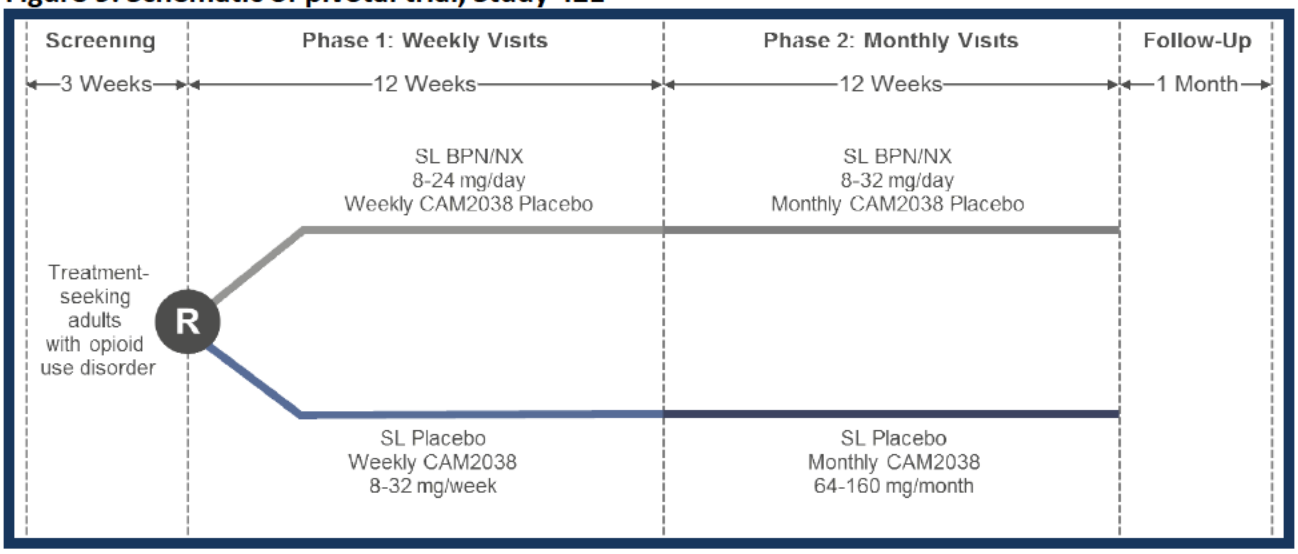
In Study 421, the Applicant sought to demonstrate that their product would be appropriate for use from the first patient visit (following tolerability of a 4mg SL BPN test dose), so that no take-home use of sublingual buprenorphine would be necessary in the real-world setting. (b) (4) Dosage adjustments could be made at weekly appointments with the maximum weekly dose being 32 mg in the first phase of the study. Patients would then transition from Once Weekly to Once Monthly CAM0238 during the second phase of the trial (in the real-world this transition would be based on clinical judgment). Dose tapering and titration did take place, per investigator decision, and per interpretation of the protocol and its amendments.

Trial Design

Study 421 was a Phase 3, double-blind, double-dummy, active-controlled (non-inferiority trial), parallel-group multicenter USA 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 four "*phases*": Screening, *Phase 1*, *Phase 2*, and Follow-up ((b) (4)

Figure 9: Schematic of pivotal trial, Study 421).

Figure 9: Schematic of pivotal trial, Study 421



Method of determining non-inferiority margin

The Applicant, with the original protocol submission, initially proposed a (b)(4)% margin as appropriate for this Study from a scientific validity perspective to meet the Agency's guidelines for non-inferiority selection[15]. On July 9, 2015, additional comments were provided to the applicant regarding the design of the clinical efficacy study, including discussion on the selection of the clinical endpoint and the justification for the non-inferiority margin. The clinical hold placed on this protocol was lifted on October 2, 2015. The study was then initiated on December 29, 2015.

The Applicant provided an amended version of the protocol in February 2016. The Applicant further modified the responder definition to be as follows: No opioids detected in at least 33% of the twelve urine toxicology results in the first twelve weeks of the study and at least 67% of urine toxicology results collected during the final twelve weeks. The Applicant also narrowed the non-inferiority margin from (b)(4)% to (b)(4)%.

Further feedback was provided by the Agency on September 1, 2016. The Agency stated that there was insufficient historical evidence for the (b)(4)% non-inferiority margin and a more

[15] FDA. Guidance for Industry Non-Inferiority Clinical Trials. March 2010. Available from: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugsgen/documents/document/ucm202140.pdf.

conservative approach with a 5% non-inferiority margin was proposed. This was based on comments made at the meeting of the Psychopharmacologic Drugs Advisory Committee that considered Braeburn's prior application for Probuphine.

On October 14, 2016, the applicant requested clarification on the selection of the non-inferiority margin prior to planned database lock on November 4, 2016, noting that the study had been initiated and that a significant increase in the sample size would be required to meet a 5% NI margin. In view of the potential public health importance of the product. on November 4, 2016, the Agency provided a response to the applicant that a 10% margin would be acceptable.

Inclusion Criteria

- Males and females, ages 18-65 years
- Diagnosis of moderate or severe opioid use disorder, per DSM-5[5]
- Treatment seeking for opioid use disorder
- No medication-assisted treatment for opioid use disorder within 60 days of study start
- Considered by the investigator to be a good candidate for BPN treatment (per history)
- Patients of childbearing potential were willing to use a reliable method of contraception during the entire study (Screening visit to Follow-up)

Exclusion Criteria

- Current diagnosis of Acquired Immune Deficiency Syndrome (AIDS)
- Current diagnosis of chronic pain requiring opioids for treatment
- DSM-5 diagnosis of moderate to severe substance use disorder on any other psychoactive substances other than opioids, caffeine, or nicotine (e.g., alcohol, cocaine, sedatives) and the non-opioid substance use disorder(s) were considered primary or co-primary, causing current (last 30 days) significant impairment and/or in the judgement of the investigator would interfere with the efficacy and safety assessments (***revised in Protocol Amendment 3***).
- Pregnant or lactating or planning to become pregnant during the study.
- Hypersensitivity or allergy to BPN or other opioids, naloxone or other opioid antagonists, or excipients of CAM2038 or SL BPN.
- Required use of agents that are strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) such as some azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., clarithromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir).
- Subjects with active signs or symptoms of hepatitis and requiring treatment. Subjects
- with no acute signs of inflammation and no clinical necessity for therapy may have been allowed at the discretion of the investigator (revised in ***Protocol Amendment 3***).
- Recent history of or current evidence of suicidal ideation or active suicidal behavior as based on the Columbia Suicide Severity Rating Scale ("Yes" to questions 4 or 5).

- Any pending legal action that could prohibit participation or compliance in the study.
- Exposure to any investigational drug within the four weeks prior to Screening.
- History of risk factors of Torsades de Pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome) or ECG demonstrating a Fridericia's corrected QT interval (QTcF) > 450 msec in males and QTcF > 470 in females at Screening.
- AST levels > 3 × the upper limit of normal (ULN), alanine aminotransferase (ALT) levels > 3 × ULN, total bilirubin > 1.5 × ULN, or creatinine > 1.5 × ULN on the Screening lab assessments, or other clinically significant lab abnormalities, which the investigator decided that the patient could not safely participate in the study.

Procedures and Schedule

Table 11: Schedule of Assessments for CAM2038 Weekly formulation in Study 421 (*phase 1*)

Study Period/Phase:	**Screenin**	**Phase 1 (Weekly Visits)**							
Month:	**-1**	**M1**					**M1-3**		
Week:	**-3 to -1**	**W1**					**W2-W11**		**W12**
Day:	**-21 to -**	**D1**[a]	**D2**	**D**	**D4**	**D5-7**	**D8**	**Weekly**[b]	
Informed Consent[c]	X								
Eligibility Criteria Review[d]	X	X							
Demographic Data and Psychosocial History	X								
Medical and Medication History/Substance Abuse and Treatment History (questionnaires)	X								
DSM-5	X								
Physical Examination[e]	X								
Weight, BMI	X	X							X
Height	X								
Vital Signs[f]	X	X[g]			X		X	Weekly	X
ECG	X	X[g]					X	Weekly	X
Biochemistry, Hematology, Urinalysis and Coagulation	X	X							X
Pregnancy Test[h]	X	X					X	Weekly	X
Hepatitis B/C, HIV[i]	X								
Injection Site Examination		X	X		X	(X)	X	Weekly	X
Dispense Treatment		X							
Urine Toxicology	X	X					X	Weekly	X
Illicit Drug Use Self-Report	X	X					X	Weekly	X
SOWS, COWS, VAS[j]	X	X	X		X	(X)	X	Weekly	X

C-SSRS[k]	X	X	X		X	(X)	X	Weekly	X
Measurement of Morning Desire to Use/Need to Use							X	Weekly	X
SL BPN/NX or SL placebo dispensing		X	X		X	(X)	X	Weekly	X
SL BPN/NX or SL placebo administration[l]		X	X	X	X	Daily	X	Daily	X
CAM2038 q1w or placebo SC		X			X	(X)	X	Weekly	X
Psychosocial Counseling		X					X	Weekly	X
Adverse Events[n]	X	X	X		X	(X)	X	Weekly	X
Concomitant Medications/Procedures	X	X	X		X	(X)	X	Weekly	X
On-Site Visits	X	X	X		X	(X)	X	Weekly	X

Abbreviations: BMI, body mass index; BPN/NX, buprenorphine/naloxone; COWS, Clinical Opiate Withdrawal Scale; C-SSRS, Columbia Suicide Severity Rating Scale; D, day; DSM-V, Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition; ECG, electrocardiogram; HIV, human immunodeficiency virus; M, month; q1w, once weekly; SC, subcutaneous; SL, sublingual; SOWS, Subjective Opiate Withdrawal Scale; VAS, visual analogue scale; W, week

[a] Subjects were randomized to one of two treatment groups (SL BPN/NX or CAM2038) after confirmation of eligibility ≥ 1 hour following an open-label 4 mg SL BPN/NX test dose. [b] A window of ± 2 days was allowed for weekly visits during Weeks 2 to 12, in addition to Week 13. [c] Subjects voluntarily provided written informed consent prior to any study-related procedures being performed. [d] Prior to randomization on Day 1, a review of the eligibility criteria was made. [e] A complete physical exam of all major body systems was performed at the Screening visit. [f] Included temperature, blood pressure, pulse rate, respiration rate. [g] Vital signs and ECG were measured at approximately 15 to 30 minutes before the test dose, approximately 15 to 30 minutes after the CAM2038/SL BPN/NX dose on Day 1 and approximately 15 to 30 minutes predose at the other visits as indicated in the table (or during the visit if no dose was given). [h] A serum pregnancy test was performed at Screening. An "in-office" urine pregnancy test was required on Day 1 PRIOR to randomization and test dose administration and weekly thereafter (for women of childbearing potential). [i] It was the investigator's responsibility to understand and comply with all laws and regulations that apply to HIV, Hepatitis B, and Hepatitis C and testing of blood. Hepatitis B/C and HIV testing was required unless a site's IRB prohibited such testing. [j] SOWS/COWS/VAS were completed each time the subject visited the clinic, as needed based on titration and dosage adjustment. On Day 1, COWS, SOWS, and VAS were completed before the test dose was administered (Baseline). COWS were completed after the test dose on Day 1 to evaluate tolerability, and on Day 2.

[k] Screening version at Visit 1 (Screening), Since Last Visit version at all subsequent visits. [l] Not to exceed 24 mg SL BPN/NX (or placebo) per day, this administration was done at home. [m] Not to exceed 32 mg CAM2038 q1w (or placebo) per week. [n] Any spontaneously reported adverse event was recorded after the subject signed the informed consent form. In addition, adverse events were elicited using a non-leading question each time the subject visited the clinic. (X) indicates as needed based on the individual subject.

Table 12: Schedule of Assessments for CAM2038 Monthly formulation in Study 421 (*phase 2*)

Study Period/Phase:	Phase 2 (Monthly Visits)						Follow-up		
Month:	M4		M5		M6		M7		
Week: [a]	W13	W14-16	W17	W18-20	W21	W22-24	(EOT) W25	W26-28	W29
Weight and BMI	X		X		X		X		
Physical Examination							X		
Vital Signs[b,c]	X		X		X		X		
ECG[c]	X		X		X		X		
Biochemistry, Hematology, Urinalysis and Coagulation	X		X		X		X		
Pregnancy Test[d]	X		X		X		X		
Injection Site Examination	X		X		X		X		X
Urine Toxicology	X		X		X		X		
Illicit Drug Use Self-Report	X		X		X		X		
Random Urine Toxicology and Illicit Drug Use Self-Report[e]	3 x random urine toxicology								
SOWS, COWS, VAS	X		X		X		X		X
C-SSRS[f]	X		X		X		X		X
Measurement of Morning Desire to Use/Need to Use	X		X		X		X		X
SL BPN/NX or SL Placebo Dispensing	X		X		X				
SL BPN/NX or SL Placebo	X	Daily	X	Daily	X	Daily			
CAM2038 q4w or Placebo SC Injection[h]	X		X		X				
Transition to Standard Care							X		
Psychosocial Counseling	X		X		X		X		
Adverse Events[i]	X		X		X		X	X	X
Concomitant Medications/Procedures	X		X		X		X	X	X
Scheduled On-site Visit	X		X		X		X		X
Telephone Contact								Weekly	

Abbreviations: BMI, body mass index; BPN/NX, buprenorphine/naloxone; COWS, Clinical Opiate Withdrawal Scale; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; EOT, end of treatment; M, month; q4w, every 4 weeks; SC, subcutaneous; SL, sublingual; SOWS, Subjective Opiate Withdrawal Scale; VAS, visual analogue scale; W, week.

[a] Treatment Visits were conducted within a window of ± 7 days for monthly visits (other than Week 13, which had a visit window of ± 2 days). If a subject missed a visit or completed a visit early or late, the original schedule was resumed at the subsequent visit such that the ensuing visits occurred as originally scheduled, relative to Day 1. [b] Included temperature, blood pressure, pulse rate, respiration rate. [c] Vital signs and ECG were measured approximately 15 to 30 minutes pre-dose and approximately 15 to 30 minutes post-dose at Week 13. At the other visits, ECG was measured approximately 15 to 30 minutes predose as indicated in the table (or during the visit if no dose is given). [d] A serum pregnancy test was performed at the End of Treatment visit (Week 25). An "in-office" urine pregnancy test was required at Weeks 13, 17 and 21 prior to injection being administered (for women of childbearing potential). [e] A total of three random urine toxicology

visits during Month 4 to Month 6, preferably once a month. Illicit drug use self-reports were also completed by the subjects at these visits. [f] C-SSRS "Since Last Visit version" was used. [g] Not to exceed 32 mg/8 mg SL BPN/NX (or placebo) per day. [h] Subjects received the first CAM2038 q4w injection (active or placebo) at the beginning of Week 13 (± 2 days). Not to exceed 160 mg CAM2038 q4w (or placebo) per month. Subjects received their last CAM2038 q4w dose at Week 21. [i] Any spontaneously reported adverse events were recorded after the subject signed the informed consent form. In addition, adverse events were elicited using a non-leading question each time the subject visited the clinic and during the telephone contacts in the Follow-up period.

Assignment to treatment, Study treatments, Blinding

All subjects who met screening criteria and consented were given a unique number and were given one, 4 mg, test dose of SL BPN and then, if the test dose was tolerated, randomized in a 1:1 blinded fashion. A central randomization, through an Interactive Web Response System, managed by DSG, Inc., was used after patients were assigned a unique number.

All study drugs were administered in a double-blind, double-dummy manner, such that subjects received both SL tablets (active BPN/NX or placebo) and SC injections (active CAM2038 Weekly/Monthly or placebo) throughout the study (except for Days 2 and 3, when only SL BPN/NX or SL placebo tablets were given). Subjects received treatment for up to 24 weeks during the study: 12 weeks during *phase 1* and 12 weeks during *phase 2*. To maintain the blind, CAM2038 and the active comparator were designed to look similar in terms of injections and tablets. However, they did not look identical. Thus, the injecting clinician did not collect patient outcomes data and the study staff did not engage the injecting clinician in patient study assignments.

CAM2038/placebo were injected in the buttocks, abdomen, thighs, and the upper back of the arms and the injection sites were rotated such that no injections were administered into the same site (most the injection sites were gluteal). The following injection schedule was used:

- CAM2038 Weekly/placebo injections were not to be administered into a previously injected site for at least 8 weeks.
- CAM2038 Monthly/placebo injections were not to be administered in a sited previously injected with CAM2038 Monthly/placebo.

During phase 2, an 8mg dose of CAM2038 Weekly could be administered as a supplement medication for symptomatic patients requiring additional treatment, per the investigator. This supplemental CAM2038 dosing occurred in both groups to maintain the treatment blinding.

Patients returned unused tablets (placebo or SL BPN/NX) to the clinic at each study visit. Unused tablets were counted and documented.

Dose Selection and Dose Adjustments

CAM 2038: Doses were selected to deliver similar exposure as the SL BPN/NX doses in clinical practice (approximating daily doses of 8-24 mg SL BPN/NX in *phase 1* and up to 32 mg SL BPN/NX in *phase 2*). The Applicant reported that, as in clinical practice, dose adjustments (increases in case of withdrawal effects or cravings or decreases for tolerability reasons) were allowed during the study at scheduled study visits during both *phase 1* and *phase 2*.

Active comparator: The study included a range of doses as used in clinical practice (8 mg to 24 mg SL BPN/NX per day in *phase 1* and up to 32 mg SL BPN/NX in *phase 2*), based on each patient's individual needs.

Subject completion, Discontinuation, and Withdrawals

Patients were free to withdraw from the study at any time. The investigator also had the right to withdraw a patient from the study if an intercurrent illness or adverse event (AE) occurred, if the patient did not cooperate, or for any reason concerning the health or well-being of the patient. A patient was required to be discontinued from the study for: safety reasons; at the request of the sponsor, regulatory agency, or IRB; lost to follow-up; treatment allocation was unblinded; death; pregnancy; need for opioid analgesics >7 days; and major protocol violations.

