CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210136Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review and Division Summary

Date	5/22/2023
Medical Officer	Gioia Guerrieri, D.O.
CDTL/Associate Division Director	Celia Winchell, M.D.
Division Director	Rigoberto Roca, M.D.
NDA/BLA #	210136
Applicant	Braeburn Inc.
Date of Submission	11/23/2022
Proprietary Name	Brixadi
Established or Proper Name	(buprenorphine extended-release) injection, for subcutaneous administration
Dosage Form(s)	Injection Weekly Formulation: 8 mg, 16 mg, 24 mg, 32 mg Monthly Formulation: 64 mg, 96 mg, 128 mg
Applicant Proposed Indication(s)/Population(s)	For the treatment of moderate to severe opioid use disorder (b) (4) (b) (4)
Applicant Proposed Dosing Regimen(s)	Patients not currently receiving buprenorphine treatment: titrate to (b) (4) Weekly in the first week then dose adjust. Patients currently receiving buprenorphine treatment: transfer to appropriate Weekly or Monthly formulation.
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	BRIXADI is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. BRIXADI should be used as part of a complete treatment plan that includes counseling and psychosocial support.
Recommended Dosing Regimen(s) (if applicable)	New Entrants to treatment: after test dose of sublingual buprenorphine, titrate to 24-32 mg Weekly in the first week then dose adjust. Adults stabilized on current buprenorphine product: transfer to appropriate Weekly or Monthly formulation.

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1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

CAM2038 (buprenorphine extended-release) injection, for subcutaneous administration use. is intended for the treatment of moderate-to-severe opioid use disorder. The Weekly formulation is for initiating treatment in patients who have tolerated a test dose of a transmucosal buprenorphine-containing product and the Monthly formulation is for patients already in established treatment with another buprenorphine-containing product (including the Weekly formulation).

Opioid use disorder 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 include non-drug (behavioral) treatment, as well as medication treatment 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. Methadone has been associated with fatal overdoses in patients and in their household contacts, including children.

Oral naltrexone (REVIA) and depot naltrexone (VIVITROL, which must be administered by a health care provider) 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. 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; additionally, this product is no longer marketed in the U.S..

In 2017, monthly subcutaneous depot formulation of buprenorphine (SUBLOCADE) was approved. Like Sublocade, Brixadi is a HCP-administered long-acting depot providing a sustained effective plasma level of buprenorphine over a prolonged period. Brixadi represents an additional option that has the potential to address several limitations of other existing treatments

The submitted clinical data show that the Brixadi weekly formulation, in doses of 24 mg and 32 mg, is able to block subjective effects of a clinically relevant dose of opioid agonist, more completely after the second weekly dose. Based on PK-PD analysis, the plasma levels delivered by the corresponding monthly doses are predicted to produce similar blockade. In a non-inferiority comparison to sublingual buprenorphine/naltrexone treatment, the effect of this blockade was shown to translate to clinical efficacy for a regimen beginning with weekly doses and transitioning to monthly doses, based the proportion of subjects whose drug use assessments met a pre- specified responder definition.

The systemic safety profile of buprenorphine is well-characterized, and the overall Brixadi safety profile appears similar. Analysis of dose-dependent adverse effects was hampered by the study design and the presentation of data but various explorations for dose-effects (in previous review cycles) did not identify concerning dose-limiting adverse effects in the doses currently proposed for marketing.

Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated at doses higher than studied in the clinical trial (16 mg weekly x 1) in a patient still dependent on a full agonist. Additionally, there may be circumstances under which the rapid discontinuation or dose reduction of buprenorphine might be desirable for a given patient. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with Brixadi for a period of time. Possibilities for surgical removal have not been explored. Patients developing intolerance to buprenorphine will require long-term monitoring by a health care professional. Foreign post-marketing to date suggests that inadequate dosing, particularly early in treatment, may be an issue for some patients. “Booster” doses to address this problem are described in labeling.

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 by ensuring healthcare settings and pharmacies are certified and only dispense Brixadi directly to a health care provider for administration by a healthcare provider.

Manufacturing quality issues which precluded approval of Brixadi (CAM2038) for use in the treatment of adult patients with moderate to severe OUD in previous review cycles have been resolved. Approval is recommended.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Opioid use disorder or OUD, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), 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 2020, the National Survey on Drug Use and Health determined that over 2.7 million Americans aged 12 and over met criteria for opioid use disorder in the past year. In 2021, the CDC reported that the estimated number of overdose deaths related to opioids in 2020 was 69,710. The most recent 2022 provisional mortality report from CDC indicated that 80,590 of the 107,000 drug overdose deaths in America, involved opioids. 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 for years, or even indefinitely.	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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	Current treatment options include non-drug (behavioral) treatment, as well as medication treatment with antagonists (naltrexone), agonists (methadone) or partial agonists (buprenorphine). o Behavioral treatment alone (individual or group counseling, self- help groups) is not effective for many patients. o 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 overdoses in patients and in their household contacts, including children. o Subdermal implant (PROBUPHINE)[1] 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. o Depot buprenorphine (SUBLOCADE) o 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. o 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 medications for OUD are subject to diversion, misuse, abuse and accidental pediatric exposure	An additional buprenorphine depot injection would be a desirable addition to the therapeutic armamentarium. o Convenience of weekly or monthly vs daily dosing; various doses offered o At steady state, provides consistent buprenorphine levels sufficient to block effects of exogenous opioids o May improve adherence o Reduces potential for diversion, misuse, abuse and accidental pediatric exposure o No surgical procedure needed

[1] No longer marketed in the US

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Evidence: The opioid blockade study, Study HS-13-478, demonstrated that after CAM2038 (weekly) injections of either 24 mg or 32 mg, on average, subjective effects of both 6 mg and 18-mg doses of hydromorphone were blocked in non-treatment-seeking subjects with OUD, although significant variation was seen across subjects. Dose-response analysis showed a decreasing number of outliers (unblocked responses) with increasing plasma levels, with very few outliers above a plasma level of 4 ng/ml. The pivotal efficacy trial, Study HS-11-421 (N=428) demonstrated that patients treated with a regimen of 12 weeks on individually determined doses of CAM2038 (weekly), followed by 12 weeks on individually-determined doses of CAM2038 (monthly) had a response rate non-inferior to patients treated with sublingual buprenorphine/naltrexone tablets (and placebo injections). CAM2038 is to be administered by a health care provider subcutaneously every week or month and provides advantages over daily dose medications for OUD in terms of patient adherence, patient convenience, and risks of abuse, misuse, and accidental exposure. Uncertainties: The design of the studies did not permit analyses by dose	CAM2038 24 mg weekly and CAM2038 32 mg weekly are capable of blocking the subjective effects of a clinically relevant dose of opioid agonist, and this blockade becomes longer-lasting after two weekly doses. The effect of this blockade was shown to translate to clinical efficacy as demonstrated by comparable outcomes in patients treated with a regimen of weekly followed by monthly CAM2038 compared with patients treated with sublingual buprenorphine/naloxone. Taken together, and considering the established efficacy of the reference product, Subutex, these studies provide substantial evidence of efficacy for CAM2038 in the treatment of moderate or severe OUD in patients who tolerate at least an initial test dose of buprenorphine. CAM2038 weekly is suitable for starting treatment, while CAM2038 (monthly) has been studied only in patients already in established treatment.
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. 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.) o In a safety database of 440 opioid-dependent patients, systemic effects of buprenorphine associated with	The systemic safety profile of buprenorphine is well-characterized, and the overall safety profile of CAM2038 appears to be similar. Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated too quickly in a patient still dependent on a full agonist. Cases of this nature have not been

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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 case was identified in the clinical development program One death occurred in a CAM2038-treated patient, due to a car-vs-pedestrian traffic accident Foreign post-marketing suggests that dose inadequacy may be an issue for some patients, requiring "booster" doses. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with CAM2038 for a period of time. Possibilities for surgical removal have not been explored. Patients developing intolerance to buprenorphine effects will require long-term monitoring by a health care professional. Buprenorphine itself can precipitate withdrawal if initiated in patients who are not yet in significant opioid withdrawal. For this reason, initial dosing is generally cautious and typically begins with a dose of 2 mg-4 mg. The starting dose of CAM2038 in the efficacy trial was divided over several visits in the first week of treatment. Clinicians may be interested in initiating CAM2038 more expeditiously, for example, administering a single 24 mg or 32 mg weekly injection at the first visit, or administering a monthly dose at the first visit. It is not known if this can be accomplished safely. CAM2038 forms a gel when injected. If patients obtain direct access to the product, there is a risk they may choose to attempt to inject the product intravenously. Notably, the consequences of intravenous injection of the contents of the pre-filled syringe are not known, it is	observed in post-marketing outside the U.S. Foreign post-marketing data suggest dose inadequacy may be an issue for some patients during titration. Additionally, there may be circumstances under which the rapid discontinuation or dose reduction of buprenorphine might be desirable for a given patient. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with CAM2038 for a period of time. It is not known whether there are possibilities for surgical removal. Patients developing intolerance to buprenorphine effects will require long- term monitoring by a health care professional. A REMS is required to ensure that CAM2038 is not distributed directly to patients, and is administered by a health care professional, to mitigate the risk of serious consequences should the product be administered intravenously.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	anticipated that there is a risk of occlusion, tissue damage, and emboli.	

2. Introduction

This is the fifth review cycle for NDA 210136 (CAM2038, proposed proprietary name Brixadi). The application was initially submitted in July 2017. Because of the potential for a depot product to mitigate risks of abuse, diversion, and accidental pediatric exposure associated with oral transmucosal buprenorphine, the application was granted a priority review because no depot formulations had been approved at the time of submission. At the conclusion of the first application cycle, NDA 210136 received a Complete Response (CR) letter. The January 19, 2018, CR letter cited significant manufacturing issues as well as concerns about the clinical datasets.

The second resubmission, submitted June 2018, adequately addressed the deficiencies of the first submission. However, between the two submissions, NDA 209819 (Sublocade, Indivior), a monthly extended-release buprenorphine injectable product, was approved for marketing and blocked the marketing of the Brixadi Monthly product because of Hatch/Waxman drug product exclusivity. The Division discussed options regarding the labelling and marketing of the Brixadi Weekly formulation. However, the Applicant chose to wait to market the Weekly formulation until the product exclusivity on Sublocade expired and agreed to resubmit NDA 210136 in 2020. Thus, the second submission for NDA 210136 received a tentative approval (TA) letter on December 28, 2018.

Between the first and third submissions for NDA 210136, the manufacturer of Brixadi, Camurus, with whom Braeburn has a marketing partnership, received marketing approval for the product under the proprietary name Buvidal (CAM2038) in November 2018, for the treatment of OUD in the European Union, European Economic Area, Australia and the United Kingdom. Since then, marketing authorizations have expanded. At the time of this review, marketing authorizations have been received in New Zealand (March 2021), Israel (December 2021), and Lebanon (February 2022). Marketing Authorization Applications are currently under review in United Arab Emirates, Tunisia, and Saudi Arabia. With this submission, updated safety information based on Camurus' marketing experience, as well as safety findings from ongoing and completed studies sponsored or supported by Braeburn are summarized.

During the third review cycle, submitted June 2020, the manufacturing facilities were inspected as part of a pre-approval inspection (PAI) for an NDA unrelated to this one, and significant Good Manufacturing Practice (GMP) deficiencies were identified. The manufacturing company (Pii) made an internal decision to shut-down those manufacturing facilities to address the deficiencies. However, after an October 2020 re-inspection, two 483 forms were issued to the manufacturer. The deficiencies in those forms covered (b) (4) It was unclear how the inspectional findings might directly impact the manufacturing of the Brixadi drug product, but the manufacturing deficiencies could not be resolved. The facility was determined to be "Official Action Indicated" (OAI) and Office of Pharmaceutical Manufacturing Assessment (OPMA) issued a recommendation to withhold approval. Therefore, the application received a

complete response (CR) letter on December 01, 2020 due to inadequacies related to manufacturing.

Similarly, During the fourth review cycle, submitted June 2021, the manufacturing facilities were inspected as part of a PAI for an NDA unrelated to this one, and significant GMP deficiencies were again identified. It remained unclear how the inspectional findings might directly impact the manufacturing of Brixadi, but the manufacturing deficiencies could not be resolved. The facility was determined again to be OAI and OPMA issued a recommendation to withhold approval. Therefore, the application received a CR letter on December 14, 2021 for inadequacies related to manufacturing.

In summary, this submission includes a manufacturing update and safety update from foreign post-marketing data. A new inspection was undertaken in conjunction with this submission and the manufacturing issues were adequately addressed, supporting approval of this application.

Product Overview
The Brixadi products include two modified-release formulations of buprenorphine in a novel Fluid Crystal technology designed for administration by subcutaneous (not intramuscular) injection to be provided ready-for-use in a prefilled syringe for the treatment of moderate-to-severe opioid use disorder (OUD) in adults. This product is available in weekly and monthly formulations, each of which contains different doses and excipients.

Table 1: Proposed Doses of the Brixadi 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		
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: Clinical Reviewer

The Brixadi Weekly formulation, at the 24 mg and 32 mg doses, respectively, provides sustained plasma levels of buprenorphine intended to block the effects of exogenous opioids over 7 days. Based on pharmacokinetic data, the Brixadi Monthly formulation is predicted to block exogenous opioids for at least 28 days. Brixadi Weekly is intended for the treatment of moderate-to-severe opioid use disorder (OUD) in patients who have tolerated at least a test dose of transmucosal buprenorphine, and Brixadi Monthly product was studied in patients who are transferring from an oral-transmucosal buprenorphine product or the Brixadi Weekly formulation. The products are intended to be used as part of a complete treatment plan to include counseling and psychosocial support. Table 2 identifies the corresponding dose of BRIXADI when switching a patient from transmucosal buprenorphine to BRIXADI (weekly) or BRIXADI (monthly), expressing the transmucosal dose equivalents in terms of Subutex or Suboxone doses. Table 3 shows how patients may be transitioned between doses of both Brixadi product formulations. Both tables are adapted from proposed drug product labeling. For dose adjustments, an additional Brixadi Weekly 8 mg injection may be administered, based on clinical judgment during a dosing interval, for a total dose of up to a maximum dose of 32 mg per week of Brixadi Weekly or 128 mg per month of Brixadi Monthly.

Table 2: Daily Doses of Sublingual Buprenorphine (Subutex, Suboxone, or Generic Product Equivalents) and Suggested Corresponding BRIXADI (Weekly) or BRIXADI (Monthly) Doses

Daily dose of sublingual buprenorphine	BRIXADI (weekly)	BRIXADI (monthly)
≤ 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

Note: One SUBOXONE® (buprenorphine and naloxone) 8 mg/2 mg sublingual tablet provides equivalent buprenorphine exposure to one SUBUTEX® (buprenorphine HCl) 8 mg sublingual tablet (b) (4) (b) (4) or one Zubsolv® (buprenorphine and naloxone) 5.7 mg/1.4 mg sublingual tablet.

Table 3: Recommended Dose When Transitioning Between BRIXADI (Weekly) and BRIXADI (Monthly)

BRIXADI (weekly)	BRIXADI (monthly)
16 mg	64 mg
24 mg	96 mg
32 mg	128 mg

(b) (4)

Comparison of exposures after CAM2038 doses to exposures after sublingual buprenorphine demonstrate that, at steady-state (4th injection), CAM2038 (weekly) and monthly deliver plasma concentrations (Cavg,ss) that are higher than the corresponding dose of sublingual buprenorphine in Braeburn's proposed conversion scheme. Based on plasma levels (see Table 4

below), the efficacy would be anticipated to be at least non-inferior to, if not superior to, the corresponding doses.

Table 4: Summary of Steady-State PK Parameters of Buprenorphine After Subcutaneous Buttock Injections of Brixadi (Weekly), Brixadi (Monthly), and SL Administration of SUBUTEX

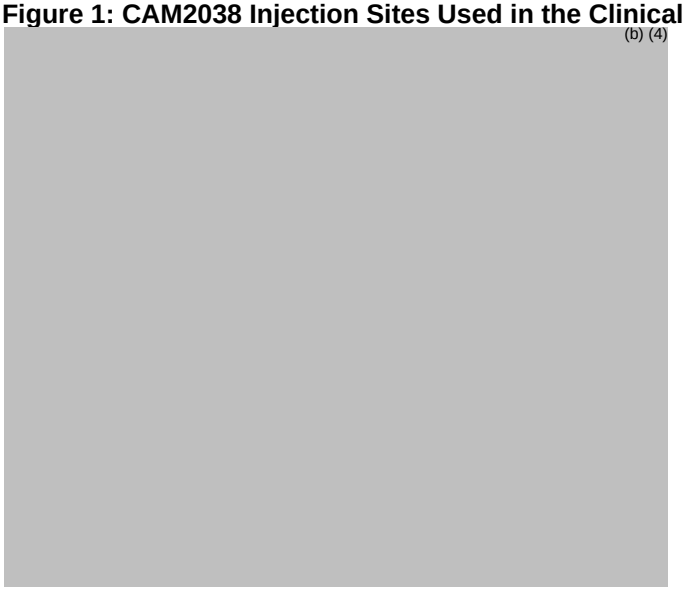
Drug product dose			C_{av} (ng/mL)			$C_{max,ss}$ (ng/mL)			C_{trough} [a] (ng/mL)		
SL BPN	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly
8 mg	16 mg	64 mg	1.2	2.1	2.0 $	4.7	4.3	4.0 $	0.7	0.8	1.3 $
16 mg	24 mg	96 mg	1.8	2.9 $	2.9 $	6.5	5.5 $	6.0 $	1.0	1.4 $	2.0 $
24 mg	32 mg	128 mg	2.5	4.2	3.9	8.2	6.9	11.1	1.4	2.6	2.1

Average value of two studies
$ Simulated
a C168h for BRIXADI (weekly), C28d for BRIXADI Monthly and C24h for Subutex

As with the previous submissions, 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 were proposed (Figure 1)[2] based on the injection sites used in the clinical program. No new sites were proposed. 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, during the clinical development program, it was poorly palpable in the subcutaneous space and diffuses into the surrounding tissue over time, leaving no mass behind. Injection site mass has, however, been reported in foreign post-marketing experience. This product is not intended to be self-administered.

[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 initial submission) after review of additional data. It is not recommended for initiation of dosing.

Figure 1: CAM2038 Injection Sites Used in the Clinical Studies



Source: page 27, Applicant's Manual of Procedures, 2018

3. Background

Buprenorphine is a partial agonist at the μ-opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain, and two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence[3]. Three other transmucosal formulations, a six-month, surgically-placed implant, and a monthly depot formulation have subsequently been approved for opioid dependence, as well as one transdermal product and one transmucosal product for pain. Approximately (b) (4) million prescriptions from outpatient retail pharmacies were dispensed and approximately (b) (4) million patients received a dispensed prescription for buprenorphine-containing tablets or film labeled for MAT during 2019. Primary care physicians accounted for 34% of dispensed prescriptions, followed by nurse practitioners (14%), psychiatrists (14%), osteopathic physicians (12%), and all others (26%).

As a partial agonist, buprenorphine produces less euphoria compared to full agonists and has an improved safety profile with respect to effects on respiration. In addition to the improved safety profile, at sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, deterring abuse of opioids by buprenorphine-maintained patients. Unfortunately, despite these features of improved safety and abuse deterrence, buprenorphine sublingual products have been increasingly identified in the illicit drug market, and it is known

[3] Subutex, buprenorphine sublingual tablets (Reckitt Benckiser (now Indivior) NDA 20732) and Suboxone, buprenorphine/naloxone sublingual tablets (Reckitt Benckiser (now Indivior) 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.

that they are diverted, abused, and misused. Additionally, they have been implicated in a number of cases of accidental poisonings of small children. Therefore, an additional depot injection which would be difficult to divert or abuse, would be less likely to be accidentally ingested by small children and offers potential advantages. In addition, a depot or implantable product that provides a sufficient plasma level of buprenorphine to block the effects of exogenous opioids, would enforce compliance so that patients could not periodically discontinue use to allow the blocking effect to dissipate in order to experience the effects of their opioids of choice. Importantly, some patients also express a preference for a long-acting treatment that reduces fluctuations in plasma levels and removes the need to think daily about taking medication.

3.1. Clinical Development of CAM2038

The clinical development of CAM20388 was undertaken with advice from the Division and was described in previous reviews. The program comprised PK studies, an inpatient opioid blockade study (HS-13-478) and a randomized, double-blind, double-dummy, active-control efficacy study (HS-11-421).

No additional information was submitted with this cycle.

3.2. Safety Concerns Related to Formulation

One potential risk associated with Brixadi, which differentiates it from transmucosal formulations of buprenorphine, is the concern that serious consequences could ensue if the product were injected intravenously. A Risk Mitigation and Evaluation Strategy (REMS) is proposed to ensure that the product is administered appropriately. Preclinical data reviewed in the previous two application submissions, suggested that if the drug product were to be administered intravenously, it would either gel rapidly and potentially block the injected vessel as it apparently did in preclinical studies (i.e., the rat tail vein), or, if the injected vein is larger and the product does not gel quickly enough, it could result in a lung embolus or eventually be lodged in other small capillaries. This raised a safety concern about the possible consequences of this type of misuse, which could involve occlusion, tissue damage, or possibly embolus. Available post-marketing data from the Buvidal program has not revealed adverse events associated with intravenous injection. However, the Buvidal product is also marketed under a restricted distribution (similar to the proposed REMS) to mitigate potential risk.

3.3. Legal and Regulatory Issues Constraining Buprenorphine Treatment

Buprenorphine is a Schedule III Controlled Substance and physicians prescribing buprenorphine must comply with the relevant aspects of the Controlled Substances Act. In addition, the provision of agonist treatment of opioid addiction is governed by certain legal requirements. Methadone treatment of opioid addiction is delivered in a closed distribution system (opioid treatment programs, OTPs) that originally required special licensing by both Federal and State authorities, under the Narcotic Addict Treatment Act of 1974 (NATA).

Unlike methadone, buprenorphine may be prescribed by health care providers outside the OTP system. The Drug Addiction Treatment Act of 2000 (DATA 2000), created an option for qualifying physicians to obtain a waiver (colloquially, "the X waiver") from the special registration requirements of the NATA to prescribe buprenorphine for OUD in office-based practice[4]. However, under the Consolidated Appropriations Act of 2023[5], new provisions allowing all DEA-licensed providers to prescribe buprenorphine were established. Therefore, Brixadi may be prescribed by any DEA-licensed prescriber and no X-waiver is required.

4. Product Quality

The CAM2038 FluidCrystal subcutaneous injection depot drug product is a sterile, yellowish to yellow clear liquid which is (b) (4) 1 mL long clear glass syringes with grey plungers.

Figure 2: Visual of Combination Product

(b) (4)

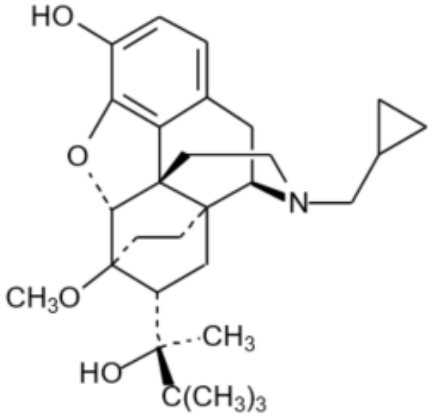
It is a lipid-based parenteral (subcutaneous injection) extended-release product (once weekly or once monthly dosing) based on the proprietary FluidCrystal (hereinafter denoted FC) injection depot technology.

The active ingredient in CAM 2038 is buprenorphine free base, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist. The molecular weight of buprenorphine free base is 467.6, and its molecular formula is C29H41NO4. Chemically, buprenorphine is (2S)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3- hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol. The structural formula is shown below.

[4] The Comprehensive Addiction and Recovery Act (CARA) of 2016 (P.L. 114-198) extended the privilege of prescribing buprenorphine in office-based settings to qualifying nurse practitioners (NPs) and physician assistants (PAs).

[5] The Consolidated Appropriations Act incorporated the Mainstreaming Addiction Treatment (MAT) Act, which removed the requirement for notification to SAMHSA and receipt of a waiver from DEA to prescribe buprenorphine, and the Medication Access and Training Expansion (MATE) Act, which created new training requirements linked to obtaining or renewing a DEA license to prescribe controlled substances.

Figure 3: Structural Formula of Buprenorphine



The CAM2038 q1w (weekly) solution consists of 50 mg buprenorphine base (BUP)/mL, 10% w/w ethanol (EtOH) and Soybean Phosphatidylcholine (SPC)/Glycerol Dioleate (GDO) in the weight ratio 50/50 to final volume. The CAM2038 q4w Monthly solution consists of 356 mg buprenorphine base (BUP)/mL, 30% w/w N-methyl-2-pyrrolidone (NMP), and SPC/GDO in the weight ratio 40/60 to the final volume. The injection products utilizing the lipid-based formulations are low viscosity liquids. When the product is injected into the subcutaneous tissue, the formulation absorbs interstitial aqueous body fluid and transforms the liquid to a highly viscous gel. According to the applicant, (b) (4) CAM2038 q1w and CAM2038 q4w drug product. No changes were made to or issues identified with the manufacturing of the drug substance. Similarly, no changes were made to the previously acceptable method and method validation data (b) (4) Refer to previous NDA reviews for buprenorphine composition data for the doses of CAM2038 q1w and CAM208 q4w formulations as well as stability and specification data (which is unchanged from the previous review).

As with previous review cycles, part of the manufacturing process for Brixadi is completed at two facilities:

1. Pharmaceutics International, Inc. (b) (4) | FEI: 3006503102 | DUNS: 049185696
2. Pharmaceutics International, Inc. (b) (4) | FEI: 1000513101 | DUNS: 878265586

In July 2020, these two facilities were inspected and significant Good Manufacturing Practice (GMP) deficiencies were identified as part of a pre-approval inspection (PAI) for an NDA unrelated to this one. The company (Pii) made an internal decision to shut-down those manufacturing facilities to address the deficiencies. After an October 2020 re-inspection, two 483 forms were issued to the manufacturer. The deficiencies in those forms covered (b) (4) The facilities were determined to be "Official Action Indicated" (OAI) and the

Office of Pharmaceutical Manufacturing Assessment (OPMA) issued a recommendation to withhold approval of NDA 210136.

During the last application review cycle, a PAI (reinspection) at the two facilities was conducted for NDA 210136 (and other applications) between July 26 and Sep 29, 2021. Deficiencies were identified (b) (4) The Applicant contracted with a third party, (b) (4) (b) (4) to provide in-person oversight of the manufacturing process. OPMA acknowledged receipt of those submissions, but due to the ongoing issues addressed during inspection, a recommendation for approval could not be made. It remained unclear if the manufacturing of Brixadi was directly impacted, but the conditions of the site were not favorable for safe manufacturing and OPMA issued a recommendation to withhold approval of NDA 210136.

With this submission, another PAI was conducted at the two Pii facilities for NDA 210136 (and other applications) in 2022. The previous inspectional findings had been addressed. The outcome of the follow-up inspection has been finalized as VAI and OPMA recommended approval of both the drug product manufacturing facility and the associated testing facility.

5. Nonclinical Pharmacology/Toxicology

The previous Pharmacology/Toxicology reviews focused on the safety of the CAM2038 formulations, and the two novel excipients, N-methyl-pyrrolidone (NMP), found in the monthly product, and glycerol dioleate (GDO), a diglyceride, found in both products. Additional details from the first two application cycles can be found in the Pharmacology/Toxicology reviews conducted by Gary Bond, PhD, Jaime D'Agostino, PhD, and Elizabeth Bolan, PhD In the second review cycle, the Applicant submitted new extractable leachable data and published and unpublished reproductive and developmental toxicity studies with NMP in lieu of new studies to address the deficiencies identified in the first review cycle. However, at the conclusion of that cycle, the review team identified two remaining concerns related to leachables, and two remaining concerns related to the reproductive and developmental toxicity of NMP that could be addressed through post-marketing requirements (PMRs). For the former, the Pharmacology/Toxicology review noted that the majority of previously identified leachables were adequately qualified and that the levels of the unidentified compounds in the formulations were predicted to be low. For the latter, the Pharmacology/Toxicology review noted the findings from the published reproductive and developmental toxicity studies with NMP would be included in labeling, and definitive GLP studies should be completed as PMRs. With the second resubmission (i.e., third review cycle), the Applicant submitted the results of fertility and early embryonic development (FEED) study in female rats testing NMP and a pre- and post-natal development (PPND) study in rats testing NMP to address the two reproductive and developmental toxicology study requirements that we communicated previously that could be submitted post marketing. Based on the third review cycle Pharmacology/Toxicology review conducted by Dr. Grace Lee, PhD, the FFED and PPND studies demonstrated there were no adverse NMP-related effects on the relevant parameters at up to 377 times the human

exposure; therefore, from the nonclinical perspective, the NDA may be approved without additional PMRs to conduct these studies. However, the Applicant has not submitted adequate leachable data or the elemental impurity evaluation to date and therefore these studies should be completed as PMRs. Refer to the PMR section of this review for the remaining nonclinical PMRs.

6. Clinical Pharmacology

No new clinical pharmacology information was submitted with this review cycle. The following summary of clinical pharmacology is based on the Clinical Pharmacology review conducted by Suresh Narahisetti, PhD. during the first two review cycles, and on the language proposed by the Division for drug labeling in the second cycle.

In Dr. Narahisetti's 2018 Clinical Pharmacology review, it was noted that trough levels of Brixadi from the upper arm site failed to meet the set bioequivalence criteria for 80 to 125% (see Table 4 and Table 7 and in the proposed label). To ensure expeditious attainment of therapeutic trough levels, the upper arm is not recommended as a site for initiation of Brixadi dosing but may be used in patients already at steady-state. This change was agreed upon at the conclusion of the second review cycle. The indented text in Arial font below is based on the Division's recommended labeling language specifically for Brixadi for this review cycle:

> Absorption
> BRIXADI is an extended-release formulation of buprenorphine designed for subcutaneous administration. BRIXADI is available in two regimens: weekly and monthly. Following single doses of BRIXADI (weekly) or BRIXADI (monthly), the buprenorphine C_{max} and AUC_{inf} increase dose-proportionally.
>
> The steady-state PK of buprenorphine following BRIXADI (weekly), BRIXADI (monthly) and their comparison to sublingual SUBUTEX across three studies are shown in Table 5. In these studies, BRIXADI (weekly) was administered for 4 or 4 to 7 weekly doses, BRIXADI (monthly) was administered for 4 monthly doses, and SUBUTEX was administered for 7 daily doses.
>
> After BRIXADI subcutaneous injection, the buprenorphine plasma concentration increases with a median time to maximum plasma concentration (t_{max}) of about 24 hours for the weekly BRIXADI and 6-10 hours for monthly BRIXADI. Based on trough levels after each dose, steady-state exposure is reached just prior to administration of the fourth weekly or monthly dose.
>
> After four repeated doses of BRIXADI (weekly) (16 mg) $AUC\tau$ (0-7d), C_{max} and C_{trough} values are ~40% higher exposure compared to the first dose. Based on cross-study comparisons, four repeated doses of BRIXADI (monthly) (128 mg) results in 68%, 65%, and 124% higher $AUC\tau$ (0-28d), C_{max} and C_{trough} values, respectively compared to the first dose.

Table 5: Summary of Steady-State PK Parameters of Buprenorphine After Subcutaneous Buttock Injections of BRIXADI (Weekly) and BRIXADI (Monthly) and SL Administration of SUBUTEX

Drug product dose			C_{av} (ng/mL)			$C_{max,ss}$ (ng/mL)			C_{trough}[a] (ng/mL)		
SL BPN	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly
8 mg	16 mg	64 mg	1.2	2.1	2.0 $	4.7	4.3	4.0 $	0.7	0.8	1.3 $
16 mg	24 mg	96 mg	1.8	2.9 $	2.9 $	6.5	5.5 $	6.0 $	1.0	1.4 $	2.0 $
24 mg	32 mg	128 mg	2.5	4.2	3.9	8.2	6.9	11.1	1.4	2.6	2.1

Source: Table 7, Physician Package Insert
* Average value of two studies
$ Simulated
a C168h for BRIXADI (weekly), C28d for BRIXADI (monthly) and C24h for Subutex

Effect of injection Site on PK of BRIXADI

After multiple dose subcutaneous injections of 32 mg BRIXADI weekly product at different injection sites (abdomen, thigh, buttock or upper arm), a comparable PK exposure was observed. However, injection in the arm site was associated with approximately 10% lower plasma levels than other sites.

Distribution:

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Elimination:

Buprenorphine is metabolized and eliminated in urine and feces. The apparent terminal plasma half-life of buprenorphine following subcutaneous injection of BRIXADI ranged between 3 to 5 days for BRIXADI (weekly) and 19 to 26 days for BRIXADI (monthly) as a result of the slow release of buprenorphine from the subcutaneous depot.

Metabolism:

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity.

Norbuprenorphine steady-state plasma concentrations in humans after subcutaneous injection of BRIXADI (weekly or monthly) are low compared to buprenorphine (AUC norbuprenorphine/ buprenorphine ratio of 0.35).