Use of concomitant medications

Patients requiring analgesic emergency treatment or anesthesia for surgery were treated with a non-opioid analgesic when possible. Opioids were permitted to be used with caution, but as higher doses might have been required for analgesic effect, there was a higher potential for toxicity with opioid administration. Concomitant use of other narcotic anesthetics, benzodiazepines, phenothiazines, other tranquilizers, or other central nervous system (CNS) depressants (including alcohol and sedative/hypnotics) may cause respiratory and CNS depression. Use of these substances was minimized during treatment with CAM2038 or SL BPN/NX. If these sedatives were required during the study, the medical monitor was consulted. Subjects were advised of the danger of concomitant use of sedatives while participating in the study. Subjects were explicitly advised of the danger of intravenous abuse of benzodiazepines and abuse of alcohol while under treatment with CAM2038 or SL BPN/NX.

Study Endpoints

Dosing

On the first day of treatment patients received an open-label 4 mg test dose of SL BPN/NX. Patients who tolerated the test dose were randomized to a 16 mg CAM2038 Weekly dose or matched placebo. In week one, patients were allowed up to two, 8 mg injections at subsequent visits as needed. Patients received an injection of CAM2038 Weekly 16, 24, or 32 mg on Day 8; matched to the dose they received in the previous seven days. The protocol envisioned that patients would receive injections at the same dose weekly for 12-weeks total and then would be transitioned to an equivalent dose of the monthly formulation for the remaining twelve weeks (*phase 2*). The protocol stipulated, however, that dose adjustments and supplemental 8 mg injections were permitted at investigator's discretion for the duration of the study.

Supplemental 8 mg doses of CAM2038 weekly were allowed during the study in both treatment arms. The SL BPN/NX dose was managed similarly. Patients were initiated on a dose of 8 mg per day, which could be adjusted in increments of 8 mg up to a total of 24 mg per day.

Primary endpoint

The primary endpoint for this study was the percentage of patients who are responders in *phase 1* and *phase 2*:

The responder definition for *phase 1* was as follows:

- No evidence of illicit opioid use during week 12 (evaluated during Week 13 visit).
- No more than one positive urinalysis in the six illicit opioid use assessments performed in weeks 10 to 12.

The responder definition for *phase 2* was as follows:

- No evidence of illicit opioid use during the week 25 visit (end of month 6).
- No more than one positive urinalysis in the six illicit opioid use assessments performed during phase 2.

Illicit opioid use was defined as either a positive urine toxicology results or a self-reported illicit opioid use. Missing results were imputed as positive. As discussed in Section 2.1, the study used a 10% non-inferiority margin for the study was agreed with the Agency prior to initiation of the study. The Agency requested a secondary analysis of the cumulative distribution function (CDF) of the percentage of urine samples negative for illicit opioids between week 5 and 25. The purpose of analyzing efficacy starting from Week 5 instead of Week 1 was to allow patients to stabilize in treatment. The percentage of negative drug use assessments was computed for each patient as the number of weeks of negative drug use assessments divided by 15. For example, if a patient had 10 weeks of negative urine samples and self-report negative for opioids, the percentage negative drug use assessments of this patient was 67%[16].

[16] The word "abstinence" is used in some parts of the protocol and study report to refer to negative drug use assessments. However, as noted above, the sampling scheme was not sufficient to establish whether or not

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). For a patient 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). There was also a requirement for opioid negative urines at specific weeks, Week 12 and Week 24 to be a responder. All urine samples were verified by subject's self-reported use.

Secondary endpoint

The secondary endpoint included cumulative distribution frequency (CDF) over treatment Weeks 4-24 for illicit opioid-negative urine samples with and without self-reports and study retention.

Statistical Analysis Plan

Analysis populations

- **Randomized Population:** All patients randomized into the treatment phase.
- **Intent-to-Treat (ITT) Population:** All subjects who have been randomized and received CAM2038 or placebo injections or received SL BPN/placebo (apart from test dose). This was to be the primary analysis population for efficacy.
- **Safety Population**: All subjects randomized and treated who received any dose of SL BPN/placebo or CAM2038/placebo injections in the treatment phase. Analyses
- based on this population will group subjects by the treatment they received regardless of the treatment they were randomized to receive. All safety analyses from this population.
- **Per Protocol Population**: All subjects in ITT population with no major protocol violations. Major protocol violation criteria were to be established prior to the database lock.

Primary endpoint and non-inferiority

The primary endpoint for this study was the percentage of patients who met the response criteria for both phases of the study. The primary efficacy analysis was conducted on the ITT population, which was defined as all randomized patients. Analyses based on this population will group patients per the treatment that they were randomized to receive, regardless of actual treatment received. Non-inferiority (NI) of CAM2038 would be concluded if the lower bound of 95% confidence interval of the difference in the response rates between CAM2038

patients were abstinent between assessments and therefore, the more precise term "negative drug use assessments" is a better representation of the findings.

and SL BPN/NX is greater than the pre-specified non-inferiority margin of 10%. The confidence interval of the difference in response rates was calculated using the normal approximation to the binomial distribution and is given by the following formula:

$$(P_T - P_C) \pm 1.96 * \sqrt{\frac{P_T(1-P_T)}{N_T} + \frac{P_C(1-P_C)}{N_c}}$$

Where, PT and PC are the observed percentages of responders in the treatment and control arms respectively, and NT and NC are the number of patients enrolled in the treatment and control arms respectively.

The Cumulative Distribution Function (CDF) endpoint was analyzed using the Wilcoxon rank-sum test. The CAM2038 arm was tested against sublingual buprenorphine for superiority at the 0.05 level. NI was not considered. Please refer to Biometrics Reviewer, Dr. Travis' statistical review for additional details.

Protocol Amendments
The protocol was first submitted on October 19, 2015, followed by five protocol amendments (November 24, 2015; December 10, 2015; February 08, 2016; October 18, 2016; November 03, 2016) and two protocol administrative changes (December 15, 2015 and March 1, 2016, respectively). Notable, key changes to the protocol are discussed in section 6.2.1 as they relate to the primary endpoint (method of determining the non-inferiority margin)

6.2.2. Study 421 Results

Compliance with Good Clinical Practices
The Applicant reported that this study was conducted in accordance with the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) guidelines and all applicable regulations.

Financial Disclosure
The Applicant provided a seemingly adequate disclosure of financial arrangements with clinical investigators, which was readily available in Module 1 (1.3.4) of the eCTD (refer to section 13.2 for additional information). Two Clinical investigators, (b) (6) at site (b) (6)

(b) (6) and (b) (6), at site (b) (6) and each received annual consultation fees of more than $25,000.00. However, each of the two sites enrolled (b) (6) subject (b) (6) The Applicant provided a disclosure of the honoraria for review. Therefore, it appears unlikely that the honoraria would have influenced the results of the clinical studies represented by those two sites.

Patient Disposition

In study 421, 600 patients were screened and 434 patients received the SL BPN/NX test dose. Three patients did not tolerate the test dose and were not randomized. Another **3 subjects did not get randomized for other reasons (site logistics, withdrawal of consent after the test dose, or subject left the site after the test dose and was lost to follow-up before randomization). Therefore, 428 patients enrolled, were randomized, and received at least one dose of study drug (215, SL BPN/NX; 213, CAM2038;**

Table 13). All patients were included in the safety, ITT and PP populations.

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Per Applicant, 57.7% of the patients were identified as completers. Of the 181 (42.3%) who discontinued the study early, approximately half (n=90) were due to withdrawal by subject request (21.0% of total subjects). Eleven (2.6%) subjects withdrew from treatment but completed the study. Seven (1.6%) subjects (1 in the SL BPN/NX group and 6 in the CAM2038 group) discontinued due to an AE. There was one death in the CAM2038 group during the study (section 8.4.1).

Withdrawal by subject and lost to follow-up was reported in both groups. More subjects in the CAM2038 group withdrew due to adverse events.

Table 13: Patient disposition in Study 421

Category of Disposition Event	Subcategory of Disposition Event	Disposition Event	CAM2038		SL BPN (Control)	
			Subject Count	%	Subject Count	%
Protocol Milestone	**Informed Consent**	Informed Consent Obtained	213	100.0	215	100.0
	Randomization	Randomized	213	100.0	215	100.0
Disposition Event	**Early Termination**	Withdrawal By Subject	44	20.7	46	21.4
		Lost To Follow-Up	27	12.7	29	13.5
		Other	9	4.2	9	4.2
		Adverse Event	6	2.8	1	0.5
		Physician Decision	4	1.9	3	1.4
		Death	1	0.5	0	0.0
		Protocol Deviation	1	0.5	0	0.0
		Pregnancy	0	0.0	1	0.5
	Study Completion	Completed	121	56.8	126	58.6

Screen failures

The study had 172 Screen Failures (SF): 166 patient SF during screening and six patient SFs after they received the SL BPN test dose on Day1 (P1D1 per Applicant) but before they received study medications. Many SFs (55.4%) were due to exclusion criteria being met. However, 44.6 % of SF's were attributed to "other" by the Applicant

Disposition coding

The Division identified seven study subjects who were listed as "completed" under DSDECOD but on subject disposition review, they were discontinued (e.g., USUBJID HS-11-421-(b) (6) and HS-11-421-(b) (6) respectively). In response to an IR (Table 9), the Applicant provided a table of 11 subjects (seven in the CAM2038 and four in the SL BPN groups) who discontinued study medication during the study, but continued to complete rest of the study visits and were thus listed as having completed the study, but discontinued study medication. These subjects represented 2.6% of the enrolled population. Reasons (N) for discontinuing the study medication included Adverse event (1); Other (4); Physician decision (2); Pregnancy (1); Withdrawal by subject (3).

Protocol Violations/Deviations

The Applicant reported one protocol violation in Study 421 with the application submission. Examples of protocol violations included violation of inclusion or exclusion criteria during the study and failure to adhere to the treatment schedule. The Applicant reported that criteria were established before the database lock.

The Applicant provided a SAS-generated PDF line listing from for the protocol deviations reported from the clinical sites. The following protocol deviations were identified as reportable by the Applicant but were not considered protocol violations:

- A subject who did not meet entry criteria
- A subject who developed withdrawal criteria but was not withdrawn
- Urine toxicology not performed at each visit
- Subject missed a study visit
- A subject received the wrong treatment, an incorrect dose, or missed a dose
- A subject that received an excluded medication
- A site administered a dose above a maximum of 32 mg SC injection dose per week or above 160 mg injection dose per four weeks
- More than one open label booster CAM2038 8 mg SC injection administered to a subject per month during Phase 2.
- An open label CAM2038 8 mg SC injection administered to a subject in Phase 1.

Per the Applicant, none of the identified deviations affected the study outcomes. A total of 87 patients reported one or more protocol deviations, the most common of which were missed study visits (N=66) and one or more missing urine toxicology samples (N=44).

In addition, and throughout the course of the review, many IR's were sent requesting additional information and clarification for cases of inconsistencies and errors that appeared to be protocol deviations with easily identifiable way to determine if they were data entry errors or the protocol deviations. Examples include:

- Reports of duplicate drug kits administered for patients
- Twenty-five subjects got their first monthly dose (in *phase* 2) more than 10 days after their last weekly injection.
- two doses of study medication given at one time
- patients missing scheduled appointments
- four subjects in *phase* 1 and two subjects in *phase* 2 received more than the protocol-defined doses of CAM2038 32 mg Weekly and 160 mg Monthly, respectively (listed as having duplicate doses).

Table of Demographic Characteristics

Table 14 below represents baseline demographics at time of randomization. All studies were conducted in the United States and no significant differences between baseline demographic characteristics were identified between groups.

Table 14: Patient Demographics in Study 421

Demographic Baseline Characteristics		CAM2038 (N=213)	SL BPN/NX (N=215) Control	Overall (N=428)
		N (%)	N (%)	N (%)
Sex	F	92 (43.2)	73 (34.0)	165 (38.6)
	M	121 (56.8)	142 (66.0)	263 (61.4)
Age	Mean years [SD]	38.7 [11.2]	38.0 [10.9]	38.4 [11.0]
	Median years	36	36	36
	Min, Max years	19, 65	18, 65	18, 65
Age Group	Age <65 years	212 (99.5)	214 (99.5)	426 (99.5)
	Age >=65 years	1 (0.5)	1 (0.5)	2 (0.5)
Race	American Indian	2 (0.9)	1 (0.5)	3 (0.7)
	Asian	1 (0.5)	0	1 (0.2)
	Black	47 (22.1)	48 (22.3)	95 (22.2)
	Native Hawaiian Or Pacific Islander	1 (0.5)	0	1 (0.2)
	White	159 (74.6)	164 (76.3)	323 (75.5)
	Other	3 (1.4)	2 (0.9)	5 (1.2)
Ethnicity	Hispanic	25 (11.7)	24 (11.2)	49 (11.4)
	Not Hispanic	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]
Hepatitis C at study entry		49 (23.0%)	50 (23.3%)	99 (23.1%)

Other Baseline Characteristics

The population of patients recruited for this study included adults who reported heroin as their primary drug of choice and injection as the preferred route of illicit opioid use, shown in **Error! Not a valid bookmark self-reference.**, below.

Table 15: Opioid Use History in Safety Population, Study 421

Category	SL BPN/NX N=215 n (%)	CAM2038 N=213 n (%)	Total N=428 n (%)
Primary opioid of use at initiation			
Heroin	151 (70.2)	152 (71.4)	303 (70.8)
Prescription opioid pain reliever	64 (29.8)	61 (28.6)	125 (29.2)
Route of illicit opioid			
Injection	110 (51.2)	114 (53.5)	224 (52.3)
Non-injection	105 (48.8)	99 (46.5)	204 (47.7)
Positive screening result for:			
Amphetamines	32 (14.9)	38 (18.0)	
Barbiturates	1 (0.5)	3 (1.4)	
Benzodiazepine	35 (16.3)	30 (14.2)	
Cocaine	53 (24.7)	53 (25.1)	
Marijuana	64 (29.8)	57 (27.0)	
Phencyclidine	0	2 (0.9)	

Source: Applicant provided Table 7, Clinical Study Report HS-11-421; Source table 14.2.14

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was measured through drug dispensing inventory management and drug accountability, per Applicant-provided protocol. Many subjects (67.1%) took at least one concomitant medication during the study (
Table 16). Overall, the most common class of concomitant medications taken during the study was opioids (22.2%), followed by anti-inflammatory medications. The use of concomitant medications was comparable between the treatment groups. Thirty-five subjects took CYP3A4 inhibitors during the study (after randomization). Of these, 11 were in the CAM2038 treatment group and 24 were in the SL BPN/NX treatment group.

Table 16: Use of concomitant medications in Study 421*

Drug Classes	CAM 2038 (N=213) N (%)	SL BPN/NX (N=215) N (%)	Total (N=428) N (%)

Patients taking at least 1 medication	145 (68.1)	142 (66)	287 (67.1)
Adrenergics/Inhalants	15 (7.0)	15 (7.0)	30 (7.0)
Antidepressants	29 (13.6)	30 (14.0)	59 (13.8)
Anti-inflammatory agents	33 (15.5)	29 (13.5)	62 (14.5)
Antipsychotics	14 (6.6)	12(5.6)	26(6.1)
Anxiolytics	17 (8.0)	21 (9.8)	38 (8.9)
Drugs for Constipation	11 (5.2)	15 (7.0)	26 (6.1)
Hypnotics and Sedatives	17 (8.0)	14 (6.5)	31 (7.2)
Opioids**	41 (19.2)	54 (25.1)	95 (22.2)
Other analgesics and antipyretics	4 (11.2)	30 (14.1)	54 (12.6)

*WHO drug ATC Class designations. Table represents most widely used drug classes by patients in the study. Derived from Applicant-provided data in Clinical Study Report HS-11-421: Table 14.1.6.2.
** On 12/20, the Application clarified that the use of opioids included patients transferring back to SL BPN or requiring it for analgesia.

Efficacy Results - Primary Endpoint

The review of efficacy and secondary analyses were conducted by Dr. Travis, of Biometrics, and are summarized below. Please refer to his review for additional details on the issues and corrections to source data that he identified In each of the analyses, the applicant combined all the patients in each arm and did not distinguish between patients receiving different dose levels of CAM2038 or SL BPN/NX. There were three patients (two CAM2038, one SL BPN/NX) which were classified as responders in the applicant's primary analysis which did not appear to meet the applicant's responder definition. These patients were classified as non-responders in the Biometrics review.

The applicant concluded CAM2038 was NI to SL BPN/NX since the lower bound of the 95% confidence interval of the difference in the percentage of responders was greater than the prespecified −10% NI margin. However, CAM2038 was not demonstrated to be superior to the SL BPN/NX.

Table 17: Applicant's Analysis of responder rate in Study 421

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)	Non-Inferiority P-value 2-sided
Responder, n (%)	36 (16.9%)	30 (13.9%)	2.9% (−3.9%, 9.8%)	< 0.001
Non-Responder, n (%)	177 (83.1%)	185 (86.0%)		

Source: Reviewer
Abbreviations: CI, Confidence interval; ITT, intent to treat; SL BPN/NX, sublingual buprenorphine/naloxone

Table provided from Dr. Travis' Primary Review

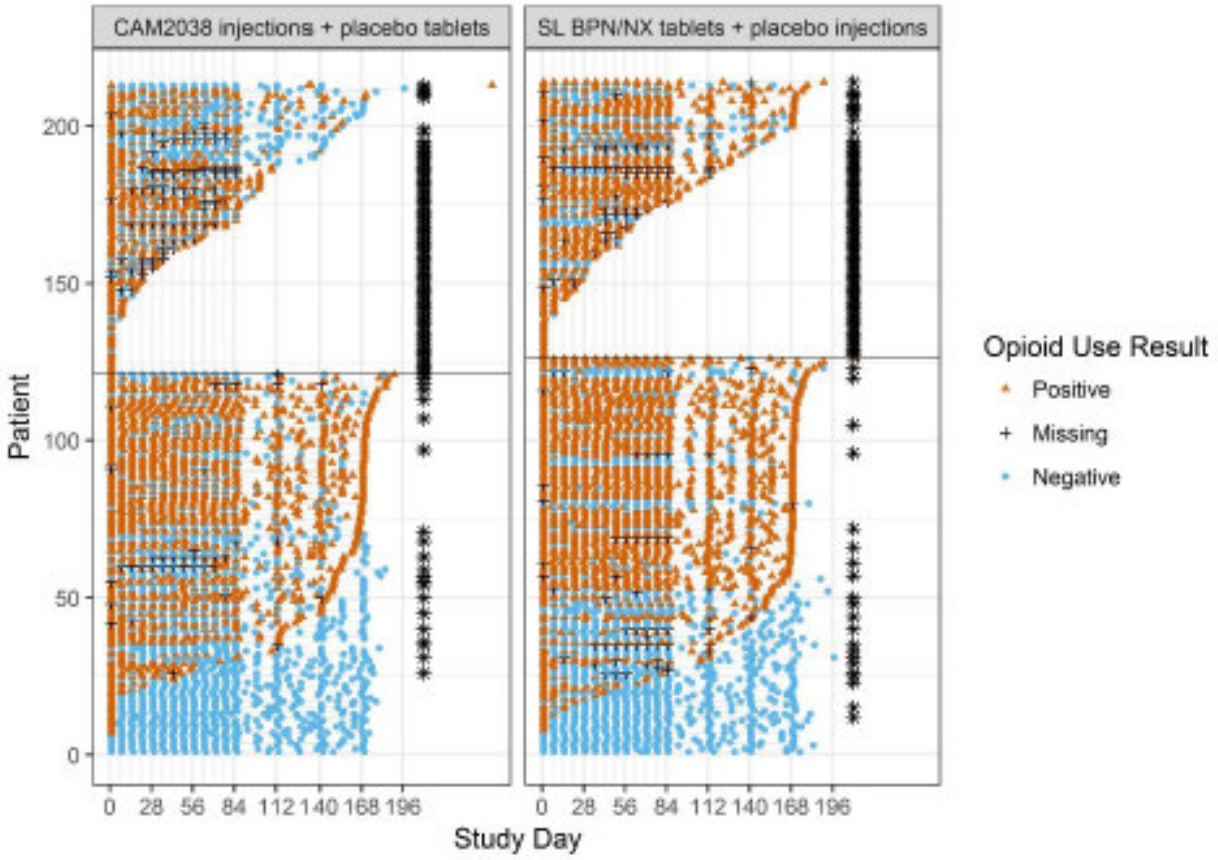
Percentage of Urine Samples negative for illicit opioids

Despite a significant difference in the overall percent of urine negative tests favoring CAM2038, per the Applicant, their analysis did not differentiate between, for example, a patient who is abstinent for half the study and then relapses to daily illicit drug use, a patient who continues to use illicit drugs daily for
half the study and then stops completely, and a patient who uses intermittently, half the days throughout the study. These patients might have 50% of their tests negative.

To allow an appreciation of the temporal sequence of patients' test results, the graphic depiction provided by Biometrics in

Figure 10,shows the results of each test for each patient. The plot also distinguishes between tests that were imputed as positive because they were missing, and actual positive tests or self-reported use. Patients with missed random tests are indicated by a star on the right side of the figure.

Figure 10: Plot of opioid use assessment results in Study 421

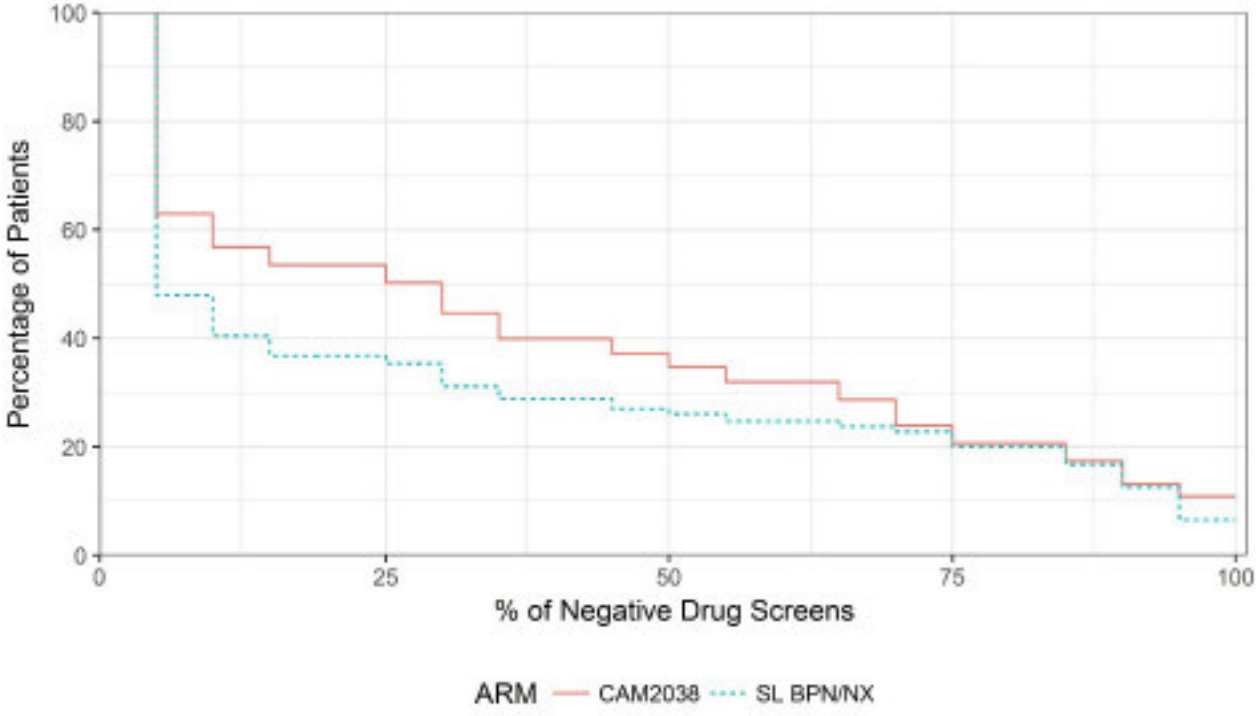


Source: Dr. Travis, Biometrics reviewer
This figure represents patients with positive, missing, or negative urine opioid assessments. Patients with missed random tests are indicated by a star on the right-hand side of the plot.

Cumulative Distribution Function (CDF) of the Percentage of Negative Opioid Use

The results of the applicant's analysis of the CDF are illustrated in Figure 11. The corresponding values plotted in the figure are shown in Table 9 and the applicant's statistical analysis of this endpoint is shown in Table 10. As you will see in Figure 5, a greater percentage of patients who received CAM2038 provided more negative urine samples and self-reported less use in Weeks 5 through 25 than patients who received sublingual buprenorphine plus naloxone. The applicant's analysis found that this difference is statistically significant in a Wilcoxon rank sum test (p = 0.004). However, the statistical significance is driven by the disparity in the number of patients with less than 70% negative opioid use assessments. There is very little difference in the right-hand side of the curves where most or all the urine assessments were negative. The clinical significance of these differences is not known.

Figure 11: CDF of percent negative opioid use in Study 421



Source: Dr. Travis, Biometrics reviewer
This figure represents the Cumulative Distribution Function (CDF) of the percentage of negative opioid Use from weeks 5 through the end of study.

Data Quality and Integrity - Reviewers' Assessment

Throughout the course of the review, increasing inconsistencies were identified in the provided datasets. A cross-section of some of those deficiencies are represented here. This sampling of identified data quality inconsistencies was extrapolated from the Division's many IRs and subsequent Applicant responses (Table 9):

- There were 158 days where 106 patients had at least 2 visits on the same day. Of these there were 21 days where 3 visits were reported on the same day and 1 day where 7 visits were reported (HS-11-421-(b) (6) Day 113).

- A total of 302 unscheduled visits for 147 patients were recorded in the SV SDTM dataset. The mean number of unscheduled visits was 2.05 and the median was 2. The maximum number of unscheduled visits for one patient was 7.

- In the first week patients were initiated on CAM2038 16 mg dose on day 1. They were then given an additional 8 mg on any subsequent visit in that week, except for one patient who received 32 mg on day 3 (HS-11-421-(b) (6)).

- 317 patients received at least one dose of the monthly formulation. There were nine visits where 8 mg doses were used in *phase 1* outside of the first 7 days. Four of these were on day eight. The other five were on days 14, 24, 36, 38, and 64. In *phase 2* it also appears that there were possibly larger doses than 8 mg used as supplemental doses but it was difficult to determine.

Dose/Dose Response

The Clinical Study Report submitted by the Applicant made no attempt to evaluate dose-response in this study, and the initially-submitted datasets did not provide information on doses received. At Agency request, additional information was received that facilitated the reviewers' attempts at dose-response analyses.

The dose of CAM2038 (*phase 1*) given to each patient during the study is shown in Figure 12 and was generated by Dr. Travis (months 1-3). The dose of CAM2038 given to each patient in *phase 2* (months 4-6) is represented in

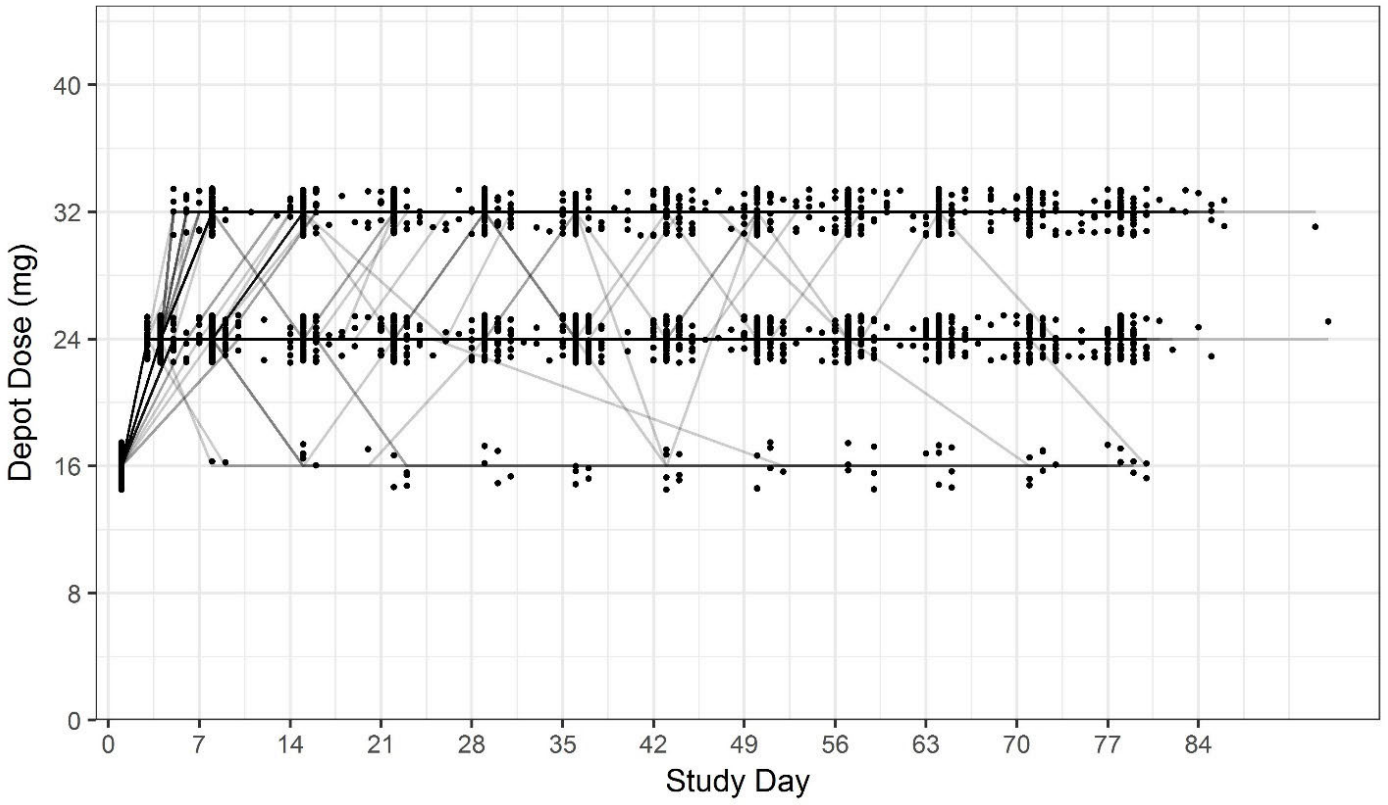
Figure 13. Per protocol, patients were then given a 16 mg injection of the weekly formulation. Patients were to return to the study site several times during the first week of the study. If the 16 mg dose was judged to be insufficient by the investigator and the patient, then up to two 8 mg "booster" doses could be administered to the patient. These 8 mg doses were added to the patient's previous dose.

On the first day of Week 2 patients received an individualized dose of either 16, 24, or 32mg of the weekly formulation. This continued until the start of Phase 2 (Week 13) when patients were transitioned to the monthly formulation. The lowest three doses of the monthly formulation, 64, 96, and 128 mg, were expected[17] to match the exposures of the three highest weekly formulation doses, 16, 24, and 32 mg, respectively. The 160 mg monthly dose was intended to provide higher exposure for patients for whom the other doses were determined to be insufficient. Some patients received additional 8 mg doses of the weekly formulation after the

[17] Note that the full evaluation of relative bioavailablity among the doses had not been completed at the time the study was initiated.

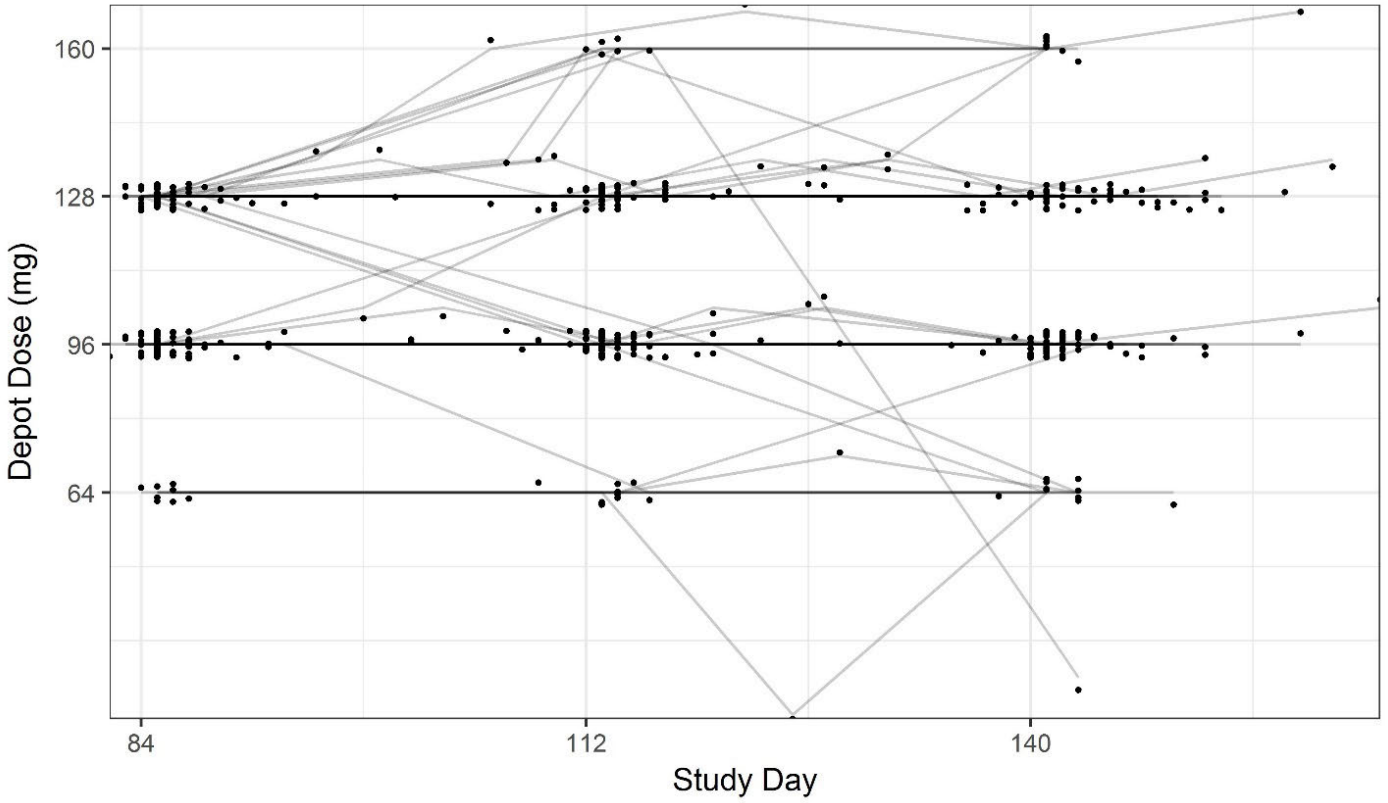
initial titration. Again, these were added to the patients' previous dose. A summary of the patient exposures to CAM2038 and placebo injections can be found in Table 18: Summary of patient exposures to CAM2038 in Study 421.

Figure 12: CAM2038 dosing pattern in *phase 1* of Study 421



Source: Dr. Travis, Biometrics reviewer

Figure 13: CAM2038 dosing pattern in *phase 2* of Study 421



Source: Dr. Travis, Biometrics reviewer

The tables above illustrate that doses were changed, both up and down, frequently, without information on what led to these dosing changes. It was not possible to determine whether any dose or regimen (e.g., the 16 mg weekly dose, which was not studied in the Blockade Study) was ineffective, or whether any was particularly poorly-tolerated.