Excretion:

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and

two unidentified buprenorphine metabolites. In urine, most of the buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Specific Populations

Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of BRIXADI has not been studied. In a pharmacokinetic study, the disposition of buprenorphine was determined after administering a 2.0/0.5 mg Suboxone (buprenorphine/naloxone) sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine in patients with hepatic impairment was compared to disposition in subjects with normal hepatic function.

In subjects with mild hepatic impairment, the changes in mean $C_{max,}$ $AUC_{0\text{-last}}$, and half-life values of buprenorphine were not clinically significant. For subjects with moderate and severe hepatic impairment, mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine were increased *[see Warnings and Precautions (5.14) and Use in Specific Populations (8.6)].*

Renal Impairment
The effect of renal impairment on the pharmacokinetics of BRIXADI has not been studied. Clinical studies of BRIXADI did not include subjects with severe renal impairment. Less than 1% is excreted as unchanged buprenorphine in urine following IV buprenorphine administration. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine [*see Use in Specific Populations (8.7)].*

Population PK analyses indicated no notable relationship between creatinine clearance and steady-state buprenorphine plasma concentrations.

HCV infection
In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine were not clinically significant in comparison to healthy subjects without HCV infection.

7. Clinical Microbiology

N/A

8. Clinical/Statistical- Efficacy

Evidence of efficacy for Brixadi Weekly and Monthly doses derive from two studies, an inpatient opioid blockade study (HS-13-478) and a randomized, double-blind, double-dummy, active-control efficacy study (HS-11-421). The blockade study demonstrated that CAM2038 24 mg weekly and CAM2038 32 mg weekly are capable of blocking the subjective effects of a clinically-relevant dose of opioid agonist, and this blockade becomes longer-lasting after two weekly doses. The effect of this blockade was shown to translate to clinical efficacy as demonstrated by comparable outcomes in patients treated with a regimen of weekly followed by monthly CAM2038 compared with patients treated with sublingual buprenorphine/naloxone in the double-blind study.

Taken together, and considering the established efficacy of the reference product, Subutex, these studies provide substantial evidence of efficacy for CAM2038 in the treatment of moderate or severe OUD in patients who tolerate at least an initial test dose of buprenorphine. CAM2038 weekly is suitable for starting treatment, while CAM2038 (monthly) has been studied only in patients already in established treatment.

The text below briefly summarizes the design and findings of these two studies using labeling language proposed by the Division. Additional detail may be found in reviews from the previous review cycles. No new efficacy data were submitted for this cycle.

8.1. Blockade study (HS-13-478)

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 indented text in Arial font below is based on the Division's recommended labeling language for this review cycle. Refer to the primary review of the blockade study, performed by CSS Medical Officer, Dr. Alan Trachtenberg, and Biostatistics Reviewer, Wei Liu, from the first review cycle (2017); and the Pharmacometrics section of the Clinical Pharmacology review, performed by Dr. Michael Bewernitz, for additional information.

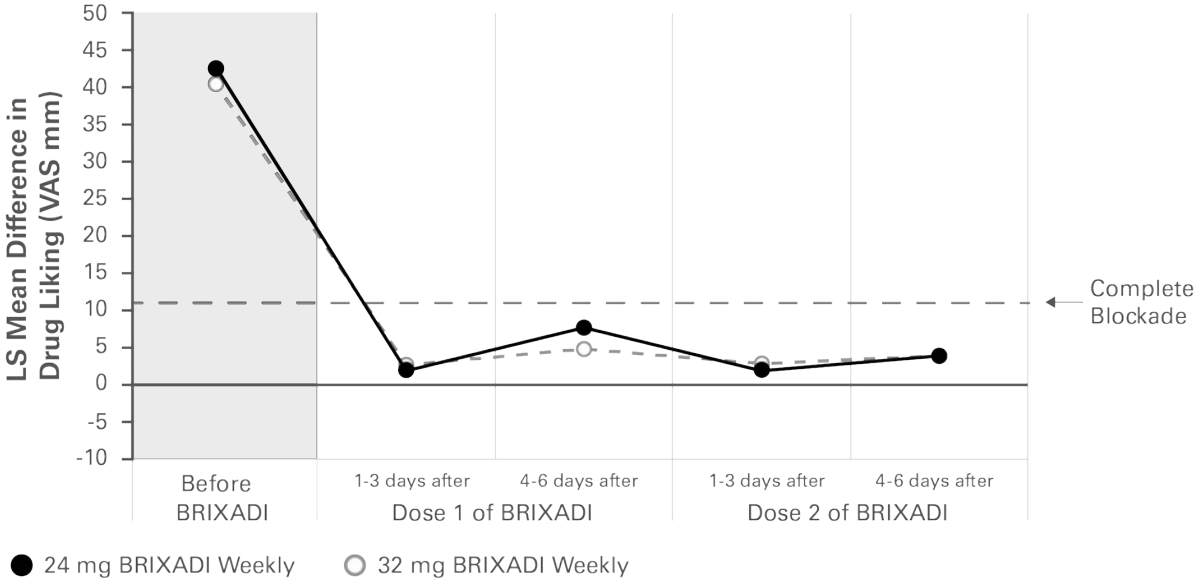
> The opioid blockade study assessed the blockade of subjective opioid effects, PK, and safety of BRIXADI weekly in 47 patients with moderate or severe opioid use disorder. Forty-six patients completed the study. Subjects were randomized to receive two injections of BRIXADI (weekly) once weekly for 2 weeks either at a 24 mg or 32 mg dose level.
>
> After stabilization on immediate-release morphine, all patients completed a 3-day qualification/baseline hydromorphone (HM) challenge session, which included intramuscular administration of 3 doses of HM (0 mg [placebo], 6 mg and 18 mg) once daily for 3 consecutive days. Patients were not exposed to buprenorphine during the baseline/qualification phase.

Following the qualification phase, eligible patients were randomly assigned to receive 2 doses of either 24 mg (22 patients) or 32 mg (24 patients) BRIXADI (weekly) with each dose administered one week apart. Two HM challenge sessions (Days 1-3 and 4-6 for the first session and Days 8-10 and 11-13 for the second session, respectively) were conducted after each dose of BRIXADI (weekly).

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

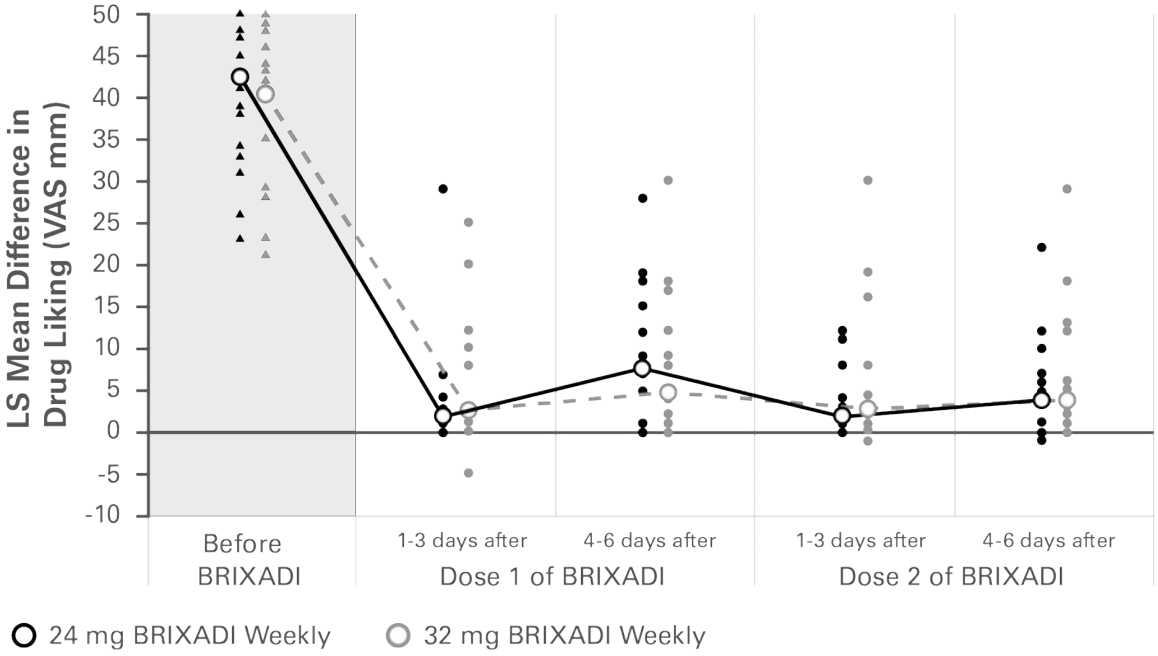
During the qualification/baseline phase, mean E_{max} scores for placebo were neutral while intramuscular hydromorphone 6 and 18 mg produced dose-related increases in the scores. Beginning with the first injection of BRIXADI (weekly) 24 mg or 32 mg weekly, no active intramuscular hydromorphone dose resulted in a mean drug liking VAS E_{max} score of 11 mm or greater when compared to placebo, which demonstrated complete blockade that was sustained throughout the first and second dosing intervals (see Figure 3). Individual subject scores are shown in Figure 4.

Figure 4: Mean Difference in Placebo-Corrected Peak Drug Liking



Source: Figure 15, Physician Package Insert

Figure 5: Mean Difference in Placebo-Corrected Peak Drug Liking With Individual Scores



Source: Figure 16, Physician Package Insert

Abuse

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

BRIXADI contains buprenorphine, a Schedule III controlled substance that can be abused similar to other opioids. Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with or referred for more intensive and structured treatment. Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines [see Warnings and Precautions (5.5)].

BRIXADI is distributed through a restricted distribution program, which is intended to prevent the direct distribution to a patient. BRIXADI should only be dispensed directly to a healthcare provider for administration by a healthcare provider. It is supplied in prefilled syringes and is intended for administration only by subcutaneous injection by a healthcare provider. The entire contents of the prefilled syringe should be administered.

Upon injection, BRIXADI spontaneously transforms from a low viscous solution to a liquid crystalline gel that encapsulates buprenorphine and releases it at a steady rate as the depot biodegrades [see Warnings and Precautions (5.1)].

Clinical monitoring for evidence at the injection site of tampering or attempting to remove the depot should be ongoing throughout treatment. No attempts to remove BRIXADI have been reported in clinical trials.

Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. Monitor patients during discontinuation of BRIXADI for symptoms of withdrawal [see Warnings and Precautions (5.8)].

Due to the long-acting nature of BRIXADI, withdrawal signs and symptoms may not be evident immediately following the discontinuation of treatment.

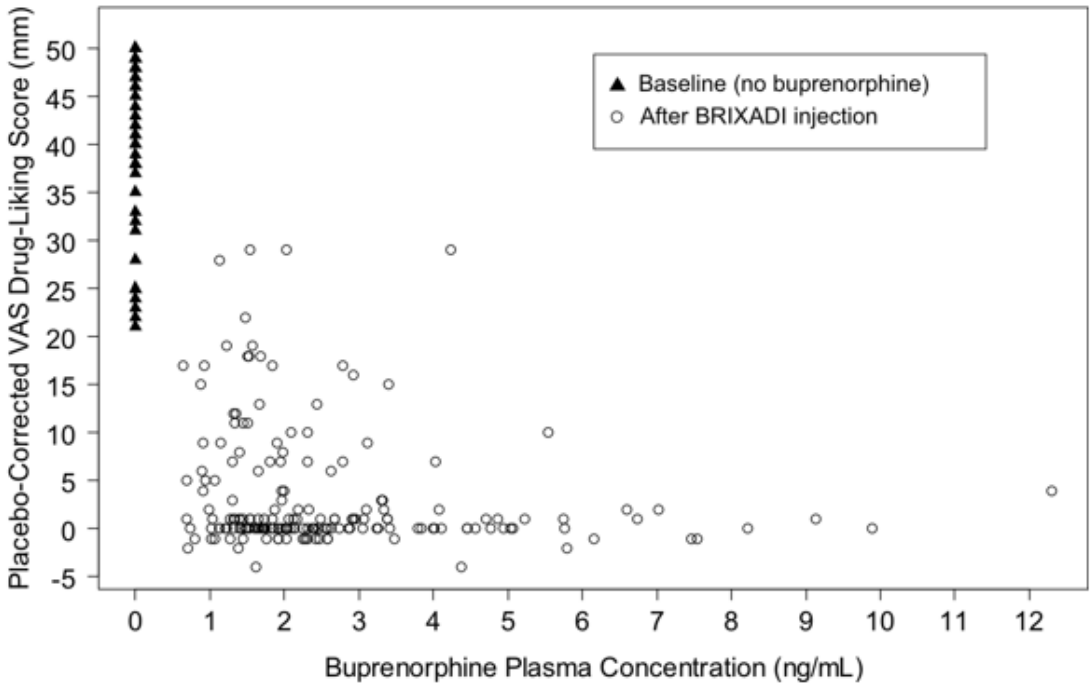
Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy [see Warnings and Precautions (5.6)].

Opioid Blockade

The opioid blockade study assessed the blockade of subjective opioid drug-liking effects and pharmacokinetics (PK) of BRIXADI (weekly) in 47 patients with moderate or severe opioid dependence. The primary endpoint was the maximum rating (Emax) on the visual analogue scale (VAS) for drug-liking. After stabilization on immediate-release morphine, all patients completed a 3-day qualification/baseline hydromorphone challenge session consisting of 3 intramuscular doses of hydromorphone (0 mg, [placebo], 6 mg, and 18 mg) once daily for 3 consecutive days in a randomized, double-blind, crossover manner. Following the qualification phase, eligible patients received 2 injections of BRIXADI (weekly) for two weeks at either the 24 mg or 32 mg level. Two hydromorphone challenge sessions (3 consecutive days each) were conducted throughout the week after each weekly injection of BRIXADI (weekly). On average, the subjective effects (e.g., drug liking [Emax]) of 6 mg or 18 mg hydromorphone was blocked following injections of BRIXADI (weekly) at the 24 mg or 32 mg levels. The variability in drug-liking scores was wider for the 18 mg than the 6 mg hydromorphone dose level. In addition, for the 18 mg hydromorphone dose challenge, the drug-liking score variability was wider towards the end of the BRIXADI (weekly) dosing interval compared to earlier in the interval (e.g. Days 4-6 versus Days 1-3; Day 11-13 versus Day 8-10). Drug-liking score variability was wider for the 24 mg BRIXADI (weekly) dose level compared to 32 mg [see Clinical Studies (14.1)]. Figure 14 illustrates the relationship between buprenorphine plasma level and drug liking after 18 mg

hydromorphone where data from the 24 mg BRIXADI (weekly) arm is pooled with data from the 32 mg BRIXADI (weekly) arm. The observed plateau for maximal response of drug-liking was reached at buprenorphine concentrations of approximately 1.5-2 ng/mL plasma levels.

Figure 6: Placebo-Corrected Drug Liking VAS vs. Plasma Buprenorphine Concentration Following 18 mg Hydromorphone Challenges for Pooled 24 mg and 32 mg Arms, From Proposed Drug-Labeling



Source: Figure 14, Physician Package Insert

8.2. Efficacy Study (HS-11-421)

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 indented text in Arial font below is based on the Division's recommended language for section 14.2 of the proposed drug label for this review cycle. Refer to the 2018 CDTL memo and the reviews conducted by Dr. Gioia Guerrieri (clinical) and Dr. James Travis (statistical) for additional information.

The efficacy and safety of BRIXADI for the treatment of opioid use disorder was evaluated in a Phase 3, 24-Week, randomized, double-blind, double-dummy, active-controlled, multicenter study in patients who met the DSM-5 criteria for

moderate or severe opioid use disorder and who were actively seeking but not currently receiving buprenorphine treatment. Patients were randomized to receive either BRIXADI injections with placebo sublingual tablets or sublingual buprenorphine/naloxone (SL BPN/NX) tablets with placebo injections. All patients received individual drug counseling for the duration of the study.

On the first day of treatment patients received an open-label 4 mg test dose of sublingual buprenorphine. Patients who tolerated the test dose (two patients did not tolerate the test dose) were randomized and given a 16 mg injection of BRIXADI (weekly) or matched placebo. During the next 6 days patients were allowed up to two further 8 mg injections as needed. Patients received an injection of 16, 24, or 32 mg on Day 8 matched to the dose they received in the previous seven days. Patients received injections weekly (every 7 days +/- 2-day window) for twelve weeks total and then transitioned to an equivalent dose of BRIXADI (monthly) (every 28 days, +/- 7-day window) for the remaining twelve weeks. Dose adjustments were permitted for the duration of the study. Supplemental 8 mg BRIXADI (weekly) injections were allowed during the second phase of the study and were also used in the active-controlled group. Overall, supplemental 8 mg injections were given to 14 patients (6.6%) in the BRIXADI arm and 17 patients (7.9%) in the SL BPN/NX arm. Table 6 shows the doses of BRIXADI (weekly) administered following the initial titration period and at the final visit before transition to BRIXADI (monthly) was allowed. Table 7 shows the first and final BRIXADI (monthly) dose administered to each patient.

Table 6: Number of Patients Receiving Each BRIXADI (Weekly) Dose at Selected Time-Points

BRIXADI (Weekly) Dose	Following Titration Period	End of Weekly Phase
16 mg	2	6
24 mg	128	84
32 mg	54	64

Table 7: Number of Patients Receiving Each BRIXADI (Monthly) Dose at Selected Time-Points

BRIXADI (Monthly) Dose	First BRIXADI (Monthly) dose	Final BRIXADI (Monthly) dose
64 mg	8	11
96 mg	84	83
128 mg	66	56
160 mg*	0	8

*not an approved strength
Source: Tables 8 and 9, Physician Package Insert

For the first twelve weeks patients completed weekly visits. For the final twelve weeks patients were transitioned to monthly visits. Patients were also required to complete three additional randomly scheduled visits during the final twelve weeks. Efficacy was evaluated using urine drug screens combined with self-reported use of illicit opioid use. Missing urine drug screen samples and/or self-reports were counted as positive for illicit opioids.

A total of 428 patients were randomized equally (215 patients in the SL BPN/NX group and 213 in the BRIXADI group). Of the randomized patients, 69.0% (147/213) of the patients in BRIXADI treatment group and 72.6% (156/215) of the patients in the SL BPN/NX treatment group completed the 24-week period. Patient demographics and baseline characteristics are provided in Table 8.

Table 8: Patient Demographics and Baseline Characteristics

	BRIXADI (N=213)	SL BPN/NX (N=215)
Mean Age (Years)	38.7	38.0
Sex %		
Male	56.8	66.0
Female	43.2	34.0
Race or Ethnicity %		
White	74.6	76.3
Black or African American	22.1	22.3
American Indian or Alaska Native	0.9	0.5
Asian	0.5	0
Native Hawaiian or Other Pacific Islander	0.5	0
Other	1.4	0.9
Primary Opioid of Use at Initiation %		
Heroin	71.4	70.2
Prescription Pain Reliever	28.6	29.8
Injectable Route %	53.5	51.2
Substance Use by Urine Toxicology Prior to Randomization %		
Amphetamines	22.1	18.6
Barbiturates	1.4	0.5
Benzodiazepine	21.1	21.9
Cocaine	30.5	32.6
Cannabinoids	34.3	36.3
Fentanyl	29.1	22.8
Phencyclidine	1.9	0.5
Medical History %		
Anxiety	14.1	18.6
Back Pain	15.5	18.6
Depression	11.7	13.0

Source: Table 10, Physician Package Insert

Table 9 below illustrates the proportion of patients who were considered to be responders. A patient was a responder if they met all of the following criteria:

- Negative opioid assessment (urinalysis and self-report) during week 12 (evaluated during Week 13 visit).
- No more than one positive opioid assessment in the three illicit opioid use assessments performed during week 9 to 11 (evaluated during visits at Weeks 10 to 12).
- Negative opioid assessment during the final month of the study.
- No more than one positive opioid assessment at the three scheduled monthly visits and three random site visits.

This responder definition was designed to identify patients who were successfully treated with both BRIXADI (weekly) (administered in the first 12 weeks of treatment) and BRIXADI (monthly) (administered in the second 12 weeks of treatment). Therefore, patients were required to have negative opioid assessments at the end of each treatment phase. Each phase also included an allowable grace period (an initial period of time when positive opioid assessments were not taken into account) and the definition also allowed for sporadic positive assessments. Based on the results of this trial, the efficacy of BRIXADI was demonstrated. Table 11 shows the response rate for each treatment arm along with the associated 95% confidence interval for their difference.

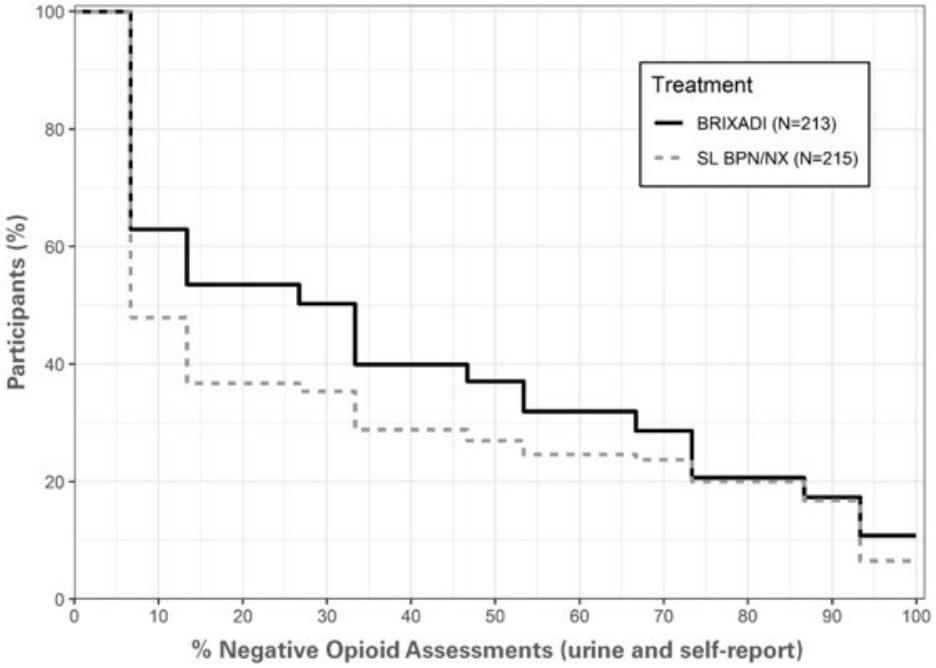
Table 9: Number (Percentage) of Patients Who Met the Responder Definition

BRIXADI Injection with placebo sublingual tablets (N=213)	SL BPN/NX Tablets with Placebo Injections (N=215)	Treatment Difference (95% CI)
36 (16.9%)	30 (14.0%)	2.9% (-3.9%, 9.8%)*

* The lower bound of the confidence interval was within the agreed upon non-inferiority threshold of −10%.
Source: Table 11, Physician Package Insert

The cumulative distribution function (CDF) of the percentage of negative opioid assessments (urine samples negative for illicit opioid use combined with self-reports negative for illicit opioid use) from Week 4 through Week 24 are shown in Figure 6 and Table 10. The figure and table are cumulative, so that a patient whose percentage of opioid-free assessments is, for example 50%, is also included at every level of negative opioid assessments below 50%. Missing values and values after premature discontinuation were considered positive. Based on the CDF of the percentage of negative opioid assessments, superiority was demonstrated with BRIXADI with statistical significance compared with SL BPN/NX. However, on the right-hand side of the curves where patients were reporting mostly negative opioid assessments (80% or greater) there was little to no difference between BRIXADI and SL BPN/NX.

Figure 7: Patients Achieving Varying Percentages of Negative Opioid Assessments (Urine and Self-Report) in Weeks 4 Through 24



Source: Figure 17, Physician Package Insert

Table 10: Patients Achieving Varying Percentage of Opioid-Negative Assessments (Urine and Self- Report) (Weeks 4-24)

Percentage of Opioid-Negative Assessments (Urine and Self Report)	Number (%) of Patients	
	BRIXADI 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: Table 12, Physician Package Insert

9. Safety

The review strategy for this cycle involved evaluating the newly-reported post-marketing information and comparing the findings to the established safety profile as documented in the previous review cycle. The post-marketing data did not demonstrate any previously unknown safety concerns regarding the risks of buprenorphine or the CAM2038 (Brixadi) drug product. The sections below detail the previous findings and any pertinent observations about the updated safety data reviewed for this submission.

Updated safety information reviewed for this cycle included:

- Applicant-provided clinical Information amendment with an overview of the safety findings of CAM2038 that occurred since the fourth application cycle (including 15-day safety reports submitted to IND 114082 from the post-marketing reports of Buvidal) through the data lock point of September 30, 2022.
- Annual Data Safety Update Report (DSUR) #8 from Camurus and Braeburn for CAM2038 safety data received from worldwide sources (February 2022).
- The 2019 Periodic Brief Risk Evaluation Report (PBRER) for Buvidal, marketed by Camurus, with a July 30, 2019 data lock, unchanged from the previous two application cycles.
- Investigator Brochure(IB) 16 (also submitted to INDs 114082 (b) (4)).
- Annual Report for IND 140724 (May 2021)
- Annual Report for IND 146193 (December 2020)
- Annual Report for IND 146501 (May 2021)

Clinical trial safety data to support Brixadi drug approval was unchanged from previous review cycles and were derived from Phase 1 PK studies, the blockade and efficacy studies described above, and a 24-week, Phase 3 open-label study, which enrolled patients who could be new to treatment ("new entrants") or already in established treatment with transmucosal buprenorphine ("transfer") (Study 499). In the clinical development of CAM2038 (Brixadi) for OUD during the initial review, 729 subjects were exposed to at least one dose of the study, which included healthy volunteers. In the pooled Phase 3 studies, 440 unique patient exposures to Brixadi were reported by the Applicant. In these studies, a total of 305 patients were exposed to Brixadi for at least 24 weeks and 132 patients were exposed for at least 48 weeks.

As of April 06, 2022, a total of 1,646 subjects[7] have been exposed to the Brixadi/Buvidal investigational drug product, CAM2038, in sponsored clinical studies and remained unchanged from the previous review cycle. No ongoing studies are being conducted under IND 114082.

(b) (4)

[7] Per Investigator Brochure version 16, the total number (b) (4) exposed to CAM2038 in the United States. And additional 60 patients were exposed to CAM2038 through the Australian trial, HS-17-585.

Additionally, Braeburn has provided product for use in three ongoing investigator-initiated studies. The updated safety information for these activities was obtained from the Applicant-provided clinical information and from annual reports submitted to the Agency (see Table 11, below). No new safety issues were identified that would alter the risk/benefit conclusion or require significant modifications of the proposed labeling.

Table 11: Investigator-Initiated Trials for Which Braeburn is Currently Providing CAM2038 (Brixadi)

Study Name	*Emergency Department- INitiated bupreNOrphine and VAlidaTIOn Network Trial (ED-INNOVATION)*	*Medication Treatment for Opioid Use Disorder in Expectant Mothers (MOMs): A Pragmatic Randomized Trial Comparing Two Buprenorphine*	*A comparative effectiveness trial of extended-release naltrexone versus extended-release buprenorphine with individuals leaving jail*
ClinicalTrials.gov Identifier	**NCT04225598**	**NCT04212065**	**NCT04408313**
Investigational New Drug Application number	**IND 146193**	**IND 140724**	**IND 146501**
Study Objectives	Evaluate implementation of emergency department (ED)-initiated buprenorphine; compare extended-release buprenorphine with sublingual buprenorphine in ED Opioid Use Disorder patients; Develop and validate electronic health record phenotypes of opioid-related illnesses; Enhance active disease surveillance; Better identify patients eligible for inclusion.	Evaluate the impact of treating opioid use disorder in pregnant women with extended- release buprenorphine, compared to sublingual buprenorphine, on maternal-infant outcomes; Testing a conceptual model of the mechanisms by which extended-release buprenorphine may improve maternal-infant outcomes, relative to sublingual buprenorphine	Determine the effectiveness of extended-release buprenorphine compared to extended-release naltrexone; To calculate the cost to the jail/county health system of implementing extended- release buprenorphine and extended-release naltrexone, and determine the relative value, including the costs associated with the interventions in the community, from a county and state-policymaker and societal perspective.

Study Status	IND contains 3 protocols: 2036 enrolled, 101 discontinued, 607 completed (studies ongoing) ten deaths(one in the CAM2038 arm: overdose unrelated to study participation). TEAEs included injection site pruritis, fatigue, and "Drug withdrawal syndrome".	Ongoing. 76 have been enrolled and continue in study (38 in the CAM 2038 group). One death reported in an 11-week old infant (2021) of a mother randomized to 16 mg sublingual buprenorphine who was delivered at term and required no intervention at delivery and exhibited no signs of withdrawal. Mother found infant unresponsive at home at undisclosed time. No SAEs in maternal group. 11 SAEs among neonates (4 in the CAM 2038 group), primarily "neonatal abstinence syndrome."	Ongoing: 153 enrolled, 10 discontinued (not for reasons related to study drugs, "refused injection"). Seven deaths reported: 6 among subjects who discontinued and received none (4) or one (3) injection in jail before release. Deaths due to drug overdoses in community (one death certificate pending). No TEAEs of interest for this review.

Source: *Reviewer*

9.1. Safety data reporting

Since the initial clinical trial safety data were submitted for review, CAM2038 (as Buvidal) in both the weekly and monthly formulations, has been marketed in multiple countries by Camurus. Per Camurus' May 2022 Annual Report, an estimated 36,000 patients have been treated.

The Applicant indicated that the data-lock for the non-IND post-marketing safety reporting for this application was September 22, 2022, and provided their summary of the Buvidal post-marketing safety data in the Clinical Information Amendment. An overview of those findings is described in the relevant subsections below.

9.1.1. Deaths

Clinical Program:

No additional deaths in the clinical program supporting this NDA were reported by the Applicant. One death was previously reported in the clinical program (during the first review cycle), in a patient treated with CAM2038 in Study 421 (a 41-year-old female with no other reported medical history was hit by a car and died on Study Day 147). There were no factors suggesting a causal link to the study drug. No overdose deaths or clearly medication-associated deaths were identified in the clinical program.

Post-marketing data:

In the previous review cycle, five reports of death were submitted to IND 114082 as the global market expansion of Buvidal (CAM2038) continued in the context of its 2018 approval. The deaths included the term "cardiorespiratory arrest" and involved males between the ages of 30-60 years with comorbid conditions, various medications, and various exposures to Buvidal. At that time, the Applicant was asked to provide a detailed summary of those events and any follow-up documentation that could be retrieved. In Summary, causality was difficult to determine, and illicit substance use was identified in some of the cases and toxicology/autopsy reports were missing from others. Please refer to the 4th Cycle clinical review for additional information.

With this submission, the Applicant provided 33 postmarketing reports of death from the global safety database through September 30, 2022. These reports included the previously reviewed cases and specific attention was made to new cases of interest related to the term cardiorespiratory arrest (N=2[8]). Most of the reported deaths reported during this review cycle were related to overdose and toxicities involving illicit substances (N=19). Two deaths were related to completed suicides.

The summary of findings from the causes of death (known or unknown) submitted by the Applicant do not change the risk-benefit profile of Brixadi.

[8] FR-CAM-22-00228 (cardiorespiratory arrest in a 33-year-old male with intentional misuse of medication and drug use) and GM-CAM-21-0004 (myocardial ischemia in a 49-year-old female).

9.1.2. Serious Adverse Events

Pre-marketing data:

A total of 20 SAEs occurred among 17 subjects of the 729 exposed to CAM2038 across the OUD treatment clinical program. None were related to injection site reactions. In Study 421, SAEs were reported in five (2.3%) of the CAM2038 group and in 13 (6%) of the SL BPN group. Accidental overdoses (3) were reported in the SL BPN group but not the CAM2038 group. One event (vomiting) was deemed plausibly related to study drug. In the second review cycle (2018), Braeburn included an SAE that occurred (b) (4) that was reported (b) (4) and should have been included in the original NDA submission. The case involved a woman who presented to the ER one day after her first injection of 8 mg CAM2038 with "acute onset altered mental status, rhabdomyolysis, acute renal failure, and markedly elevated liver transaminases leading to acute liver failure." The patient recovered. Because hepatic effects are known to be associated with buprenorphine, that event did not change the overall assessment of Brixadi.