Table 18: Summary of patient exposures to CAM2038 in Study 421

Dose (mg)	Formulation	Number of Patients Exposed	
		CAM2038	SL BPN/NX
8	Weekly	200	196
16	Weekly	213	215
24	Weekly	146	156
32	Weekly	84	89
64	Monthly	11	5
96	Monthly	89	84
128	Monthly	68	74
160	Monthly	9	9

Source: Dr. Travis, Biometrics reviewer
Table represents the number of patients exposed to each dose and formulation of CAM2038 (and placebo injections) in Study 421.

Durability of Response

Study 421 was a 24-week clinical trial divided into two "*phases*", each phase lasting 12-weeks and comprised of CAM2038 Weekly or Monthly formulations, respectively. Thus, the efficacy of the combined formulations was not studied beyond 24-weeks. Further, the efficacy of each formulation was not studied independently, longer than 12-weeks.

Additional Analyses Conducted on the Individual Trial

Analysis by Sex, Race, and Age

For analysis by sex, overall, females responded at a higher rate than males in the study in both treatment groups. For the analysis by race, patients who identified as black or African American responded at a much lower rate than patients who identified as white. One possible cause of this is a difference is the primary opioid of use at initiation. Ninety-five percent (95%) of patients who identified as black or African American reported heroin as their primary opioid at initiation compared to 64% for patients who identified as white (

Table 19).

Table 19: Analysis by demographic subgroup in Study 421

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)
Sex			
Male	17/121 (14.0%)	18/142 (12.7%)	1.4% (-6.9%, 9.6%)
Female	19/92 (20.7%)	12/73 (16.4%)	4.2% (-7.6%, 16.1%)
Race			
White	31/159 (18.4%)	27/164 (16.5%)	3.0% (-5.3%, 11.4%)
Black or African American	3/47 (6.4%)	2/48 (4.2%)	2.2% (-6.8%, 11.2%)
American Indian or Alaska native	1/2 (50%)	1/1 (100%)	-50% (-119%, 19%)
Asian	1/1 (100%)	0/0 (NA)	NA
Other	1/3 (33.3%)	0/0 (NA)	NA
Age			
< 36 years old	19/99 (19.2%)	11/100 (11%)	8.2% (-1.7%, 18.1%)
≥ 36 years old	17/114 (14.9%)	19/115 (16.5%)	-1.6% (-11.0%, 7.8%)

Source: Applicant-provided submission 13

Analysis by opioid use history

Additional analyses on opioid use history were performed by Dr. Travis, Biometrics reviewer. Opioid use history was categorized by two different variables: primary opioid of use at initiation and route of illicit use. Primary opioid of use at initiation divided patients into two categories: primarily heroin user, and primarily prescription opioid pain reliever user. Route of administration was used to divide the patient population into two groups: those who had recently injected either intravenously or intramuscularly, and those who had not (Table 20).

Patients reported as primary heroin users who received SL BPN/NX had a lower response rate (4.6%) than seen overall (14.4%) while primary heroin users who received CAM2038 had a similar response rate (15.8%) to the overall CAM2038 response rate (17.8%). Patients who primarily used prescription opioid pain relievers had a higher response rate in both treatment groups compared to the overall rate. The same effect is seen for injection vs non-injection users in both treatment groups. While these results appear to be consistent with the expectation that patients with more severe opioid use disorder would be more likely to benefit from the

enforced compliance of depot formulations, this analysis is post-hoc (b) (4)
(b) (4)

Table 20: Analysis of Patient population by opioid use history in Study 421

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)
Primary opioid of use at initiation			
Heroin	22/152 (14.5%)	7/151 (4.6%)	9.8% (3.3%, 16.4%)
Prescription opioid pain reliever	14/61 (23.0%)	23/64 (35.9%)	-13.0% (-28.8%, 2.8%)
Route of illicit opioid			
Injection	17/113 (15.0%)	8/11 (7.2%)	7.8% (-0.3%, 16.0%)
Non-injection	19/100 (19.0%)	22/104 (21.2%)	-2.2% (-13.1%, 8.8%)

Source: Biometrics reviewer, Dr. Travis

7. Integrated Review of Effectiveness

7.1. Additional Efficacy Considerations

Other Considerations and Relevant Benefits

Much of the clinical review process included multiple communications with the Applicant, in the form of Information requests, to identify if the submitted application had sound evidence of effectiveness to meet the Agency's statutory evidentiary standard. It was evident, particularly after the AC meeting, that a product with the features of CAM2038 holds clinical-meaningfulness to both patients and clinical providers and that the clinical benefit of a product with flexible Weekly and Monthly formulations and multiple dosing regimens is desirable in a clinical setting.

However, in designing a single clinical trial (Study 421) that incorporated two dosing regimens, used supplemental dosing, and had relatively frequent dose changes, the Applicant provided

data that made the process of determining clinical efficacy and meaningfulness, particularly by dose, difficult.

Moreover, the datasets were submitted in such a way that, although the Division was able to file the Application, several requests were sent to the Applicant during the review process to provide updated and corrected datasets for review, ultimately leading to the identification of an issue resulting in multiple errors in the submitted data.

Despite the review issues of this application, the availability of two formulations (Weekly and Monthly); convenient dosing (four doses in the Weekly formulation and three in the Monthly formulation); and the availability of a supplemental 8 mg Weekly dose to augment the patient's treatment regimen, are benefits of the CAM2038 product and were noted in the AC panel's comments during the AC meeting held on 11/1/2017. Additionally, because CAM2038 can be administered after a single test dose of transmucosal buprenorphine, this product has the potential to be used early on in MAT or, potentially, in emergency room settings where treatment can be initiated before the patient follows up with a provider. Thus, CAM2038 could provide several clinical benefits for the treatment of OUD.

However, interpreting the efficacy of CAM2038 by dose in the primary pivotal efficacy trial (Study 421) proved difficult. First, the Applicant chose to combine the efficacy evaluation of the CAM Weekly and Monthly formulations into a single clinical trial that assessed the two formulations in two *phases*, each lasting 12-weeks. Thus, the efficacy of each formulation was not studied independently. Second, several data inconsistencies were identified throughout the course of the review and narratives were not provided by the Applicant to assuage the concerns that a transparent audit of data could provide a clear understanding that the raw data and subsequently generated datasets were the same data.

8. Review of Safety

8.1. Safety Review Approach

The safety evaluation of this application was based primarily on the pivotal efficacy study 421 and the supporting open-label study 499. This review revealed no safety findings that would preclude approval of this application, or necessitate other regulatory action. However, upon review, not all CAM2038 doses proposed by the Applicant appear to have demonstrated adequate exposures at the highest doses. Specifically, The CAM2038 Monthly 160 mg dose had few overall patient exposures and represented a much higher plasma concentration of BPN than the currently marketed-approved maximum dose of daily buprenorphine. Moreover, as noted above, the submitted datasets were found to have numerous errors, so findings based on analysis of those datasets must be viewed as tentative.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Across all studies in the clinical development of CAM2038 for OUD, 729 subjects were exposed to at least one dose of the study drug (this included healthy volunteers). In the pooled Phase 3 studies, 440 unique patient exposures to CAM2038 were reported by the Applicant. The safety analysis set was defined as all patients with OUD who took at least one dose of CAM2038 and had a post-baseline safety assessment (N=594;Table 21).

Table 21: Overall patient exposure to CAM2038 in the clinical program

Duration of Exposure	CAM2038 Weekly (N=531)	CAM2038 Monthly (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%)**

Table 21 Source: Extracted from the Applicant-provided Summary of Clinical Safety, Table 7

The value in the CAM2038 column does not necessarily match the sum of the CAM2038 Weekly and CAM2038 Monthly columns. For example (and per Applicant), if a patient was treated for 3 weeks with 24 mg CAM2038 Weekly, 5 weeks with 32 mg CAM2038 Weekly and 40 weeks with 128 mg CAM2038 Monthly, the patient was not included as treated for at least 48 weeks with CAM2038 Weekly or CAM2038 Monthly but in the total column for CAM2038. Thus, the patient would appear as treated for at least 8 weeks with CAM2038 Weekly; at least 24 weeks with CAM2038 Weekly; and at least 48 weeks with CAM2038.

Table 22 and

Table 23, provided by the Applicant, illustrate in more detail the extent of cumulative exposure to the doses in each formulation of CAM2038 in the pooled Phase 3 studies. Of note, seven patients were exposed to weekly CAM2038 doses (any dose) for at least 48 weeks. Similarly, 22 patients were exposed to any CAM2038 Monthly formulation for at least 48 weeks of duration. Note that in both tables, the total represents all patients exposed to at least one injection of the given dose, but patients exposed for less than 4 weeks are not shown in any row. In terms of cumulative exposure to CAM2038 in the pooled Phase 3 studies, 402 patients with OUD were exposed to the Weekly and 309 patients were exposed to the Monthly formulations.

Table 22: Cumulative Exposure to CAM2038 Weekly by weeks of treatment in the pooled Phase 3 Studies

	CAM2038 q1w 8mg (N=335)	CAM2038 q1w 16mg (N=316)	CAM2038 q1w 24mg (N=255)	CAM2038 q1w 32mg (N=135)
Exposed for at least 4 weeks	45 (13.4%)	47 (14.9%)	170 (66.7%)	105 (77.8%)
Exposed for at least 8 weeks	18 (5.4%)	35 (11.1%)	132 (51.8%)	85 (63.0%)
Exposed for at least 12 weeks	12 (3.6%)	23 (7.3%)	40 (15.7%)	22 (16.3%)
Exposed for at least 24 weeks	6 (1.8%)	14 (4.4%)	28 (11.0%)	12 (8.9%)
Exposed for at least 48 weeks	4 (1.2%)	1 (0.3%)	1 (0.4%)	1 (0.7%)
In HS-11-421 and HS-14-499 the same subject can be exposed to both q1w and q4w doses				

Source: Applicant's page 33 of ISS Additional Tables; Table 2.2.6

Table 23: Cumulative Exposure to CAM2038 Monthly by weeks of treatment in the pooled Phase 3 studies

	CAM2038 q4w 64mg (N=71)	CAM2038 q4w 96mg (N=178)	CAM2038 q4w 128mg (N=125)	CAM2038 q4w 160mg (N=31)
Exposed for at least 4 weeks	71 (100.0%)	178 (100.0%)	125 (100.0%)	31 (100.0%)
Exposed for at least 8 weeks	52 (73.2%)	131 (73.6%)	95 (76.0%)	22 (71.0%)
Exposed for at least 12 weeks	44 (62.0%)	114 (64.0%)	78 (62.4%)	15 (48.4%)
Exposed for at least 24 weeks	29 (40.8%)	40 (22.5%)	30 (24.0%)	14 (45.2%)
Exposed for at least 48 weeks	8 (11.3%)	9 (5.1%)	4 (3.2%)	1 (3.2%)
In HS-11-421 and HS-14-499 the same subject can be exposed to both q1w and q4w doses				

Source: Applicant's page 34 of ISS Additional Tables; Table 2.2.6
Represents patient cumulative exposure to the Monthly formulation in Studies 421 and 499

Table 24 shows the proposed doses for marketing and cumulative exposures to CAM2038 in the pooled phase 3 studies.

Table 24: Cumulative Exposure and PK relationship to CAM2038 in Phase 3 Studies

CAM2038 Weekly dose	Exposed (N)	**CAM2038 Monthly dose**	Exposed (N)
8 mg	**335**	64 mg	**71**
16 mg	**316**	96 mg	**178**
24 mg*	**255**	128 mg¥	**125**
32 mg*¥	**135**	160 mg¥	**31**

This table represents the cumulative exposures, not unique exposures, to CAM2038 in the Weekly and Monthly formulations in the pooled Phase 3 Studies (421 and 499, respectively).
*CAM2038 Weekly doses used in blockade study 478
¥ Doses with higher Cavg steady values compared with daily dosing of SL BPN 24 mg. These doses were used in the comparative bioavailability studies (the 128, 160, and 32 mg monthly and weekly doses, respectively) reviewed by the Clinical Pharmacology team and referenced in Section 4.5.
The doses highlighted in blue (CAM2038 24 mg Weekly and 96 mg Monthly) were mathematically modeled by the Applicant for bioavailability comparisons.

The Applicant proposes that either the Weekly or Monthly formulation of CAM2038 could be used (b) (4) Two of the proposed doses were evaluated in the Blockade study 478 (CAM2038 Weekly 24mg and 32 mg). The cumulative exposures represent anyone who got at least injection of a particular dose. Correlating availabile PK data with the results of the blockade study and numbers of relative exposures in the context of the safety dataset, helped determine that CAM2038 appears to be tolerated relatively well. However, determining a dose/adverse event relationship was difficult.

Exposure by dose and formulation in Study 421

In study 421, most patients were exposed to the CAM2038 24 mg Weekly formulation [n=108 (50.7%)] and the 96 mg Monthly formulation [n=83 (52.5%)]. Both of those doses correlate with an average of 16 mg of SL BPN daily dosing, per Applicant. The number of patients exposed to doses higher those mentioned, the 32 mg Weekly formulation and the 128 mg and 160 mg Monthly formulations, respectively, were much lower. However, the 32 mg Weekly dose was also examined in Study 478, the opioid blockade study, and was effective in blocking the effects of hydromorphone; and the plasma exposures associated with 128 mg Monthly formulation, if the source data is accurate, did not exceed the observed levels associated with clinical dosing of SL BPN.

Clinician considerations to alternate Weekly and Monthly CAM2038 dosing formulations

In pre-marketing discussions, the Division encouraged Braeburn to use protocol-specified stability criteria for advancing patients from weekly to monthly dosing, or, at a minimum, to capture the criteria that were used by investigators in making these determinations. Braeburn elected not to include criteria for dose switching into the protocol. In response to an IR, dated October 25, 2017, the Applicant provided physician-determined criteria used for switching patients between formulations. Although there was a fixed time-point for switching from Weekly to Monthly CAM2038 in Study 421 (Week 13), the same criteria was used for both Phase 3 studies:

- Has the patient been on a stable dose of Weekly CAM2038 (or placebo injection) with no fluctuations in doses in the past 4 weeks?
- Does the patient show minimal subjective and no objective withdrawal symptoms (based on SOWS ≤ 7 and COWS ≤ 5?
- Does the patient exhibit a decrease desire to use based on VAS scores with 50% minimum reduction from baseline scores?
- Does the patient exhibit diminished use of illicit opioids according the investigator's discretion?

Because of the design of the study, patients not meeting the above criteria might have been switched to monthly dosing at Week 13 of Study 421.

Pooling strategy and rationale
Limitations to pooling included the comparison of studies that included several dose changes with two formulations (Studies 421 and 499, respectively); varying study designs; and the inherit difficulty of evaluating adverse events by dose and by formulation (Weekly vs Monthly).

Explorations of dose-adverse event
Explorations of dose-AE were challenging because three doses were administered within each of two CAM2038 product formulations. Further, the designs of each study reviewed were different and specific dose to AE proved difficult. The ability to assess safety by specific dose and formulation (dose-AE) was limited in review of the ISS. Several Information Requests (IR's) were sent to the Applicant to obtain datasets with tabulations that would enable us evaluate AE's based on CAM2038 dosing and formulation but the clinical studies were not designed in a way to determine AEs by formulation. This complicated the review, in that it was difficult to determine if an AE that could have delayed onset (e.g, hepatic enzyme elevations) was attributed to the CAM2038 Weekly or Monthly formulations because the patients were exposed to a continuum of both. Additional IRs were sent to obtain clarification on missing data and subject-specific data irregularities (e.g., patients being marked as "completers" who discontinued study participation).

Study 421
The safety population was defined as all enrolled and randomized patients who received at least one dose of study medication during the study phase and who had at least one post-baseline assessment (N=213). The duration (mean) of exposure to CAM2038 during both *phase 1* and *phase 2* of the study was 127.4 (62.88) days, or 18.2 weeks. Refer to

Table 13 for patients in the CAM2038 group who completed the study compared with the subjects randomized to the active comparator (SL BPN/NX).

Study 499
In the supportive OL, Phase 3 Study 499, 156 were included in the safety population (128, who were already in treatment with SL BPN/NX at entry ("transfers") and 28 patients representing new entrants to BPN treatment). In this population, median duration of exposure to CAM2038 was 48 weeks (range: 47-50 weeks). Because the study was OL, all patients were exposed to the drug. Further, because it was difficult to interpret dose by time exposure, particularly in Study 499 (although the issue was present in both Phase 3 studies), the Division asked the Applicant to provide additional information to show dose administration by time. On October 20, 2017, the Applicant provided several graphics that showed timelines of CAM2038 dosing and

formulations (including supplemental 8 mg CAM2038 weekly dosing). Figure 14 shows the dosing pattern and supplemental CAM2038 use in select patients who represented transfers to CAM2038 from SL BPN and received at least one dose of supplemental BPN dosing.

Figure 14: Dosing pattern and supplemental use of CAM2038 in "Transfers" to treatment in Study 499

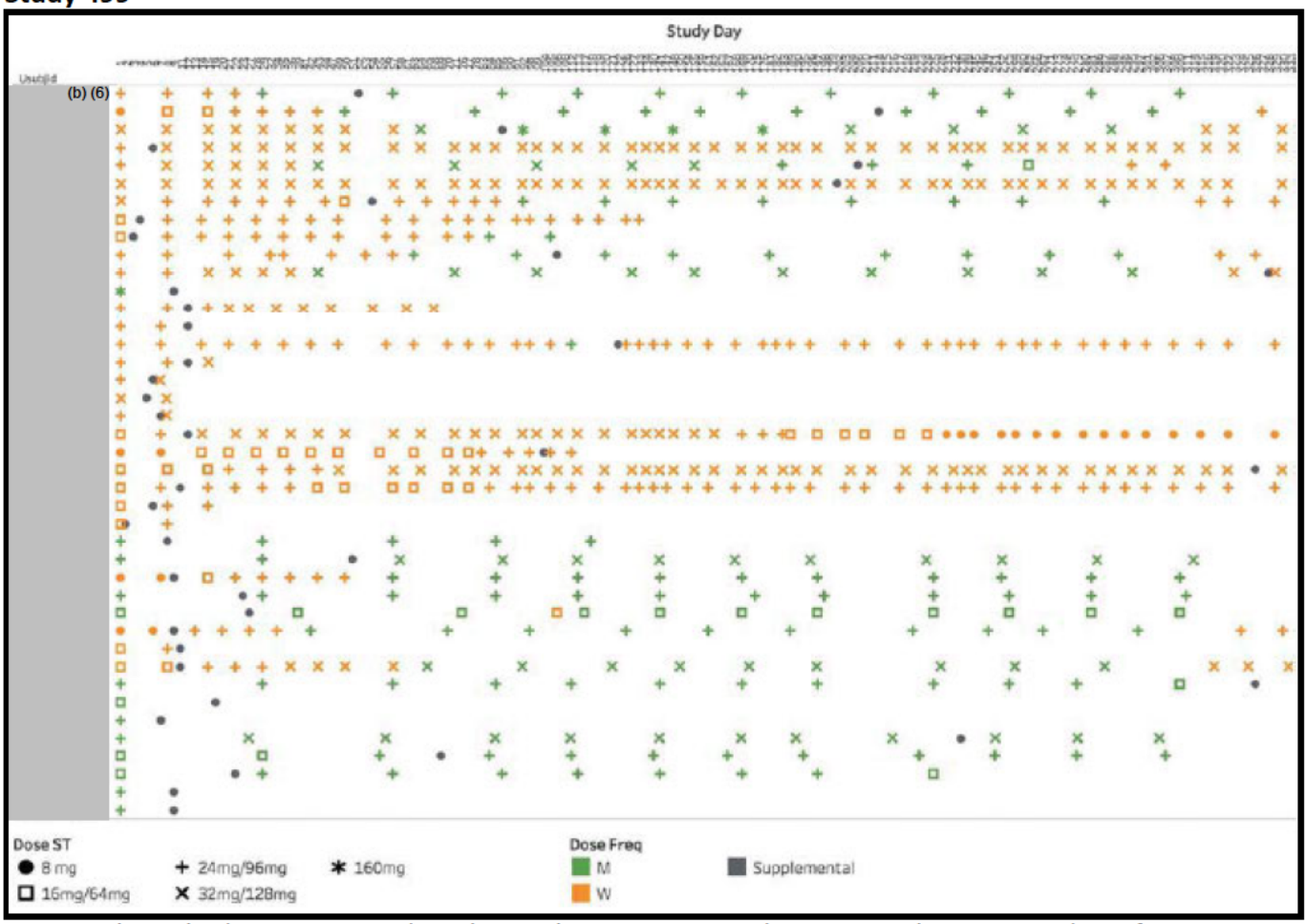
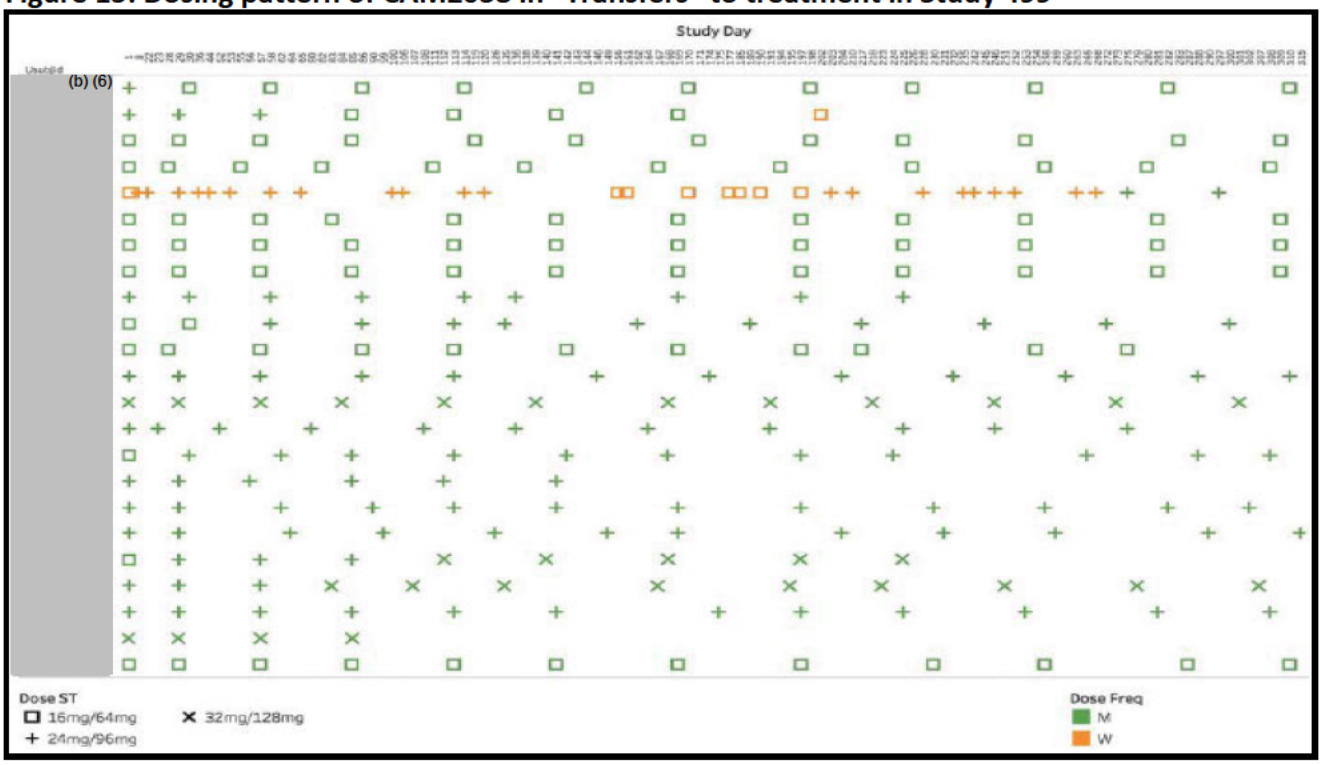


Figure 14 shows the dosing pattern and supplemental CAM2038 use in select patients who represented transfers to CAM2038 from SL BPN and received at least one dose of supplemental BPN dosing

Error! Not a valid bookmark self-reference. shows the dosing pattern by time in the "transfers" to BPN treatment without supplemental CAM2038 Weekly dosing in Study 499.

Figure 15: Dosing pattern of CAM2038 in" Transfers" to treatment in Study 499

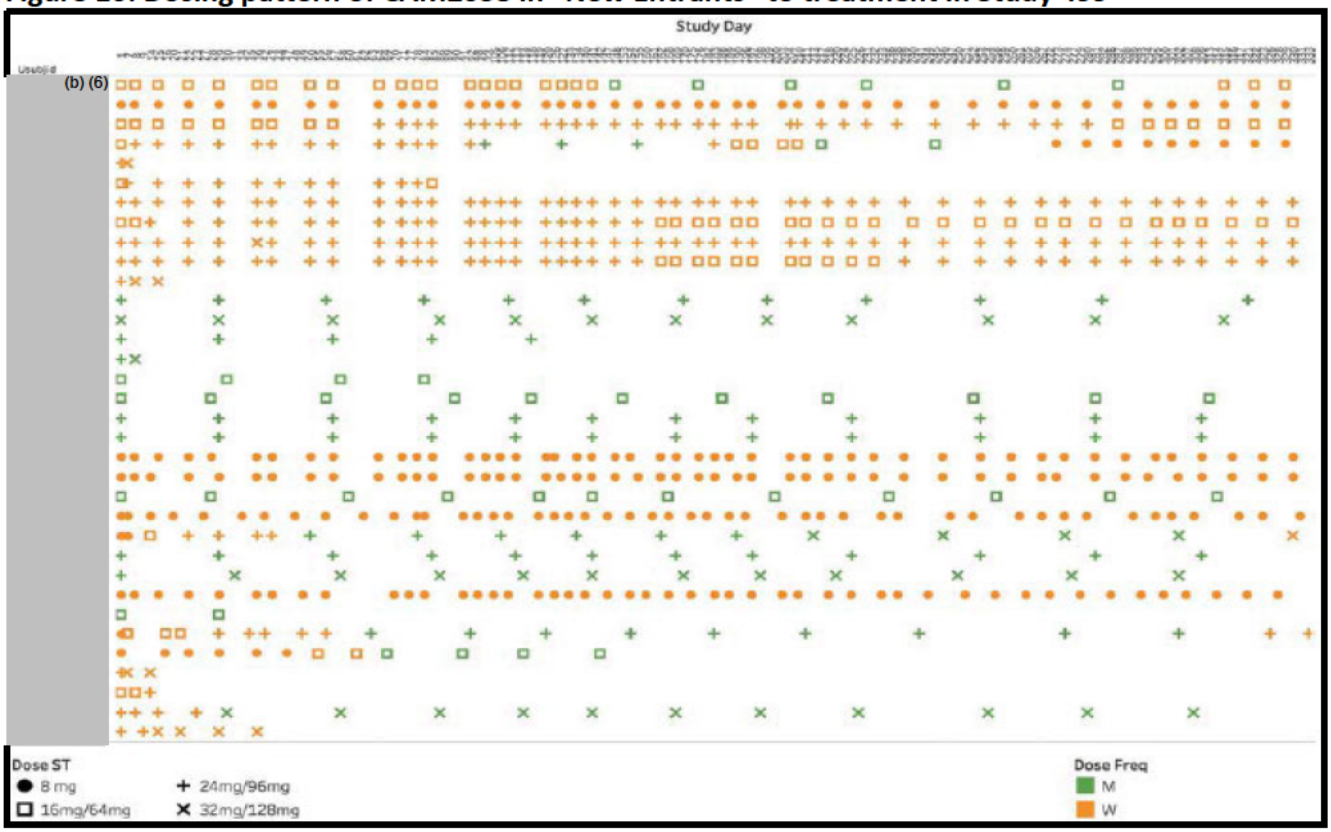


This Applicant=provided figure shows that dosing pattern in transfers to CAM2038 from SL BPN. Specifically, this group shows the dosing pattern without supplemental CAM2038 use.

Figure 16 shows a snapshot of the dosing patterns in Study 499 for "new entrants" to treatment: patients who received initiated CAM2038 after the 4mg test dose of BPN. The intention of displaying these figures is to demonstrate the extreme variability of dosing and formulation used in the OL study and how few "New Entrants" to treatment were ever

transitioned to the CAM2038 Monthly formulation in Study 499.

Figure 16: Dosing pattern of CAM2038 in "New Entrants" to treatment in Study 499



This Applicant=provided figure shows that dosing pattern in New Entrants to CAM2038 from SL BPN.

8.2.2. Relevant characteristics of the safety population:

Study 421

The safety population (New Entrants to BPN treatment) did not differ from that of the Efficacy population and, despite a small database of total exposures with both CAM2038 formulations, the safety findings appeared to be representative of the target population; allowing for generalizability of the safety findings in this review. Because the proposed drug targets a population of opiate drug abusers, approximately 50% of whom were former intravenous drug abusers, many of them had a history of hepatitis and elevated liver function tests. Please refer to Table 14 and Other Baseline Characteristics

The population of patients recruited for this study included adults who reported heroin as their primary drug of choice and injection as the preferred route of illicit opioid use, shown in **Error! Not a valid bookmark self-reference.**, below. APPEARS THIS WAY ON ORIGINAL

Table 15 in section 6.2 for a review of the patient population and baseline demographics for Study 421.

Study 499

Similar to Study 421, the patient population of Study 499 (N=227) comprised of many of the same baseline characteristics (including former IVDA's and patients with a history of hepatitis C/elevated liver function tests) with few other demographic differences (Table 25). The primary differences between patients in Study 499 compared with Study 421 were in the patient selection criteria (new entrants to treatment versus transfers from current BPN treatment) and allocation to CAM2038 dosing groups (which makes pooling Dose/AE data difficult).

Of the 227 patients enrolled, 156 were included in the safety population (128, receiving SL BPN/NX at entry; 28, new to BPN treatment). In this population, median duration of exposure to study drug was 48 weeks (range: 47-50 weeks).

Table 25: Demographics and Baseline Clinical Characteristics of Patients in Study 499

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

Abbreviations: BMI, body mass index; BPN, buprenorphine; SD, standard deviation; SL BPN, sublingual buprenorphine; US, United States.
Source: Table 14.1.2.1 and Table 14.1.3.1.

8.2.3. **Adequacy of the safety database:**

In general, the common adverse events associated with CAM2038 treatment were similar to those seen with sublingual buprenorphine treatment. The review of the hepatic effects and effects on cardiac conduction, were also consistent with buprenorphine's expected effects. The most notable aspect of the safety data is 1) the number of discontinuations in the CAM2038 program (which did not differ significantly from the active control group and might reflect the population recruited for the clinical trials) and 2) that the safety database for exposures to doses of CAM2038 greater than 24 mg Weekly and 90 mg Monthly were small, which made it difficult to generalize safety information for a dose higher than those; particularly the CAM2038 160 mg Monthly, which has a higher steady state plasma concentration that exceeds the recommended maximum dose of 24 mg SL BPN.

A novel aspect of this product is that CAM2038 is an injectable depot and a product of this nature has not yet been reviewed by this division at the time of NDA submission. Thus, the review of this application has raised questions about specific risks associated with the OUD patient population using an injectable product. For instance, among OUD with a former intravenous drug abuse (IVDA) history, the sight of a syringe can elicit cravings in patients in recovery. In Study 421 of the CAM2038 program, 52.3% of the patient population was comprised of previous IVDAs, which approximates the percent of the former IVDA population included in the clinical program.

No data on the consequence of accidental or intentional intravenous administration of CAM2038 (a subcutaneous drug product) was provided by the Applicant, nor was it requested at the time of NDA submission. The Applicant did acknowledge the potential risk of misuse of their product (b) (4)

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

On face, the safety assessments contained within the application were sufficient to file the application and adequately monitor for potential adverse events that have been observed with buprenorphine. The case report forms (CRFs) provided adequate summaries for each patient.

I audited CRFs to evaluate the consistency of adverse event information reported across the CRF, the narrative summary, and the individual trial adverse event tabulations (ae.xpt) for the following three subjects in Study 421:

Site	Subject
	(b) (6)

The adverse event information was found to be consistent across the above three documents for these four subjects. However, text fields in the Study Reports presented numeric differences in the presentation of the "Serious TEAEs"; "SAEs"; "Nonfatal SAEs". For example, there were several instances where the text report (in the Study Report Body) of an adverse event did not align with the SAS line items or the text/table reports did not match the symptom severity as defined in the protocol (e.g., "requiring hospitalization" meets criteria for an SAE but several hospitalization events were listed as non-serious AEs). Another example of organizational inconsistency was the designation of subject (b) (6) as having had a "Moderate TEAE" when he was hospitalized for a seizure with dehydration, hypokalemia, hyperglycemia, and illicit substance withdrawal symptoms.

There were several instances of term-matching inconsistencies that did not preclude the ability to conduct a safety review but did complicate it. In Study 421, no severity table was provided for categorizing AEs (an AE severity table was provided for Study 499). This made it more difficult to identify serious AEs in the pivotal study. Further, AEs by dose were not provided with original submission. AEs in the provided safety dataset were listed by an EPOCH of "treatment" with no ability (from the provided dataset) to easily determine what *phase* of the study the patient experienced an adverse event (e.g., a patient (b) (6) was listed having two AEs, 12-weeks apart, which would indicate that the AEs occurred in both *phases* of the study).

8.3.2. **Categorization of Adverse Events**

An AE was defined as any new untoward medical occurrence or worsening of a preexisting medical condition regardless of causal relationship with treatment. Each reported AE required a complete and thorough description on the AE case report form (CRF). An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or increase in severity of a preexisting abnormality, temporally associated with the use of a medicinal (investigational) product, whether considered related to the medicinal (investigational) product or not.

A treatment emergent adverse event (TEAE) was defined as any AE with an onset date on or after date of randomization, or any ongoing event on the date of first dose that worsened in severity after date of randomization. Per the Applicant, only TEAEs with an onset date prior to date of last dose + 30 days were tabulated in summary tables. TEAEs considered by the

investigator to be 'possibly', 'probably', or 'definitely' related to study drug were classified as study drug-related events.

A SAE was any untoward medical occurrence at any dose that:

- Resulted in death.
- Was life-threatening
- An Important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Required inpatient hospitalization or caused prolongation of existing hospitalization.
- Resulted in persistent or significant disability/incapacity.
- Was a congenital anomaly/birth defect
- Pregnancy

Adverse event investigator terms were coded to Preferred Terms using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 and 18.1 terminology. The categories of adverse event preferred terms of interest included 'Hepatic', 'Suicide', 'Mood', 'Cardiovascular', and, 'Overdose, Abuse, and Dependence'. I assessed the accuracy of the Applicant's coding process by examining the variables AEVNAM1A (reported term) and PT_TXT (Preferred Term) in the adverse event tabulation dataset (ae.xpt) using JMP, version 6.2. Coding was judged to be reasonably accurate.

In addition, I audited an approximate 5% sample of reported adverse events from the ISS dataset adae.xpt in Studies 427 and 499 to compare the reported (verbatim) term (AETERM) with the coded (or preferred) term. I identified no deficiencies in adverse event coding from this audit. However, during the course of my review of the safety data, I noticed instances where multiple coded terms could represent very similar adverse events (e.g., heart palpitations and tachycardia). For purposes of this review, all preferred terms reflective of one condition, (e.g., increased heart rate) were combined.

Deaths, non-fatal serious adverse events (SAEs) and adverse events (AE) leading to discontinuation were also examined from Studies 421 and 499 and are described under sections 8.4.1, 8.4.2, 8.4.3 and 8.4.4.