Post-marketing data:

The Applicant submitted a tabulation of cumulative serious adverse drug reactions from post-marketing data sources and do not necessarily reflect individual cases. The Applicant reported that, at the time of the data lock, a total of 2403 reports were reviewed from all post-marketing sources and 199 of them were assessed as serious. The reports were consistent with cases reported from the previous review cycle, as well postmarketing reports submitted to IND 114082. The summary included the following system organ classes: Blood and lymphatic system disorders (1)[9]; Cardiac Disorders (10)[10]; Ear and Labrinth Disorders (1)[11]; Gastrointestinal disorders (8)[12]; General disorders and administration site conditions (30)[13]; Hepatobiliary disorders (5)[14]; Immune system disorders (1)[15]; Infections and infestations (8)[16]; Injury, poisoning and procedural complications (34)[17]; Investigations (4)[18]; Metabolism and nutrition

[9] Splenic hemorrhage

[10] Cardiorespiratory arrest (3), myocardial ischemia (2), acute cardiac event, acute myocardial infarction, arrythmia, arteriosclerosis, superventricular tachycardia

[11] deaf

[12] Nausea (2), vomit(2), abdominal pain, , gastrointestinal hemorrhage, hematemesis, intestinal obstruction

[13] Death, described above(10), drug withdrawal syndrome (3), drug withdrawal syndrome neonatal (3), peripheral edema (3), face edema (2), injection site necrosis (2), drug ineffective, drug interaction, , gait disturbance, generalized

[14] Drug induced liver injury, hepatic cytolysis, hepatitis, hepatitis acute, liver injury.

[15] Hypersensitivity

[16] Hepatitis C (2), bronchitis, cellulitis, infection, injection site abscess, pneumonia, septic shock

[17] Toxicity to various agents (11), overdose (6), alcohol poisoning (2), poisoning (2), rib fracture (2), road traffic accident (2), clavicle fracture, fall, head injury, drug titration error, intentional product misuse, labelled drug-food interaction issue, postoperative delirium, product label confusion, splenic rupture

[18] Blood pressure decreased, electrocardiogram QT prolonged, oxygen saturation decreased weight increased;

disorders (6)[19]; Musculoskeletal and connective tissue disorders (2)[20]; Nervous system disorders (17)[21]; Pregnancy, puerperium, and perinatal conditions (14)[22]; Psychiatric (21)[23]; Renal and urinary disorders (6)[24]; Respiratory, thoracic and mediastinal disorders (17)[25]; Skin and subcutaneous tissue disorders (2)[26]; Surgical and medical procedures (5)[27], and Vascular disorders (6)[28].

Review of the summary of these findings submitted by the Applicant do not change the known risk-benefit profile of Brixadi.

9.1.3. Dropouts and/or Dose Reductions Due to Adverse Effects

Pre-marketing data:
Adverse reactions led to premature discontinuation in 10 (4.7%) patients in the group receiving BRIXADI compared to 5 (2.3%) patients in the sublingual buprenorphine/naloxone group, during the double-blind study.

Post-marketing data:
No new information related to AEs leading to discontinuation were submitted in this review cycle. Three cases of events consistent with precipitated withdrawal leading to dose reductions due to AEs were identified. If anything, a pattern of CAM2038 dosing increase within 2-3 weeks after transferring to CAM2038 (also observed in previous review cycles) from another buprenorphine product was identified. Refer to section 9.1.8 and 9.2.1 for additional information on inadequate dosing and precipitated withdrawal.

[19] Type-1 diabetes mellitus (2), cachexia, dehydration, hypervolemia, hypokalemia
[20] Costochondritis, rhabdomyolysis
[21] Loss of consciousness (3), altered state of consciousness (2), seizure (2), depressed level of consciousness, epilepsy, head discomfort, hypoesthesia, loss of consciousness, migraine, neuroleptic malignant syndrome, sedation, serotonin syndrome, unresponsive to stimuli.
[22] Spontaneous abortions (6), pre-eclampsia (2), failed induction of labor, fetal growth restriction, fetal hypokinesia, fetal macrosomia, HELLP syndrome, jaundice neonatal.
[23] Drug abuse (7), confusional state (2), hallucination (2), agitation, anger, completed suicide, depression, disorientation, hallucination auditory,, psychotic disorder, psychotic symptom, suicidal ideation, suspected suicide
[24] Acute kidney injury (3), urinary retention (2), renal impairment
[25] Asphyxia (2), aspiration (2), acute respiratory failure, asthma, choking, dyspnea, hypoxia, interstitial lung disease, neonatal respiratory distress, obstructive sleep apnea syndrome, pulmonary hypertension, respiratory depression, respiratory distress, respiratory failure, respiratory symptom
[26] erythema multiforme, skin ulcer.
[27] Cesarean section (3), arm amputation (confirmed unrelated to study drug), endotracheal intubation
[28] Deep vein thrombosis (2), circulatory collapse, hemorrhage (related to spontaneous abortion), peripheral ischemia, superficial vein thrombosis

9.1.4. Injection Site Reactions

Pre-marketing data:

In the clinical program, injection site reactions were reported by approximately 20% of patients (Patients in the sublingual buprenorphine arm received placebo injections). The indented text in Arial font below summarizes the clinical trials safety database and is based on the agreed-upon language for section 6.1 of the proposed drug label during the previous review cycle and carried forward for drug labeling in this review cycle:

> Injection site reactions in the double-blind study are presented in Table below. The majority of injection site-related adverse events were mild or moderate in severity. No injection site reactions were reported as severe intensity.

Table 12: Injection-Site Reactions in the Double-Blind Phase 3 Study: ≥ 2% of Patients Receiving BRIXADI

Preferred Term (PT)[a]	BRIXADI Total[b] (N=213) n(%)	SL BPN/NX[c] (N=215) n(%)
Administration site reactions[d]	**44 (20.7%)**	**49 (22.8%)**
Injection site pain	21 (9.9%)	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%)

a = Injection site reactions (ISR) that occurred in ≥2% of patients receiving BRIXADI, in the controlled trial, HS-11-421. Patients are represented once per PT.
b = This group includes patients exposed to varying doses of both the BRIXADI weekly and monthly formulations.
c = SL BPN/NX denotes the active comparator: subjects assigned to daily buprenorphine with sham (placebo) injections. Patients randomized to this group could also receive a supplemental 'booster' injection of BRIXADI (weekly), 8 mg, per protocol.
d = The ISRs that occurred in ≥2% of the patients randomized to BRIXADI were reported under the HGLT of Administration site reactions. However, ISRs were also identified under the Bacterial infectious disorders HGLT (of which, there were three injection site related cellulitis reactions in the BRIXADI group and one in the SL BPN/NX group, respectively) but those numbers did not rise to level of reporting. Tabulation included all events coded as treatment-emergent and injection site reactions, regardless of treatment-emergent flags.
Source: Table 6, Physician Package Insert

Post-marketing data:

A total of 554 injection site reactions were submitted by the Applicant from Buvidal postmarketing reports and are listed the table below, which highlights ISRs from post-marketing sources from July 31, 2019 through September 30, 2022. Two terms of interest were addressed in this review: "injection site mass" and "injection site necrosis." The term "injection site mass" was not commonly reported in the clinical trials data. However, it has been increasingly reported in the postmarketing setting for Buvidal and was observed by the Applicant and described in the two previous review cycles. As a result, the Applicant updated product labeling to reflect that a palpable mass may be observed after dosing. With this submission, 83 cases of ISRs coded as "injection site mass" were included in the updated safety

information.. Regarding “injection site necrosis” the Applicant reported two additional postmarketing cases of patients treated with Buvidal 64 mg who experienced injection site necrosis requiring treatment/debridement. In response to the reports (which total three, since 2019), the Applicant proposed the following language to the postmarketing section of Brixadi labeling to adequately inform prescribers of the risk of this event:

“Injection site abscess, ulceration and necrosis: Cases of injection site abscess,

ulceration and necrosis have been reported after treatment initiation.”

Table 13: Injection- Site Reactions Received from Postmarketing Sources through September 30. 2022

MedDRA PT	Number of ISRs
Injection site pain	113
Injection site erythema	83
Injection site mass	83
Injection site swelling	58
Injection site pruritus	54
Injection site rash	19
Injection site bruising	18
Injection site inflammation	14
Injection site induration	13
Injection site nodule	12
Injection site warmth	12
Injection site reaction	8
Injection site hematoma	7
Injection site hemorrhage	7
Injection site discomfort	6
Injection site vesicles	5
Injection site injury	4
Injection site urticaria	4
Injection site discoloration	3
Injection site extravasation	3
Injection site necrosis	3
Injection site scab	3
Injection site discharge	2
Injection site ulcer	2
Injection site deformation	1
Injection site dermatitis	1
Injection site dryness	1
Injection site eczema	1
Injection site hypersensitivity	1
Injection site hypoesthesia	1
Injection site irritation	1
Injection site laceration	1
Injection site movement impairment	1
Injection site muscle weakness	1
Injection site nerve damage	1
Injection site oedema	1
Injection site panniculitis	1
Injection site papule	1

Injection site scar	1
Total	554

Adapted from Applicant-provided clinical information

The following injection site necrosis narratives were reported by the Applicant in the Clinical Information Amendment under the subsection 'Injection Site Reactions' during this review cycle. These cases are line-listed in Table 13:

- GB-CAM-22-00106 (2022BBN00059): A male patient who was treated with Buvidal 64mg and experienced an injection site reaction that become necrotic.
- AU-CAM-22-00341 (2022BBN00133). A female patient who was treated with Buvidal 64mg and experienced injection site necrosis.
- AU-CAM-20-00071: A week to ten days after Buvidal administration the patient experienced skin necrosis. The patient had a yellow top form over the skin where the injection had been given. The patient plucked the top off, with no pain. Subsequent dose was administered without events or concerns. The physician stated the possibility that Buvidal was administered intradermally, but he was not able to confirm since he had not witnessed the administration. Action taken with Buvidal regarding the reaction was not provided.

The premarketing findings taken together with the results received from post-marketing data sources, indicate that injection site mass might be reported after US marketing and that injection site necrosis is a less common but potential injection site risk. The frequency of pain, erythema, swelling, and pruritis reports with this submission are also higher than predicted based on the clinical trial database, but are not unexpected with an injectable product. Product labeling includes the risks of ISRs.

9.1.5. Hepatic

Premarketing data:

Hepatic adverse events are referenced in the Division's agreed upon labeling language for sections 5, 8, and 12 (see listed language above in Clinical Pharmacology). One suspected case of hepatitis (case AU-CAM-19-00051) was reported from a single, investigator-initiated study (dBC2531) in Australia, which involved a 36-year-old subject who experienced hepatitis acute six days after initiating treatment with CAM2038. Treatment with CAM2038 was interrupted as a response to the event which resolved 9 days later. In a follow-up received by Camurus after the data lock date of the DSUR, the causality of this event was re-assessed to not related to CAM2038. Review of the extremely limited case information yielded no additional information.

Postmarketing data:

Four cases of serious hepatic adverse event were identified from post-marketing sources during this review cycle, one of which was a published case report of drug-induced liver injury of an unknown brand of buprenorphine and was not reviewed. The remaining three involved Buvidal dosing of 8-16 mg (weekly formulation). Two of those cases were related to hepatitis without

liver impairment. The drug was withdrawn in one patient (after dosing of 8 mg Buvidal) and the other patient remained on treatment. The fourth case of hepatic impairment was reported in the context of death in a 33-year-old male (FR-CAM-22-00228) who had been treated with an unknown buprenorphine product, was found after a fall in the context of 'cardiorespiratory arrest' with multiple organs affected. Because the relationship of the event to buprenorphine and unknown buprenorphine product, causality to Buvidal could not be assessed.

From the data reviewed, nothing in the DSUR or post-market reports provided by the Applicant require modification of the labeling agreed upon in previous review cycles.

9.1.6. Cardiac

Premarketing data:
In the pre-marketing program, clinically significant ECG abnormalities reported as an AE occurred in 10 patients treated with CAM2038 (studies 549, 478, 421, and 499), in addition to a few cases of mild to moderate QT prolongation. Data were reviewed by the QT-IRT team during the first review cycle.

Post-marketing data:
Several reports of cardiac events (of any severity) from postmarketing sources from July 31, 2019 through September 30, 2022 were summarized by the Applicant during this review cycle[29]. Cases involving the outcome of death are described above in section 9.1.1. No reports adverse drug experiences were reported with ECG abnormalities that were independent of cases presented elsewhere in this review. One postmarketing adverse drug experience related to cardiac event (not described elsewhere) was reported during this review cycle and included the report of a non-ST elevation myocardial infarction in a male estimated to be in his mid-40's who had been treated with Buvidal 128 mg monthly for an unknown period of time. The event occurred one week before next injection was planned. Patient was hospitalized and treated. Outcome of continued Buvidal therapy unknown. Deemed "not related" in follow-up by Applicant (case 2022BBN00028).

During the third review cycle, DAAP undertook a comprehensive review of all available information about the cardiac effects of buprenorphine, including mechanistic studies performed by the Division of Applied Regulatory Science. A review of the material considered, prepared by Dr. Daniel Foster, documented the overall conclusion that the observed QT prolongation with buprenorphine does not appear to be mediated by hERG channels and that buprenorphine is unlikely to be pro-arrhythmic when used alone. Accordingly, new language was recommended for sections 5.15 (Warnings and Precautions) and 12.2 (Clinical Pharmacology) of the proposed drug label during that review cycle and carried forward to this one:

[29] Eighteen MeDRA terms reported since 2019 under the SOC "Cardiac disorders"; 10 were coded as serious and 8 were coded as non-serious. These terms do not reflect individual patients.

5.15 QTc Prolongation

Some studies demonstrate a modest QTc prolongation of uncertain clinical significance. This effect does not appear to be mediated by hERG channels and buprenorphine is unlikely to be pro-arrhythmic when used alone. The effect of combining buprenorphine with other QT-prolonging agents is not known *[see Clinical Pharmacology (12.2)].*

12.2 Pharmacodynamics

…

Cardiac Electrophysiology

Thorough QT studies with buprenorphine products have demonstrated modest QT prolongation ≤15 msec. Two categorical analyses of cardiovascular-specific adverse events among patients exposed to buprenorphine demonstrated no proarrhythmic potential. One Holter monitoring study demonstrated no arrhythmia. An analysis of medical literature provided no evidence for causal association between buprenorphine and Torsades de Pointes.

9.1.7. CNS/Respiratory Depression

Pre-marketing data:

Symptoms such as somnolence and sedation were not commonly reported in the safety database. One patient [CAM3028 (weekly) 32 mg] discontinued study medication due to sedation. No TEAEs potentially associated with respiratory depression were reported in patients treated with CAM2038.

Post-marketing data:

Two postmarketing cases of respiratory depression were submitted with this review cycle:

- AU-CAM-21-00371 (“neonatal respiratory distress”): A female infant born via elective lower segment Caesarean section at 34.1 weeks of gestation to a mother that was being treated with insulin for gestational diabetes and with Buvidal 128 mg (monthly formulation) every 3 weeks experienced reduced fetal movements. The preterm infant was admitted to the neonatal intensive care unit where she was treated for respiratory distress with secondary pulmonary hypertension, neonatal jaundice, and neonatal abstinence syndrome. Prematurity and the mother's gestational diabetes were reported as factors that might have caused neonatal respiratory distress with secondary pulmonary hypertension. The infant was discharged home at 22 days and no medications. The mother remained on Buvidal post-partum. Additional information not provided.

- AU-CAM-22-00403 ("respiratory failure"): An approximately 50-year-old female was treated with Buvidal 64 mg monthly and then titrated to 96 mg monthly due to subjective withdrawal. The day after the 96 mg monthly injection, the patient had been drinking alcohol and was admitted to an intensive care unit with type 2 respiratory failure, bronchial infection, and aspiration. The patient was treated for a chest infection with unspecified antibiotics, as well as for aspiration. The events resolved. Buvidal was withdrawn.

These findings did not appear to change the overall safety profile of Brixadi.

9.1.8. Inadequate dosing

Of the many cases submitted for review with this application cycle, using the standardized MedDRA query "drug withdrawal reactions," 10 postmarketing reports involved patients complaining of withdrawal at or around 2-weeks following the dosing of monthly Buvidal[30] . In most cases, the event resolved with increasing doses of Buvidal. These cases did not describe the syndrome of precipitated withdrawal as much as they described sub-therapeutic dosing of Buvidal.

These findings did not change the overall safety profile of Brixadi.

9.1.9. Medication errors

Premarketing data:
In the clinical development program, no studies were performed to evaluate whether lower doses of either formulation could be combined to yield exposures equivalent to the mathematical sum of the doses of CAM2038 (e.g., 2 x 16 mg Weekly formulation compared to 1 x 32 mg Weekly formulation). The proposed label cautions against combining doses in this fashion. Instances of investigators making such substitutions were recorded in the clinical trials submitted with the first review cycle and may be predicted to occur after marketing. However, review of post-marketing data submitted with this application cycle, did not reveal situations where providers reported combinations of doses to achieve a desired mathematical sum. Last, only one report of "package difficult to open" was reported and this did not result in a medication error.

Post Marketing data:
With this submission, 25 medication errors were reported. The errors included:

- Incorrect dose/product administered, described as different monthly doses or monthly instead of weekly administered (9)
- Improper technique, resulting in product leaking from injection site (6)

[30] Monthly dosing formulations varied. A similar pattern was also observed with the weekly formulations in an equal number of cases, occurring 3-4 days after injection.

- Improper technique, resulting in swelling, pain, or mass at site (4)
- Improper technique, intramuscular delivery (4)
- Syringe malfunction with product left behind in syringe (2)

This finding did not change the overall safety profile of Brixadi but reflects the importance of cross-checking the order with the dispensed drug and proper injection technique

9.1.10. Common AEs

The systemic safety profile for CAM3038, when given by a HCP in clinical trials, was broadly consistent with the known safety profile of transmucosal buprenorphine. The indented text in Arial font below from the proposed labeling summarizes the findings from the clinical program for Brixadi.

> Adverse reactions commonly reported after BRIXADI administration (≥5%, regardless of dose and regimen) in the double-blind study, were injection site pain (9.9%), headache (7.5%), constipation (7.5%), nausea (7.0%), injection site erythema (6.6%), injection site pruritis (6.1%), Insomnia (5.6%), and urinary tract infection (5.2%).
>
> Table shows the adverse reactions for BRIXADI compared with the active-control group (SL BPN/NX) in the double-blind study.

Table 14: Adverse Reactions in the Phase 3 Double-Blind Study: ≥ 2% of Patients Receiving BRIXADI (Excluding Injection-Site Reactions)

System Organ Class (SOC) Preferred Term (PT)[a]	**BRIXADI Total[b]** (N=213) **n(%)**	**SL BPN/NX[c]** (N=215) **n(%)**
Cardiac disorders	**6 (2.8%)**	**9 (4.2%)**
Tachycardia	5 (2.3)	5 (2.3)
Gastrointestinal disorders	**43 (20.2%)**	**45 (20.9%)**
Constipation	16 (7.5)	16 (7.4)
Diarrhea	6 (2.8)	7 (3.3)
Nausea	15 (7.0)	17 (7.9)
Vomiting	9 (4.2)	8 (3.7)
Infections and infestations	**42 (19.7%)**	**50 (23.3%)**
Urinary tract infection	11 (5.2)	10 (4.7)
Upper respiratory tract infection	9 (4.2)	9 (4.2)
Musculoskeletal and connective tissue disorders	**20 (9.4%)**	**22 (10.2%)**
Arthralgia	7 (3.3)	3 (1.4)
Nervous system disorders	**27 (12.7%)**	**27 (12.6%)**
Headache	16 (7.5)	17 (7.9)
Psychiatric disorders	**20 (9.4%)**	**20 (9.3%)**
Anxiety	6 (2.8)	7 (3.3)
Insomnia	12 (5.6)	6 (2.8)

a = report of adverse reactions that occurred in ≥ 2% of the patients randomized to BRIXADI in Study HS-11-421. Patients are represented once per PT; b = This group includes all subjects exposed to varying doses of both the BRIXADI (weekly) and BRIXADI (monthly) formulations.; c = SL BPN/NX denotes the active comparator: patients assigned to daily buprenorphine with sham (placebo) injections. Patients randomized to this group could also receive a 'booster' injection of BRIXADI (weekly), 8 mg, per protocol.; All patients in Study 421 received a single test dose of 4 mg SL BPN/NX before randomization into either arm.
Source: Table 5, Physician Package Insert

9.2. Other Safety Concerns

Certain concerns not observed in the clinical trials were identified as areas of particular interest that might arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated in a patient still dependent on a full agonist.

9.2.1. Precipitated Withdrawal

Pre-marketing data:

Buprenorphine itself can precipitate withdrawal if initiated in patients who are not yet in significant opioid withdrawal. For this reason, initial dosing is generally cautious and typically begins with a sublingual dose of 2 mg- 4 mg. Some of the doses of CAM2038 contain a large amount of buprenorphine. In new entrants to treatment, the clinical trials included a test dose of 4 mg sublingual buprenorphine and then initiated treatment with a 16 mg weekly dose. Two

patients did not tolerate the test dose. The Applicant reported that no patient experienced precipitated withdrawal due to CAM2038.

Post-marketing data:
A total of 104 cases of withdrawal were reported by the Applicant using the standardized MedDRA query "withdrawal syndrome" (76), "drug withdrawal syndrome" (22), and "drug withdrawal syndrome neonatal (7)[31]" and were submitted for review from post-marketing reports.

On review, and consistent with the previous review cycle, some patients appeared to experience precipitated withdrawal while others complained of effects consistent with dose inadequacy, described as "not sufficient", need for supplemental buprenorphine dosing continued dose titration, or dosing Buvidal in shorter intervals (N=22) [refer to section 9.1.8].

These findings did not change the overall safety profile of CAM2038.

9.2.2. Consequences of Intravenous Injection

In the clinical development program, CAM2038 was administered in a supervised setting by HCPs. If a patient, household contact, or associate were to obtain access to CAM2038, the pre-filled syringe containing a Schedule III opioid might be an attractive target for abuse by the intravenous route. Therefore, given the route of administration of CAM2038, it is predicted that injection into a vessel could result in the formation of a gel or solid, with resulting occlusion and possibly tissue damage or embolus. Clinical review of the ongoing clinical trial adverse event data and provided post-marketing data revealed no cases involving intravenous injection of Buvidal.

9.2.3. Serotonin Syndrome

No reports of serotonin syndrome were submitted with this review cycle. In a previous review cycle, one post-marketing case report[32] of serotonin syndrome was submitted to IND 114082 on 9-04-2020 (after the data lock) and was included in the primary review of the third application submission. The case involved a 41-year-old female from Australia with a history of OUD, insomnia, anxiety, and major depressive disorder. The patient was transferred to Buvidal, 16 mg Weekly on (b) (6) from 12 mg daily dosing of Subutex. Concomitant medications included amitriptyline, escitalopram, and diazepam. The patient was titrated to Buvidal 24 mg Weekly on (b) (6) then titrated to 32 mg Weekly on (b) (6) then transferred to Buvidal 128 mg Monthly on (b) (6) at the same time amitriptyline dosing increased from 10 mg to 20 mg. Symptoms of hot and cold flushes, yawning, "sweating profusely", cannot concentrate",

[31] The postmarketing cases of neonatal withdrawal syndrome were also listed as Neonatal Abstinence syndrome and were difficult to assess. The Applicant posited that 3 of the 7 cases met criteria for neonatal opioid withdrawal syndrome. Adjunctive medication (e.g., morphine, phenobarbital) was provided to the neonate in approximately half of the cases.
[32] Case reference number AU-CAM-20-00143 (2020BBN00021)

and "feeling foggy" were reported. Diazepam was discontinued, amitriptyline dosing was decreased and a physical exam on (b) (6) yielded normal vital signs, and 5 mm pupils that were reactive to light. The event was marked "resolved" on (b) (6), and the patient received her second dose of Buvidal 128 mg Monthly.

No reports of serotonin syndrome were identified in the clinical trials for CAM2038. In review of this case, it is possible that the presenting symptoms were related to Buvidal. Because serotonin syndrome is listed in (b) (4) the drug label (and in the drug labels of other buprenorphine products), this finding did not change the risk-benefit profile of Brixadi.

9.2.4. Seizure

No post-marketing case reports of seizure were reported with this review cycle.

One post-marketing case report of seizure[33], following Buvidal administration in the context of a medication error, was submitted to IND 114082 on 10-16-2020, during the third review cycle. A 50-year-old Australian male with a history of alcohol use and chronic pain [treated with Norspan (buprenorphine patch, unknown dose)], presented to an emergency department acutely intoxicated. The sequence of events is unknown, but the patient was physically restrained in the emergency department in order to receive an 8 mg injection of Buvidal Weekly. However, 128 mg Buvidal Monthly was administered. The patient experienced a seizure and was transferred to ICU where naloxone was administered.

Of note, no reports of seizure were identified in the clinical trials for CAM2038. In review of this case, it is possible that the presenting symptoms were related to Buvidal in the context of alcohol intoxication. Additional details of the case are unknown. Although "seizure" is not listed in the Warnings and Precautions section of the drug label (or in the drug labels of other buprenorphine products), clinical studies have been published on the onset of seizures following buprenorphine overdose and are a risk factor in alcohol withdrawal. At this time and in the context of the event described, the finding does not change the risk-benefit profile of Brixadi.

10. Advisory Committee Meeting

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

[33] Case reference number AU-CAM-20-00180 (2020BBN00032)

application.[34] No additional Advisory Committee input was sought for subsequent application cycles.

11. Pediatrics

Braeburn received a full waiver of the Pediatric Research Equity Act (PREA) requirements on the basis of infeasibility. The prevalence of OUD in the pre-adolescent population is very low, and this product would not be suitable for treating iatrogenic opioid dependence (i.e., physical dependence without meeting criteria for OUD). Prevalence in adolescents under age 17 is also too low for feasible study.

12. Other Relevant Regulatory Issues

12.1. Exclusivity

No exclusivity concerns exist with this submission. However, in 2018, during the second application cycle, the administrative records related to the approval of NDAs 204442 and 209819 were reviewed and the Exclusivity Board determined that the 3-year exclusivity for Sublocade (NDA 209819) would block the approval of the Brixadi monthly depot product. The Board recommended that Brixadi's weekly depot product should not be blocked. At that time, Braeburn expressed that they were not willing to entertain separating the Weekly and Monthly Brixadi product formulations. Therefore, only a combined label was negotiated during the second review cycle and the tentative approval (TA) was issued applying to both formulations. Braeburn timed the 2020 review cycle of NDA 210136 (third resubmission) to align with the expiration of Sublocade's 3-year exclusivity for Sublocade[35].

13. Labeling

The submitted proposed labeling is in Physician's Labeling Rule (PLR) format and is similar to the previously agreed-upon label from the third review cycle. The previous cycle included revisions to Section 6 regarding injection site mass and insufficient dosing and revisions to

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[34] A verbatim transcript of this meeting is available on the FDA website at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm535446.htm

[35] In April 2019, Braeburn filed an action with the federal district court for the District of Columbia, in an effort to overturn that 3-year exclusivity period (which blocked Brixadi from final approval for marketing). After a court hearing in July 2019, the Court's Chief Judge did not overturn FDA's decision. Braeburn was notified that they could resubmit their application in June 2020, to request final approval of Brixadi, because Sublocade's exclusivity expires in November 2020. Further, and in order to eliminate the risk of further exclusivity periods blocking Brixadi from marketing approval, Braeburn also filed a Citizen Petition in April 2019, That Citizen Petition requested that FDA review the orphan designation granted to Sublocade. FDA reviewed the conditions of the orphan designation and granted Braeburn's Citizen Petition. Thus, the risk of Brixadi being blocked from marketed approval through November 2024 was eliminated.

Section 9 (inclusion of descriptive text to reflect buprenorphine class labeling changes[36]). With this submission, minor revisions were made by Braeburn and the Division, primarily to remove (b) (4)

14. Postmarketing Recommendations

14.1. Risk Evaluation and Mitigation Strategies (REMS)

With this submission, Braeburn agreed to keep and revise the agreed-upon Risk Evaluation and Mitigation Strategy (REMS) from the third and fourth review cycles, which was reviewed by the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology. Consistent with the previous review cycle, DRISK has determined that a REMS with elements to assure safe use (ETASU) is needed to ensure the benefits of CAM2038 (Brixadi) outweigh its risks. Consistent with previous review cycles, the REMS should include restricted distribution with CAM2038 being dispensed only in healthcare settings that are certified. The goal of the Brixadi REMS is to mitigate the risk of serious harm or death that could result from intravenous self-administration by ensuring healthcare settings and pharmacies are certified and only dispense Brixadi directly to a healthcare provider for administration by a healthcare professional.

The elements of the REMS are:

- Elements to assure safe use to ensure that health care settings and pharmacies that dispense BRIXADI are specially certified;
- An implementation system; and,
- A timetable for submission of assessments of the REMS.

Materials include:

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

14.2. Postmarketing Requirements (PMRs) and Commitments (PMCs)

A postmarketing trial will be required to evaluate whether Brixadi can safely be initiated at a full blocking dose of either formulation (e.g., 24-32 mg weekly and 64-96 mg monthly) without titration over the initial week of treatment without causing precipitated withdrawal. This is expected to be of great interest to clinicians who see patients in Emergency Department settings where treatment could be expeditiously initiated.

[36] Derived from the 2019 FDA Draft Guidance (Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products-Content and Format Guidance for Industry).

The following post-marketing studies were required at the time of the previous tentative approval action and are still outstanding:

1. Conduct a study to quantitate the level of elemental impurities that could be leached from the container closure system over the course of the shelf-life and provide a toxicological risk assessment to justify the safety of the levels detected.

2. Conduct a study using validated methods to confirm the identity of the unspecified (b) (4) the unidentified compound with relative retention time (RRT) of (b) (4) minutes, the unknown compound containing (b) (4) with RRT of (b) (4) min, and the unknown compound (b) (4) with RRT of (b) (4) min that were detected in your leachable studies above the safety concern threshold of 5 mcg/day and the levels of the identified leachables (b) (4) (b) (4) and provide a toxicological risk assessment for each of these compounds and any other compounds detected at ≥5 mcg/day.

14.3. Associate Division Director Comments

The efficacy and safety of Brixadi (weekly) and Brixadi (monthly) were demonstrated in data submitted and reviewed in previous review cycles. Review of the safety update included in this submission does not identify any new concerns that alter the overall assessment of the risk/benefit ratio for this product.

In this review cycle, as with the previous one, contract manufacturing and testing facilities were inspected as part of a pre-approval inspection (PAI). Good Manufacturing Practice (GMP) deficiencies previously identified have been addressed, and OPMA has recommended approval.

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/

CELIA J WINCHELL
05/23/2023 12:35:55 PM

Cross-Discipline Team Leader Review and Division Summary

Date	12/15/2021
Medical Officer	Gioia Guerrieri, D.O.
CDTL/Associate Division Director	Celia Winchell, M.D.
Division Director	Rigoberto Roca, M.D.
NDA/BLA #	210136
Applicant	Braeburn Inc.
Date of Submission	6/15/2021
Proprietary Name	Brixadi
Established or Proper Name	(buprenorphine extended-release) injection, for subcutaneous administration
Dosage Form(s)	Injection Weekly Formulation: 8 mg, 16 mg, 24 mg, 32 mg Monthly Formulation: 64 mg, 96 mg, 128 mg
Applicant Proposed Indication(s)/Population(s)	For the treatment of moderate to severe opioid use disorder (b) (4) (b) (4)
Applicant Proposed Dosing Regimen(s)	Patients not currently receiving buprenorphine treatment: titrate to (b) (4) Weekly in the first week then dose adjust. Patients currently receiving buprenorphine treatment: transfer to appropriate Weekly or Monthly formulation.
Recommendation on Regulatory Action	*Complete Response*
Recommended Indication(s)/Population(s) (if applicable)	BRIXADI is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. BRIXADI should be used as part of a complete treatment plan that includes counseling and psychosocial support.
Recommended Dosing Regimen(s) (if applicable)	New Entrants to treatment: after test dose of sublingual buprenorphine, titrate to 24-32 mg Weekly in the first week then dose adjust. Adults stabilized on current buprenorphine product: transfer to appropriate Weekly or Monthly formulation.

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1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

CAM2038 (buprenorphine extended-release) injection, for subcutaneous administration use. is intended for the treatment of moderate-to-severe opioid use disorder; the Weekly formulation is for initiating treatment in patients who have tolerated a test dose of a transmucosal buprenorphine-containing product; the Monthly formulation is for patients already in established treatment with another buprenorphine-containing product (including the Weekly formulation).

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 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. 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.

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. 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; additionally, this product is no longer marketed in the U.S..

A monthly subcutaneous depot formulation of buprenorphine (SUBLOCADE) was approved in 2017 Like Sublocade, Brixadi is a HCP-administered long-acting depot providing a sustained effective plasma level of buprenorphine over a prolonged period. Brixadi represents an additional option that has the potential to address several limitations of other existing treatments

The submitted clinical data show that the Brixadi weekly formulation, in doses of 24 mg and 32 mg, is able to block subjective effects of a clinically relevant dose of opioid agonist, more completely after the second weekly dose. Based on PK-PD analysis, the plasma levels delivered by the corresponding monthly doses are predicted to produce similar blockade. In a non-inferiority comparison to sublingual buprenorphine/naltrexone treatment, the effect of this blockade was shown to translate to clinical efficacy for a regimen beginning with weekly doses and transitioning to monthly doses, based the proportion of subjects whose drug use assessments met a pre- specified responder definition.

The systemic safety profile of buprenorphine is well-characterized, and the overall Brixadi safety profile appears similar. Analysis of dose-dependent adverse effects was hampered by the study design and the presentation of data but various explorations for dose-effects (in the previous review cycle) did not identify concerning dose-limiting adverse effects in the doses currently proposed for marketing.

Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated at doses higher than studied in the clinical trial (16 mg weekly x 1) in a patient still dependent on a full agonist. Additionally, there may be circumstances under which the rapid discontinuation or dose reduction of buprenorphine might be desirable for a given patient. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with Brixadi for a period of time. Possibilities for surgical removal have not been explored. Patients developing intolerance to buprenorphine will require long-term monitoring by a health care professional. Foreign post-marketing to date suggests that inadequate dosing, particularly early in treatment, may be an issue for some patients. “Booster” doses to address this problem are described in labeling.

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 by ensuring healthcare settings and pharmacies are certified and only dispense Brixadi directly to a health care provider for administration by a healthcare provider.

Because of manufacturing quality issues, approval of Brixadi (CAM2038) for use in the treatment of adult patients with moderate to severe OUD cannot be recommended at this time.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Opioid use disorder or OUD, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), 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 2020, the National Survey on Drug Use and Health determined that over 2.7 million Americans aged 12 and over met criteria for opioid use disorder in the past year. In 2021, the CDC reported that the estimated number of overdose deaths related to opioids in 2020 was 69,710. 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 for years, or even indefinitely.	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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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). o Behavioral treatment alone (individual or group counseling, self- help groups) is not effective for many patients. o 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 overdoses in patients and in their household contacts, including children. o Subdermal implant (PROBUPHINE)[1] 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. o Depot buprenorphine (SUBLOCADE) o 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. o 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	An additional buprenorphine depot injection would be a desirable addition to the therapeutic armamentarium. o Convenience of weekly or monthly vs daily dosing; various doses offered o At steady state, provides consistent buprenorphine levels sufficient to block effects of exogenous opioids o May improve adherence o Reduces potential for diversion, misuse, abuse and accidental pediatric exposure o No surgical procedure needed

[1] No longer marketed in the US

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Evidence: The opioid blockade study, Study HS-13-478, demonstrated that after CAM2038 (weekly) injections of either 24 mg or 32 mg, on average, subjective effects of both 6 mg and 18-mg doses of hydromorphone were blocked in non-treatment-seeking subjects with OUD, although significant variation was seen across subjects. Dose-response analysis showed a decreasing number of outliers (unblocked responses) with increasing plasma levels, with very few outliers above a plasma level of 4 ng/ml. The pivotal efficacy trial, Study HS-11-421 (N=428) demonstrated that patients treated with a regimen of 12 weeks on individually determined doses of CAM2038 (weekly), followed by 12 weeks on individually-determined doses of CAM2038 (monthly) had a response rate non-inferior to patients treated with sublingual buprenorphine/naltrexone tablets (and placebo injections). CAM2038 is to 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. Uncertainties: The design of the studies did not permit analyses by dose	CAM2038 24 mg weekly and CAM2038 32 mg weekly are capable of blocking the subjective effects of a clinically relevant dose of opioid agonist, and this blockade becomes longer-lasting after two weekly doses. The effect of this blockade was shown to translate to clinical efficacy as demonstrated by comparable outcomes in patients treated with a regimen of weekly followed by monthly CAM2038 compared with patients treated with sublingual buprenorphine/naloxone. Taken together, and considering the established efficacy of the reference product, Subutex, these studies provide substantial evidence of efficacy for CAM2038 in the treatment of moderate or severe OUD in patients who tolerate at least an initial test dose of buprenorphine. CAM2038 weekly is suitable for starting treatment, while CAM2038 (monthly) has been studied only in patients already in established treatment.
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. 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.) o In a safety database of 440 opioid-dependent patients, systemic effects of buprenorphine associated with	The systemic safety profile of buprenorphine is well-characterized, and the overall safety profile of CAM2038 appears to be similar. Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated too quickly in a patient still dependent on a full agonist. Cases of this nature have not been

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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 case was identified in the clinical development program One death occurred in a CAM2038-treated patient, due to a car-vs-pedestrian traffic accident Foreign post-marketing suggests that dose inadequacy may be an issue for some patients, requiring "booster" doses. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with CAM2038 for a period of time. Possibilities for surgical removal have not been explored. Patients developing intolerance to buprenorphine effects will require long-term monitoring by a health care professional. Buprenorphine itself can precipitate withdrawal if initiated in patients who are not yet in significant opioid withdrawal. For this reason, initial dosing is generally cautious and typically begins with a dose of 2 mg-4 mg. The starting dose of CAM2038 in the efficacy trial was divided over several visits in the first week of treatment. Clinicians may be interested in initiating CAM2038 more expeditiously, for example, administering a single 24 mg or 32 mg weekly injection at the first visit, or administering a monthly dose at the first visit. It is not known if this can be accomplished safely. CAM2038 forms a gel when injected. If patients obtain direct access to the product, there is a risk they may choose to attempt to inject the product intravenously. Notably, the consequences of intravenous injection of the contents of the pre-filled syringe are not known, it is	observed in post-marketing outside the U.S. Foreign post-marketing data suggest dose inadequacy may be an issue for some patients during titration. Additionally, there may be circumstances under which the rapid discontinuation or dose reduction of buprenorphine might be desirable for a given patient. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with CAM2038 for a period of time. It is not known whether there are possibilities for surgical removal. Patients developing intolerance to buprenorphine effects will require long- term monitoring by a health care professional. A REMS is required to ensure that CAM2038 is not distributed directly to patients, and is administered by a health care professional, to mitigate the risk of serious consequences should the product be administered intravenously. The deficiencies observed at the manufacturing site preclude approval at this time.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	anticipated that there is a risk of occlusion, tissue damage, and emboli. The manufacturing site for this product has had a number of concerning inspectional findings, and at this time, it does not appear that the product can be manufactured adequately.	

2. Introduction

This is the fourth review cycle for NDA 210136 (CAM2038, proposed proprietary name Brixadi). The application was initially submitted in July 2017. Because of the potential for a depot product to mitigate risks of abuse, diversion, and accidental pediatric exposure associated with oral transmucosal buprenorphine, the application was granted a priority review because no depot formulations had been approved at the time of submission. At the conclusion of the first application cycle, NDA 210136 received a Complete Response (CR) letter. The January 19, 2018, CR letter cited significant manufacturing issues as well as concerns about the clinical datasets.

The second resubmission, submitted June 2018, adequately addressed the deficiencies of the first submission. However, between the two submissions, NDA 209819 (Sublocade, Indivior), a monthly extended-release buprenorphine injectable product, was approved for marketing and blocked the marketing of the Brixadi Monthly product because of Hatch/Waxman drug product exclusivity. The Division discussed options regarding the labelling and marketing of the Brixadi Weekly formulation. However, the Applicant chose to wait to market the Weekly formulation until the product exclusivity on Sublocade expired and agreed to resubmit NDA 210136 in 2020. Thus, the second submission for NDA 210136 received a tentative approval (TA) letter on December 28, 2018.

Between the first and third submissions for NDA 210136, the manufacturer of Brixadi, Camurus, with whom Braeburn has a marketing partnership, received marketing approval for the product under the proprietary name Buvidal (CAM2038) in November 2018, for the treatment of OUD in the European Union, European Economic Area (Norway and Iceland), Australia and the United Kingdom. The current submission provides updated safety information based on Camurus' marketing experience, as well as safety findings from ongoing and completed studies sponsored or supported by Braeburn.

During the third review cycle, submitted June 2020, the manufacturing facilities were inspected as part of a pre-approval inspection (PAI) for an NDA unrelated to this one, and significant Good Manufacturing Practice (GMP) deficiencies were identified. The manufacturing company (Pii) made an internal decision to shut-down those manufacturing facilities to address the deficiencies. However, after an October 2020 re-inspection, two 483 forms were issued to the manufacturer. The deficiencies in those forms covered (b) (4) It was unclear how the inspectional findings might directly impact the manufacturing of the Brixadi drug product, but the manufacturing deficiencies could not be resolved. The facility was determined to be "Official Action Indicated" and Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued a recommendation to withhold approval. Therefore, the application received a complete response (CR) letter on December 01, 2020 due to inadequacies related to manufacturing.

This submission includes a safety update from foreign post-marketing data, and Braeburn's assertion that the manufacturing concerns at the contract manufacturer, Pii, have been addressed. In addition, a new inspection was undertaken in conjunction with this submission.

Product Overview

The Brixadi products include two modified-release formulations of buprenorphine in a novel Fluid Crystal technology designed for administration by subcutaneous (not intramuscular) injection to be provided ready-for-use in a prefilled syringe for the treatment of moderate-to-severe opioid use disorder (OUD) in adults. This product is available in weekly and monthly formulations, each of which contains different doses and excipients.

Table 1: Proposed Doses of the Brixadi 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		
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: Clinical Reviewer

The Brixadi Weekly formulation, at the 24 mg and 32 mg doses, respectively, provides sustained plasma levels of buprenorphine intended to block the effects of exogenous opioids over 7 days. Based on pharmacokinetic data, the Brixadi Monthly formulation is predicted to block exogenous opioids for at least 28 days. Brixadi Weekly is intended for the treatment of moderate-to-severe opioid use disorder (OUD) in patients who have tolerated at least a test dose of transmucosal buprenorphine, and Brixadi Monthly product was studied in patients who are transferring from an oral-transmucosal buprenorphine product or the Brixadi Weekly formulation. The products are intended to be used as part of a complete treatment plan to include counseling and psychosocial support. Table 2 identifies the corresponding dose of BRIXADI when switching a patient from transmucosal buprenorphine to BRIXADI (weekly) or BRIXADI (monthly), expressing the transmucosal dose equivalents in terms of Subutex or

Suboxone doses. Table 3 shows how patients may be transitioned between doses of both Brixadi product formulations. Both tables are adapted from proposed drug product labeling. For dose adjustments, an additional Brixadi Weekly 8 mg injection may be administered, based on clinical judgment during a dosing interval, for a total dose of up to a maximum dose of 32 mg per week of Brixadi Weekly or 128 mg per month of Brixadi Monthly.

Table 2: Daily Doses of Sublingual Buprenorphine (Subutex, Suboxone, or Generic Product Equivalents) and Suggested Corresponding BRIXADI (Weekly) or BRIXADI (Monthly) Doses

Daily dose of sublingual buprenorphine	BRIXADI (weekly)	BRIXADI (monthly)
≤ 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

Note: One SUBOXONE® (buprenorphine and naloxone) 8 mg/2 mg sublingual tablet provides equivalent buprenorphine exposure to one SUBUTEX® (buprenorphine HCl) 8 mg sublingual tablet (b) (4) (b) (4) or one Zubsolv® (buprenorphine and naloxone) 5.7 mg/1.4 mg sublingual tablet.

Table 3: Recommended Dose When Transitioning Between BRIXADI (Weekly) and BRIXADI (Monthly)

BRIXADI (weekly)	BRIXADI (monthly)
16 mg	64 mg
24 mg	96 mg
32 mg	128 mg

(b) (4)

Comparison of exposures after CAM2038 doses to exposures after sublingual buprenorphine demonstrate that, at steady-state (4th injection), CAM2038 (weekly) and monthly deliver plasma concentrations (Cavg,ss) that are higher than the corresponding dose of sublingual buprenorphine in Braeburn's proposed conversion scheme. Based on plasma levels (see Table 4 below), the efficacy would be anticipated to be at least non-inferior to, if not superior to, the corresponding doses.

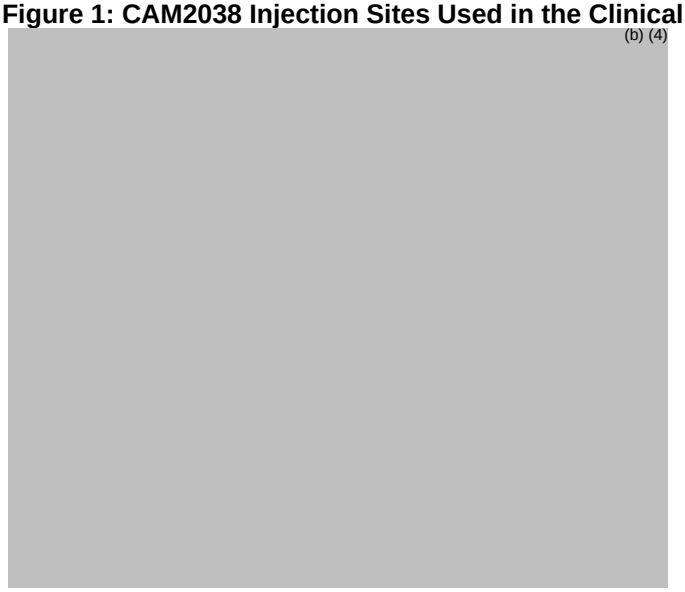
Table 4: Summary of Steady-State PK Parameters of Buprenorphine After Subcutaneous Buttock Injections of Brixadi (Weekly), Brixadi (Monthly), and SL Administration of SUBUTEX

Drug product dose			C_{av} (ng/mL)			$C_{max,ss}$ (ng/mL)			C_{trough} [a] (ng/mL)		
SL BPN	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly
8 mg	16 mg	64 mg	1.2	2.1	2.0 $	4.7	4.3	4.0 $	0.7	0.8	1.3 $
16 mg	24 mg	96 mg	1.8	2.9 $	2.9 $	6.5	5.5 $	6.0 $	1.0	1.4 $	2.0 $
24 mg	32 mg	128 mg	2.5	4.2	3.9	8.2	6.9	11.1	1.4	2.6	2.1

Average value of two studies
$ Simulated
a C168h for BRIXADI (weekly), C28d for BRIXADI Monthly and C24h for Subutex

As with the previous two submissions, 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 were proposed (Figure 1)[2] based on the injection sites used in the clinical program. No new sites were proposed. 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.

Figure 1: CAM2038 Injection Sites Used in the Clinical Studies



Source: page 27, Applicant's Manual of Procedures, 2018

[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 initial submission) after review of additional data. It is not recommended for initiation of dosing.

3. Background

Buprenorphine is a partial agonist at the μ-opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain, and two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence[3]. Three other transmucosal formulations, a six-month, surgically-placed implant, and a monthly depot formulation have subsequently been approved for opioid dependence, as well as one transdermal product and one transmucosal product for pain. Approximately (b) (4) million prescriptions from outpatient retail pharmacies were dispensed and approximately (b) (4) million patients received a dispensed prescription for buprenorphine-containing tablets or film labeled for MAT during 2019. Primary care physicians accounted for 34% of dispensed prescriptions, followed by nurse practitioners (14%), psychiatrists (14%), osteopathic physicians (12%), and all others (26%).

As a partial agonist, buprenorphine produces less euphoria compared to full agonists and has an improved safety profile with respect to effects on respiration. In addition to the improved safety profile, at sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, deterring abuse of opioids by buprenorphine-maintained patients. Unfortunately, despite these features of improved safety and abuse deterrence, buprenorphine 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 a number of cases of accidental poisonings of small children. Therefore, an additional depot injection which would be difficult to divert or abuse, would be less likely to be accidentally ingested by small children and offers potential advantages. In addition, a depot or implantable product that provides a sufficient plasma level of buprenorphine to block the effects of exogenous opioids, would enforce compliance so that patients could not periodically discontinue use to allow the blocking effect to dissipate in order to experience the effects of their opioids of choice. Importantly, some patients also express a preference for a long-acting treatment that reduces fluctuations in plasma levels and removes the need to think daily about taking medication.

3.1. Clinical Development of CAM2038

The clinical development of CAM20388 was undertaken with advice from the Division and was described in previous reviews. The program comprised PK studies, an inpatient opioid blockade study (HS-13-478) and a randomized, double-blind, double-dummy, active-control efficacy study (HS-11-421).

[3] Subutex, buprenorphine sublingual tablets (Reckitt Benckiser (now Indivior) NDA 20732) and Suboxone, buprenorphine/naloxone sublingual tablets (Reckitt Benckiser (now Indivior) 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.

No additional information was submitted with this application.

3.2. Safety Concerns Related to Formulation

One potential risk associated with Brixadi, which differentiates it from transmucosal formulations of buprenorphine, is the concern that serious consequences could ensue if the product were injected intravenously. A Risk Mitigation and Evaluation Strategy (REMS) is proposed to ensure that the product is administered appropriately. Preclinical data reviewed in the previous two application submissions, suggested that if the drug product were to be administered intravenously, it would either gel rapidly and potentially block the injected vessel as it apparently did in preclinical studies (i.e., the rat tail vein), or, if the injected vein is larger and the product does not gel quickly enough, it could result in a lung embolus or eventually be lodged in other small capillaries. This raised a safety concern about the possible consequences of this type of misuse, which could involve occlusion, tissue damage, or possibly embolus. Available post-marketing data from the Buvidal program has not revealed adverse events associated with intravenous injection. However, the Buvidal product is also marketed under a restricted distribution (similar to the proposed REMS) to mitigate potential risk.

3.3. Legal and Regulatory Issues Constraining Buprenorphine Treatment

Buprenorphine is a Schedule III Controlled Substance and physicians prescribing buprenorphine must comply with the relevant aspects of the Controlled Substances Act. In addition, the provision of agonist treatment of opioid addiction is governed by certain legal requirements. Unlike methadone, buprenorphine may be prescribed by physicians meeting certain requirements. Methadone treatment of opioid addiction is delivered in a closed distribution system (opioid treatment programs, OTPs) that originally required special licensing by both Federal and State authorities, under the Narcotic Addict Treatment Act of 1974.

Under the provisions the Drug Addiction Treatment Act of 2000 (DATA 2000), qualifying physicians may obtain a waiver from the special registration requirements in the Narcotic Addict Treatment Act of 1974, and its enabling regulations, to treat opioid addiction with Schedule III, IV, and V opioid medications that have been specifically approved by FDA for that indication, and to prescribe and/or dispense these medications in treatment settings other than licensed OTPs, including in office-based settings[4]. The Applicant has been advised by DEA that the physician who prescribes CAM 2038 must be DATA-waived, or practicing in an OTP where DATA waivers are not required. The product may be injected by a non-waived health care provider.

[4] The Comprehensive Addiction and Recovery Act (CARA) of 2016 (P.L. 114-198) extended the privilege of prescribing buprenorphine in office-based settings to qualifying nurse practitioners (NPs) and physician assistants (PAs).

4. Product Quality

The CAM2038 FluidCrystal subcutaneous injection depot drug product is a sterile, yellowish to yellow clear liquid which is [redacted] (b) (4) 1 mL long clear glass syringes with grey plungers.

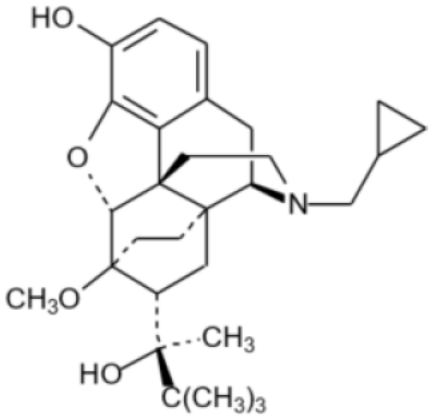
Figure 2: Visual of Combination Product

[redacted] (b) (4)

It is a lipid-based parenteral (subcutaneous injection) extended-release product (once weekly or once monthly dosing) based on the proprietary FluidCrystal (hereinafter denoted FC) injection depot technology.

The active ingredient in CAM 2038 is buprenorphine free base, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist. The molecular weight of buprenorphine free base is 467.6, and its molecular formula is C29H41NO4. Chemically, buprenorphine is (2S)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3- hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol. The structural formula is shown below.

Figure 3: Structural Formula of Buprenorphine



The CAM2038 q1w (weekly) solution consists of 50 mg buprenorphine base (BUP)/mL, 10% w/w ethanol (EtOH) and Soybean Phosphatidylcholine (SPC)/Glycerol Dioleate (GDO) in the weight ratio 50/50 to final volume. The CAM2038 q4w Monthly solution consists of 356 mg

buprenorphine base (BUP)/mL, 30% w/w N-methyl-2-pyrrolidone (NMP), and SPC/GDO in the weight ratio 40/60 to the final volume. The injection products utilizing the lipid-based formulations are low viscosity liquids. When the product is injected into the subcutaneous tissue, the formulation absorbs interstitial aqueous body fluid and transforms the liquid to a highly viscous gel. According to the applicant, (b) (4) CAM2038 q1w and CAM2038 q4w drug product. No changes were made to or issues identified with the manufacturing of the drug substance. Similarly, no changes were made to the previously acceptable method and method validation data (b) (4) Refer to previous NDA reviews for buprenorphine composition data for the doses of CAM2038 q1w and CAM208 q4w formulations as well as stability and specification data (which is unchanged from the previous review).

As with previous review cycles, part of the manufacturing process for Brixadi is completed at two facilities:

1. Pharmaceutics International, Inc. (b) (4) | FEI: 3006503102 | DUNS: 049185696
2. Pharmaceutics International, Inc. (b) (4) | FEI: 1000513101 | DUNS: 878265586

In July 2020, during the last application review cycle, these two facilities were inspected and significant Good Manufacturing Practice (GMP) deficiencies were identified as part of a pre-approval inspection (PAI) for an NDA unrelated to this one. The company (Pii) made an internal decision to shut-down those manufacturing facilities to address the deficiencies. After an October 2020 re-inspection, two 483 forms were issued to the manufacturer. The deficiencies in those forms covered (b) (4) The facilities were determined to be "Official Action Indicated" (OAI) and the Office of Pharmaceutical Manufacturing Assessment (OPMA) issued a recommendation to withhold approval of NDA 210136.

With this submission, a PAI (reinspection) at the two facilities was conducted for NDA 210136 (and other applications) between July 26 and Sep 29, 2021. Significant inspectional findings were again noted. At the time of this review, the outcome of the follow-up inspection has not been finalized as OAI; however the recommendation based on the inspection is to withhold approval for both the drug product manufacturing facility and the principal facility for drug product testing because of the issues/repeat observations identified. In the context of these inspectional findings, it remains unclear if the manufacturing of Brixadi is directly impacted, but the conditions of the site are not favorable for safe manufacturing.

Braeburn contracted with a third party, (b) (4) to provide in-person oversight of the manufacturing process. OPMA acknowledges receipt of these submissions, but is unable to comment on the proposal. Due to the ongoing issues addressed during inspection, a recommendation for approval cannot be made.

5. Nonclinical Pharmacology/Toxicology

The previous Pharmacology/Toxicology reviews focused on the safety of the CAM2038 formulations, and the two novel excipients, N-methyl-pyrrolidone (NMP), found in the monthly product, and glycerol dioleate (GDO), a diglyceride, found in both products. Additional details from the previous two application cycles can be found in the Pharmacology/Toxicology reviews conducted by Gary Bond, Ph.D., Jaime D'Agostino, Ph.D., and Elizabeth Bolan, Ph.D. In the second review cycle, the Applicant submitted new extractable and leachable data to address the deficiencies identified in the first review cycle. However, at the conclusion of that cycle, the review team identified three remaining concerns that could be addressed through post-marketing requirements (noting that the majority of previously identified leachables were adequately qualified and that the levels of the unidentified compounds in the formulations were predicted to be low. With this review cycle, the Application submitted the results of two reproductive and developmental toxicology studies to address two of the original nonclinical post-marketing requirements (PMRs 3 and 4). However, the Applicant did not submit new leachable data or the elemental impurity analysis. Refer to the PMR section of this review for the remaining nonclinical PMRs.

6. Clinical Pharmacology

No new clinical pharmacology information was submitted with this review cycle. The following summary of clinical pharmacology is based on the Clinical Pharmacology review conducted by Suresh Narahansetti, PhD. during the first two review cycles, and on the language proposed by the Division for drug labeling in the second cycle.

In Dr. Narahansetti's 2018 Clinical Pharmacology review, it was noted that trough levels of Brixadi from the upper arm site failed to meet the set bioequivalence criteria for 80 to 125% (see Table 4 and Table 7 and in the proposed label). To ensure expeditious attainment of therapeutic trough levels, the upper arm is not recommended as a site for initiation of Brixadi dosing but may be used in patients already at steady-state. This change was agreed upon at the conclusion of the second review cycle. The indented text in Arial font below is based on the Division's recommended labeling language specifically for Brixadi for this review cycle:

> Absorption
> BRIXADI is an extended-release formulation of buprenorphine designed for subcutaneous administration. BRIXADI is available in two regimens: weekly and monthly. Following single doses of BRIXADI (weekly) or BRIXADI (monthly), the buprenorphine C_{max} and AUC_{inf} increase dose-proportionally.
>
> The steady-state PK of buprenorphine following BRIXADI (weekly), BRIXADI (monthly) and their comparison to sublingual SUBUTEX across three studies are shown in Table 5. In these studies, BRIXADI (weekly) was administered for 4 or

4 to 7 weekly doses, BRIXADI (monthly) was administered for 4 monthly doses, and SUBUTEX was administered for 7 daily doses.

After BRIXADI subcutaneous injection, the buprenorphine plasma concentration increases with a median time to maximum plasma concentration (t_{max}) of about 24 hours for the weekly BRIXADI and 6-10 hours for monthly BRIXADI. Based on trough levels after each dose, steady-state exposure is reached just prior to administration of the fourth weekly or monthly dose.

After four repeated doses of BRIXADI (weekly) (16 mg) AUCτ (0-7d), C_{max} and C_{trough} values are ~40% higher exposure compared to the first dose. Based on cross-study comparisons, four repeated doses of BRIXADI (monthly) (128 mg) results in 68%, 65%, and 124% higher AUCτ (0-28d), C_{max} and C_{trough} values, respectively compared to the first dose.

Table 5: Summary of Steady-State PK Parameters of Buprenorphine After Subcutaneous Buttock Injections of BRIXADI (Weekly) and BRIXADI (Monthly) and SL Administration of SUBUTEX

Drug product dose			C_{av} (ng/mL)			$C_{max,ss}$ (ng/mL)			C_{trough}[a] (ng/mL)		
SL BPN	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly
8 mg	16 mg	64 mg	1.2	2.1	2.0 $	4.7	4.3	4.0 $	0.7	0.8	1.3 $
16 mg	24 mg	96 mg	1.8	2.9 $	2.9 $	6.5	5.5 $	6.0 $	1.0	1.4 $	2.0 $
24 mg	32 mg	128 mg	2.5	4.2	3.9	8.2	6.9	11.1	1.4	2.6	2.1

Source: Table 7, Physician Package Insert
* Average value of two studies
$ Simulated
a C168h for BRIXADI (weekly), C28d for BRIXADI (monthly) and C24h for Subutex

Effect of injection Site on PK of BRIXADI
After multiple dose subcutaneous injections of 32 mg BRIXADI weekly product at different injection sites (abdomen, thigh, buttock or upper arm), a comparable PK exposure was observed. However, injection in the arm site was associated with approximately 10% lower plasma levels than other sites.

Distribution:
Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Elimination:
Buprenorphine is metabolized and eliminated in urine and feces. The apparent terminal plasma half-life of buprenorphine following subcutaneous injection of BRIXADI ranged between 3 to 5 days for BRIXADI (weekly) and 19 to 26 days for BRIXADI (monthly) as a result of the slow release of buprenorphine from the subcutaneous depot.

Metabolism:
Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity.

Norbuprenorphine steady-state plasma concentrations in humans after subcutaneous injection of BRIXADI (weekly or monthly) are low compared to buprenorphine (AUC norbuprenorphine/ buprenorphine ratio of 0.35).

Excretion:
A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of the buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Specific Populations

Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of BRIXADI has not been studied. In a pharmacokinetic study, the disposition of buprenorphine was determined after administering a 2.0/0.5 mg Suboxone (buprenorphine/naloxone) sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine in patients with hepatic impairment was compared to disposition in subjects with normal hepatic function.

In subjects with mild hepatic impairment, the changes in mean $C_{max,}$ $AUC_{0\text{-last}}$, and half-life values of buprenorphine were not clinically significant. For subjects with moderate and severe hepatic impairment, mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine were increased *[see Warnings and Precautions (5.14) and Use in Specific Populations (8.6)].*

Renal Impairment
The effect of renal impairment on the pharmacokinetics of BRIXADI has not been studied. Clinical studies of BRIXADI did not include subjects with severe renal impairment. Less than 1% is excreted as unchanged buprenorphine in urine following IV buprenorphine administration. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine [*see Use in Specific Populations (8.7)].*

Population PK analyses indicated no notable relationship between creatinine clearance and steady-state buprenorphine plasma concentrations.

HCV infection
In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine were not clinically significant in comparison to healthy subjects without HCV infection.

7. Clinical Microbiology

N/A

8. Clinical/Statistical- Efficacy

Evidence of efficacy for Brixadi Weekly and Monthly doses derive from two studies, an inpatient opioid blockade study (HS-13-478) and a randomized, double-blind, double-dummy, active-control efficacy study (HS-11-421). The blockade study demonstrated that CAM2038 24 mg weekly and CAM2038 32 mg weekly are capable of blocking the subjective effects of a clinically-relevant dose of opioid agonist, and this blockade becomes longer-lasting after two weekly doses. The effect of this blockade was shown to translate to clinical efficacy as demonstrated by comparable outcomes in patients treated with a regimen of weekly followed by monthly CAM2038 compared with patients treated with sublingual buprenorphine/naloxone in the double-blind study.

Taken together, and considering the established efficacy of the reference product, Subutex, these studies provide substantial evidence of efficacy for CAM2038 in the treatment of moderate or severe OUD in patients who tolerate at least an initial test dose of buprenorphine. CAM2038 weekly is suitable for starting treatment, while CAM2038 (monthly) has been studied only in patients already in established treatment.

The text below briefly summarizes the design and findings of these two studies using labeling language proposed by the Division. Additional detail may be found in reviews from the previous review cycles. No new efficacy data were submitted for this cycle.

8.1. Blockade study (HS-13-478)

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 indented text in Arial font below is based on the Division's recommended labeling language for this review cycle. Refer to the primary review of the blockade study, performed by CSS Medical Officer, Dr. Alan Trachtenberg, and Biostatistics Reviewer, Wei Liu, from the first

review cycle (2017); and the Pharmacometrics section of the Clinical Pharmacology review, performed by Dr. Michael Bewernitz, for additional information.

The opioid blockade study assessed the blockade of subjective opioid effects, PK, and safety of BRIXADI weekly in 47 patients with moderate or severe opioid use disorder. Forty-six patients completed the study. Subjects were randomized to receive two injections of BRIXADI (weekly) once weekly for 2 weeks either at a 24 mg or 32 mg dose level.

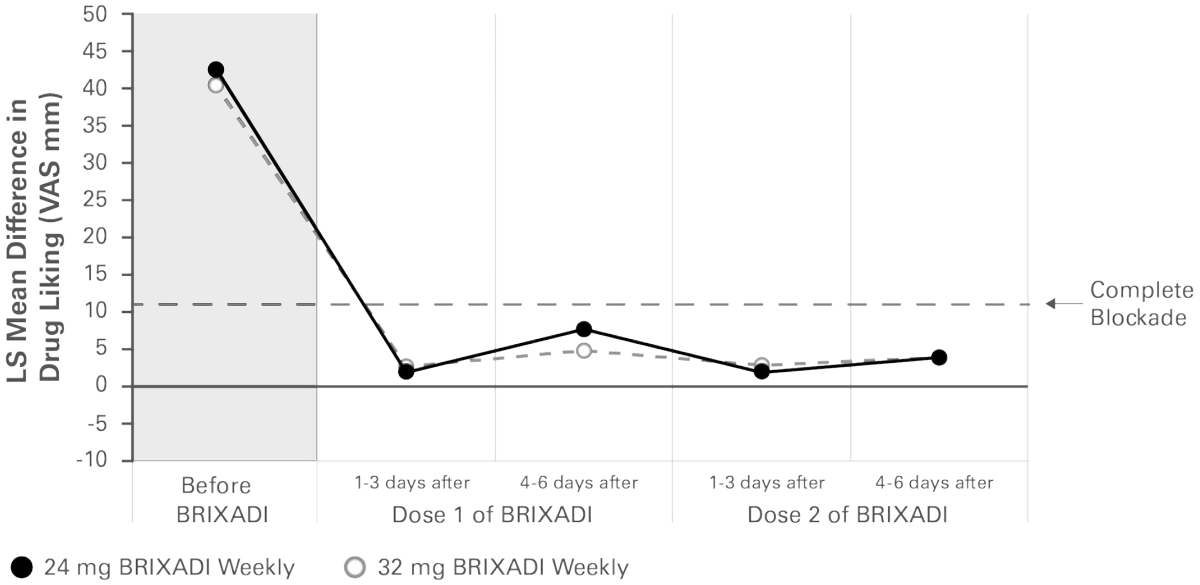
After stabilization on immediate-release morphine, all patients completed a 3-day qualification/baseline hydromorphone (HM) challenge session, which included intramuscular administration of 3 doses of HM (0 mg [placebo], 6 mg and 18 mg) once daily for 3 consecutive days. Patients were not exposed to buprenorphine during the baseline/qualification phase.