8.3.3. **Routine Clinical Tests**

Study 421

Visits were conducted weekly for 12-weeks in *phase 1* and every four weeks for 12 weeks in *phase 2*.

The following safety endpoints were assessed throughout the study:

- Rating scales: COWS, SOWS, VAS, and CSSR-S were administered at baseline and weekly for *phase 1* (and monthly in *phase 2*) of Study 421.
- Adverse events at each visit.
- Vital signs at each visit. Vital signs included: temperature, weight, systolic and diastolic blood pressure, pulse, and respiratory rate and were conducted at baseline and at each scheduled visit.
- Laboratory testing (hematology, chemistry) was done at baseline and end of *phase* in *phase 1* and every 4-weeks in *phase 2*. 12-lead ECGs were obtained at baseline and weeks 11 and end of phase in *phase 1* and every 4-weeks in *phase 2*.

Study 499

Visits were conducted in accordance to the treatment regimen the patients were allocated to (CAM2038 Weekly for New Entrants to treatment) and guided by clinician decision. The following safety endpoints were assessed throughout the study:

- Rating scales: COWS, SOWS, VAS, and CSSR-S were administered at baseline and weekly for patients on the weekly formulation and monthly for patients on the monthly formulation.
- Adverse events at each visit (weekly or monthly).
- Vital signs at each visit (weekly or monthly). Vital signs included: temperature, weight, systolic and diastolic blood pressure, pulse, and respiratory rate and were conducted at baseline and at each scheduled visit.
- Laboratory testing (hematology, chemistry) was done at baseline and end of treatment (week 49).
- 12-lead ECGs were performed after the first administration of CAM2038 Weekly or CAM2038 Monthly (prior to dosing at Week 2 for CAM2038 Weekly or Week 5 for CAM2038 Monthly). During the study, ECGs were performed after dose increases (excluding the initial dose titration and supplemental injections) and after intake of QT-extending drugs or CYP3A4 inhibitors.

No significant differences or abnormalities between groups were identified in routine clinical tests.

8.4. Safety Results

8.4.1. Deaths

Study 421

One death was reported for a patient randomized to CAM2038: a 41-year-old female with no other reported medical history and no concomitant medications taken within 30 days of the start of the event. On Day 147 (b) (6) at approximately 1:30 am, she attempted to cross a 4-lane street when she was hit by a car and died instantly (motor vehicle accident). Her last visit was day 143 (b) (6) Week 21. She was reported as doing “fairly well” and was described by the site as "happy, no evidence of depression and/or sadness, and was on her way to the beach following the visit." Per Applicant, there was no evidence of suicidal ideation during the study or at the last visit. She denied using any substance since her last visit; however, urine drug screen was positive for marijuana and benzoylecgonine. The urine toxicology labs were negative for opiates. After reviewing the case, it appears that the death was not related to CAM2038.

Study 499: No deaths were reported for OL Study 499.

Supportive pooled studies: No deaths were reported in pooled studies 307 or 549.

8.4.2. Serious Adverse Events

The Applicant reported a total of 20 events in 17 subjects (2.3%) across all 729 subjects (including healthy volunteers) receiving CAM2038. These SAE’s included road traffic accident and seizure that were reported in 2 patients each; all other SAEs were reported in 1 patient each. One treatment-related SAE (vomiting) occurred within 30 days after the last dose of CAM2038 16mg Weekly, per Applicant (Table 26).

Table 26: Summary of Applicant-provided SAE’s in the CAM2038 clinical program

Category	Severity	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%)

Source: derived from applicant-provided summary of clinical safety, Table 26
Abbreviations: SAE, serious adverse event
Table represents Applicant-provided AE by severity in the entire clinical program (including Healthy Volunteers).

The pattern of SAEs did not identify novel systemic findings inconsistent with the known safety profile of buprenorphine. No SAEs were related to injection site injury, per the Applicant. However, a serious TEAE of injection site reaction, that leads to study discontinuation, could have qualified as an SAE. Narratives of SAE's did not appear misleading.

Study 421

The Applicant reported five (2.3%) SAEs in the CAM2038 group (including one death) compared with 13 (6.0%) in the SL/BPN group in Study 421. These included vomiting leading to hospitalization[18], non-cardiac chest pain[19], suicidal ideation[20], and spontaneous abortion (that did not lead to study discontinuation). These cases were verified with the submitted line listings but were not clearly described in the Study report. Of the five reported SAE's the vomiting leading to hospitalization did appear related to CAM2038, as the Applicant had reported. This male had a history of gastroesophageal reflux disease, esophageal tears, and self-induced vomiting. He experienced vomiting leading to hospitalization on day four of CAM2038. The case of non-cardiac chest pain in occurred in a 51-year-old Caucasian male on day 21 of CAM2038 treatment. He had a history of gastric ulcers, atrial fibrillation and coronary

[18] Subject (b) (6)
[19] Subject (b) (6)
[20] Subject (b) (6)

artery disease and went to the hospital after substernal burning pain did not resolve with nitroglycerin. Other concomitant medications included diltiazem, duloxetine, baclofen, amitriptyline, pregabalin, and tizanidine. Hospitalization did not reveal cardiac origin of pain (including serial, negative troponins, echocardiogram, ECG, and cardiac stress test). The Applicant reported that the event was not due to the study medication. Upon review of the case, it would seem unlikely that the event was due to CAM2038. In the case of the suicidal ideation (SI) in the 23-year-old Caucasian male, who continued in the study, he was admitted to the hospital on day 141 of the study due to agitation and SI in the context of intoxication (cocaine, benzodiazepines, and cannabis). He was released from the hospital on quetiapine after his mood improved and he continued in the study. This event did not appear related to CAM2038.

The summary of *non-fatal* serious adverse events in Table 31, included the death, previously discussed, and did not elucidate the number of SAEs from the number of patients who experienced them. SAEs in the control group included seizure in a patient with a known history of epilepsy and was identified as having abused benzodiazepines, accidental overdose (3) an intentional overdose (with suicidal ideations status post intoxication (1). On independent review of the Applicant-provided dataset, by body system, per severe adverse events, the above SAE's were included except for two (tooth abscess and dental caries) in the CAM2038 group. Several more severe AEs were reported in the SL BPN/NX, which is consistent with the Applicant-provided data. These included Accidental overdose (3), elevated liver enzymes (5) Cellulitis (2; not related to injection site reactions), and one each of the following: tooth abscess, arthralgia, backpain, decreased libido, suicidal ideation (related to drug use), localized infection and cellulitis (not related to study injections), substance induced mood disorder, overdose, hematuria, COPD, osteomyelitis, and sepsis (not related to study drug).

Study 499

15 SAE's in 13 subjects were identified in study 499 in the overall safety population (N=227). However, in another text document, the number of patients who experienced an SAE in 499 was 12 (5.3%). Eight of the SAE's resulted in hospitalization. In the identified safety population (N=156), nine SAE's were reported. (

Table 27). Because Study 499 was OL there was no comparator group.

Table 27: Summary of Serious AE's in Study 499

	Overall Safety Population			Full Exposure Safety Population		
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 (%)	Currently Receiving SL BPN/NX N=128 n (%)	New to BPN Treatment N=28 n (%)	Total CAM2038 N=156 n (%)
At least one SAE	10 (5.3)	2 (5.4)	12 (5.3)	8 (6.3)	1 (3.6)	9 (5.8)
Infections and infestations	1 (0.5)	1 (2.7)	2 (0.9)	1 (0.8)	1 (3.6)	2 (1.3)
Cellulitis	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Pneumonia	0	1 (2.7)	1 (0.4)	0	1 (3.6)	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.1)	0	2 (0.9)	2 (1.6)	0	2 (1.3)
Follicular thyroid cancer	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Malignant melanoma	1 (0.5)	0	1 (0.4)	1 0.8)	0	1 (0.6)
Nervous system disorders	1 (0.5)	1 (2.7)	2 (0.9)	1 (0.8)	0	1 (0.6)
Seizure	1 (0.5)	1 (2.7)	2 (0.9)	1 (0.8)	0	1 (0.6)
Psychiatric disorders	2 (1.1)	0	2 (0.9)	1 (0.8)	0	1 (0.6)
Psychotic disorder	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Substance-induced psychotic disorder	1 (0.5)	0	1 (0.4)	0	0	0
Cardiac disorders	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Ventricular tachycardia	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Gastrointestinal disorders	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Duodenitis	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
General disorders and administration site conditions	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Drug withdrawal syndrome	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)

No SAE's were reported for studies 307, 478, or 549.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The number of patients and healthy volunteers exposed to CAM2038 and discontinued from any study in the entire clinical development program was 226 (31.0%). However, the number of participants who were reported as discontinued due to an AE in the clinical development program was lower [12 (1.6%) out of the 729 exposures, which included healthy volunteers]. Other listed reasons for discontinuation included physician decision (n=13), lack of efficacy (n=12), lost to follow-up (n=45), withdrawal by subject (n=87), and other (n=11). Narratives of discontinuations did not appear misleading.

The following protocol specified criteria were used to determine if a subject was listed as discontinued from the study:

- Discretion of the study investigator or sponsor
- in the event of an adverse event
- if the patient was lost to follow-up
- If a patient withdrew themselves from the study

The following criteria were used to determine subject study discontinuation by the investigator or Applicant:

- Patient refused or was unable to adhere to the study protocol
- Major protocol violation (e.g., violation of inclusion or exclusion criteria during the
- study, failure to adhere to the treatment schedule)
- Pregnancy
- Physician's discretion

Study 421

Per the Summary of AEs leading to discontinuation in Study report 421, the numbers of discontinuations were comparable between in both the CAM2038 and placebo-treated patients [n =7 (3.3%) in the CAM2038 group and n=3 (1.3%) in the control (SL BPN/Placebo injection) group, respectively (

Table 28). However, a comparative review of the Applicant's Integrated Summary of Safety (ISS), (listed as Summary of Clinical Safety in Module 2), reported six discontinuations due to an AE in the CAM2038 group and one discontinuation in the SL BPN/NX group, respectively. The ISS report was consistent with

Table 13, the patient disposition of Study 421, which was generated from the Applicant-provided dataset. I was able to find narratives to the patients who discontinued in Study 421 and the 421 Study Report appeared to represent the accurate number of discontinuations in

each group. A request was sent to the Applicant to audit their data and ensure accuracy among the reports generated from the data.

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Table 28: Enumeration of Dropouts and Discontinuations in Study 421

System Organ Class/Preferred Term	SL BPN/NX N=215 n (%)	CAM2038 N=213 n (%)	Total N=428 n (%)
General disorders and administration site conditions	2 (0.9)	5 (2.3)	7 (1.6)
Drug withdrawal syndrome	1 (0.5)	0	1 (0.2)
Injection site erythema	0	1 (0.5)	1 (0.2)
Injection site pain	0	2 (0.9)	2 (0.5)
Injection site pruritus	1 (0.5)	1 (0.5)	2 (0.5)
Injection site reaction	1 (0.5)	2 (0.9)	3 (0.7)
Injection site swelling	0	1 (0.5)	1 (0.2)
Non-cardiac chest pain	0	1 (0.5)	1 (0.2)
Ulcer	0	1 (0.5)	1 (0.2)
Gastrointestinal disorders	0	2 (0.9)	2 (0.5)
Nausea	0	1 (0.5)	1 (0.2)
Oesophageal rupture	0	1 (0.5)	1 (0.2)
Vomiting	0	2 (0.9)	2 (0.5)
Infections and infestations	1 (0.5)	0	1 (0.2)
Sepsis	1 (0.5)	0	1 (0.2)
Metabolism and nutrition disorders	0	1 (0.5)	1 (0.2)
Dehydration	0	1 (0.5)	1 (0.2)
Nervous system disorders	0	1 (0.5)	1 (0.2)
Sedation	0	1 (0.5)	1 (0.2)

Abbreviations: SL BPN/NX, sublingual buprenorphine /naloxone; SOC, system organ class; TEAE, treatment-emergent adverse event.
Notes: SOCs are presented in order of decreasing incidence in the Total column. Within each SOC, TEAEs are ordered by decreasing incidence in the Total column and then alphabetically for terms with like incidence.
Denominators for percentages were N, the total number of subjects overall. At each level of subject summarization, a subject was counted only once if the subject reported 1 or more events.
Only events that started on or after first dose date and within 30 days of last dose date were summarized.
Source: Table 14.3.10.1

Source: Applicant Table 14.3.10.1, From 421 Study report "Treatment-Emergent Adverse Events That Led to Discontinuation of Study Drug (Safety Population)" Non-Fatal Serious adverse events are not repeated here. Events that led to dropouts and discontinuations with the following terms, 'relapse criteria met' or 'failure to meet randomization criteria', 'lost to follow-up', 'study withdrawal by subject', or 'protocol non-compliance/violation', are not reported in this table.

Study 499

Table 29, provided by the Applicant, highlights the discontinuations in the study (not the safety population, which is smaller).

Table 29: TEAEs that led to discontinuation in Study 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 (%)
Discontinued due to a TEAE	3 (1.6)	0	3 (1.3)
General disorders and administration site conditions	2 (1.1)	0	2 (0.9)
Injection site swelling	2 (1.1)	0	2 (0.9)
Injection site erythema	1 (0.5)	0	1 (0.4)
Injection site pain	1 (0.5)	0	1 (0.4)
Injection site pruritus	1 (0.5)	0	1 (0.4)
Injury, poisoning and procedural complications	1 (0.5)	0	1 (0.4)
Facial bones fracture	1 (0.5)	0	1 (0.4)
Intervertebral disc injury	1 (0.5)	0	1 (0.4)
Lower limb fracture	1 (0.5)	0	1 (0.4)
Multiple injuries	1 (0.5)	0	1 (0.4)
Pharyngeal injury	1 (0.5)	0	1 (0.4)
Road traffic accident	1 (0.5)	0	1 (0.4)
Skull fractured base	1 (0.5)	0	1 (0.4)
Spinal fracture	1 (0.5)	0	1 (0.4)
Upper limb fracture	1 (0.5)	0	1 (0.4)

Abbreviations: SOC, system organ class; TEAE, treatment-emergent adverse event.
SOCs are presented in order of decreasing incidence in the Total column for the Overall Safety population. Within each SOC, TEAEs are ordered by decreasing incidence in the Total column and then alphabetically for terms with like incidence.
Denominators for percentages were N, the total number of subjects overall. At each level of subject summarization, a subject was counted only once if the subject reported 1 or more events.
Only events that started on or after first dose date and within 30 days of last dose date were summarized.
Source: Table 14.3.7.1

In the OL study 499, the Applicant reported that three patients withdrew (1.3%) due to an AE (per the CRF). Two of them discontinued due to injection site TEAE's (0.9%)[21] and one discontinued to several TEAEs (due to a road traffic accident). However, on review and in the Study Report, the Applicant identified two other study discontinuations due to "pain in

[21] Subjects (b) (6)

extremity" (in a patient new to BPN treatment)[22] and an abnormal ECG[23] (in a patient who was transferred from SL BPN/NX). Of the 70 patients (30.8%) who discontinued the study, approximately half (n=33) were due to withdrawal by subject request (14.5% of total subjects). Thirteen patients (5.7%) were lost to follow-up, and 12 (5.3%) discontinued due to lack of efficacy. According to study report, four patients who completed 48 weeks of treatment were subsequently lost to follow-up. Line listings were provided by the Applicant. The most common type of event leading to discontinuation in all studies was "lost to follow-up".

Table 30 shows the reason for study discontinuations by study and treatment group across all studies in the clinical program, per the ISS, provided by the applicant.

Table 30: Reasons for Study Discontinuation by Study and Treatment Group Across All Studies

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

8.4.4. Significant Adverse Events

[22] Subject (b) (6)
[23] Subject (b) (6)

Cardiovascular effects, hepatic effects, and injection site reactions are of concern among opioids and injectables. Each of these event types are reviewed below in their representative sections. This section will focus on non-fatal Serious adverse events. Further discussion of events of concern is found in Sections 8.4.9 (QT) and 8.5 (Submission-specific safety concerns).

Study 421

Per the Applicant, 18 (4.2%) subjects, 13 (6.0%) in the SL BPN/NX group and 5 (2.3%) in the CAM2038 group, experienced at least 1 non-fatal SAE. None of the non-fatal SAEs were reported at the injection site or in association with an injection site reaction. One patient (CAM2038 group) was reported as having an SAE related to study drug (vomiting). Fifteen (3.5%) patients, 12 (5.6%) in the SL BPN/NX group and three (1.4%) in the CAM2038 group, were hospitalized.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The adverse event profile of SL BPN has been previously characterized in the safety database for buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets. The adverse event tables from the approved labeling (see 13.2). Table 31 illustrates the most common adverse events in the pooled Phase 3 studies in the CAM2038 development program. TEAE's for Studies. Specific findings for Studies 421 and 499 are outlined below. Despite these numbers being fewer than what is listed in the product label for Subutex, an audit of these results did not yield alternate findings.

Table 31: Common Treatment-Emergent Adverse Events (≥ 5%) in the Pooled Phase 3 studies

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%)
Urinary tract infection	12 (3.0%)	12 (3.9%)
Constipation	19 (4.7%)	3 (1.0%)
Nasopharyngitis	17 (4.2%)	6 (1.9%)

CAM2038 TEAEs identified in >5% of the patient population in both the Weekly and Monthly formulations in the Pooled phase 3 Studies, 421 and 499 (derived from Applicant-provided ISS).

8.4.6. Laboratory Findings

In Study 421, the Applicant reported that exposure to CAM2038 did not reveal significant differences in lab abnormalities compared with SL BPN/NX and the submitted cases of lab abnormalities did not exceed what is reported with buprenorphine products. Most of the TEAEs related to laboratory values were with liver enzymes (Table 32).