Following the qualification phase, eligible patients were randomly assigned to receive 2 doses of either 24 mg (22 patients) or 32 mg (24 patients) BRIXADI (weekly) with each dose administered one week apart. Two HM challenge sessions (Days 1-3 and 4-6 for the first session and Days 8-10 and 11-13 for the second session, respectively) were conducted after each dose of BRIXADI (weekly).

The primary endpoint was the peak effect (E_{max}) on a 100-mm bipolar (i.e., 50=neutral response) “Drug Liking” Visual Analog Scale (VAS). The pre-defined upper bound of the 95% CI for complete blockade of drug liking was an 11 mm difference between VAS E_{max} scores obtained for HM doses compared with placebo.

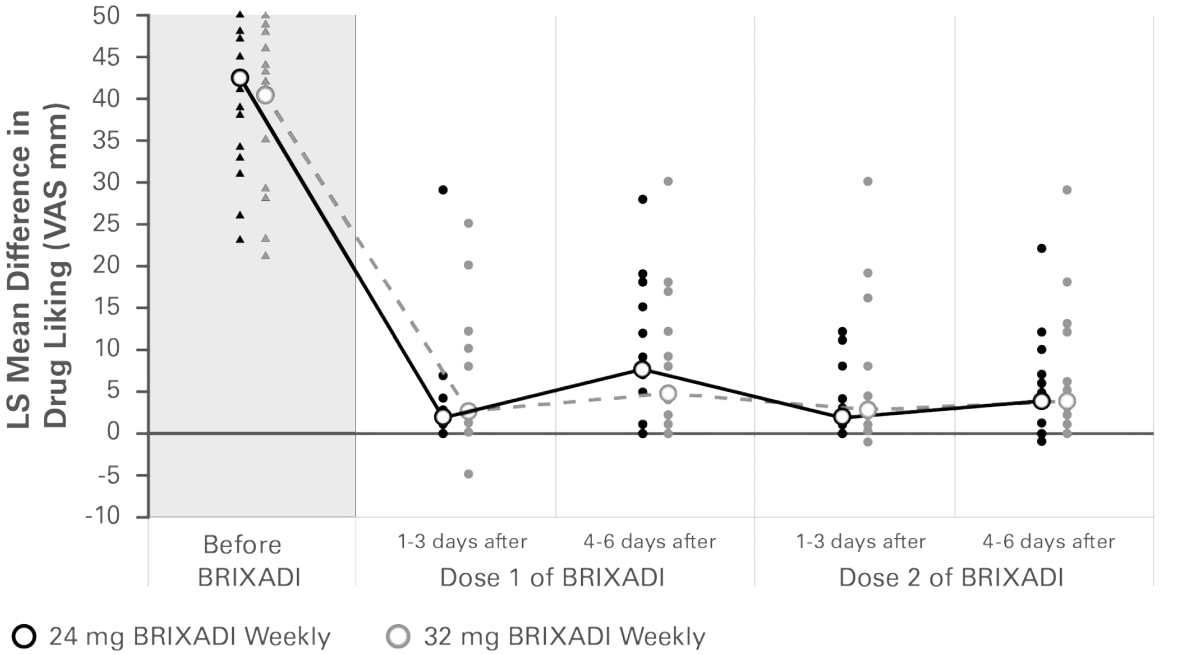
During the qualification/baseline phase, mean E_{max} scores for placebo were neutral while intramuscular hydromorphone 6 and 18 mg produced dose-related increases in the scores. Beginning with the first injection of BRIXADI (weekly) 24 mg or 32 mg weekly, no active intramuscular hydromorphone dose resulted in a mean drug liking VAS E_{max} score of 11 mm or greater when compared to placebo, which demonstrated complete blockade that was sustained throughout the first and second dosing intervals (see Figure 3). Individual subject scores are shown in Figure 4.

Figure 4: Mean Difference in Placebo-Corrected Peak Drug Liking



Source: Figure 15, Physician Package Insert

Figure 5: Mean Difference in Placebo-Corrected Peak Drug Liking With Individual Scores



Source: Figure 16, Physician Package Insert

Abuse

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

BRIXADI contains buprenorphine, a Schedule III controlled substance that can be abused similar to other opioids. Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with or referred for more intensive and structured treatment. Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines [see Warnings and Precautions (5.5)].

BRIXADI is distributed through a restricted distribution program, which is intended to prevent the direct distribution to a patient. BRIXADI should only be dispensed directly to a healthcare provider for administration by a healthcare provider. It is supplied in prefilled syringes and is intended for administration only by subcutaneous injection by a healthcare provider. The entire contents of the prefilled syringe should be administered.

Upon injection, BRIXADI spontaneously transforms from a low viscous solution to a liquid crystalline gel that encapsulates buprenorphine and releases it at a steady rate as the depot biodegrades [see Warnings and Precautions (5.1)].

Clinical monitoring for evidence at the injection site of tampering or attempting to remove the depot should be ongoing throughout treatment. No attempts to remove BRIXADI have been reported in clinical trials.

Dependence
Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. Monitor patients during discontinuation of BRIXADI for symptoms of withdrawal [see Warnings and Precautions (5.8)].

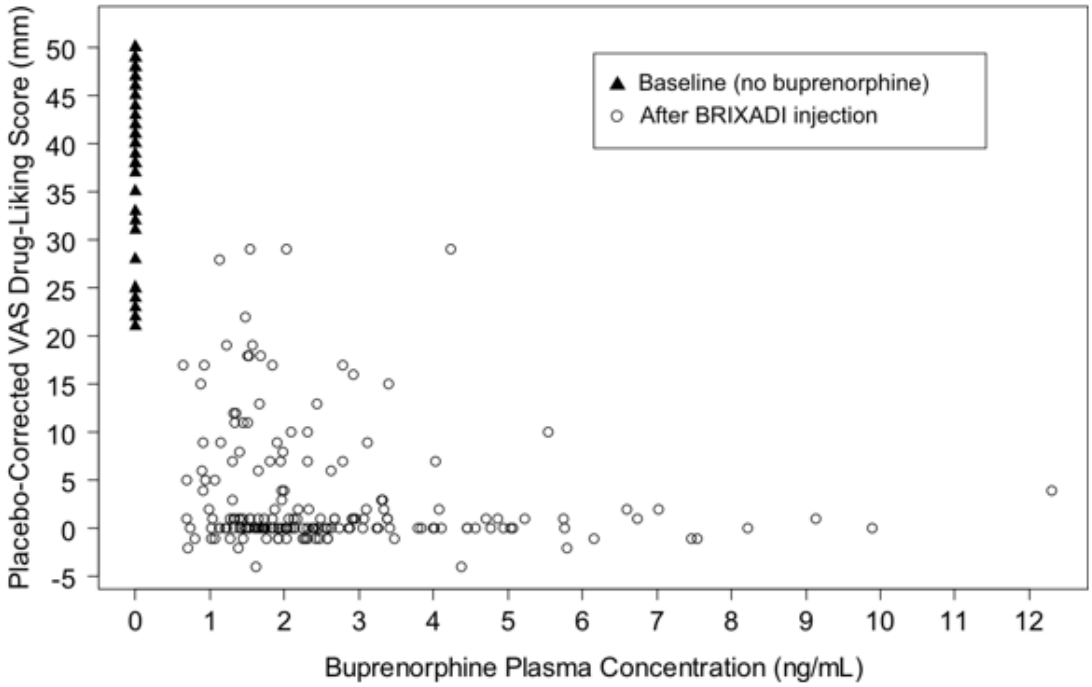
Due to the long-acting nature of BRIXADI, withdrawal signs and symptoms may not be evident immediately following the discontinuation of treatment.

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy [see Warnings and Precautions (5.6)].

Opioid Blockade
The opioid blockade study assessed the blockade of subjective opioid drug-liking effects and pharmacokinetics (PK) of BRIXADI (weekly) in 47 patients with moderate or severe opioid dependence. The primary endpoint was the maximum

rating (Emax) on the visual analogue scale (VAS) for drug-liking. After stabilization on immediate-release morphine, all patients completed a 3-day qualification/baseline hydromorphone challenge session consisting of 3 intramuscular doses of hydromorphone (0 mg, [placebo], 6 mg, and 18 mg) once daily for 3 consecutive days in a randomized, double-blind, crossover manner. Following the qualification phase, eligible patients received 2 injections of BRIXADI (weekly) for two weeks at either the 24 mg or 32 mg level. Two hydromorphone challenge sessions (3 consecutive days each) were conducted throughout the week after each weekly injection of BRIXADI (weekly). On average, the subjective effects (e.g., drug liking [Emax]) of 6 mg or 18 mg hydromorphone was blocked following injections of BRIXADI (weekly) at the 24 mg or 32 mg levels. The variability in drug-liking scores was wider for the 18 mg than the 6 mg hydromorphone dose level. In addition, for the 18 mg hydromorphone dose challenge, the drug-liking score variability was wider towards the end of the BRIXADI (weekly) dosing interval compared to earlier in the interval (e.g. Days 4-6 versus Days 1-3; Day 11-13 versus Day 8-10). Drug-liking score variability was wider for the 24 mg BRIXADI (weekly) dose level compared to 32 mg [see Clinical Studies (14.1)]. Figure 14 illustrates the relationship between buprenorphine plasma level and drug liking after 18 mg hydromorphone where data from the 24 mg BRIXADI (weekly) arm is pooled with data from the 32 mg BRIXADI (weekly) arm. The observed plateau for maximal response of drug-liking was reached at buprenorphine concentrations of approximately 1.5-2 ng/mL plasma levels.

Figure 6: Placebo-Corrected Drug Liking VAS vs. Plasma Buprenorphine Concentration Following 18 mg Hydromorphone Challenges for Pooled 24 mg and 32 mg Arms, From Proposed Drug-Labeling



Source: Figure 14, Physician Package Insert

8.2. Efficacy Study (HS-11-421)

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 indented text in Arial font below is based on the Division's recommended language for section 14.2 of the proposed drug label for this review cycle. Refer to the 2018 CDTL memo and the reviews conducted by Dr. Gioia Guerrieri (clinical) and Dr. James Travis (statistical) for additional information.

> The efficacy and safety of BRIXADI for the treatment of opioid use disorder was evaluated in a Phase 3, 24-Week, randomized, double-blind, double-dummy, active-controlled, multicenter study in patients who met the DSM-5 criteria for moderate or severe opioid use disorder and who were actively seeking but not currently receiving buprenorphine treatment. Patients were randomized to receive either BRIXADI injections with placebo sublingual tablets or sublingual buprenorphine/naloxone (SL BPN/NX) tablets with placebo injections. All patients received individual drug counseling for the duration of the study.

On the first day of treatment patients received an open-label 4 mg test dose of sublingual buprenorphine. Patients who tolerated the test dose (two patients did not tolerate the test dose) were randomized and given a 16 mg injection of BRIXADI (weekly) or matched placebo. During the next 6 days patients were allowed up to two further 8 mg injections as needed. Patients received an injection of 16, 24, or 32 mg on Day 8 matched to the dose they received in the previous seven days. Patients received injections weekly (every 7 days +/- 2-day window) for twelve weeks total and then transitioned to an equivalent dose of BRIXADI (monthly) (every 28 days, +/- 7-day window) for the remaining twelve weeks. Dose adjustments were permitted for the duration of the study. Supplemental 8 mg BRIXADI (weekly) injections were allowed during the second phase of the study and were also used in the active-controlled group. Overall, supplemental 8 mg injections were given to 14 patients (6.6%) in the BRIXADI arm and 17 patients (7.9%) in the SL BPN/NX arm. Table 6 shows the doses of BRIXADI (weekly) administered following the initial titration period and at the final visit before transition to BRIXADI (monthly) was allowed. Table 7 shows the first and final BRIXADI (monthly) dose administered to each patient.

Table 6: Number of Patients Receiving Each BRIXADI (Weekly) Dose at Selected Time-Points

BRIXADI (Weekly) Dose	Following Titration Period	End of Weekly Phase
16 mg	2	6
24 mg	128	84
32 mg	54	64

Table 7: Number of Patients Receiving Each BRIXADI (Monthly) Dose at Selected Time-Points

BRIXADI (Monthly) Dose	First BRIXADI (Monthly) dose	Final BRIXADI (Monthly) dose
64 mg	8	11
96 mg	84	83
128 mg	66	56
160 mg*	0	8

*not an approved strength
Source: Tables 8 and 9, Physician Package Insert

For the first twelve weeks patients completed weekly visits. For the final twelve weeks patients were transitioned to monthly visits. Patients were also required to complete three additional randomly scheduled visits during the final twelve weeks. Efficacy was evaluated using urine drug screens combined with self-

reported use of illicit opioid use. Missing urine drug screen samples and/or self-reports were counted as positive for illicit opioids.

A total of 428 patients were randomized equally (215 patients in the SL BPN/NX group and 213 in the BRIXADI group). Of the randomized patients, 69.0% (147/213) of the patients in BRIXADI treatment group and 72.6% (156/215) of the patients in the SL BPN/NX treatment group completed the 24-week period. Patient demographics and baseline characteristics are provided in Table 8.

Table 8: Patient Demographics and Baseline Characteristics

	BRIXADI (N=213)	SL BPN/NX (N=215)
Mean Age (Years)	38.7	38.0
Sex %		
Male	56.8	66.0
Female	43.2	34.0
Race or Ethnicity %		
White	74.6	76.3
Black or African American	22.1	22.3
American Indian or Alaska Native	0.9	0.5
Asian	0.5	0
Native Hawaiian or Other Pacific Islander	0.5	0
Other	1.4	0.9
Primary Opioid of Use at Initiation %		
Heroin	71.4	70.2
Prescription Pain Reliever	28.6	29.8
Injectable Route %	53.5	51.2
Substance Use by Urine Toxicology Prior to Randomization %		
Amphetamines	22.1	18.6
Barbiturates	1.4	0.5
Benzodiazepine	21.1	21.9
Cocaine	30.5	32.6
Cannabinoids	34.3	36.3
Fentanyl	29.1	22.8
Phencyclidine	1.9	0.5
Medical History %		
Anxiety	14.1	18.6
Back Pain	15.5	18.6
Depression	11.7	13.0

Source: Table 10, Physician Package Insert

Table 9 below illustrates the proportion of patients who were considered to be responders. A patient was a responder if they met all of the following criteria:

- Negative opioid assessment (urinalysis and self-report) during week 12 (evaluated during Week 13 visit).
- No more than one positive opioid assessment in the three illicit opioid use assessments performed during week 9 to 11 (evaluated during visits at Weeks 10 to 12).
- Negative opioid assessment during the final month of the study.
- No more than one positive opioid assessment at the three scheduled monthly visits and three random site visits.

This responder definition was designed to identify patients who were successfully treated with both BRIXADI (weekly) (administered in the first 12 weeks of treatment) and BRIXADI (monthly) (administered in the second 12 weeks of treatment). Therefore, patients were required to have negative opioid assessments at the end of each treatment phase. Each phase also included an allowable grace period (an initial period of time when positive opioid assessments were not taken into account) and the definition also allowed for sporadic positive assessments. Based on the results of this trial, the efficacy of BRIXADI was demonstrated. Table 11 shows the response rate for each treatment arm along with the associated 95% confidence interval for their difference.

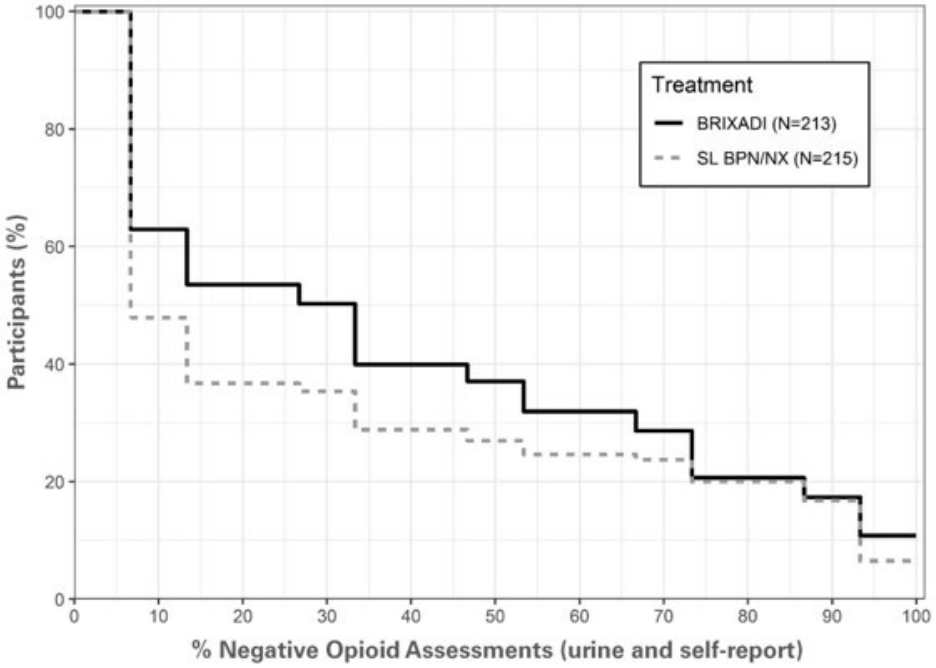
Table 9: Number (Percentage) of Patients Who Met the Responder Definition

BRIXADI Injection with placebo sublingual tablets (N=213)	SL BPN/NX Tablets with Placebo Injections (N=215)	Treatment Difference (95% CI)
36 (16.9%)	30 (14.0%)	2.9% (-3.9%, 9.8%)*

* The lower bound of the confidence interval was within the agreed upon non-inferiority threshold of −10%.
Source: Table 11, Physician Package Insert

The cumulative distribution function (CDF) of the percentage of negative opioid assessments (urine samples negative for illicit opioid use combined with self-reports negative for illicit opioid use) from Week 4 through Week 24 are shown in Figure 6 and Table 10. The figure and table are cumulative, so that a patient whose percentage of opioid-free assessments is, for example 50%, is also included at every level of negative opioid assessments below 50%. Missing values and values after premature discontinuation were considered positive. Based on the CDF of the percentage of negative opioid assessments, superiority was demonstrated with BRIXADI with statistical significance compared with SL BPN/NX. However, on the right-hand side of the curves where patients were reporting mostly negative opioid assessments (80% or greater) there was little to no difference between BRIXADI and SL BPN/NX.

Figure 7: Patients Achieving Varying Percentages of Negative Opioid Assessments (Urine and Self-Report) in Weeks 4 Through 24



Source: Figure 17, Physician Package Insert

Table 10: Patients Achieving Varying Percentage of Opioid-Negative Assessments (Urine and Self- Report) (Weeks 4-24)

Percentage of Opioid-Negative Assessments (Urine and Self Report)	Number (%) of Patients	
	BRIXADI 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: Table 12, Physician Package Insert

9. Safety

The review strategy for this cycle involved evaluating the newly-reported post-marketing information and comparing the findings to the established safety profile as documented in the previous review cycle. The post-marketing data did not demonstrate any previously unknown safety concerns regarding the risks of buprenorphine or the Brixadi drug product. The sections below detail the previous findings and any pertinent observations about the updated safety data reviewed for this submission.

Updated safety information reviewed for this cycle included:

- A Clinical Information amendment providing an overview of the safety findings of CAM2038 that occurred since the third application cycle (including 15-day safety reports submitted to IND from the post-marketing reports of Buvidal) with a cut-ff date of April 30, 2021.
- Annual Data Safety Update Report (DSUR) #7 from Camurus and Braeburn for CAM2038 safety data received from worldwide sources (data lock February 19, 2021).
- The 2019 Periodic Brief Risk Evaluation Report (PBRER) for Buvidal, marketed by Camurus, with a July 30, 2019 data lock, unchanged from the previous application cycle.
- Investigator Brochure 15(also submitted to INDs 114082 (b) (4)).
- Annual Report for IND 140724 (May 2021)
- Annual Report for IND 146193 (December 2020)
- Annual Report for IND 146501 (May 2021)

Clinical trial safety data to support Brixadi drug approval was unchanged from previous review cycles and were derived from Phase 1 PK studies, the blockade and efficacy studies described above, and a 24-week, Phase 3 open-label study, which enrolled patients who could be new to treatment ("new entrants") or already in established treatment with transmucosal buprenorphine ("transfer") (Study 499). In the clinical development of CAM2038 (Brixadi) for OUD during the initial review, 729 subjects were exposed to at least one dose of the study, which included healthy volunteers. In the pooled Phase 3 studies, 440 unique patient exposures to Brixadi were reported by the Applicant. In these studies, a total of 305 patients were exposed to Brixadi for at least 24 weeks and 132 patients were exposed for at least 48 weeks.

As of April 08, 2021, a total of 1,646 subjects[6] have been exposed to the Brixadi/Buvidal investigational drug product, CAM2038, in sponsored clinical studies.

(b) (4)

[6] With the Applicant-provided reporting interval ending 12/31/2020, the total number (b) (4) exposed to CAM2038 in the United States. And additional 60 patients were exposed to CAM2038 through the Australian trial, HS-17-585.

At the time of DSUR #7, two clinical trials were completed (not for support of this application), with no ongoing commercial clinical trials. The first, (b) (4) (b) (4) investigating CAM2038 (b) (4) The second, sponsored by Camurus (Sweden), was an open-label, active comparator, multi-center Australian clinical trial comparing both formulations of CAM2038 to a buprenorphine standard of care in adults with OUD (trial HS-17-585).

Additionally, Braeburn has provided product for use in three ongoing investigator-initiated studies. The updated safety information for these activities was obtained from the Applicant-provided clinical information and from annual reports submitted to the Agency (see Table 11, below). No new safety issues were identified that would alter the risk/benefit conclusion or require significant modifications of the proposed labeling.

Table 11: Investigator-Initiated Trials for Which Braeburn is Currently Providing CAM2038 (Brixadi)

Study Name	*Emergency Department- INitiated bupreNOrphine and VAlidaTIOn Network Trial (ED-INNOVATION)*	*Medication Treatment for Opioid Use Disorder in Expectant Mothers (MOMs): A Pragmatic Randomized Trial Comparing Two Buprenorphine*	*A comparative effectiveness trial of extended-release naltrexone versus extended-release buprenorphine with individuals leaving jail*
ClinicalTrials.gov Identifier	**NCT04225598**	**NCT04212065**	**NCT04408313**
Investigational New Drug Application number	**IND 146193**	**IND 140724**	**IND 146501**
Study Objectives	Evaluate implementation of emergency department (ED)-initiated buprenorphine; compare extended-release buprenorphine with sublingual buprenorphine in ED Opioid Use Disorder patients; Develop and validate electronic health record phenotypes of opioid-related illnesses; Enhance active disease surveillance; Better identify patients eligible for inclusion.	Evaluate the impact of treating opioid use disorder in pregnant women with extended- release buprenorphine, compared to sublingual buprenorphine, on maternal-infant outcomes; Testing a conceptual model of the mechanisms by which extended-release buprenorphine may improve maternal-infant outcomes, relative to sublingual buprenorphine	Determine the effectiveness of extended-release buprenorphine compared to extended-release naltrexone; To calculate the cost to the jail/county health system of implementing extended- release buprenorphine and extended-release naltrexone, and determine the relative value, including the costs associated with the interventions in the community, from a county and state-policymaker and societal perspective.

Study Status	Ongoing: 95 enrolled, 7 discontinued, 55 stayed in study. No deaths. No SAEs. One TEAE related to precipitated withdrawal.	Ongoing. 13 have been enrolled and continue in study. No Deaths. No SAEs. No TEAEs of interest for this review.	Ongoing: 32 enrolled, 10 discontinued (not for reasons related to study drugs). One death in incarcerated patient due to suspected overdose. No SAEs, No TEAEs of interest for this review. Patients are randomized to one of two treatments and study remains blinded at this time.

Source: *Reviewer, adapted from Applicant-provided, clinical information amendment*

9.1. Safety data reporting

Since the initial clinical trial safety data were submitted for review, CAM2038 (as Buvidal) in both the weekly and monthly formulations, has been marketed in twelve countries[7] by Camurus. Per Camurus' May 2021 company presentation[8], almost 18,000 patients have been treated[9].

Braeburn indicated that the data-lock for the non-IND post-marketing safety reporting for this application was December, 2020 and provided their summary of the Buvidal post-marketing safety data in the Clinical Information Amendment. An overview of those findings is described in the relevant subsections below.

9.1.1. Deaths

Clinical Program:

No additional deaths in the clinical program supporting this NDA were reported by the Applicant. One death was previously reported in the clinical program (during the first review cycle), in a patient treated with CAM2038 in Study 421 (a 41-year-old female with no other reported medical history was hit by a car and died on Study Day 147). There were no factors suggesting a causal link to the study drug.

[7] From the 2021 Applicant-Provided Clinical Information Amendment: Buvidal was made commercially available in Australia, Austria, Belgium, Denmark, Finland, Germany, Iceland, Ireland, Norway, Spain, Sweden, and United Kingdom. In Australia it is provided in hospitals and specialist drug rehabilitation clinics through the Patient Familiarization Program.

[8] https://www.camurus.com/wp-content/uploads/2021/05/Camurus-company-presentation-May-2021.pdf

[9] Per Camurus' 2020 annual report, ~ 14,000 patients had been treated with Buvidal: https://www.camurus.com/wp-content/uploads/2021/04/Camurus-Annual-Report-2020.pdf

No new deaths were reported in the DSUR for this reporting period[10] and no overdose deaths or clearly medication-associated deaths were identified in the clinical program.

Post-marketing data:

One new death was reported to the Agency by Braeburn in the clinical information safety amendment update with this review cycle (GB-CAM-21-00192, listed below). In addition, three expedited non-IND MedWatch case reports were submitted by the Applicant to IND 114082 July 2021. These cases were obtained from Buvidal post-marketing sources and provided by Camurus to Braeburn after Camurus was made aware of them from a British presentation. No details of those reports were made available and are therefore excluded from this review.

A summary of deaths related to the post-marketing safety data base of Buvidal (2019-2021) is outlined below in Table 12. The summary of findings from the causes of death (known or unknown) submitted by the Applicant do not change the risk-benefit profile of Brixadi.

[10] One fatality was reported to Braeburn by Camurus in the third review cycle of NDA 210136 and involved a 68-year-old male with OUD a history of end-stage renal disease who died from sepsis and had participated in trial HS-17-585 (now completed). The patient continued treatment with CAM2038 in the Special Access Scheme until Buvidal was marketed in Australia. Review of the events confirm that the death was likely not related to Buvidal.

Table 12: Summary of Deaths Obtained from Postmarketing Sources through April 30, 2021

Case Reference #	Date of event [initial receipt date to IND 114082], location	Age in years (sex), Past Medical History	Buvidal/ CAM2038 dose (duration)	Case description	Reported to NDA 210136
GB-CAM-20-00032*	(b) (6) [3-24-2020], UK	63 (M), HCV**, alcohol use disorder, OUD, "mental disorder, unspecified"	16 mg Weekly (10 weeks)	Patient was started on Buvidal (b) (6) after transfer from oral buprenorphine, 6 mg daily (duration unknown). 14 days after the most recent dose of Buvidal had been administered, outreach team attended home address (when patient had missed appointment) and the patient was found dead at home. At his last appointment, the patient-reported "sickness and loose stool" and was referred to a primary care doctor. The treatment team called the patient the next day, who reported symptom improvement and declined seeking additional treatment. Not deemed related to the study drug by Camurus. Autopsy report and concomitant medications not reported.	Y
SE-CAM-20-00091	(b) (6) [6-18-2020], Sweden	35 (M), OUD, chronic liver disease, bipolar disorder, attention deficit hyperactivity disorder	96 mg Monthly (20 weeks)	Patient began treatment with Buvidal 24 mg Weekly in (b) (6) (transferred from Suboxone, 16 mg daily since (b) (6)). Treatment switched to Buvidal Monthly, 96 mg, (b) (6) for severe OUD. Laboratory results were "unremarkable" (b) (6) but did not include buprenorphine levels. 8-days after last Buvidal Monthly dosing (b) (6), the patient was found dead. The patient was not hospitalized before death, per MedWatch report, but per the Applicant, the patient was in a custodial setting and known to the facility for attempting to obtain illicit substances. Autopsy revealed elevated levels of plasma and urine buprenorphine, elevated levels of norbuprenorphine, and enlarged liver. "Other narcotic drugs detected, including methylphenidate" but details remained unavailable Per the Applicant, methylphenidate was not prescribed preceding death. Concomitant medications included: duloxetine, lithium citrate, metformin, olanzapine,	Y

Case Reference #	Date of event [initial receipt date to IND 114082], location	Age in years (sex), Past Medical History	Buvidal/ CAM2038 dose (duration)	Case description	Reported to NDA 210136
				simvastatin,budesonide/formoterol, and methylphenidate hydrochloride. Autopsy report not available to Applicant (Braeburn) and the contribution of Buvidal to death could not be determined based on the information provided. This case is listed as "overdose" under serious adverse events.T	
AU-CAM-20-00181	(b) (6) [9-17-2020], Australia	32 (M), OUD, "psychiatric condition, unspecified", and HCV	96 mg Monthly (7 weeks)	Patient died 3-weeks after second dose of Buvidal 96 mg. Patient was in a custodial setting, experienced dizziness, loss of consciousness, subsequent cardiac arrest and death during the course of pushing a wheelbarrow. Concomitant medications included olanzapine and glecaprevir/pibrentasvir. Follow-up toxicology, and autopsy results were unavailable. Per the Applicant, the contribution of Buvidal to death could not be determined. Based on the information provided, Buvidal cannot be excluded as a contributing factor.	Y
AU-CAM-20-00182	(b) (6) [9-17-2020], Australia	34 (M), OUD, hypertension, hypercholesterolemia, obesity (160 kg), diabetes mellitus, and "psychiatric condition, unspecified"	8 mg Weekly (one day)	Patient was dosed with Buvidal, 8 mg, on (b) (6) after a test dose of SL buprenorphine. He was found in cardiopulmonary arrest on (b) (6) the day after Buvidal dosing. Resuscitation was attempted but unsuccessful. Concomitant medications included fenofibrate, paliperidone, quetiapine, escitalopram, metformin/dapagliflozin, simvastatin, atorvastatin, metoprolol, dulaglutide, perindopril. Follow-up toxicology, and autopsy results were not available. Per the Applicant, the contribution of Buvidal to death could not be determined. Based on the information provided, Buvidal cannot be excluded as a contributing factor.	Y

Case Reference #	Date of event [initial receipt date to IND 114082], location	Age in years (sex), Past Medical History	Buvidal/ CAM2038 dose (duration)	Case description	Reported to NDA 210136
GB-CAM-21-00192	Submitted with NDA 210136 on June 15, 2021	45 (M), OUD, cocaine use disorder, drug abuse	128 mg monthly (one day)	On (b) (6) the patient presented to treatment clinic in opioid withdrawal. The patient's concurrent medical history included cocaine use and heroin addiction with recent use of approximately 1g heroin smoked daily. He was noted to be 'quite anxious' at assessment and his urine drug screen was positive for heroin and cocaine. The same day, the patient initiated treatment with Buvidal 128 mg for heroin addiction. After 15 minutes of observation, the patient left without adverse effects. The following morning, on (b) (6) the patient informed the treatment clinic that he was experiencing opioid withdrawal symptoms (specific symptoms were not reported), nausea and vomiting. Patient was prescribed metoclopramide 10 mg, and the medication was collected at the pharmacy by the patient. On the same day, approximately 4 hours later, the patient contacted the clinic again in distress reporting difficulty breathing. When the ambulance arrived at his home, he had already experienced a cardiac event. The patient died at home, despite attempts at resuscitation. Toxicology report is pending. Per the Applicant, the contribution of Buvidal to death could not be determined. Based on the information provided, Buvidal cannot be excluded as a contributing factor.	Y

This table reflects Applicant-provided updates about each death submitted to the Agency through April 2021
**Case reported by non-medical professional*
*** HCV= hepatitis C virus*
Source: Clinical Reviewer

9.1.2. Serious Adverse Events

Pre-marketing data:

A total of 20 SAEs occurred among 17 subjects of the 729 exposed to CAM2038 across the OUD treatment clinical program. None were related to injection site reactions. In Study 421, SAEs were reported in five (2.3%) of the CAM2038 group and in 13 (6%) of the SL BPN group. Accidental overdoses (3) were reported in the SL BPN group but not the CAM2038 group. One event (vomiting) was deemed plausibly related to study drug. In the second review cycle (2018), Braeburn included an SAE that occurred (b) (4) that was reported (b) (4) and should have been included in the original NDA submission. The case involved a woman who presented to the ER one day after her first injection of 8 mg CAM2038 with "acute onset altered mental status, rhabdomyolysis, acute renal failure, and markedly elevated liver transaminases leading to acute liver failure." The patient recovered. Because hepatic effects are known to be associated with buprenorphine, that event did not change the overall assessment of Brixadi.

Post-marketing data:

The Applicant submitted a tabulation of cumulative serious adverse drug reactions from post-marketing data sources and do not necessarily reflect individual cases. The Applicant reported that, at the time of the data lock, a total of 494 reports were reviewed from all post-marketing sources and 30 of them were assessed as serious. The summary included the following system organ classes: Gastrointestinal disorders (3)[11], General disorders and administration site conditions (6)[12], Immune system disorders (1)[13], Injury, poisoning and procedural complications (7)[14], Investigations (2)[15], Metabolism and nutrition disorders (1)[16], Musculoskeletal and connective tissue disorders (1)[17], Nervous system disorders (9)[18], Pregnancy, puerperium, and

[11] Abdominal pain, nausea, vomit

[12] These were unchanged from the previous application cycle: death (GB-CAM-20-00032 described above), drug ineffective, Drug interaction, drug withdrawal syndrome (2), peripheral edema

[13] Unchanged from the previous application cycle: hypersensitivity

[14] Toxicity to various agents, drug titration error, postoperative delirium, overdose (SE-CAM-20-00091), product label confusion, rib fracture, road traffic accident.

[15] Unchanged from the previous application cycle: Weight increased; Oxygen Saturation decreased

[16] Hypokalemia

[17] Rhabdomyolysis

[18] Depressed level of consciousness, epilepsy, hypoesthesia, loss of consciousness, migraine, neuroleptic malignant syndrome, seizure, serotonin syndrome, unresponsive to stimuli.

perinatal conditions (2)[19], Psychiatric (6)[20], Renal and urinary disorders (1)[21], Respiratory, thoracic and mediastinal disorders (2)[22],Skin and subcutaneous tissue disorders (1)[23], and Vascular disorders (3)[24].

My review of the summary of these findings submitted by the Applicant do not change the understood risk-benefit profile of Brixadi.

9.1.3. Dropouts and/or Dose Reductions Due to Adverse Effects

Pre-marketing data:
Adverse reactions led to premature discontinuation in 10 (4.7%) patients in the group receiving BRIXADI compared to 5 (2.3%) patients in the sublingual buprenorphine/naloxone group, during the double-blind study.

Post-marketing data:
No new information concerning AEs leading to discontinuation were submitted in this review cycle. Other than two cases of events consistent with precipitated withdrawal, no dose reductions due to AEs were identified. If anything, a pattern of CAM2038 dosing increase within 2-3 weeks after transferring to CAM2038 (also observed in the previous review cycle) from another buprenorphine product was identified. Refer to section 9.1.8 and 9.2.1 for additional information on inadequate dosing and precipitated withdrawal.

9.1.4. Injection Site Reactions

Pre-marketing data:
In the clinical program, injection site reactions were reported by approximately 20% of patients (Patients in the sublingual buprenorphine arm received placebo injections). The indented text in Arial font below summarizes the clinical trials safety database and is based on the agreed-upon language for section 6.1 of the proposed drug label during the previous review cycle and carried forward for drug labeling in this review cycle:

[19] Unchanged from the previous application cycle: spontaneous abortions
[20] Unchanged from the previous application cycle: agitation, anger, disorientation, auditory hallucination, drug abuse, psychotic symptoms
[21] Acute Kidney Injury, urinary retention
[22] Acute respiratory failure, hypoxia
[23]Unchanged from the previous application cycle: skin ulcer in case E2B_00000051 (2019BBN00029): A patient was hospitalized due to leg ulcer, five days after receiving the first injection of Buvidal 16 mg in an unknown location. This did not appear related to an injection site reaction.
[24] Hemorrhage (related to spontaneous abortion), circulatory collapse, DVT

Injection site reactions in the double-blind study are presented in Table 13 below. The majority of injection site-related adverse events were mild or moderate in severity. No injection site reactions were reported as severe intensity.

Table 13: Injection-Site Reactions in the Double-Blind Phase 3 Study: ≥ 2% of Patients Receiving BRIXADI

Preferred Term (PT)[a]	BRIXADI Total[b] (N=213) n(%)	SL BPN/NX[c] (N=215) n(%)
Administration site reactions[d]	**44 (20.7%)**	**49 (22.8%)**
Injection site pain	21 (9.9%)	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%)

a = Injection site reactions (ISR) that occurred in ≥2% of patients receiving BRIXADI, in the controlled trial, HS-11-421. Patients are represented once per PT.
b = This group includes patients exposed to varying doses of both the BRIXADI weekly and monthly formulations.
c = SL BPN/NX denotes the active comparator: subjects assigned to daily buprenorphine with sham (placebo) injections. Patients randomized to this group could also receive a supplemental 'booster' injection of BRIXADI (weekly), 8 mg, per protocol.
d = The ISRs that occurred in ≥2% of the patients randomized to BRIXADI were reported under the HGLT of Administration site reactions. However, ISRs were also identified under the Bacterial infectious disorders HGLT (of which, there were three injection site related cellulitis reactions in the BRIXADI group and one in the SL BPN/NX group, respectively) but those numbers did not rise to level of reporting. Tabulation included all events coded as treatment-emergent and injection site reactions, regardless of treatment-emergent flags.
Source: Table 6, Physician Package Insert

Of note, in the Investigator Brochure, version 14 (data lock of February 19, 2020), results from study HS-17-585 were reported (the study was completed in the year prior). HS-17-585 was an Australian trial that compared efficacy, safety, treatment satisfaction, quality of life and health economics of CAM2038 to those of standard of care BPN treatment in 24 weeks of treatment. In the CAM2038 treatment group, the two most frequently occurring adverse drug reactions (in ≥5% of patients) were injection site pain (11 patients [18.3%]) and injection site mass (10 patients [16.7%]). Injection site mass was seen in three patients (1.4%) exposed to CAM2038 in Study 421.

Post-marketing data:

Twenty-two cases of ISRs coded as "injection site mass" were included in the updated safety information. This term was not commonly reported in the clinical trials data and, as with the previous review cycle, labeling was updated to reflect that a palpable mass may be observed after dosing. Table 14 shows reported ISRs from post-marketing sources from July 31, 2019 through June 2021. No other new ISR terms from the updated safety information were reported that requires a changes to proposed labeling.

Table 14: Injection- Site Reactions Received from Postmarketing Sources

MedDRA PT	Number of ISRs
Injection site pain	33
Injection site erythema	31
Injection site swelling	24
Injection site pruritus	20
Injection site mass	22
Injection site rash	9
Injection site inflammation	8
Injection site nodule	8
Injection site bruising	7
Injection site induration	5
Injection site hematoma	5
Injection site extravasation	3
Injection site haemorrhage[25]	2
Injection site injury	2
Injection site reaction	2
Injection site discolouration	2
Injection site urticaria	2
Injection site vesicles	2
Injection site warmth	2
Injection site cyst	1
Injection site eczema	1
Injection site hypoaesthesia	1
Injection site movement impairment	1
Injection site necrosis	1
Injection site scab	1
Injection site scar	1
Total	**196**

Adapted from Applicant-provided clinical information

The following injection site reaction narratives were reported by the Applicant in the Clinical Information Amendment under the subsection 'Injection Site Reactions' during this review cycle. Five were assessed as "unlisted" per the Company Core Data Sheet because they had not been previously reported, or because they were more severe than previously reported (some were submitted as non-IND safety reports to IND. These cases are included in the summary of Table 14 and included:

- GB-CAM-19-00070 (Injection site pain): A patient experienced pain that 'made him cry' (severe) following Buvidal injection. It was thought than an air bubble in the pre-filled syringe may have been a contributing factor. On the same day, the pain resolved with no sequelae.

[25] During the previous review cycle, injection site hemorrhage and hematoma were related to case number FI-CAM-20-00057: A Finnish patient with medical history of asthma, sleep apnea, type-2 diabetes and morbid obesity who experienced several ISRs after receiving her first dose of Buvidal 96 mg monthly. These included bleeding, hematoma and puncture mark at the injection site, stinging pain, and a burning and itching feeling in the arm. In addition, a rash appeared after injection that extended to the neck and slightly over the elbow. Action was taken and outcome was not reported. No new cases were identified with this review cycle.

- AU-CAM-20-00041 (Injection site cyst): A patient developed an injection site cyst, bruising, induration, and mild pink discoloration after two separate injections of monthly Buvidal. At the time of reporting, the injection site bruising had resolved, but the other ISRs were still present at the first injection site. Treatment with Buvidal was discontinued.
- GB-CAM-20-00006 (Injection site mass): A patient experienced bumps under skin at the Buvidal injection sites. Lipohypertrophy (unlisted) was suspected as a possible cause. Approximately 3 months after starting treatment with weekly Buvidal, the patient was switched to monthly Buvidal in order to reduce number of doses and the events resolved.
- SE-CAM-20-00072 (Injection site movement impairment): A patient after receiving his second weekly dose of Buvidal reported right upper arm swelling which had a big 'boil' at the injection site, centered over the triceps. The subcutaneous swelling was 8-10 cm, solid in consistency with no heat increase or redness. The patient experienced pain when pressure was applied and due to the swelling, had difficulty stretching his arm. No effect on peripheral blood flow was observed. Two further injections have not resulted in further reactions. The events resolved and treatment with Buvidal continued.
- AU-CAM-20-00071 (Injection site necrosis): A week to ten days after Buvidal administration the patient experienced skin necrosis. The patient had a yellow top form over the skin where the injection had been given. The patient plucked the top off, with no pain. Subsequent dose was administered without events or concerns. The physician stated the possibility that Buvidal was administered intradermally, but he was not able to confirm since he had not witnessed the administration. Action taken with Buvidal regarding the reaction was not provided.
- FI-CAM-20-00193 (Injection site eczema): A patient experienced drug eruption and injection site eczema. At the time of this report, the events were resolving. Action taken with Buvidal in management of the events was not reported.
- AU-CAM-20-00078 (Injection site scar): A patient experienced an injection site scar on his abdomen where a buprenorphine depot was administered. It is unclear if the patient received Buvidal or Sublocade. Action taken with Buvidal regarding the reaction was not provided.
- GB-CAM-20-00186 (Injection site scab): the patient experienced injection site abscess, and injection site scabbing. Action taken with buprenorphine in management of the reactions was reported as not applicable.

The pre-marketing findings taken together with the results received from post-marketing data sources, indicate that injection site mass might be reported after US marketing. The frequency of pain, erythema, swelling, and pruritis reports with this submission are also higher than predicted base on the clinical trial database, but are not unexpected with an injectable product. Labeling already reflects the risk of ISRs.

9.1.5. Hepatic

Premarketing data:

Hepatic adverse events are referenced in the Division's agreed upon labeling language for sections 5, 8, and 12 (see listed language above in Clinical Pharmacology). One suspected case of hepatitis (case AU-CAM-19-00051) was reported from a single, investigator-initiated study (dBC2531) in Australia, which involved a 36-year-old subject who experienced hepatitis acute six days after initiating treatment with CAM2038. Treatment with CAM2038 was interrupted as

a response to the event which resolved 9 days later. In a follow-up received by Camurus after the data lock date of the DSUR, the causality of this event was re-assessed to not related to CAM2038. Review of the extremely limited case information yielded no additional information.

Postmarketing data:
No new cases of serious hepatic adverse event were identified from post-marketing sources during this review cycle[26].

In addition to the case mentioned above, two other cases were reported in the previous cycle. One of the cases (GB-CAM-20-00032) was described above and reported as a death. This was the 63-year-old male with a history of hepatitis C. The second case (FI-CAM-20-00042) occurred in Finland in a 44-year-old male who was hospitalized with shortness of breath, peripheral edema, and abdominal pain 3-weeks after receiving the 96 mg Monthly dose of Buvidal. Significant concurrent medical history included chronic viral hepatitis C, insomnia, depression, in addition to severe OUD. On exam, the patient had bile duct calculi and elevated liver enzymes. The symptoms resolved and the patient was discharged and continued Buvidal treatment.

From the data reviewed, nothing in the DSUR or post-market reports provided by the Applicant require modification of the labeling agreed upon in previous review cycles.

9.1.6. Cardiac

Premarketing data:
In the pre-marketing program, clinically significant ECG abnormalities reported as an AE occurred in 10 patients treated with CAM2038 (studies 549, 478, 421, and 499), in addition to a few cases of mild to moderate QT prolongation. Data were reviewed by the QT-IRT team during the first review cycle.

Post-marketing data:
No adverse drug experiences of ECG abnormalities or serious cardiac events (of any severity) were reported in the completed investigational trials or from post-marketing reports during this review cycle[27].

[26] Case AU-CAM-20-00024 was submitted by the Applicant following a MedDRA SMQ search and deemed not be a hepatic event upon review. This was a patient with a preexisting history of HCV who switched from Suboxone daily treatment to Buvidal monthly treatment and who, two weeks later, developed diarrhea (treated with loperamide), runny nose, and restlessness, similar to a previous episode of opioid withdrawal, per the report. Buvidal monthly dose was increased, and the patient was stable for the following 3 months. All the events were assessed as non-serious by the Applicant and no lab abnormalities were provided or referenced.
[27] One expedited 15-day safety report was submitted during the previous review cycle on 6-29-2020 to IND 114082 involving Buvidal administration in a 62-year-old Norwegian male with OUD (reference number NO-CAM-20-00108) who experienced SVT and QTc prolongation and hospitalization after Buvidal dosing of 64 mg (formulation

During the previous review cycle, DAAP undertook a comprehensive review of all available information about the cardiac effects of buprenorphine, including mechanistic studies performed by the Division of Applied Regulatory Science. A review of the material considered, prepared by Dr. Daniel Foster, documented the overall conclusion that the observed QT prolongation with buprenorphine does not appear to be mediated by hERG channels and that buprenorphine is unlikely to be pro-arrhythmic when used alone. Accordingly, new language was recommended for sections 5.15 (Warnings and Precautions) and 12.2 (Clinical Pharmacology) of the proposed drug label during that review cycle and carried forward to this one:

> 5.15 QTc Prolongation
>
> Some studies demonstrate a modest QTc prolongation of uncertain clinical significance. This effect does not appear to be mediated by hERG channels and buprenorphine is unlikely to be pro-arrhythmic when used alone. The effect of combining buprenorphine with other QT-prolonging agents is not known *[see Clinical Pharmacology (12.2)].*
>
> 12.2 Pharmacodynamics
>
> …
>
> Cardiac Electrophysiology
>
> Thorough QT studies with buprenorphine products have demonstrated modest QT prolongation ≤15 msec. Two categorical analyses of cardiovascular-specific adverse events among patients exposed to buprenorphine demonstrated no proarrhythmic potential. One Holter monitoring study demonstrated no arrhythmia. An analysis of medical literature provided no evidence for causal association between buprenorphine and Torsades de Pointes.

9.1.7. CNS/Respiratory Depression

Pre-marketing data:

Symptoms such as somnolence and sedation were not commonly reported in the safety database. One patient [CAM3028 (weekly) 32 mg] discontinued study medication due to sedation. No TEAEs potentially associated with respiratory depression were reported in patients treated with CAM2038.

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not provided). On review, the dosing of the drug was administered after document ECG changes and arrythmia the week prior. The patient recovered and action with the medication was unknown.

Post-marketing data:
No cases of respiratory depression were reported that are not covered elsewhere. With the previous review cycle, one case of potential "overmedication" was reported and is listed above under Serious Adverse Events. This case was reported (b) (4)

These findings did not appear to change the overall safety profile of Brixadi.

9.1.8. Inadequate dosing

Of the 25 cases submitted for review with this application cycle, using the standardized MedDRA query "drug withdrawal reactions," sevenpost-marketing reports involved patients complaining of withdrawal at or after 2-weeks following treatment initiation with Buvidal, 128 mg monthly. In most cases, the event resolved with increasing doses of Buvidal. These cases did not describe the syndrome of precipitated withdrawal as much as they described sub-therapeutic dosing of Buvidal.

,

These findings did not change the overall safety profile of Brixadi.

9.1.9. Medication errors

Premarketing data:
In the clinical development program, no studies were performed to evaluate whether lower doses of either formulation could be combined to yield exposures equivalent to the mathematical sum of the doses of CAM2038 (e.g., 2 x 16 mg Weekly formulation compared to 1 x 32 mg Weekly formulation). The proposed label cautions against combining doses in this fashion. Instances of investigators making such substitutions were recorded in the clinical trials submitted with the first review cycle and may be predicted to occur after marketing. However, review of post-marketing data submitted with this application cycle, did not reveal situations where providers reported combinations of doses to achieve a desired mathematical sum. Last, only one report of "package difficult to open" was reported and this did not result in a medication error.

Post Marketing data:
With the previous submission, one report of a significant medication error was identified in post-marketing sources. A patient was administered 128 mg CAM2038 Monthly (Buvidal) instead of 8 mg CAM2038 Weekly (Buvidal), as was prescribed. The event occurred in an Australian emergency department and was related to a serious AE in a patient (refer to section 9.2.4 below for clinical details). No details regarding the causality of the medication error were provided because they were unavailable to the Applicant. This case is now included in the serious adverse event tabulation provided by the Applicant. This finding did not change the overall safety profile of Brixadi but reflects the importance of cross-checking the order with the dispensed drug.

9.1.10. Common AEs

The systemic safety profile for CAM3038, when given by a HCP in clinical trials, was broadly consistent with the known safety profile of transmucosal buprenorphine. The indented text in Arial font below from the proposed labeling summarizes the findings from the clinical program.

> Adverse reactions commonly reported after BRIXADI administration (≥5%, regardless of dose and regimen) in the double-blind study, were injection site pain (9.9%), headache (7.5%), constipation (7.5%), nausea (7.0%), injection site erythema (6.6%), injection site pruritis (6.1%), Insomnia (5.6%), and urinary tract infection (5.2%).
>
> Table 15 shows the adverse reactions for BRIXADI compared with the active-control group (SL BPN/NX) in the double-blind study.

Table 15: Adverse Reactions in the Phase 3 Double-Blind Study: ≥ 2% of Patients Receiving BRIXADI (Excluding Injection-Site Reactions)

System Organ Class (SOC) Preferred Term (PT)[a]	**BRIXADI Total[b]** (N=213) **n(%)**	**SL BPN/NX[c]** (N=215) **n(%)**
Cardiac disorders	**6 (2.8%)**	**9 (4.2%)**
Tachycardia	5 (2.3)	5 (2.3)
Gastrointestinal disorders	**43 (20.2%)**	**45 (20.9%)**
Constipation	16 (7.5)	16 (7.4)
Diarrhea	6 (2.8)	7 (3.3)
Nausea	15 (7.0)	17 (7.9)
Vomiting	9 (4.2)	8 (3.7)
Infections and infestations	**42 (19.7%)**	**50 (23.3%)**
Urinary tract infection	11 (5.2)	10 (4.7)
Upper respiratory tract infection	9 (4.2)	9 (4.2)
Musculoskeletal and connective tissue disorders	**20 (9.4%)**	**22 (10.2%)**
Arthralgia	7 (3.3)	3 (1.4)
Nervous system disorders	**27 (12.7%)**	**27 (12.6%)**
Headache	16 (7.5)	17 (7.9)
Psychiatric disorders	**20 (9.4%)**	**20 (9.3%)**
Anxiety	6 (2.8)	7 (3.3)
Insomnia	12 (5.6)	6 (2.8)

a = report of adverse reactions that occurred in ≥ 2% of the patients randomized to BRIXADI in Study HS-11-421. Patients are represented once per PT; b = This group includes all subjects exposed to varying doses of both the BRIXADI (weekly) and BRIXADI (monthly) formulations.; c = SL BPN/NX denotes the active comparator: patients assigned to daily buprenorphine with sham (placebo) injections. Patients randomized to this group could also receive a 'booster' injection of BRIXADI (weekly), 8 mg, per protocol.; All patients in Study 421 received a single test dose of 4 mg SL BPN/NX before randomization into either arm.
Source: Table 5, Physician Package Insert

9.2. Other Safety Concerns

Certain concerns not observed in the clinical trials were identified as areas of particular interest that might arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated in a patient still dependent on a full agonist.

9.2.1. Precipitated Withdrawal

Pre-marketing data:
Buprenorphine itself can precipitate withdrawal if initiated in patients who are not yet in significant opioid withdrawal. For this reason, initial dosing is generally cautious and typically begins with a sublingual dose of 2 mg- 4 mg. Some of the doses of CAM2038 contain a large amount of buprenorphine. In new entrants to treatment, the clinical trials included a test dose of 4 mg sublingual buprenorphine and then initiated treatment with a 16 mg weekly dose. Two patients did not tolerate the test dose. The Applicant reported that no patient experienced precipitated withdrawal due to CAM2038.

Post-marketing data:
A total of 48cases using the standardized MedDRA query “drug withdrawal”. “drug withdrawal syndrome”, and “withdrawal syndrome” were submitted for review from post-marketing reports (28 new cases with this application cycle). On review, some patients appeared to experience precipitated withdrawal (N=2) while others complained of effects consistent with dose inadequacy or need for continued dose titration (N=34) [refer to section 9.1.8].

These findings did not change the overall safety profile of CAM2038.

9.2.2. Consequences of Intravenous Injection

In the clinical development program, CAM2038 was administered in a supervised setting by HCPs. If a patient, household contact, or associate were to obtain access to CAM2038, the pre-filled syringe containing a Schedule III opioid might be an attractive target for abuse by the intravenous route. Therefore, given the route of administration of CAM2038, it is predicted that injection into a vessel could result in the formation of a gel or solid, with resulting occlusion and possibly tissue damage or embolus. Clinical review of the ongoing clinical trial adverse event data and provided post-marketing data revealed no cases involving intravenous injection of Buvidal.

9.2.3. Serotonin Syndrome

No new reports of serotonin syndrome were submitted in this review cycle. With the previous review cycle, one post-marketing case report[28] of serotonin syndrome was submitted to IND 114082 on 9-04-2020 (after the data lock) and was included in my review. The case involved a 41-year-old female from Australia with a history of OUD, insomnia, anxiety, and major depressive disorder. The patient was transferred to Buvidal, 16 mg Weekly on (b) (6) from 12 mg daily dosing of Subutex. Concomitant medications included amitriptyline, escitalopram, and diazepam. The patient was titrated to Buvidal 24 mg Weekly on (b) (6) then titrated to 32 mg Weekly on (b) (6) then transferred to Buvidal 128 mg Monthly on (b) (6) at the same time amitriptyline dosing increased from 10 mg to 20 mg. Symptoms of hot and cold flushes, yawning, "sweating profusely", cannot concentrate", and "feeling foggy" were reported. Diazepam was discontinued, amitriptyline dosing was decreased and a physical exam on (b) (6) yielded normal vital signs, and 5 mm pupils that were reactive to light. The event was marked "resolved" on (b) (6) and the patient received her second dose of Buvidal 128 mg Monthly.

No reports of serotonin syndrome were identified in the clinical trials for CAM2038. In review of this case, it is possible that the presenting symptoms were related to Buvidal. Because serotonin syndrome is listed in (b) (4) the drug label (and in the drug labels of other buprenorphine products), this finding did not change the risk-benefit profile of Brixadi.

9.2.4. Seizure

No post-marketing case reports of seizure were reported with this review cycle.

One post-marketing case report of seizure[29], following Buvidal administration in the context of a medication error, was submitted to IND 114082 on 10-16-2020, during the previous review cycle. A 50-year-old Australian male with a history of alcohol use and chronic pain [treated with Norspan (buprenorphine patch, unknown dose)], presented to an emergency department acutely intoxicated. The sequence of events is unknown, but the patient was physically restrained in the emergency department in order to receive an 8 mg injection of Buvidal Weekly. However, 128 mg Buvidal Monthly was administered. The patient experienced a seizure and was transferred to ICU where naloxone was administered.

Of note, no reports of seizure were identified in the clinical trials for CAM2038. In review of this case, it is possible that the presenting symptoms were related to Buvidal in the context of alcohol intoxication. Additional details of the case are unknown. Although "seizure" is not listed in the Warnings and Precautions section of the drug label (or in the drug labels of other

[28] Case reference number AU-CAM-20-00143 (2020BBN00021)
[29] Case reference number AU-CAM-20-00180 (2020BBN00032)

buprenorphine products), clinical studies have been published on the onset of seizures following buprenorphine overdose and are a risk factor in alcohol withdrawal. At this time and in the context of the event described, the finding does not change the risk-benefit profile of Brixadi.

10. Advisory Committee Meeting

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] No additional Advisory Committee input was sought for the second or third cycle.

11. Pediatrics

Braeburn received a full waiver of the Pediatric Research Equity Act (PREA) requirements on the basis of infeasibility. The prevalence of OUD in the pre-adolescent population is very low, and this product would not be suitable for treating iatrogenic opioid dependence (i.e., physical dependence without meeting criteria for OUD). Prevalence in adolescents under age 17 is also too low for feasible study.

12. Other Relevant Regulatory Issues

12.1. Exclusivity

No exclusivity concerns exist with this submission. However, in 2018, during the second application cycle, the administrative records related to the approval of NDAs 204442 and 209819 were reviewed and the Exclusivity Board determined that the 3-year exclusivity for Sublocade (NDA 209819) would block the approval of the Brixadi monthly depot product. The Board recommended that Brixadi's weekly depot product should not be blocked. At that time, Braeburn expressed that they were not willing to entertain separating the Weekly and Monthly Brixadi product formulations. Therefore, only a combined label was negotiated during the second review cycle and the tentative approval (TA) was issued applying to both formulations. Braeburn timed the 2020 review cycle of NDA 210136 (third resubmission) to align with the expiration of Sublocade's 3-year exclusivity for Sublocade[31].

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[30] A verbatim transcript of this meeting is available on the FDA website at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm535446.htm

[31] In April 2019, Braeburn filed an action with the federal district court for the District of Columbia, in an effort to overturn that 3-year exclusivity period (which blocked Brixadi from final approval for marketing). After a court hearing in July 2019, the Court's Chief Judge did not overturn FDA's decision. Braeburn was notified that they could resubmit their application in June 2020, to request final approval of Brixadi, because Sublocade's exclusivity expires in November 2020. Further, and in order to eliminate the risk of further exclusivity periods blocking Brixadi from marketing approval, Braeburn also filed a Citizen Petition in April 2019, That Citizen Petition requested that FDA review the orphan designation granted to Sublocade. FDA reviewed the conditions of the

13. Labeling

The submitted proposed labeling is in Physician's Labeling Rule (PLR) format and is similar to the previously agreed-upon label from the third review cycle. The previous cycle included revisions to Section 6 regarding injection site mass and insufficient dosing and revisions to Section 9 (inclusion of descriptive text to reflect buprenorphine class labeling changes[32]). With this submission, minor revisions were made by Braeburn and the Division. The Patient Labeling Team was consulted to review those changes and made recommendations for formatting changes to improve readability.

14. Postmarketing Recommendations

14.1. Risk Evaluation and Mitigation Strategies (REMS)

With this submission, Braeburn agreed to keep the agreed-upon Risk Evaluation and Mitigation Strategy (REMS) from the third (2020) review cycle, which was reviewed by the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology. Consistent with the previous review cycle, DRISK has determined that a REMS with elements to assure safe use (ETASU) is needed to ensure the benefits of CAM2038 outweigh its risks. Consistent with previous review cycles, the REMS should include restricted distribution with CAM2038 being dispensed only in healthcare settings that are certified. The goal of the BRIXADI REMS is to mitigate the risk of serious harm or death that could result from intravenous self-administration by ensuring healthcare settings and pharmacies are certified and only dispense BRIXADI directly to a healthcare provider for administration by a healthcare professional.

The elements of the REMS are:

- Elements to assure safe use to ensure that health care settings and pharmacies that dispense BRIXADI are specially certified;
- An implementation system; and,
- A timetable for submission of assessments of the REMS.

Materials include:

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

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orphan designation and granted Braeburn's Citizen Petition. Thus, the risk of Brixadi being blocked from marketed approval through November 2024 was eliminated.

[32] Derived from the 2019 FDA Draft Guidance (Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products-Content and Format Guidance for Industry).

The REMS content was largely agreed upon during previous cycles and final materials were submitted July 06. 2021. In response to the Applicants submission, DRISK sent an information request (IR) on 10/15/2021 for additional documentation to support the Brixadi non-compliance protocol, Audit Plan, and elements of the Key Performance Indicator (KPI) for the risk management plan. The Applicant provided the requested documentation on 10/22/2021 and 11/08/2021 and DRISK determined that the response to IR was adequate.

14.2. Postmarketing Requirements (PMRs) and Commitments (PMCs)

Two postmarketing trials will be required to evaluate whether Brixadi can safely be initiated (b) (4) This is expected to be of great interest to clinicians who see patients in Emergency Department settings where treatment could be expeditiously initiated.

The following non-clinical post-marketing studies were required at the time of the previous tentative approval action and are still outstanding:

1. Evaluate elemental impurity levels in at least three batches of drug product on stability at 12 and 24 months or provide adequate extraction data to characterize the elemental impurities that could be leached from the container closure system using suitable solvents (e.g., nitric acid for elementals from glass).

2. Conduct a study to confirm, using validated methods, the identity of the unspecified (b) (4) the unidentified compound with relative retention time (RRT) of (b) (4) minutes, the unknown compound containing (b) (4) with RRT of (b) (4) min, and the unknown compound with (b) (4) with RRT of (b) (4) min that were detected in your leachable studies above the safety concern threshold of 5 mcg/day and the levels of the identified leachables (b) (4) (b) (4) Evaluate at least three batches of your to-be-marketed drug product at multiple timepoints over the course of your stability studies to identify trends in leachable levels over time. Base the final safety assessment on the maximum predicted levels of leachables identified in individual batches to determine the safe level of exposure via the label-specified route of administration. Do not combine samples from different batches. Once chemical identification is confirmed for the unknown compounds, provide a toxicological risk assessment for each of these compounds and any other compounds detected at ≥5 mcg/day.

14.3. Associate Division Director Comments

The efficacy and safety of Brixadi (weekly) and Brixadi (monthly) were demonstrated in data submitted and reviewed in previous review cycles (cycles one and two). Review of the safety update included in this submission does not identify any new concerns that alter the overall assessment of the risk/benefit ratio for this product.

However, product quality issues remain and preclude approval at this time. In this review cycle, as with the previous one, contract manufacturing and testing facilities were inspected as part of a pre-approval inspection (PAI). The 2021 inspection was again prioritized by ORA due to the importance of the Brixadi product and was completed in September. Significant ongoing Good Manufacturing Practice (GMP) deficiencies were identified. The reinspection also identified deficiencies (b) (4)

Braeburn, aware of the deficiencies, contracted with a third party, (b) (4) to monitor and provide quality control over manufacturing and provided assurances that the observed deficiencies would not affect the Brixadi product. However, because of ongoing concerns at the manufacturing plant, OPMA has not commented on this plan and recommends that approval be withheld.

Given the nature of the quality system deficiencies observed, a follow-up inspection is warranted before approval could be considered. This could take place in the context of review of another application manufactured at the same site, or as part of review of a resubmission of this application. Neither a clock extension (not normally permitted for response to 483s) or a missed PDUFA date seem appropriate under these circumstances, because it is not clear how readily the manufacturing concerns can be addressed, and the time frame for resolving them is not known.

A Complete Response letter will be sent to Braeburn citing deficiencies at the manufacturing facility. At the same time, OPMA will send a Post-Action Letter to Pii.

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/

CELIA J WINCHELL
12/15/2021 10:57:06 AM

GIOIA M GUERRIERI
12/15/2021 11:44:17 AM

Cross-Discipline Team Leader Review and Division Summary

Date	12/1/2020
Medical Officer	Gioia Guerrieri, D.O.
CDTL/Associate Division Director	Celia Winchell, M.D.
Division Director	Rigoberto Roca, M.D.
NDA/BLA #	210136
Applicant	Braeburn Inc.
Date of Submission	6/01/2020
Proprietary Name	Brixadi
Established or Proper Name	(buprenorphine extended-release) injection, for subcutaneous administration
Dosage Form(s)	Injection Weekly Formulation: 8 mg, 16 mg, 24 mg, 32 mg Monthly Formulation: 64 mg, 96 mg, 128 mg
Applicant Proposed Indication(s)/Population(s)	For the treatment of moderate to severe opioid use disorder (b) (4) (b) (4)
Applicant Proposed Dosing Regimen(s)	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.
Recommendation on Regulatory Action	*Complete Response*
Recommended Indication(s)/Population(s) (if applicable)	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.
Recommended Dosing Regimen(s) (if applicable)	New Entrants to treatment: after test dose of sublingual buprenorphine, titrate to 24-32 mg Weekly in the first week then dose adjust. Adults stabilized on current buprenorphine product: transfer to appropriate Weekly or Monthly formulation.

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1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

CAM2038 (buprenorphine extended-release) injection, for subcutaneous administration use is intended for the treatment of moderate-to-severe opioid use disorder; the Weekly formulation is for initiating treatment in patients who have tolerated a test dose of a transmucosal buprenorphine-containing product; the Monthly formulation is for patients already in established treatment with another buprenorphine-containing product (including the Weekly formulation).

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 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.

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. 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. 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. Similar to the recently-approved subcutaneous depot formulation of buprenorphine, Sublocade, Brixadi has the potential to address several limitations of existing treatments.

The submitted clinical data show that the Brixadi weekly formulation, in doses of 24 mg and 32 mg, is able to block subjective effects of a clinically-relevant dose of opioid agonist, more completely after the second weekly dose. Based on PK-PD analysis, the plasma levels delivered by the corresponding monthly doses are predicted to produce similar blockade. In a non-inferiority comparison to sublingual buprenorphine/naltrexone treatment, the effect of this blockade was shown to translate to clinical efficacy for a regimen beginning with weekly doses and transitioning to monthly doses, based the proportion of subjects whose drug use assessments met a pre- specified responder definition.