Table 32: Laboratory-related TEAEs in Study 421

Preferred Term	SL BPN/NX N=215 n (%)	CAM2038 N=213 n (%)	Total N=428 n (%)
Alanine aminotransferase increased	4 (1.9)	4 (1.9)	8 (1.9)
Aspartate aminotransferase increased	4 (1.9)	4 (1.9)	8 (1.9)
Gamma-glutamyltransferase increased	3 (1.4)	2 (0.9)	5 (1.2)
Blood glucose increased[a]	3 (1.4)	1 (0.5)	4 (0.9)
Hepatic enzyme increased	2 (0.9)	2 (0.9)	4 (0.9)
Haematocrit decreased	2 (0.9)	0	2 (0.5)
Haemoglobin decreased	2 (0.9)	0	2 (0.5)
Lipase increased	0	2 (0.9)	2 (0.5)
Liver function test abnormal	2 (0.9)	0	2 (0.5)
White blood cell count increased[a]	2 (0.9)	0	2 (0.5)
Blood creatine phosphokinase increased	0	1 (0.5)	1 (0.2)
Blood glucose decreased	0	1 (0.5)	1 (0.2)
Blood potassium increased	1 (0.5)	0	1 (0.2)
Blood urine present	0	1 (0.5)	1 (0.2)
Mean cell haemoglobin concentration (low)	1 (0.5)	0	1 (0.2)
Mean cell haemoglobin decreased	1 (0.5)	0	1 (0.2)
Red blood cell count decreased	1 (0.5)	0	1 (0.2)

[a] One of the 2 cases of white blood cell count increased occurred in the context of infection (Subject (b) (6)); 1 of the 4 cases of blood glucose increased occurred in a subject with diabetes type 2 (Subject (b) (6) CAM2038).
Abbreviations: SL BPN/NX, sublingual buprenorphine /naloxone; TEAE, treatment-emergent adverse event
Note: TEAEs are ordered by decreasing incidence in the Total column and then alphabetically for terms with like incidence.
Denominators for percentages were N, the total number of subjects overall. At each level of subject summarization, a subject was counted only once if the subject reported 1 or more events.
Only events that started on or after first dose date and within 30 days of last dose date were summarized.
Source: Table 14.3.5.1; Listing 16.2.7.1

Mean laboratory findings[24] were not summarized in tables by the Applicant in the 421 Study report but were available for review in the provided SAS table outputs (by week of treatment) and in the provided datasets. Further, laboratory findings were not presented by dose, only by treatment arm (CAM2038 compared with SL BPN/NX). Inspection of reported laboratory data (specifically change from baseline at week 25/end-of-treatment) revealed no remarkable findings or differences between groups. It was not possible to ascertain laboratory changes by CAM2038 dose. Of note, laboratory reference ranges were not submitted with the application but were presented in such a way that the review could be conducted.

In Study 499, the Applicant reported very few (6) laboratory-related TEAEs in the Safety population (N=156;Table 33). Patients who had multiple abnormal events were counted once and only events that started on or after the first dose date and within 30-days of the last dose were summarized. From the data provided, it appears that CAM2038 does not pose a specific laboratory abnormality risk compared with commercially available BPN products.

Table 33: Laboratory-related TEAEs in the Safety population of Study 499

	Overall Safety Population			Full Exposure Safety Population		
Preferred Term	Currently Receiving SL BPN/NX N=190 n (%)	New to BPN Treatment N=37 n (%)	Total CAM2038 N=227 n (%)	Currently Receiving SL BPN/NX N=128 n (%)	New to BPN Treatment N=28 n (%)	Total CAM2038 N=156 n (%)
Blood creatine phosphokinase increased	1 (0.5)	1 (2.7)	2 (0.9)	1 (0.8)	1 (3.6)	2 (1.3)
Blood creatinine increased	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Blood lactic acid increased	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Blood urea increased	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Liver function test abnormal	0	1 (2.7)	1 (0.4)	0	1 (3.6)	1 (0.6)

Source: Applicant provided Table 14.3.2.1

8.4.7. **Vital Signs**

[24] Basophils, eosinophils, hemoglobin, hematocrit, leukocytes, monocytes, neutrophils, platelets, amylase, lipase, albumin; liver function tests (AST, ALT, alkaline phosphatase, bilirubin); and electrolytes.

In Study 421, vital-sign[25] related TEAEs, did not appear to exceed vital sign changes with known BPN products and affected 10.8% of the safety population (N=156). None of the preferred terms were reported as SAEs and only one was attributed to the study drug (weight decreased). The Applicant reported that the vital sign related TEAEs were of mild-moderate intensity and did not lead to discontinuation, which appeared, on face, to be accurate (Table 34).

Mean vital signs were not summarized in tables by the Applicant in the 421 Study Report but were available for review in the provided SAS table outputs (by week of treatment) and dataset. Further, laboratory findings were not presented by dose, only by treatment arm (CAM2038 compared with SL BPN/NX). Inspection of reported vital signs (specifically change from baseline at week 25/end-of-treatment) revealed no remarkable findings. It was not possible to ascertain vital signs by CAM2038 dose.

Table 34: Vital-sign related TEAEs in Study 421

Preferred Term	SL BPN/NX N=215 n (%)	CAM2038 N=213 n (%)	Total N=428 n (%)
Tachycardia	5 (2.3)	5 (2.3)	10 (2.3)
Pyrexia	3 (1.4)	3 (1.4)	6 (1.4)
Weight decreased	3 (1.4)	3 (1.4)	6 (1.4)
Hypertension	2 (0.9)	0	2 (0.5)
Bradycardia	1 (0.5)	0	1 (0.2)

Source: Applicant provided table 14.3.5.1
A patient was counted only once for a vital sign related TEAE if they experienced more than one TEAE. Events that started on or after the first dose and within 30 days of the last dose were included.

Similarly, in Study 499, vital-sign related TEAEs, did not appear to exceed vital sign changes with known BPN products and affected 10.8% of the safety population (N=156). None of the preferred terms were reported as SAEs (
Table 35).

Table 35: Vital-sign related TEAEs in Study 499

[25] Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), temperature (Celsius), respiratory rate (breaths/min), weight (kg), height (cm),BMI (kg/m^2), ECGs.

Preferred Term	Overall Safety Population			Full Exposure Safety Population		
	Currently Receiving SL BPN/NX N=190 n (%)	New to BPN Treatment N=37 n (%)	Total CAM2038 N=227 n (%)	Currently Receiving SL BPN/NX N=128 n (%)	New to BPN Treatment N=28 n (%)	Total CAM2038 N=156 n (%)
Hypertension	7 (3.7)	1 (2.7)	8 (3.5)	7 (5.5)	1 (3.6)	8 (5.1)
Abnormal loss of weight	3 (1.6)	0	3 (1.3)	2 (1.6)	0	2 (1.3)
Pyrexia	3 (1.6)	0	3 (1.3)	3 (2.3)	0	3 (1.9)
Tachycardia	3 (1.6)	0	3 (1.3)	2 (1.6)	0	2 (1.3)
Dyspnoea exertional	1 (0.5)	0	1 (0.4)	0	0	0
Heart rate irregular	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Underweight	1 (0.5)	0	1 (0.4)	0	0	0
Weight increased	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)

Source: Applicant provided Table 14.3.2.1; and Table 14.3.2.2

8.4.8. Electrocardiograms (ECGs)

A signal for QT prolongation has been identified in a study of transdermal buprenorphine used for analgesia. The extent of prolongation noted was considered to meet the threshold for regulatory concern, a value which is used to determine whether or not the effect of a drug on the QT/QTc interval in target patient populations should be studied intensively during later stages of drug development. Electrocardiogram (ECG) parameters were evaluated from the Applicant-provided data for the pooled phase 3 studies, and elevations above baseline have been noted. The data confirm that QT prolongation may be seen in patients treated with buprenorphine. In study 421, more ECG related TEAE's reported in the SL BPN arm than the group randomized to CAM2038 (seven versus three, respectively), which is supportive for the concept that ECG irregularities are related buprenorphine. A high-level summary of from the Interdisciplinary Review Team for QT Studies review can be found in 8.4.9.

Study 421

Table 36 presents the percent of patients who had an ECG-related TEAE, per Applicant. Within both groups, ECG-related events were few and they affected less than 1% of the safety population. The events were considered mild to moderate and did not lead to discontinuation of CAM2038 or SL BPN/NX. Narratives were provided and in my review of them, they did not appear misleading.

Table 36: ECG-related TEAEs in Study 421

Preferred Term	SL BPN/NX N=215 n (%)	CAM2038 N=213 n (%)	Total N=428 n (%)
Electrocardiogram abnormal	2 (0.9)	1 (0.5)	3 (0.7)
Atrial fibrillation	0	1 (0.5)	1 (0.2)
Defect conduction intraventricular	1 (0.5)	0	1 (0.2)
Electrocardiogram QT prolonged	1 (0.5)	0	1 (0.2)
Electrocardiogram ST segment elevation	0	1 (0.5)	1 (0.2)
Electrocardiogram T wave amplitude decreased	1 (0.5)	0	1 (0.2)
Myocardial infarction	1 (0.5)	0	1 (0.2)
Sinus tachycardia	1 (0.5)	0	1 (0.2)

Source; Applicant provided Table 14.3.5.1

Study 499

In the safety population (N=156), two patients (1.3%) had at least 1 ECG-related TEAE, which included myocardial ischemia and tachycardia (Table 37). A female[26] was reported with myocardial ischemia on day 337 of treatment (transfer to CAM2038), completed the study and the event was considered a TEAE of mild intensity and not related to the study drug. No narrative was provided and the Applicant reported the issue as resolved with no interruption in treatment.

Another female[27] (also a transfer to CAM2038) experienced a serious TEAE of tachycardia on day 313, which resulted in hospitalization. CAM2038 was not discontinued and the Applicant did report it as related to CAM2038. The patient had reported 3-5 highly caffeinated energy drinks prior to the episode and became unresponsive while driving. Concomitant medications included buspirone, citalopram, Lisinopril, and omeprazole. ECG revealed atrial flutter. The patient was provided an implantable defibrillator and continued the study. Per the Applicant, the hospitalist attributed the event to the caffeine drink. This appeared to be a reasonable assessment with the provided information.

Table 37: ECG-related TEAEs in Study 499

[26] Subject (b) (6)
[27] Subject (b) (6)

Preferred Term	Overall Safety Population			Full Exposure Safety Population		
	Currently Receiving SL BPN/NX N=190 n (%)	New to BPN Treatment N=37 n (%)	Total CAM2038 N=227 n (%)	Currently Receiving SL BPN/NX N=128 n (%)	New to BPN Treatment N=28 n (%)	Total CAM2038 N=156 n (%)
Electrocardiogram QT prolonged	1 (0.5)	0	1 (0.4)	0	0	0
Electrocardiogram QRS complex abnormal	1 (0.5)	0	1 (0.4)	0	0	0
Myocardial ischaemia	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)
Ventricular tachycardia	1 (0.5)	0	1 (0.4)	1 (0.8)	0	1 (0.6)

Source: Applicant provided Tables 14.3.2.1 and 14.3.2.2

8.4.9. QT

A formal review by the Interdisciplinary Review Team for QT Studies (QT-IRT) was performed (refer to the 11/27/2017 review; reference ID: 4185454). The materials submitted with this application supported an absence of large mean (i.e., 20 ms) increases in the QTc interval for CAM2038 at the time of expected maximum BPN exposure for CAM2038 compared to a baseline where patients had been taking BPN (with low systemic exposure). These results did not reveal a specific concern for CAM2038. The data used for the QT-IRT assessment was obtained from Studies 307, 426, 487, 421, 499, and 599, respectively.

8.4.10. Immunogenicity

Non-Applicable

8.5. Analysis of Submission-Specific Safety Issues

Because CAM2038 is a subcutaneous injectable product with novel excipients within each formulation, significant attention was given to injection site reactions and tolerability. Further, given the known characteristics of buprenorphine products, a review emphasis was also placed on the hepatic effects of CAM2038.

8.5.1. Injection site reactions

Study 421

The injection site reaction data presented here by preferred term for CAM2038 is from the two pooled Phase 3 studies presented in the Summary of Clinical Safety. Injection site reactions are presented by formulation (Weekly versus Monthly) and dose in Table 38 and Table 39. Of note, injection site reactions in the CAM2038 group of the controlled Phase 3 study, HS-11-421, were comparable to the SL BPN injection site reactions reported by patients exposed to placebo injections, in terms of type of reaction (pain, erythema, swelling, and pruritus) and percent of injection site reactions reported [n=40 (18.8 %) and n=48 (22.3%) in the CAM2038 and active comparator groups, respectively]. This suggests that buprenorphine, itself, is not responsible for tissue reactions over and above those of vehicle.

The data in Table 38 and Table 39, below (extracted from page 532 of the Applicant-provided ISS), represent numbers of reactions and not individual patients with reported reactions, which was 20 and 19 in the CAM2038 and SL/BPN groups, respectively. Overall, more injection site reactions occurred in the Weekly versus the Monthly formulation but that might be due to more patients were exposed to the Weekly formulation and had more frequent visits than the patients exposed to the Monthly formulation.

Table 38: CAM2038 Weekly injection site reactions by dose in Study 421

	8 mg	16 mg	24 mg	32 mg
	n (%)	n (%)	n (%)	n (%)
Patients with at least 1 AE	10(2.7%)	15 (4.2%)	34 (11.9%)	42 (18.3%)
Treatment related AE's	10	32	122	106
AE's per injection	0.011	0.03	0.05	0.06

Number (n) and percent (%) of injection site reactions in the Applicant-provided Safety Population for the CAM Weekly formulation.

Table 39: CAM2038 Monthly injection site reactions by dose in Study 421

	64 mg	96 mg	128 mg	160 mg
	n (%)	n (%)	n (%)	n (%)
Patients with at least 1 AE	4(4.5%)	18 (9.4%)	11 (6.8%)	7 (11.1%)
Treatment related AE's	12	59	21	9
AE's per injection	0.03	0.08	0.04	0.04

Number (n) and percent (%) of injection site reactions in the Applicant provided Safety Population for the CAM Monthly formulation.

Study 499

In the Safety population (N=157), 14.7% reported injection site pain and 12.8% reported injection site swelling. No discontinuations resulted from those. Two injection site reactions were reported as moderate TEAEs in Study 499 (a mild injection site reaction of erythema and a moderate infection with erythema, pruritus, and discharge). No injection site SAEs reported.

8.5.2. Hepatic Effects

Buprenorphine has been associated with hepatitis, abnormal liver function tests (LFTs), and other hepatic events. The Warnings and precautions section of current labeling for sublingual buprenorphine (as Suboxone) includes safety labeling regarding hepatitis and hepatic events (found in product labeling). The Applicant reported no "Hy's Law"[28,29] cases in the clinical development program, which are considered indicative of potential drug-induced liver injury. On review, the provided data appears consistent with these reports, although several patients experienced asymptomatic elevations in liver function tests that resolved. The CAM2038 safety database revealed no new hepatic safety concerns beyond those previously identified.

Study 421

[28] Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

[29] Excerpt from Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

No subject was missing baseline hepatic function tests but several patients in each group were missing post-baseline liver function tests (N=36 (16.9%)) in the CAM2038 group and N= 41 (19.1%) in the control group, respectively). No subject was identified as having experienced Hy's law, although one subject in the SL BPN/NX group experienced a flare of his underlying Hepatitis C, which is reflected in the significant abnormalities seen in Table 40.

Table 40: Evaluation of hepatic tests on patients in Study 421

Liver Lab Test	CAM2038 N = 213			SL BPN /NX N = 215		
ALT ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	49	17	7.98	47	21	9.77
3x ULN	14	9	4.23	25	9	4.19
5x ULN	4	3	1.41	18	7	3.26
10x ULN	0	0	0.00	5	3	1.40
20x ULN	0	0	0.00	3	2	0.93
AST ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	60	22	10.33	43	19	8.84
3x ULN	13	6	2.82	20	10	4.65
5x ULN	1	1	0.47	9	4	1.86
10x ULN	0	0	0.00	5	3	1.40
20x ULN	0	0	0.00	1	1	0.47
ALP ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	0	0	0.00	2	1	0.47
3x ULN	0	0	0.00	1	1	0.47
5x ULN	0	0	0.00	0	0	0.00
10x ULN	0	0	0.00	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00
TB ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
1.5x ULN	4	2	0.94	1	1	0.47
2x ULN	0	0	0.00	1	1	0.47
3x ULN	0	0	0.00	0	0	0.00

All scores are post-baseline. Subject scores may be counted more than once in that they will be counted in all conditions (e.g., 2x, 3x, 5x) that apply. ALT= alanine aminotransferase; AST= aspartate aminotransferase; ALP= alkaline phosphatase; TB= total bilirubin

A shift from normal-to-high in LFT's was observed in alanine aminotransferase (ALT), with 5.6% of the CAM2038 patients compared with 4.2% of the control group. Similarly, the same normal-to-high shift was observed with aspartate aminotransferase (AST) and bilirubin (6.0% and 1.3% in the CAM2038 group and 4.2% and 0.5% in the SL BPN/NX group, respectively). Although there were no statistical differences between these labs, I would have anticipated a trend in the opposite direction for the CAM2038 group, given that it is presumed that an injectable form of BPN would bypass first pass metabolism.

Study 499

No subject was missing baseline hepatic function tests but several patients in each group were missing post-baseline liver function tests. Twenty-four (12.6%) in the transfer to treatment group and nine (24.3%) in the new entrants to treatment group, were missing post-baseline liver lab tests. No subject was identified as having experienced Hy's law (

Table 41, below).