The safety profile of buprenorphine is well-characterized, and the overall Brixadi safety profile appears similar. Analysis of dose-dependent adverse effects was hampered by the study design and the presentation of data but various explorations for dose-effects (in the previous review cycle) did not identify concerning dose-limiting adverse effects in the doses currently proposed for marketing. However, safety regarding the Brixadi drug product could not be concluded during this review cycle due to quality concerns at the two primary sites of manufacturing that could not be resolved.

Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated at doses higher than studied in the clinical trial (16 mg weekly x 1) in a patient still dependent on a full agonist. Additionally, there may be circumstances under which the rapid discontinuation or dose reduction of buprenorphine might be desirable for a given patient. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with Brixadi for a period of time. Possibilities for surgical removal have not been explored. Patients developing intolerance to buprenorphine will require long-term monitoring by a health care professional.

Moderate-to-severe opioid use disorder is a serious and life-threatening condition and the need for more treatment options and greater access to treatment is clear. Brixadi, as a HCP-administered long-acting depot providing a sustained effective plasma level of buprenorphine over a prolonged period, has the potential to address some of the limitations of available options.

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 by ensuring healthcare settings and pharmacies are certified and only dispense Brixadi directly to a health care provider for administration by a healthcare provider.

Because of manufacturing quality issues unrelated to the clinical review, approval of CAM2038 for use in the treatment of adult patients with moderate to severe OUD cannot be recommended at this time.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Opioid use disorder or OUD, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), 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 over2.1 million Americans aged 12 and over met criteria for either opioid abuse or dependence. In 2015, the CDC reported that drug overdose was the leading cause of accidental death in the US, with 52,404 lethal drug overdoses in 2015. Of these, 20,101 overdose deaths were related to prescription pain relievers, and 12,990 overdose deaths were related to heroin. 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 for years, or even indefinitely.	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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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). o Behavioral treatment alone (individual or group counseling, self- help groups) is not effective for many patients. o 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 overdoses in patients and in their household contacts, including children. o 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. o Depot buprenorphine (SUBLOCADE) o 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. o 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	An additional buprenorphine depot injection would be a desirable addition to the therapeutic armamentarium. o Convenience of weekly or monthly vs daily dosing o Provides consistent buprenorphine levels sufficient to block effects of exogenous opioids o Improves adherence o Reduces potential for diversion, misuse, abuse and accidental pediatric exposure o No surgical procedure needed

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Evidence: The opioid blockade study, Study HS-13-478, demonstrated that after CAM2038 (weekly) injections of either 24 mg or 32 mg, on average, subjective effects of both 6 mg and 18-mg doses of hydromorphone were blocked in non-treatment-seeking subjects with OUD, although significant variation was seen across subjects. Dose-response analysis showed a decreasing number of outliers (unblocked responses) with increasing plasma levels, with very few outliers above a plasma level of 4 ng/ml. The pivotal efficacy trial, Study HS-11-421 (N=428) demonstrated that patients treated with a regimen of 12 weeks on individually-determined doses of CAM2038 (weekly), followed by 12 weeks on individually-determined doses of CAM2038 (monthly) had a response rate non-inferior to patients treated with sublingual buprenorphine/naltrexone tablets (and placebo injections). CAM2038 is to 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. Uncertainties: The design of the studies did not permit analyses by dose	CAM2038 24 mg weekly and CAM2038 32 mg weekly are capable of blocking the subjective effects of a clinically-relevant dose of opioid agonist, and this blockade becomes longer-lasting after two weekly doses. The effect of this blockade was shown to translate to clinical efficacy as demonstrated by comparable outcomes in patients treated with a regimen of weekly followed by monthly CAM2038 compared with patients treated with sublingual buprenorphine/naloxone. Taken together, and considering the established efficacy of the reference product, Subutex, these studies provide substantial evidence of efficacy for CAM2038 in the treatment of moderate or severe OUD in patients who tolerate at least an initial test dose of buprenorphine. CAM2038 weekly is suitable for starting treatment, while CAM2038 (monthly) has been studied only in patients already in established treatment.
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. 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.) o In a safety database of 440 opioid-dependent patients, systemic effects of buprenorphine associated with	The safety profile of buprenorphine is well-characterized, and the overall safety profile of CAM2038 appears to be similar. Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated too quickly in a patient still dependent on a full

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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 case was identified in the clinical development program One death occurred in a CAM2038-treated patient, due to a car-vs-pedestrian traffic accident Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with CAM2038 for a period of time. Possibilities for surgical removal have not been explored. Patients developing intolerance to buprenorphine effects will require long-term monitoring by a health care professional. Buprenorphine itself can precipitate withdrawal if initiated in patients who are not yet in significant opioid withdrawal. For this reason, initial dosing is generally cautious and typically begins with a dose of 2 mg-4 mg. The starting dose of CAM2038 in the efficacy trial was divided over several visits in the first week of treatment. Clinicians may be interested in initiating CAM2038 more expeditiously, for example, administering a single 24 mg or 32 mg weekly injection at the first visit, or administering a monthly dose at the first visit. It is not known if this can be accomplished safely. CAM2038 forms a gel when injected. If patients obtain direct access to the product, there is a risk they may choose to attempt to inject the product intravenously. Notably, the consequences of intravenous injection of the contents of the pre-filled syringe are not known, it is anticipated that there is a risk of occlusion, tissue damage, and emboli.	agonist. Cases of this nature have not been observed in post-marketing outside the U.S. Additionally, there may be circumstances under which the rapid discontinuation or dose reduction of buprenorphine might be desirable for a given patient. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with CAM2038 for a period of time. It is not known whether there are possibilities for surgical removal. Patients developing intolerance to buprenorphine effects will require long- term monitoring by a health care professional. A REMS is required to ensure that CAM2038 is not distributed directly to patients, and is administered by a health care professional, to mitigate the risk of serious consequences should the product be administered intravenously.

2. Introduction

This is the third review cycle for NDA 210136 (CAM2038, brand name Brixadi). The application was initially submitted in July 2017. Because of the potential for a depot product to mitigate risks of abuse, diversion, and accidental pediatric exposure associated with oral transmucosal buprenorphine, the application was granted a priority review because no depot formulations had been approved. At the conclusion of the first application cycle, NDA 210136 received a Complete Response (CR) letter. The January 19, 2018, CR letter cited significant manufacturing issues as well as concerns about the clinical datasets.

The second resubmission, submitted June 2018, adequately addressed the deficiencies of the first submission. However, between the two submissions, NDA 209819 (Sublocade, Indivior), a monthly extended-release buprenorphine injectable product, was approved for marketing and blocked the marketing of the Brixadi Monthly product because of Hatch/Waxman drug product exclusivity. The Division discussed options regarding the labelling and marketing of the Brixadi Weekly formulation. However, the Applicant chose to wait to market the Weekly formulation until the product exclusivity on Sublocade expired and agreed to resubmit NDA 210136 in 2020. Thus, the second submission for NDA 210136 received a tentative approval (TA) letter on December 28, 2018.

Between the first and third submissions for NDA 210136, the manufacturer of Brixadi, Camurus, with whom Braeburn has a marketing partnership, received marketing approval for the product under the proprietary name Buvidal (CAM2038) in November 2018, for the treatment of OUD in the European Union and Australia and the United Kingdom. The current submission provides updated safety information based on Camurus' marketing experience, as well as safety findings from ongoing studies sponsored or supported by Braeburn.

The Brixadi products include two modified-release formulations of buprenorphine in a novel Fluid Crystal technology designed for administration by subcutaneous (not intramuscular) injection to be provided ready-for-use in a prefilled syringe for the treatment of moderate-to-severe opioid use disorder (OUD) in adults. This product is available in weekly and monthly formulations, each of which contains different doses and excipients.

Table 1: Proposed Doses of the Brixadi 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		
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: Clinical Reviewer

The Brixadi Weekly formulation, at the 24 mg and 32 mg doses, respectively, provides sustained plasma levels of buprenorphine intended to block the effects of exogenous opioids over 7 days. Based on pharmacokinetic data, the Brixadi Monthly formulation is predicted to block exogenous opioids for at least 28 days. Brixadi Weekly is intended for the treatment of moderate-to-severe opioid use disorder (OUD) in patients who have tolerated at least a test dose of transmucosal buprenorphine, and Brixadi Monthly product was studied in patients who are transferring from an oral-transmucosal buprenorphine product or the Brixadi Weekly formulation. The products are intended to be used as part of a complete treatment plan to include counseling and psychosocial support. Table 2 identifies the corresponding dose of BRIXADI when switching a patient from transmucosal buprenorphine to BRIXADI (weekly) or BRIXADI (monthly), expressing the transmucosal dose equivalents in terms of Subutex or Suboxone doses. Table 3 shows how patients may be transitioned between doses of both Brixadi product formulations. Both tables are adapted from proposed drug product labeling. For dose adjustments, an additional Brixadi Weekly 8 mg injection may be administered, based on clinical judgment during a dosing interval, for a total dose of up to a maximum dose of 32 mg per week of Brixadi Weekly or 128 mg per month of Brixadi Monthly.

Table 2: Daily Doses of Sublingual Buprenorphine (Subutex, Suboxone, or Generic Product Equivalents) and Suggested Corresponding BRIXADI (Weekly) or BRIXADI (Monthly) Doses

Daily dose of sublingual buprenorphine	BRIXADI (weekly)	BRIXADI (monthly)
≤ 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

Note: One SUBOXONE® (buprenorphine and naloxone) 8 mg/2 mg sublingual tablet provides equivalent buprenorphine exposure to one SUBUTEX® (buprenorphine HCl) 8 mg sublingual tablet (b) (4) (b) (4) or one Zubsolv® (buprenorphine and naloxone) 5.7 mg/1.4 mg sublingual tablet.

Table 3: Recommended Dose When Transitioning Between BRIXADI (Weekly) and BRIXADI (Monthly)

BRIXADI (weekly)	BRIXADI (monthly)
16 mg	64 mg
24 mg	96 mg
32 mg	128 mg

(b) (4)

Comparison of exposures after CAM2038 doses to exposures after sublingual buprenorphine demonstrate that, at steady-state (4th injection), CAM2038 (weekly) and monthly deliver plasma concentrations (Cavg,ss) that are higher than the corresponding dose of sublingual buprenorphine in Braeburn's proposed conversion scheme. Based on plasma levels (see Table 4 below), the efficacy would be anticipated to be at least non-inferior to, if not superior to, the corresponding doses.

Table 4: Summary of Steady-State PK Parameters of Buprenorphine After Subcutaneous Buttock Injections of Brixadi (Weekly), Brixadi (Monthly), and SL Administration of SUBUTEX

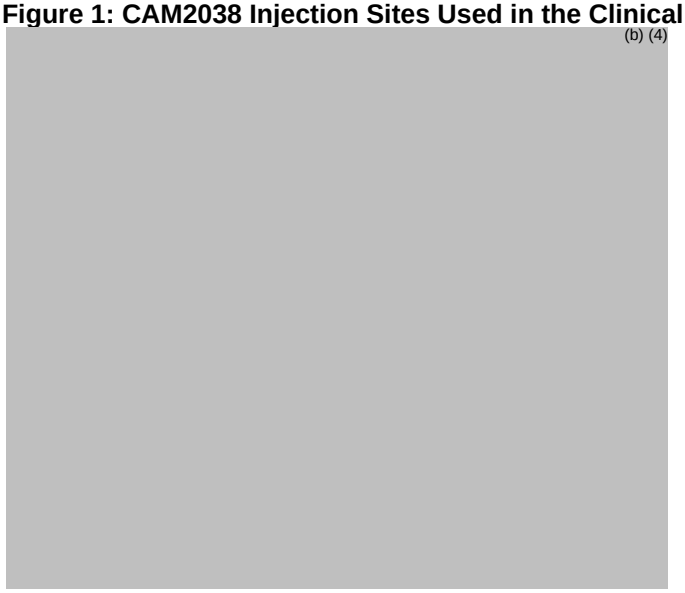
Drug product dose			C_{av} (ng/mL)			$C_{max,ss}$ (ng/mL)			C_{trough}[a] (ng/mL)		
SL BPN	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly
8 mg	16 mg	64 mg	1.2	2.1	2.0 $	4.7	4.3	4.0 $	0.7	0.8	1.3 $
16 mg	24 mg	96 mg	1.8	2.9 $	2.9 $	6.5	5.5 $	6.0 $	1.0	1.4 $	2.0 $
24 mg	32 mg	128 mg	2.5	4.2	3.9	8.2	6.9	11.1	1.4	2.6	2.1

Average value of two studies
$ Simulated
a C168h for BRIXADI (weekly), C28d for BRIXADI Monthly and C24h for Subutex

As with the previous two submissions, 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 were proposed (Figure 1)[1] based on the injection sites used in the clinical program. No new sites were proposed. 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.

Figure 1: CAM2038 Injection Sites Used in the Clinical Studies



Source: page 27, Applicant's Manual of Procedures, 2018

3. Background

Buprenorphine is a partial agonist at the μ-opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain, and two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence[2]. Three other transmucosal formulations, a six-month, surgically-placed implant, and a monthly depot formulation have subsequently been approved for opioid dependence, as well as one

[1] 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 initial submission) after review of additional data. It is not recommended for initiation of dosing.

[2] Subutex, buprenorphine sublingual tablets (Reckitt Benckiser (now Indivior) NDA 20732) and Suboxone, buprenorphine/naloxone sublingual tablets (Reckitt Benckiser (now Indivior) 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.

transdermal product and one transmucosal product for pain. Approximately (b) (4) million prescriptions from outpatient retail pharmacies were dispensed and approximately (b) (4) million patients received a dispensed prescription for buprenorphine-containing tablets or film labeled for MAT during 2019. Primary care physicians accounted for 34% of dispensed prescriptions, followed by nurse practitioners (14%), psychiatrists (14%), osteopathic physicians (12%), and all others (26%). The authority to prescribe buprenorphine for office-based treatment of OUD was expanded to include Nurse Practitioners and Physician's Assistants fairly recently, so the distribution of specialties may be expected to change in the future.

As a partial agonist, buprenorphine produces less euphoria compared to full agonists and has an improved safety profile with respect to effects on respiration. In addition to the improved safety profile, at sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, deterring abuse of opioids by buprenorphine-maintained patients. Unfortunately, despite these features of improved safety and abuse deterrence, buprenorphine 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 a number of cases of accidental poisonings of small children. Therefore, an additional depot injection which would be difficult to divert or abuse, would be less likely to be accidentally ingested by small children and offers potential advantages. In addition, a depot or implantable product that provides a sufficient plasma level of buprenorphine to block the effects of exogenous opioids, would enforce compliance so that patients could not periodically discontinue use to allow the blocking effect to dissipate in order to experience the effects of their opioids of choice. Importantly, some patients also express a preference for a long-acting treatment that reduces fluctuations in plasma levels and removes the need to think daily about taking medication.

3.1. Clinical Development of CAM2038

The clinical development of CAM20388 was undertaken with advice from the Division and was described in the previous two application submissions. The program comprised PK studies, an inpatient opioid blockade study (HS-13-478) and a randomized, double-blind, double-dummy, active-control efficacy study (HS-11-421).

No additional information was submitted with this application.

3.2. Safety Concerns Related to Formulation

One potential risk associated with Brixadi, which differentiates it from the transmucosal formulations of buprenorphine, is the concern that serious consequences could ensue if the product were injected intravenously. A Risk Mitigation and Evaluation Strategy (REMS) is proposed to ensure that the product is administered appropriately. Preclinical data reviewed in the previous two application submissions, suggested that if the drug product were to be administered intravenously, it would either gel rapidly and potentially block the injected vessel as it apparently did in preclinical studies (i.e., the rat tail vein), or, if the injected vein is larger

and the product does not gel quickly enough, it could result in a lung emboli or eventually be lodged in other small capillaries. This raised a safety concern about the possible consequences of this type of misuse, which could involve occlusion, tissue damage, or possibly embolus. Available post-marketing data from the Buvidal program has not revealed events associated with intravenous injection. However, the Buvidal product is also marketed under a restricted distribution (similar to the proposed REMS) to mitigate potential risk.

3.3. Legal and Regulatory Issues Constraining Buprenorphine Treatment

Buprenorphine is a Schedule III Controlled Substance and physicians prescribing buprenorphine must comply with the relevant aspects of the Controlled Substances Act. In addition, the provision of agonist treatment of opioid addiction is governed by certain legal requirements. Unlike methadone, buprenorphine may be prescribed by physicians meeting certain requirements. Methadone treatment of opioid addiction is delivered in a closed distribution system (opioid treatment programs, OTPs) that originally required special licensing by both Federal and State authorities, under the Narcotic Addict Treatment Act of 1974.

Under the provisions the Drug Addiction Treatment Act of 2000 (DATA 2000), qualifying physicians may obtain a waiver from the special registration requirements in the Narcotic Addict Treatment Act of 1974, and its enabling regulations, to treat opioid addiction with Schedule III, IV, and V opioid medications that have been specifically approved by FDA for that indication, and to prescribe and/or dispense these medications in treatment settings other than licensed OTPs, including in office-based settings[3]. The Applicant has been advised by DEA that the physician who prescribes CAM 2038 must be DATA-waived, or practicing in an OTP where DATA waivers are not required. The product may be injected by a non-waived health care provider.

4. Product Quality

The CAM2038 FluidCrystal subcutaneous injection depot drug product is a sterile, yellowish to yellow clear liquid which is [redacted] (b) (4) 1 mL long clear glass syringes with grey plungers.

[3] The Comprehensive Addiction and Recovery Act (CARA) of 2016 (P.L. 114-198) extended the privilege of prescribing buprenorphine in office-based settings to qualifying nurse practitioners (NPs) and physician assistants (PAs) until Oct. 1, 2021.

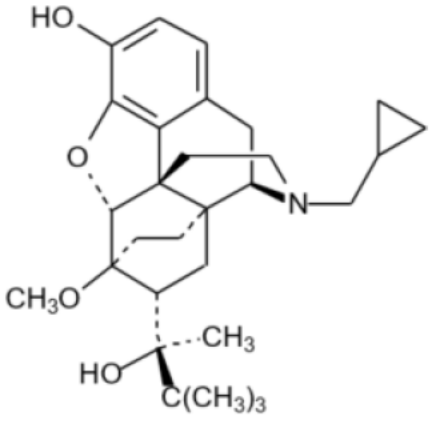
Figure 2: Visual of Combination Product

(b) (4)

It is a lipid-based parenteral (subcutaneous injection) extended-release product (once weekly or once monthly dosing) based on the proprietary FluidCrystal (hereinafter denoted FC) injection depot technology.

The active ingredient in CAM 2038 is buprenorphine free base, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist. The molecular weight of buprenorphine free base is 467.6, and its molecular formula is C29H41NO4. Chemically, buprenorphine is (2S)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3- hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol. The structural formula is shown below.

Figure 3: Structural Formula of Buprenorphine



The CAM2038 q1w (weekly) solution consists of 50 mg buprenorphine base (BUP)/mL, 10% w/w ethanol (EtOH) and Soybean Phosphatidylcholine (SPC)/Glycerol Dioleate (GDO) in the weight ratio 50/50 to final volume. The CAM2038 q4w Monthly solution consists of 356 mg buprenorphine base (BUP)/mL, 30% w/w N-methyl-2-pyrrolidone (NMP), and SPC/GDO in the weight ratio 40/60 to the final volume. The injection products utilizing the lipid-based formulations are low viscosity liquids. When the product is injected into the subcutaneous tissue, the formulation absorbs interstitial aqueous body fluid and transforms the liquid to a highly viscous gel. According to the applicant, (b) (4) CAM2038 q1w and CAM2038 q4w drug

product. No changes were made to or issues identified with the manufacturing of the drug substance. Similarly, no changes were made to the previously acceptable method and method validation data (b) (4) Refer to previous NDA review for buprenorphine composition data for the doses of CAM2038 q1w and CAM208 q4w formulations as well as stability and specification data (which is unchanged from the previous review).

Part of the manufacturing process for Brixadi is completed at two facilities:

1. Pharmaceutics International, Inc. (b) (4) | FEI: 3006503102 | DUNS: 049185696
2. Pharmaceutics International, Inc. (b) (4) | FEI: 1000513101 | DUNS: 878265586

In July 2020, the facilities were inspected as part of a pre-approval inspection (PAI) for an NDA unrelated to this one, and significant Good Manufacturing Practice (GMP) deficiencies were identified. The company (Pii) made an internal decision to shut-down those manufacturing facilities to address the deficiencies. After an October 2020 re-inspection, two 483 forms were issued to the manufacturer. The deficiencies in those forms covered (b) (4)

It is not clear how the inspectional findings might directly impact the manufacturing of the Brixadi drug product. However, at the time of this review, the deficiencies have not been resolved. The facility was determined to be "Official Action Indicated" and Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued a recommendation to withhold approval.

5. Nonclinical Pharmacology/Toxicology

The previous Pharmacology/Toxicology reviews focused on the safety of the CAM2038 formulations, and the two novel excipients, N-methyl-pyrrolidone (NMP), found in the monthly product, and glycerol dioleate (GDO), a diglyceride, found in both products. Additional details from the previous two application cycles can be found in the Pharmacology/Toxicology reviews conducted by Gary Bond, Ph.D., Jaime D'Agostino, Ph.D., and Elizabeth Bolan, Ph.D. In the second review cycle, the Applicant submitted new extractable and leachable data to address the deficiencies identified in the first review cycle. However, at the conclusion of that cycle, the review team identified three remaining concerns that could be addressed through post-marketing requirements (noting that the majority of previously identified leachables were adequately qualified and that the levels of the unidentified compounds in the formulations were predicted to be low. With this review cycle, the Application submitted the results of two reproductive and developmental toxicology studies to address two of the original nonclinical post-marketing requirements (PMRs 3 and 4). However, the Applicant did not submit new leachable data or the elemental impurity analysis. Refer to the PMR section of this review for the remaining nonclinical PMRs.

6. Clinical Pharmacology

No new clinical pharmacology information was submitted with this review cycle. The following summary of clinical pharmacology is based on the Clinical Pharmacology review conducted by Suresh Narahansetti, PhD. during the first two review cycles, and on the language proposed by the Division for drug labeling in the second cycle.

In Dr. Narahansetti's 2018 Clinical Pharmacology review, it was noted that trough levels of Brixadi from the upper arm site failed to meet the set bioequivalence criteria for 80 to 125% (see Table (b) (4) Table 7 and in the proposed label). To ensure expeditious attainment of therapeutic trough levels, the upper arm is not recommended as a site for initiation of Brixadi dosing but may be used in patients already at steady-state. This change was agreed upon at the conclusion of the second review cycle. The indented text in Arial font below is based on the Division's recommended labeling language specifically for Brixadi for this review cycle:

> Absorption
> BRIXADI is an extended-release formulation of buprenorphine designed for subcutaneous administration. BRIXADI is available in two regimens: weekly and monthly. Following single doses of BRIXADI (weekly) or BRIXADI (monthly), the buprenorphine C_{max} and AUC_{inf} increase dose-proportionally.
>
> The steady-state PK of buprenorphine following BRIXADI (weekly), BRIXADI (monthly) and their comparison to sublingual SUBUTEX across three studies are shown in Table 5. In these studies, BRIXADI (weekly) was administered for 4 or 4 to 7 weekly doses, BRIXADI (monthly) was administered for 4 monthly doses, and SUBUTEX was administered for 7 daily doses.
>
> After BRIXADI subcutaneous injection, the buprenorphine plasma concentration increases with a median time to maximum plasma concentration (t_{max}) of about 24 hours for the weekly BRIXADI and 6-10 hours for monthly BRIXADI. Based on trough levels after each dose, steady-state exposure is reached just prior to administration of the fourth weekly or monthly dose.
>
> After four repeated doses of BRIXADI (weekly) (16 mg) $AUC\tau$ (0-7d), C_{max} and C_{trough} values are ~40% higher exposure compared to the first dose. Based on cross-study comparisons, four repeated doses of BRIXADI (monthly) (128 mg) results in 68%, 65%, and 124% higher $AUC\tau$ (0-28d), C_{max} and C_{trough} values, respectively compared to the first dose.

Table 5: Summary of Steady-State PK Parameters of Buprenorphine After Subcutaneous Buttock Injections of BRIXADI (Weekly) and BRIXADI (Monthly) and SL Administration of SUBUTEX

Drug product dose			C_{av} (ng/mL)			$C_{max,ss}$ (ng/mL)			C_{trough}[a] (ng/mL)		
SL BPN	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly
8 mg	16 mg	64 mg	1.2	2.1	2.0 $	4.7	4.3	4.0 $	0.7	0.8	1.3 $
16 mg	24 mg	96 mg	1.8	2.9 $	2.9 $	6.5	5.5 $	6.0 $	1.0	1.4 $	2.0 $
24 mg	32 mg	128 mg	2.5	4.2	3.9	8.2	6.9	11.1	1.4	2.6	2.1

Source: Table 7, Physician Package Insert
* Average value of two studies
$ Simulated
a C168h for BRIXADI (weekly), C28d for BRIXADI (monthly) and C24h for Subutex

Effect of injection Site on PK of BRIXADI

After multiple dose subcutaneous injections of 32 mg BRIXADI weekly product at different injection sites (abdomen, thigh, buttock or upper arm), a comparable PK exposure was observed. However, injection in the arm site was associated with approximately 10% lower plasma levels than other sites.

Distribution:

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Elimination:

Buprenorphine is metabolized and eliminated in urine and feces. The apparent terminal plasma half-life of buprenorphine following subcutaneous injection of BRIXADI ranged between 3 to 5 days for BRIXADI (weekly) and 19 to 26 days for BRIXADI (monthly) as a result of the slow release of buprenorphine from the subcutaneous depot.

Metabolism:

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity.

Norbuprenorphine steady-state plasma concentrations in humans after subcutaneous injection of BRIXADI (weekly or monthly) are low compared to buprenorphine (AUC norbuprenorphine/ buprenorphine ratio of 0.35).

Excretion:

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of the buprenorphine

and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Specific Populations

Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of BRIXADI has not been studied. In a pharmacokinetic study, the disposition of buprenorphine was determined after administering a 2.0/0.5 mg Suboxone (buprenorphine/naloxone) sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine in patients with hepatic impairment was compared to disposition in subjects with normal hepatic function.

In subjects with mild hepatic impairment, the changes in mean $C_{max,}$ $AUC_{0\text{-last}}$, and half-life values of buprenorphine were not clinically significant. For subjects with moderate and severe hepatic impairment, mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine were increased *[see Warnings and Precautions (5.14) and Use in Specific Populations (8.6)].*

Renal Impairment
The effect of renal impairment on the pharmacokinetics of BRIXADI has not been studied. Clinical studies of BRIXADI did not include subjects with severe renal impairment. Less than 1% is excreted as unchanged buprenorphine in urine following IV buprenorphine administration. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine [*see Use in Specific Populations (8.7)].*

Population PK analyses indicated no notable relationship between creatinine clearance and steady-state buprenorphine plasma concentrations.

HCV infection
In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine were not clinically significant in comparison to healthy subjects without HCV infection.

7. Clinical Microbiology

N/A

8. Clinical/Statistical- Efficacy

Evidence of efficacy for Brixadi Weekly and Monthly doses derive from two studies, an inpatient opioid blockade study (HS-13-478) and a randomized, double-blind, double-dummy, active-control efficacy study (HS-11-421). The blockade study demonstrated that CAM2038 24 mg weekly and CAM2038 32 mg weekly are capable of blocking the subjective effects of a clinically-relevant dose of opioid agonist, and this blockade becomes longer-lasting after two weekly doses. The effect of this blockade was shown to translate to clinical efficacy as demonstrated by comparable outcomes in patients treated with a regimen of weekly followed by monthly CAM2038 compared with patients treated with sublingual buprenorphine/naloxone in the double-blind study.

Taken together, and considering the established efficacy of the reference product, Subutex, these studies provide substantial evidence of efficacy for CAM2038 in the treatment of moderate or severe OUD in patients who tolerate at least an initial test dose of buprenorphine. CAM2038 weekly is suitable for starting treatment, while CAM2038 (monthly) has been studied only in patients already in established treatment.

The text below briefly summarizes the design and findings of these two studies using labeling language proposed by the Division. Additional detail may be found in reviews from the previous review cycles. No new efficacy data were submitted for this cycle.

8.1. Blockade study (HS-13-478)

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 indented text in Arial font below is based on the Division's recommended labeling language for this review cycle. Refer to the primary review of the blockade study, performed by CSS Medical Officer, Dr. Alan Trachtenberg, and Biostatistics Reviewer, Wei Liu, from the first review cycle (2017), and the Pharmacometrics section of the Clinical Pharmacology review performed by Dr. Michael Bewernitz for additional information.

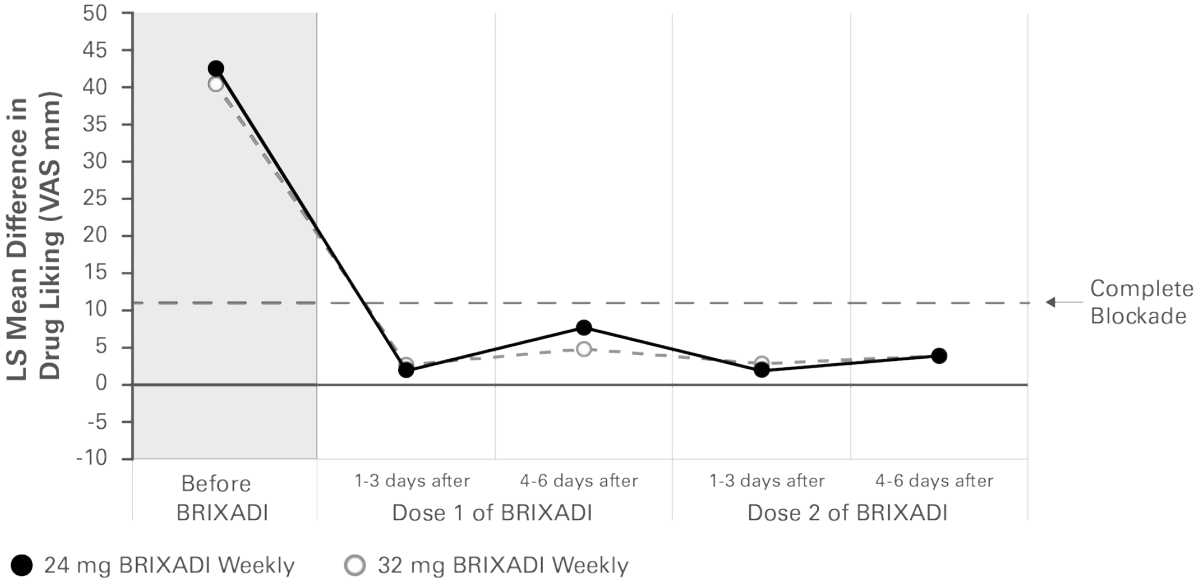
> The opioid blockade study assessed the blockade of subjective opioid effects, PK, and safety of BRIXADI weekly in 47 patients with moderate or severe opioid use disorder. Forty-six patients completed the study. Subjects were randomized to receive two injections of BRIXADI (weekly) once weekly for 2 weeks either at a 24 mg or 32 mg dose level.
>
> After stabilization on immediate-release morphine, all patients completed a 3-day qualification/baseline hydromorphone (HM) challenge session, which included intramuscular administration of 3 doses of HM (0 mg [placebo], 6 mg and 18 mg) once daily for 3 consecutive days. Patients were not exposed to buprenorphine during the baseline/qualification phase.

Following the qualification phase, eligible patients were randomly assigned to receive 2 doses of either 24 mg (22 patients) or 32 mg (24 patients) BRIXADI (weekly) with each dose administered one week apart. Two HM challenge sessions (Days 1-3 and 4-6 for the first session and Days 8-10 and 11-13 for the second session, respectively) were conducted after each dose of BRIXADI (weekly).