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Table 41: Evaluation of hepatic tests on patients in Study 499

Liver Lab Test	Currently Receiving N = 190			NEW TO BPN Treatment N = 37		
ALT ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	4	4	2.11	1	1	2.70
3x ULN	0	0	0.00	1	1	2.70
5x ULN	0	0	0.00	1	1	2.70
10x ULN	0	0	0.00	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00
AST ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	2	1	0.53	1	1	2.70
3x ULN	0	0	0.00	1	1	2.70
5x ULN	0	0	0.00	1	1	2.70
10x ULN	0	0	0.00	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00
ALP ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	0	0	0.00	0	0	0.00
3x ULN	0	0	0.00	0	0	0.00
5x ULN	0	0	0.00	0	0	0.00
10x ULN	0	0	0.00	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00
TB ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
1.5x ULN	0	0	0.00	0	0	0.00
2x ULN	0	0	0.00	0	0	0.00
3x ULN	0	0	0.00	0	0	0.00

All scores are post-baseline. Subject scores may be counted more than once in that they will be counted in all conditions (e.g., 2x, 3x, 5xthat apply). ALT= alanine aminotransferase; AST= aspartate aminotransferase; ALP= alkaline phosphatase; TB= total bilirubin

8.6. Safety Analyses by Demographic Subgroups

No additional analyses were performed. In general, there were no significant differences between groups that warranted further analysis at the time of this review. In terms of demographic differences by sex, there were few differences between the Pooled Phase 3 studies. Using long-term Study baseline characteristic data from Study 499 (Table 42), the differences between Males and Females were unremarkable:

Table 42: Demographic Baseline Characteristics by Sex in Study 499

Disposition Term	Sex	Currently Receiving N=190		NEW TO BPN Treatment N=37		Overall N=227	
		Count	%	Count	%	Count	%
Adverse Event	M	2	1.7	1	4.2	3	2.1
	F	1	1.4	0	0.0	1	1.2
Completed	F	51	71.8	9	69.2	60	71.4
	M	81	68.1	16	66.7	97	67.8
Lack Of Efficacy	M	8	6.7	0	0.0	8	5.6
	F	4	5.6	0	0.0	4	4.8
Lost To Follow-Up	F	2	2.8	4	30.8	6	7.1
	M	2	1.7	5	20.8	7	4.9
Other	F	1	1.4	0	0.0	1	1.2
	M	1	0.8	0	0.0	1	0.7
Physician Decision	M	4	3.4	0	0.0	4	2.8
	F	1	1.4	0	0.0	1	1.2
Pregnancy	F	1	1.4	0	0.0	1	1.2
	M	0	0.0	0	0.0	0	0.0
Withdrawal By Subject	M	21	17.6	2	8.3	23	16.1
	F	10	14.1	0	0.0	10	11.9

The Count column shows the count of subjects in each demographic group per arm whose last disposition event is the disposition term shown. The % column shows the proportion of the demographic group in each arm that the count represents.

8.7. Specific Safety Studies/Clinical Trials

No additional safety studies were conducted, as a specific safety signal was not identified

during the course of this review.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No formal assessments of human carcinogenicity were performed by the Applicant and no tumors or malignancies were identified during the course of the review. Thus, there was no indication that neoplastic investigations of the CAM2038 product would need to be conducted.

8.8.2. Human Reproduction and Pregnancy

Two pregnancies were reported in the Pooled Phase 3 studies of the CAM2038 Clinical program. One of those pregnancies (in a female exposed to CAM038) resulted in an early spontaneous abortion and the patient continued in the study. No additional pregnancy information was provided and no data on lactating women could be obtained. The Division of Pediatric and Maternal Health (SPMH) was not consulted to review the application materials but was consulted to review the proposed label and PLLR section of the draft label.

8.8.3. Pediatrics and Assessment of Effects on Growth

The Applicant received a full waiver (with an agreed iPSP) for the proposed indication of (b) (4) The CAM2038 product triggered the Pediatric Research Equity Act (PREA) as a new dosage form, new dosing regimen and new route of administration. The Division responded that the use and addiction of opioids in younger teens is not increasing. The use of this product for the proposed indication is most likely to occur in older teens 17 to 19 years of age. The Pediatric Review Committee (PeRC) subsequently agreed with the division to grant a full waiver in all pediatric patients for the following reason:

> *Studies are impossible or highly impractical because there are too few patients who will require medically assisted treatment (MAT).*

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Buprenorphine is controlled Schedule III of the Controlled Substances Act. Abuse liability and language for the corresponding sections of labeling were reviewed by the CMC and CSS reviewers.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

No postmarketing studies have been conducted on this product. It is not yet approved for use.

8.9.2. Expectations on Safety in the Postmarket Setting

During product development, CAM2038 was administered by a health care provider in a clinical setting. No data was provided on the take-home use or self-administration of CAM2038 by product by patients and that is not how the studies were conducted. No extraction studies (of the CAM2038 product after administration) were performed, nor was there a request to do so.

A risk exists that patients, many of whom have a history of intravenous drug abuse and drug misuse, could improperly self-administer CAM2038 if they were to have access to the product. Thus, the potential exists whereby a life-threatening situation could develop or have untoward consequences.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues, beyond those that were already mentioned in the course of this review and that were associated with the development of a REMS, are identified at this time.

8.10. Integrated Assessment of Safety

Overall, no new safety signals were identified in the review of the CAM2038 program that differentiate the overall safety profile from that established for other buprenorphine products. However, longer-term evaluations by dose and formulation were not explored independently by the Applicant. Therefore, it is difficult to evaluate the product by dose or by formulation in order to clearly identify a dose/AE relationship. This was particularly evident in the longer-term exposure to the CAM2038 160 mg Monthly formulation.

The overall safety database of CAM2038 appeared to be consistent with the known safety profile of buprenorphine. Further, despite the lack of any comparable products with the fluid crystal technology, no serious injection site reactions (ISRs) were identified and relatively few ISRs led to study discontinuation, per Applicant-provided materials.

In summary, the greatest concern with the CAM2038 product, at this time, is with the reliability of the data provided with this application. Several deficiencies were identified across the review teams involved with this application. When and if the source data can be verified and validated and if the data can be presented in such a way as to show a clear exposure by dose and formulation, a more definitive review can be made about this drug product.

9. Advisory Committee Meeting and Other External Consultations

A joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held on November 1, 2017 for the CAM2038 application[30] Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA, and from Braeburn Pharmaceuticals, Inc. The meeting was called to order by Rajesh Narendran, MD (Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS (Designated Federal Officer). Approximately 210 people attended for the meeting. There were 13 Open Public Hearing speakers. The committees discussed new drug application (NDA) 210136, buprenorphine subcutaneous injection, submitted by Braeburn Pharmaceuticals, Inc., for treatment of opioid dependence. Below is a summary of the Discussion, voting questions, and responses to the voting questions.

Advisory Committee Members (standing and temporary) in Attendance and Voting:

- **Psychopharmacologic Drugs Advisory Committee Members Present:** Satish Iyengar, PhD; Rajesh Narendran, MD (Chairperson)**;** David Pickar, MD; Erick H. Turner, MD; Kim O. Witczak (Consumer Representative)

- **Temporary Members Present:** G. Caleb Alexander, MD, PhD; Kathleen T. Brady, MD, PhD; Chester Buckenmaier, II, MD; Melinda Campopiano, MD; Kathleen M. Carroll, PhD; Daniel Ciccarone, MD, MPH; Adam J. Gordon, MD, MPH, FACP, FASAM; Daniel L. Krinsky, MS, RPh; Sabrina Numann (Patient Representative)

[30] A verbatim transcript of this meeting is available on the FDA website at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm535446.htm

Subsequent Discussion and Voting Questions Submitted to the Advisory Committee:

- ***DISCUSSION:*** *Discuss whether the provided safety data sufficiently support the use of all of the proposed doses and formulations of CAM2038, given that the steady-state plasma exposures associated with some doses/formulations exceed those associated with the highest labeled dose of the reference product, Subutex? If not, describe which doses have adequate safety data.*

  Committee Discussion: *The majority of the committee members agreed that unsafe side effects were not observed with CAM2038. A few members commented that the clinical trial design mimics real world practice and is reflective of an effectiveness rather than efficacy trial, which should predict its success in treating opioid use disorders. However, other members disagreed and commented that the inherent design of the clinical trial, which did not allow for the collection of highly controlled data to predict the safety and efficacy of the CAM2038 doses investigated, was disappointing and a drawback. The members also were unclear about how seeing more data will change the risk vs. benefit ratio with respect to what we know already based on the experience with sublingual buprenorphine Several members voiced concern that one cannot conclude the highest doses were safe. In addition, concerns about the lack of real time longitudinal data (beyond 3 months) were raised by some members. Please see the transcript for details of the committee discussion.*

- ***DISCUSSION:*** *Discuss whether the provided safety data sufficiently support the proposed indefinite use of both the weekly and monthly formulations.*

  Committee Discussion: *Most members of the committee agreed that the data is sufficient to support its use in a chronic disease. One member commented that the pragmatic trial design gives confidence that it can be administered in a chronic disease and that 6 months seems reasonable. However, some members disagreed, and stated that the lack of long term data especially for the highest doses to which very few individuals were exposed in a concern. Other noted that there are some concerns with respect to elevated liver function tests (LFTs) and there needs to be more frequent LFT monitoring at higher doses. In addition, several committee members thought there was a need for more information on the removal of the depot dose and the potential medical and surgical complications that may arise from it. Please see the transcript for details of the committee discussion.*

1. **VOTE: Do the provided safety data support:**
   A) all of the proposed doses

B) some of the proposed doses
C) none of the proposed doses

A:1 B:17 C:2 Abstain: 0

Committee Discussion: *The majority of the committee members agreed that safety data support some of the proposed doses for the above stated reasons (see answers to question #2).* (b) (4) (b) (4) *Please see the transcript for details of the committee discussion.*

2. VOTE: Do the data from the clinical trial, taken together with the results of the blockade study, provide substantial evidence of effectiveness of CAM2038 weekly and monthly formulations for the treatment of opioid use disorder in patients who are newly initiating buprenorphine treatment for:
A) all of the proposed doses
B) some of the proposed doses
C) none of the proposed doses

A: 2 B: 17 C:1 Abstain: 0

Committee Discussion: *The majority of the committee members voted that the data from the clinical trial, taken together with the blockade study, provide substantial evidence of effectiveness of CAM2038 weekly and monthly formulations for the treatment of opioid use disorder in patients who are newly initiating buprenorphine treatment for some of the doses (for stated reasons see answers to question #1). Please see the transcript for details of the committee discussion.*

- ***DISCUSSION:*** *Discuss the pros and cons of the restricted distribution under a Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risks that might ensue from direct distribution of CAM2038 to patients.*

  a. *What barriers to access may arise from implementing a restricted distribution system?*
  b. *What systemic or institutional barriers might be anticipated for a restricted distribution system?*
  c. *What modifications might address barriers to access while mitigating risk?*
  d. *Is the proposed REMS sufficient, or are other measures needed?*

Committee Discussion: *The majority of the committee members agreed and supported the need for the FDA's proposed addition to the REMS to include a one-time certification of health care settings that order and dispense CAM2038 to put systems in place from being dispensed directly to the patient. Some members commented that it may be too difficult to implement the REMS from a policy standpoint because of differences in State laws. The members also noted that the need for community pharmacists to be aware of patients use of CAM2038 via sharing of medication lists. Some members had reservations about the drug being dispensed to providers for administration to patients in a pre-filled syringe, questioning whether that presentation would increase the risk for abuse by intravenous injection. Please see the transcript for details of the committee discussion.*

3. VOTE: Do you recommend approval of this application?

A) all of the proposed doses
B) some of the proposed doses
C) none of the proposed doses

A: 0 B: 17 C: 3 Abstain: 0

Committee Discussion: *The majority of the committee members recommended approval for some of the proposed doses. The committee members voting "C" expressed concerns over the trial design being problematic, and limited clinical data. Please see the transcript for details of the committee discussion.*

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The Applicant submitted proposed labeling in Physician's Labeling Rule (PLR) format with annotations. As of this review, labeling has been reviewed in detail but has not been approved. Modifications have been made to several sections but definitive recommendations are contingent on provision of adequate source data.

10.2. Nonprescription Drug Labeling

Non-applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

The Applicant did not initially submit a REMS proposal, working under the assumption that DATA 2000-waived HCP's administering CAM2038 directly to the patient and not through a retail pharmacy, would be sufficient to mitigate abuse, misuse, and overdose.

The Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology worked with the Applicant and encouraged them to submit a REMS proposal. After the submission, DRISK determined that a REMS with elements to assure safe use (ETASU) would be needed to ensure the benefits of CAM2038 outweigh its risks. The REMS should include restricted distribution with CAM2038 only being dispensed in healthcare settings that are certified.

At the time of this review, DRISK had not finalized their review and specific recommendations regarding the CAM2038 REMS were outstanding. However, all buprenorphine products that currently have an indication for MAT of OUD are approved with REMS (Suboxone/Subutex REMS, the shared system Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS and the Probuphine REMS, and the recently-approved Sublocade REMS). As an injectable depot, CAM2038 differs significantly from the oral transmucosal formulations of buprenorphine and from Probuphine, but the risks are not expected to differ significantly from those associated with the recently approved Sublocade product.

Therefore, it is anticipated, that, if the CAM2038 product is approved, it will have a REMS similar to that which was proposed with the Sublocade product. The following materials are recommended as part of the CAM2038 REMS**:**

Enrollment Forms:

Healthcare Setting and Pharmacy:

1. Healthcare Setting and Pharmacy Enrollment Form

Communication Materials

2. Dear Healthcare Provider REMS Letter
3. Fact Sheet

Other Materials

4. REMS Program Website

12. Postmarketing Requirements and Commitments

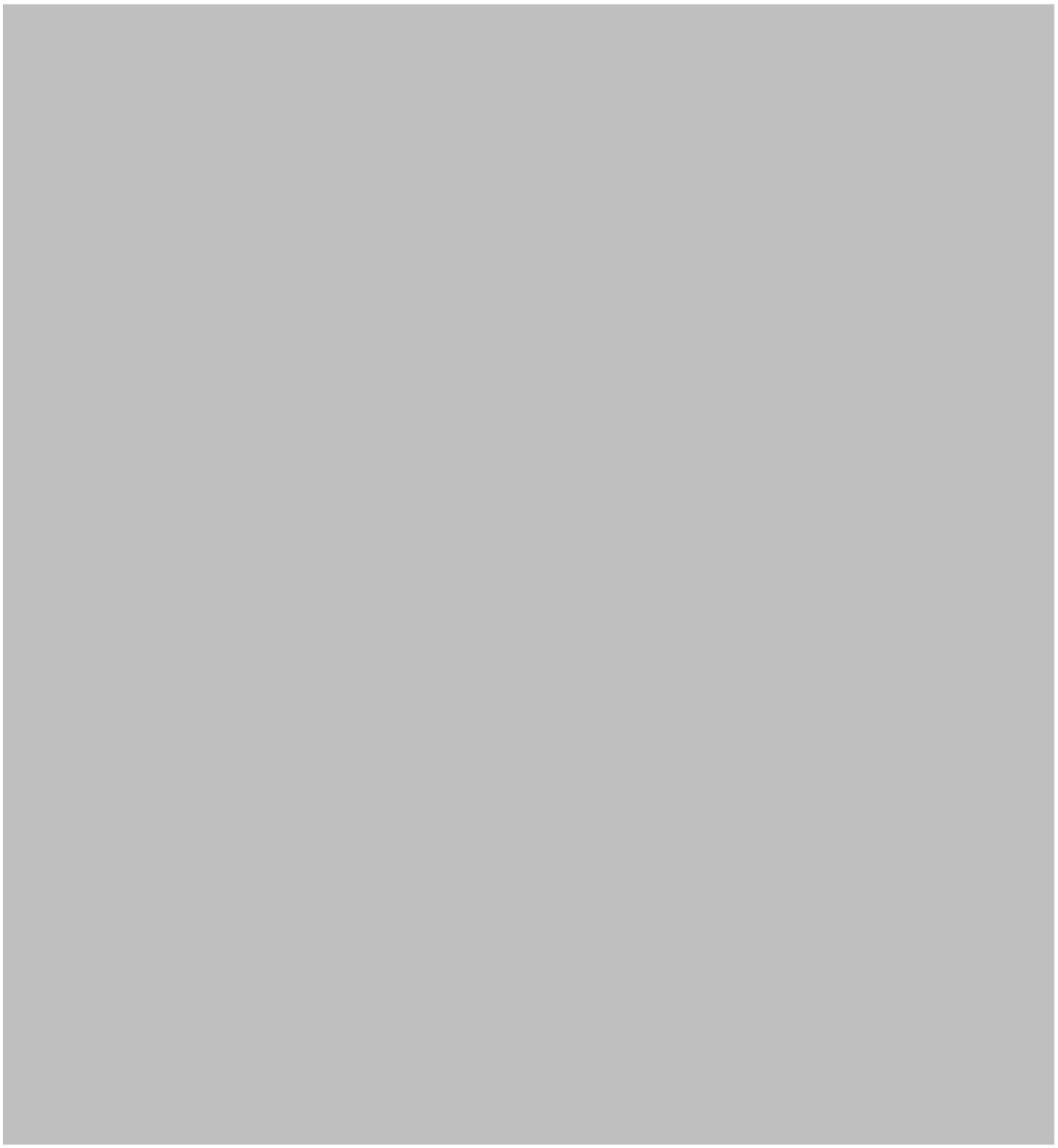
At the time of this review, postmarketing requirements had not been discussed with the Applicant.

13. Appendices

13.1. References

Applicable references were included in-text or as footnotes.

13.2. Subutex Drug Product Label:



13.3. Financial Disclosure

The Applicant submitted the certification of financial disclosure of clinical investigators in compliance with 21 CFR Part 54.2(e) [Table 43]. Three investigators participated in arrangements in which they were compensated for equipment, consultations, or honoraria. Those investigators are listed as: (b) (6) None of the other investigators listed had financial interests or disclosures to report. The Applicant reported that no clinical investigator reported participating in any financial arrangement with the Applicant whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study.

Table 43: Financial Disclosures Relative to Covered Clinical Studies: 421, 499, 478

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list)
Total number of investigators across studies identified: 251		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: Three received honoraria or compensation for consultations Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GIOIA M GUERRIERI
12/29/2017

CELIA J WINCHELL
01/12/2018