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

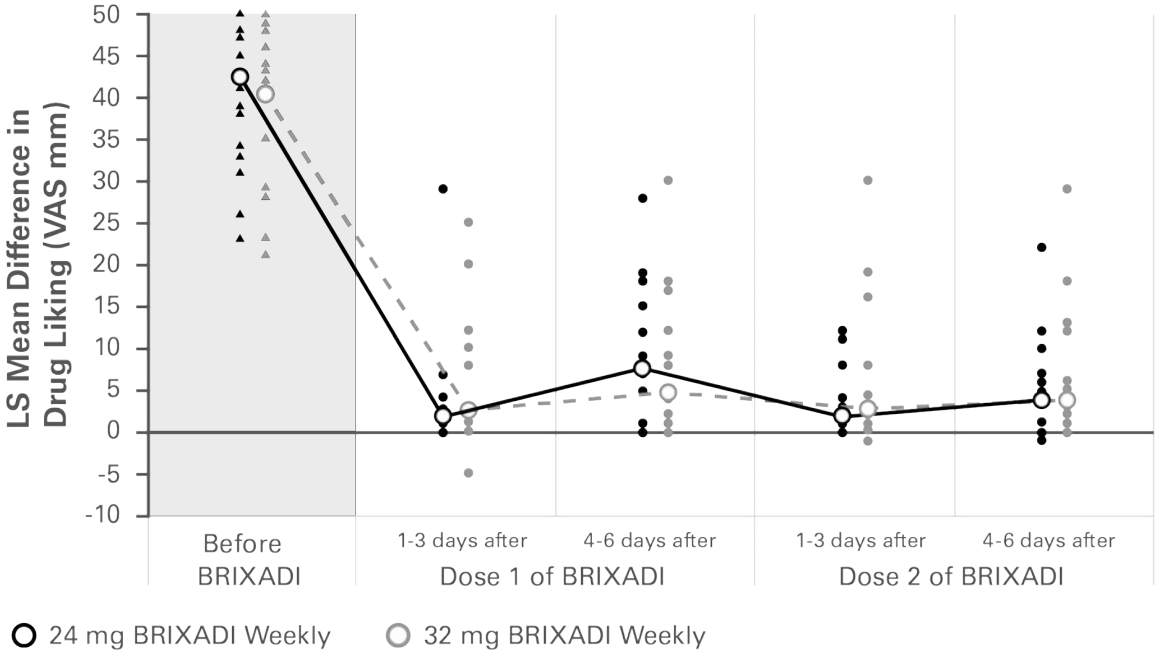
During the qualification/baseline phase, mean E_{max} scores for placebo were neutral while intramuscular hydromorphone 6 and 18 mg produced dose-related increases in the scores. Beginning with the first injection of BRIXADI (weekly) 24 mg or 32 mg weekly, no active intramuscular hydromorphone dose resulted in a mean drug liking VAS E_{max} score of 11 mm or greater when compared to placebo, which demonstrated complete blockade that was sustained throughout the first and second dosing intervals (see Figure 3). Individual subject scores are shown in Figure 4.

Figure 4: Mean Difference in Placebo-Corrected Peak Drug Liking



Source: Figure 15, Physician Package Insert

Figure 5: Mean Difference in Placebo-Corrected Peak Drug Liking With Individual Scores



Source: Figure 16, Physician Package Insert

Abuse

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

BRIXADI contains buprenorphine, a Schedule III controlled substance that can be abused similar to other opioids. Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with or referred for more intensive and structured treatment. Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines [see Warnings and Precautions (5.5)].

BRIXADI is distributed through a restricted distribution program, which is intended to prevent the direct distribution to a patient. BRIXADI should only be dispensed directly to a healthcare provider for administration by a healthcare provider. It is supplied in prefilled syringes and is intended for administration only by subcutaneous injection by a healthcare provider. The entire contents of the prefilled syringe should be administered.

Upon injection, BRIXADI spontaneously transforms from a low viscous solution to a liquid crystalline gel that encapsulates buprenorphine and releases it at a steady rate as the depot biodegrades [see Warnings and Precautions (5.1)].

Clinical monitoring for evidence at the injection site of tampering or attempting to remove the depot should be ongoing throughout treatment. No attempts to remove BRIXADI have been reported in clinical trials.

Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. Monitor patients during discontinuation of BRIXADI for symptoms of withdrawal [see Warnings and Precautions (5.8)].

Due to the long-acting nature of BRIXADI, withdrawal signs and symptoms may not be evident immediately following the discontinuation of treatment.

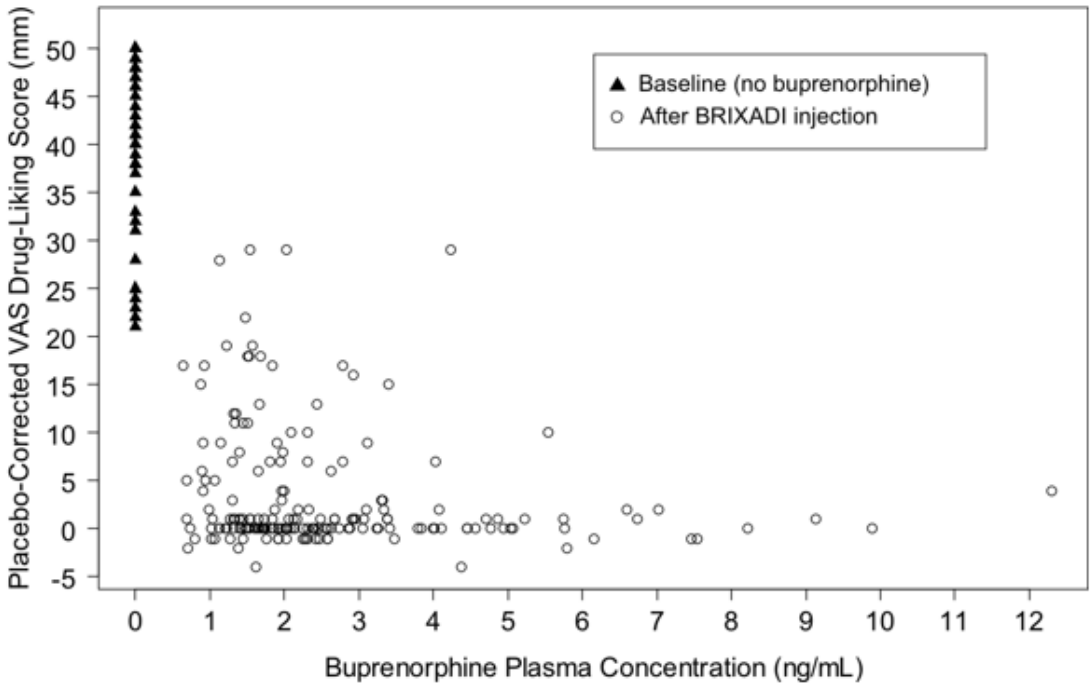
Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy [see Warnings and Precautions (5.6)].

Opioid Blockade

The opioid blockade study assessed the blockade of subjective opioid drug-liking effects and pharmacokinetics (PK) of BRIXADI (weekly) in 47 patients with moderate or severe opioid dependence. The primary endpoint was the maximum rating (Emax) on the visual analogue scale (VAS) for drug-liking. After stabilization on immediate-release morphine, all patients completed a 3-day qualification/baseline hydromorphone challenge session consisting of 3 intramuscular doses of hydromorphone (0 mg, [placebo], 6 mg, and 18 mg) once daily for 3 consecutive days in a randomized, double-blind, crossover manner. Following the qualification phase, eligible patients received 2 injections of BRIXADI (weekly) for two weeks at either the 24 mg or 32 mg level. Two hydromorphone challenge sessions (3 consecutive days each) were conducted throughout the week after each weekly injection of BRIXADI (weekly). On average, the subjective effects (e.g., drug liking [Emax]) of 6 mg or 18 mg hydromorphone was blocked following injections of BRIXADI (weekly) at the 24 mg or 32 mg levels. The variability in drug-liking scores was wider for the 18 mg than the 6 mg hydromorphone dose level. In addition, for the 18 mg hydromorphone dose challenge, the drug-liking score variability was wider towards the end of the BRIXADI (weekly) dosing interval compared to earlier in the interval (e.g. Days 4-6 versus Days 1-3; Day 11-13 versus Day 8-10). Drug-liking score variability was wider for the 24 mg BRIXADI (weekly) dose level compared to 32 mg [see Clinical Studies (14.1)]. Figure 14 illustrates the relationship between buprenorphine plasma level and drug liking after 18 mg

hydromorphone where data from the 24 mg BRIXADI (weekly) arm is pooled with data from the 32 mg BRIXADI (weekly) arm. The observed plateau for maximal response of drug-liking was reached at buprenorphine concentrations of approximately 1.5-2 ng/mL plasma levels.

Figure 6: Placebo-Corrected Drug Liking VAS vs. Plasma Buprenorphine Concentration Following 18 mg Hydromorphone Challenges for Pooled 24 mg and 32 mg Arms, From Proposed Drug-Labeling



Source: Figure 14, Physician Package Insert

8.2. Efficacy Study (HS-11-421)

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 indented text in Arial font below is based on the Division's recommended language for section 14.2 of the proposed drug label for this review cycle. Refer to the 2018 CDTL memo and the reviews conducted by Dr. Gioia Guerrieri (clinical) and Dr. James Travis (statistical) for additional information.

The efficacy and safety of BRIXADI for the treatment of opioid use disorder was evaluated in a Phase 3, 24-Week, randomized, double-blind, double-dummy, active-controlled, multicenter study in patients who met the DSM-5 criteria for

moderate or severe opioid use disorder and who were actively seeking but not currently receiving buprenorphine treatment. Patients were randomized to receive either BRIXADI injections with placebo sublingual tablets or sublingual buprenorphine/naloxone (SL BPN/NX) tablets with placebo injections. All patients received individual drug counseling for the duration of the study.

On the first day of treatment patients received an open-label 4 mg test dose of sublingual buprenorphine. Patients who tolerated the test dose (two patients did not tolerate the test dose) were randomized and given a 16 mg injection of BRIXADI (weekly) or matched placebo. During the next 6 days patients were allowed up to two further 8 mg injections as needed. Patients received an injection of 16, 24, or 32 mg on Day 8 matched to the dose they received in the previous seven days. Patients received injections weekly (every 7 days +/- 2-day window) for twelve weeks total and then transitioned to an equivalent dose of BRIXADI (monthly) (every 28 days, +/- 7-day window) for the remaining twelve weeks. Dose adjustments were permitted for the duration of the study. Supplemental 8 mg BRIXADI (weekly) injections were allowed during the second phase of the study and were also used in the active-controlled group. Overall, supplemental 8 mg injections were given to 14 patients (6.6%) in the BRIXADI arm and 17 patients (7.9%) in the SL BPN/NX arm. Table 6 shows the doses of BRIXADI (weekly) administered following the initial titration period and at the final visit before transition to BRIXADI (monthly) was allowed. Table 7 shows the first and final BRIXADI (monthly) dose administered to each patient.

Table 6: Number of Patients Receiving Each BRIXADI (Weekly) Dose at Selected Time-Points

BRIXADI (Weekly) Dose	Following Titration Period	End of Weekly Phase
16 mg	2	6
24 mg	128	84
32 mg	54	64

Table 7: Number of Patients Receiving Each BRIXADI (Monthly) Dose at Selected Time-Points

BRIXADI (Monthly) Dose	First BRIXADI (Monthly) dose	Final BRIXADI (Monthly) dose
64 mg	8	11
96 mg	84	83
128 mg	66	56
160 mg*	0	8

*not an approved strength
Source: Tables 8 and 9, Physician Package Insert

For the first twelve weeks patients completed weekly visits. For the final twelve weeks patients were transitioned to monthly visits. Patients were also required to complete three additional randomly scheduled visits during the final twelve weeks. Efficacy was evaluated using urine drug screens combined with self-reported use of illicit opioid use. Missing urine drug screen samples and/or self-reports were counted as positive for illicit opioids.

A total of 428 patients were randomized equally (215 patients in the SL BPN/NX group and 213 in the BRIXADI group). Of the randomized patients, 69.0% (147/213) of the patients in BRIXADI treatment group and 72.6% (156/215) of the patients in the SL BPN/NX treatment group completed the 24-week period. Patient demographics and baseline characteristics are provided in Table 8.

Table 8: Patient Demographics and Baseline Characteristics

	BRIXADI (N=213)	**SL BPN/NX (N=215)**
Mean Age (Years)	38.7	38.0
Sex %		
Male	56.8	66.0
Female	43.2	34.0
Race or Ethnicity %		
White	74.6	76.3
Black or African American	22.1	22.3
American Indian or Alaska Native	0.9	0.5
Asian	0.5	0
Native Hawaiian or Other Pacific Islander	0.5	0
Other	1.4	0.9
Primary Opioid of Use at Initiation %		
Heroin	71.4	70.2
Prescription Pain Reliever	28.6	29.8
Injectable Route %	53.5	51.2

	BRIXADI (N=213)	SL BPN/NX (N=215)
Substance Use by Urine Toxicology Prior to Randomization %		
Amphetamines	22.1	18.6
Barbiturates	1.4	0.5
Benzodiazepine	21.1	21.9
Cocaine	30.5	32.6
Cannabinoids	34.3	36.3
Fentanyl	29.1	22.8
Phencyclidine	1.9	0.5
Medical History %		
Anxiety	14.1	18.6
Back Pain	15.5	18.6
Depression	11.7	13.0

Source: Table 10, Physician Package Insert

Table 9 below illustrates the proportion of patients who were considered to be responders. A patient was a responder if they met all of the following criteria:

- Negative opioid assessment (urinalysis and self-report) during week 12 (evaluated during Week 13 visit).
- No more than one positive opioid assessment in the three illicit opioid use assessments performed during week 9 to 11 (evaluated during visits at Weeks 10 to 12).
- Negative opioid assessment during the final month of the study.
- No more than one positive opioid assessment at the three scheduled monthly visits and three random site visits.

This responder definition was designed to identify patients who were successfully treated with both BRIXADI (weekly) (administered in the first 12 weeks of treatment) and BRIXADI (monthly) (administered in the second 12 weeks of treatment). Therefore, patients were required to have negative opioid assessments at the end of each treatment phase. Each phase also included an allowable grace period (an initial period of time when positive opioid assessments were not taken into account) and the definition also allowed for sporadic positive assessments. Based on the results of this trial, the efficacy of BRIXADI was demonstrated. Table 11 shows the response rate for each treatment arm along with the associated 95% confidence interval for their difference.

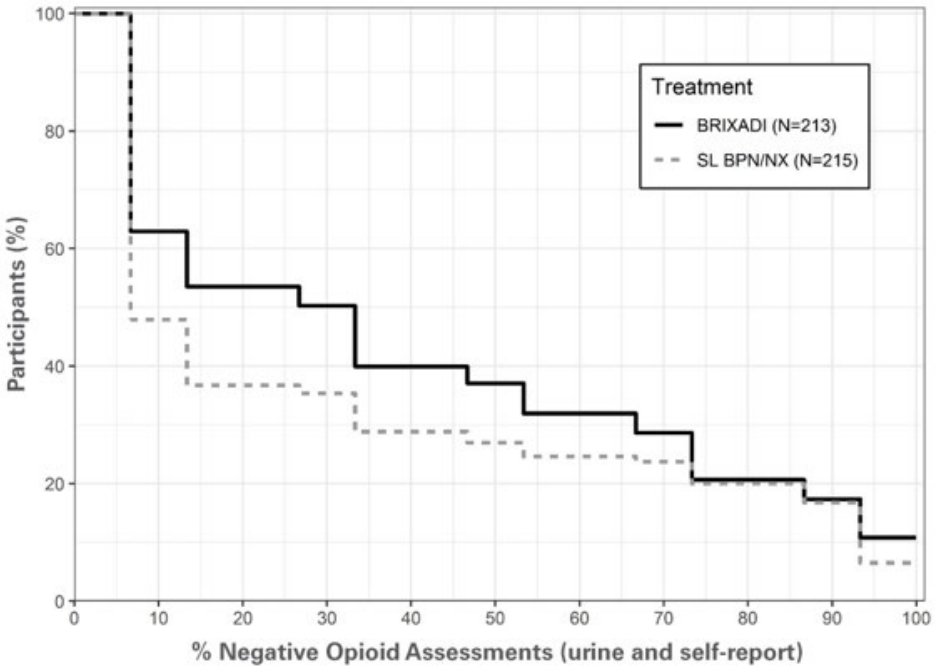
Table 9: Number (Percentage) of Patients Who Met the Responder Definition

BRIXADI Injection with placebo sublingual tablets (N=213)	SL BPN/NX Tablets with Placebo Injections (N=215)	Treatment Difference (95% CI)
36 (16.9%)	30 (14.0%)	2.9% (-3.9%, 9.8%)*

* The lower bound of the confidence interval was within the agreed upon non-inferiority threshold of −10%.
Source: Table 11, Physician Package Insert

The cumulative distribution function (CDF) of the percentage of negative opioid assessments (urine samples negative for illicit opioid use combined with self-reports negative for illicit opioid use) from Week 4 through Week 24 are shown in Figure 6 and Table 10. The figure and table are cumulative, so that a patient whose percentage of opioid-free assessments is, for example 50%, is also included at every level of negative opioid assessments below 50%. Missing values and values after premature discontinuation were considered positive. Based on the CDF of the percentage of negative opioid assessments, superiority was demonstrated with BRIXADI with statistical significance compared with SL BPN/NX. However, on the right-hand side of the curves where patients were reporting mostly negative opioid assessments (80% or greater) there was little to no difference between BRIXADI and SL BPN/NX.

Figure 7: Patients Achieving Varying Percentages of Negative Opioid Assessments (Urine and Self-Report) in Weeks 4 Through 24



Source: Figure 17, Physician Package Insert

Table 10: Patients Achieving Varying Percentage of Opioid-Negative Assessments (Urine and Self- Report) (Weeks 4-24)

Percentage of Opioid-Negative Assessments (Urine and Self Report)	Number (%) of Patients	
	BRIXADI 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: Table 12, Physician Package Insert

9. Safety

The review strategy for this cycle involved evaluating the newly-reported post-marketing information and comparing the findings to the established safety profile as documented in the previous review cycle. The post-marketing data did not demonstrate any previously-unknown safety concerns regarding the risks of buprenorphine or the Brixadi drug product. The sections below detail the previous findings and any pertinent observations about the updated safety data reviewed for this submission.

Updated safety information reviewed for this cycle included:

- A Clinical Information amendment providing an overview of the safety findings of CAM2038 that occurred since the second application cycle (including 15-day safety reports submitted to IND from post-marketing).
- Annual Data Safety Update Report (DSUR) #6 from Camurus and Braeburn for CAM2038 safety data received from worldwide sources (data lock 2/2020).
- The 2019 Periodic Brief Risk Evaluation Report (PBRER) for Buvidal, marketed by Camurus, with a July 30, 2019 data lock).
- Investigator Brochures 12, 13, and 14 submitted to INDs 114082 (b) (4).
- Response to a June 20, 2020 Information Request from the Division.

(b) (4)

Clinical trial safety data to support Brixadi drug approval was unchanged from the first two NDA review cycles (2017 and 2018) and were derived from Phase 1 PK studies, the blockade and efficacy studies described above, and a 24-week, Phase 3 open-label study, which enrolled patients who could be new to treatment ("new entrants") or already in established treatment with transmucosal buprenorphine ("transfer") (Study 499). In the clinical development of CAM2038 (Brixadi) for OUD during the initial review, 729 subjects were exposed to at least one dose of the study, which included healthy volunteers. In the pooled Phase 3 studies, 440 unique patient exposures to Brixadi were reported by the Applicant. In these studies, a total of 305 patients were exposed to Brixadi for at least 24 weeks and 132 patients were exposed for at least 48 weeks.

As of April 30, 2020, a total of 1,520 subjects have been exposed to the Brixadi/Buvidal investigational drug product in sponsored clinical studies. An additional 67 patients were exposed in one investigator-initiated Australian study with no new adverse events reported to the IB. Additionally, Braeburn (b) (4) has provided product for use in several ongoing investigator-initiated studies. The updated safety information for these activities was submitted at Agency request, on July 10, 2020, and are recruiting but have enrolled only one subject (see Table 11, below).

Table 11: Investigator-Initiated Trials for Which Braeburn is Currently Providing CAM2038 (Brixadi)

Study Name	*Emergency Department- INitiated bupreNOrphine and VAlidaTIOn Network Trial (ED-INNOVATION)*	*Medication Treatment for Opioid Use Disorder in Expectant Mothers (MOMs): A Pragmatic Randomized Trial Comparing Two Buprenorphine*	*A comparative effectiveness trial of extended release naltrexone versus extended-release buprenorphine with individuals leaving jail*
ClinicalTrials.gov Identifier	**NCT04225598**	**NCT04212065**	**NCT04408313**
Study Objective	Evaluate implementation of emergency department-initiated buprenorphine; compare extended release buprenorphine with sublingual buprenorphine in Emergency Department Opioid Use Disorder patients; develop and validate electronic health record phenotypes of opioid- related illnesses to characterize emergency department visits, enhance active disease surveillance, and better identify patients eligible for inclusion.	Evaluate the impact of treating opioid use disorder in pregnant women with extended- release buprenorphine, compared to sublingual buprenorphine, on maternal-infant outcomes. Testing a conceptual model of the mechanisms by which extended-release buprenorphine may improve maternal-infant outcomes, relative to sublingual buprenorphine, is a secondary trial objective.	To determine the effectiveness of extended-release buprenorphine compared to extended-release naltrexone. Aim 2. To calculate the cost to the jail/county health system of implementing extended-release buprenorphine and extended-release naltrexone, and determine the relative value, including the costs associated with the interventions in the community, from a county and state-policymaker and societal perspective.
Recruitment Status	Recruiting (FPFV 6/19/20)	Recruiting (no patients enrolled)	Not yet recruiting

Source: adapted from Applicant-provided, Clinical information amendment

9.1. Safety data reporting

Since the initial clinical trial safety data were submitted for review, CAM2038 (as Buvidal) in both the weekly and monthly formulations, has been marketed in seven countries[5]. Camurus estimated Buvidal patient exposure from marketing experience is to be a total of 4082 patient-

[5] From the 2019 Periodic Benefit-Risk Evaluation report, Buvidal was made commercially available in Denmark, Germany, Finland, Sweden, Norway and United Kingdom and was provided in Australia in hospitals and specialist drug rehabilitation clinics through the Patient Familiarization Program.

months, resulting from (b) (4) mg of buprenorphine distributed worldwide[6]. The Applicant reported that since distribution, 7,500 patients have been treated.

Braeburn indicated that the data-lock for post-marketing safety reporting for this application was April 30, 2020 and provided their summary of the Buvidal post-marketing safety data in the Clinical Information Amendment. The submitted data included a list of five expedited post-marketing Buvidal safety reports from February 20, 2020 to April 30, 2020. An overview of those findings are described in the relevant subsections below.

9.1.1. Deaths

Clinical Program:

No additional deaths in the clinical program supporting this NDA were reported by the Applicant. One death was previously reported in the clinical program, in a patient treated with CAM2038 in Study 421 (a 41-year-old female with no other reported medical history was hit by a car and died on Study Day 147). There were no factors suggesting a causal link to the study drug.

No deaths occurred in the clinical development program of CAM2038 in the DSUR for this reporting period. However, Camurus did mention that they received one fatal report from a Special Access Scheme (SAS) in Australia, but the death was assessed as not related to CAM2038. In response to an Agency information request (see below for verbatim text from the Division), the Applicant provided details of this SAS case. The fatality involved a 68-year-old male with a history of end-stage renal disease who died from sepsis. He previously participated in Study HS-17-585 (completed) and continued treatment with CAM2038 through the SAS until Buvidal was marketed in Australia. Review of the events confirm that the death was likely not related to Buvidal.

No overdose deaths or clearly medication-associated deaths were identified in the clinical program.

Post-marketing data:

One death was submitted by the Applicant to IND 114082 as an expedited case report from Buvidal post-marketing sources provided by Camurus in support of this review and is outlined below.

Three additional deaths that were provided to Braeburn after the data lock date and were submitted to IND 114082 between 6-18-2020 and 9-18-2020 (as 7-day expedited safety reports) were included in this review and are referenced in Table 12 by date of death event and date reported to IND 114082.

[6] Obtained from Buvidal's first reporting interval, November 20, 2018- July 30, 2019, during which (b) (4) Buvidal units were sold.

Table 12: Summary of Deaths Obtained From Postmarketing Sources

Case Reference #	Date of event [initial receipt date to IND 114082], location	Age in years (sex), PMH*	Buvidal dose	Case description	Reported to NDA 210136
GB-CAM-20-00032	(b) (6) [3-24-2020], UK	63 (M), HCV**, alcohol use disorder, OUD, "mental disorder, unspecified"	16 mg Weekly	Patient was started on Buvidal (b) (6) after transfer from oral buprenorphine, 6 mg daily (duration unknown). 14 days after the most recent dose of Buvidal had been administered, outreach team attended home address (when patient had missed appointment) and the patient was found dead at home. At his last appointment, the patient-reported "sickness and loose stool" and was referred to a primary care doctor. The treatment team called the patient the next day, who reported symptom improvement and declined seeking additional treatment. Not deemed related to the study drug by Camurus. Autopsy report and concomitant medications unavailable.	Y
SE-CAM-20-00091	(b) (6) [6-18-2020], Sweden	35 (M), chronic liver disease, bipolar disorder, attention deficit hyperactivity disorder	96 mg Monthly	Patient began treatment with Buvidal 24 mg Weekly in (b) (6) (transferred from Suboxone, 16 mg daily since (b) (6)). Treatment switched to Buvidal Monthly, 96 mg, (b) (6) for severe OUD. Laboratory results were "unremarkable" (b) (6) but did not include buprenorphine levels. 8-days after last Buvidal Monthly dosing (b) (6), the patient was found dead. The patient was not hospitalized before death, per MedWatch report, but per the Applicant, the patient was in a custodial setting and known to the facility for attempting to obtain illicit substances. Autopsy revealed elevated levels of plasma and urine buprenorphine, elevated levels of norbuprenorphine, and enlarged liver. "Other narcotic drugs detected, including methylphenidate" but details unavailable. Per the Applicant, methylphenidate was not prescribed preceding death. Concomitant medications included: duloxetine, lithium citrate, metformin, olanzapine, simvastatin,	N

Case Reference #	Date of event [initial receipt date to IND 114082], location	Age in years (sex), PMH*	Buvidal dose	Case description	Reported to NDA 210136
				budesonide/formoterol, and methylphenidate hydrochloride. Autopsy report not available to Applicant (Braeburn) and the contribution of Buvidal to death could not be determined. Based on the information provided, Buvidal cannot be excluded as a contributing factor.	
AU-CAM-20-00181	(b) (6) [9-17-2020], Australia	32 (M), OUD, "psychiatric condition, unspecified", and HCV	96 mg Monthly	Patient died 3-weeks after second dose of Buvidal 96 mg. Patient was in a custodial setting, experienced dizziness, loss of consciousness, subsequent cardiac arrest and death. Concomitant medications included olanzapine and glecaprevir/pibrentasvir. Follow-up toxicology, and autopsy results are pending at the time of this review. Per the Applicant, the contribution of Buvidal to death could not be determined. Based on the information provided, Buvidal cannot be excluded as a contributing factor.	N
AU-CAM-20-00182	(b) (6) [9-17-2020], Australia	34 (M), OUD, hypertension, hypercholesterolemia, obesity (160 kg), diabetes mellitus, and "psychiatric condition, unspecified"	8 mg Weekly	Patient was dosed with Buvidal, 8 mg, on (b) (6) after a test dose of SL buprenorphine. He was found dead with no apparent cause of death on (b) (6) the day after Buvidal dosing. Concomitant medications included paliperidone, quetiapine, escitalopram, metformin, atorvastatin, metoprolol, dulaglutide, perindopril. Follow-up toxicology, and autopsy results are pending at the time of this review. Per the Applicant, the contribution of Buvidal to death could not be determined. Based on the information provided, Buvidal cannot be excluded as a contributing factor.	N

This table reflects Applicant-provided updates about each death submitted to the Agency on October 5, 2020
**PMH = past medical history*
*** HCV= hepatitis C virus*
Source: Clinical Reviewer

The following Information request was sent to the Applicant on September 25, 2020:

> We note there have been at least four post-marketing reports of sudden death/unwitnessed death ("found dead") in patients treated with Buvidal (CAM2038/Brixadi). These deaths include case reference numbers, GB-CAM-20-00032, SE-CAM-20-00091, AU-CAM-20-00181, and AU-CAM-20-00182. We also note the additional, fatal, report mentioned in DSUR #6 that, "was received from the special access scheme in Australia, but the death was assessed as not related to CAM2038." No information about that special access scheme case was provided.
>
> Submit any additional information about these five cases, including autopsy reports or any other details of the events that were not included in the expedited safety reports. Additionally, search both the clinical trials database and the post-marketing database for any similar cases, involving sudden/unexpected deaths, unwitnessed deaths ("found dead"), or other unexplained deaths. Provide a tabulation of cases with brief summaries, as well as a detailed narrative for each case.
>
> We appreciate that your access to relevant data might be limited. However, we would like to see an overall assessment of these cases and conclusions as to what the findings might mean and what your recommendations are, or what you propose to do next.

The Applicant replied to the information request on October 5, 2020 and provided a summary and assessment of the reported unknown causes of deaths, which are listed in Table 12 and occurred since the last review cycle. At the time of this review, two of the unknown causes of death are pending toxicology and autopsy results. The Applicant acknowledged that, based on the information provided, a causal relationship between Buvidal and the sudden deaths could not be determined and the cases are being closely monitored. Of note, three of the four cases included concomitant use of atypical antipsychotic medications, which can be a risk factor for cardiac adverse events. However, at the time of this review, the summary of findings from the unknown causes of death do not change the risk-benefit profile Brixadi.

9.1.2. Serious Adverse Events

Pre-marketing data:

A total of 20 SAEs (including the fatality described above) occurred among 17 subjects of the 729 exposed to CAM2038 across the OUD treatment clinical program. None were related to injection site reactions. In Study 421, SAEs were reported in five (2.3%) of the CAM2038 group and in 13 (6%) of the SL BPN group. Accidental overdoses (3) were reported in the SL BPN group but not the CAM2038 group. One event (vomiting) was deemed plausibly related to study drug. In the second review cycle (2018), Braeburn included an SAE that occurred (b) (4) (b) (4) was reported (b) (4) and should

have been included in the original NDA submission. The case involved a woman who presented to the ER one day after her first injection of 8 mg CAM2038 with "acute onset altered mental status, rhabdomyolysis, acute renal failure, and markedly elevated liver transaminases leading to acute liver failure." The patient recovered. Because, hepatic effects are known to be associated with buprenorphine, that event did not change the overall assessment of Brixadi.

Post-marketing data:

The Applicant submitted a tabulation of serious adverse drug reactions (N=22) from post-marketing data sources. This included the following system organ classes: Gastrointestinal disorders (1)[7], General disorders and administration site conditions (6)[8], Immune system disorders (1)[9], Injury, poisoning and procedural complications (1)[10], Investigations (2)[11], Nervous system disorders (1)[12], Pregnancy, puerperium and perinatal conditions (2)[13], Psychiatric (6)[14], Skin and subcutaneous tissue disorders(1)[15], and Vascular disorders(1)[16].

Not submitted to the NDA was an expedited 15-day Safety report submitted to IND 114082 on 6-19-2020, after the data lock date. The case involved "post-operative delirium" in a 49-year-old Australian male (reference number AU-CAM-20-00092) who was hospitalized for a proctocolectomy due to ulcerative colitis and received his first dose of Buvidal 96 mg "Weekly" on (b) (6) after one week of Suboxone treatment for OUD. Concomitant medication included diazepam, 10 mg. On (b) (6) (three days after Buvidal dosing), the patient was involved in a motor vehicle accident and re-hospitalized for rib fractures and post-operative delirium. The patient recovered. No additional information was provided. Given the paucity of available information, Buvidal causality cannot be ruled out and, of note, the prescribed 96 mg dose formulation of Buvidal is monthly, not weekly. However, the report was lacking detail to the extent that the dosing regimen employed was also unclear.

These findings did not change the overall safety profile of Brixadi.

[7] Abdominal pain
[8] Death (GB-CAM-20-00032 described above), drug ineffective, Drug interaction, drug withdrawal syndrome (2), peripheral edema
[9] hypersensitivity
[10] Toxicity to various agents
[11] Weight increased; Oxygen Saturation decreased
[12] Depressed level of consciousness
[13] Spontaneous abortions
[14] Agitation, anger, disorientation, auditory hallucination, drug abuse, psychotic symptoms
[15] Skin ulcer in case E2B_00000051 (2019BBN00029): A patient was hospitalized due to leg ulcer, five days after receiving the first injection of Buvidal 16 mg in an unknown location. This did not appear related to an injection site reaction.
[16] Hemorrhage (related to spontaneous abortion)

9.1.3. Dropouts and/or Dose Reductions Due to Adverse Effects

Pre-marketing data:
Adverse reactions led to premature discontinuation in 10 (4.7%) patients in the group receiving BRIXADI compared to 5 (2.3%) patients in the sublingual buprenorphine/naloxone group, during the double-blind study.

Post-marketing data:
No new information about discontinuations due to AEs leading to discontinuation and no dose reductions due to AEs were identified. If anything, a pattern of CAM2038 dosing increase within 2-3 weeks after transferring to CAM2038 from another buprenorphine product was identified.

9.1.4. Injection Site Reactions

Pre-marketing data:
In the clinical program, injection site reactions were reported by approximately 20% of patients. (Patients in the sublingual buprenorphine arm received placebo injections.) The indented text in Arial font below summarizes the clinical trials safety database and is based on the Division's recommended language for section 6.1 of the proposed drug label for this review cycle:

> Injection site reactions in the double-blind study are presented in Table 13 below. The majority of injection site-related adverse events were mild or moderate in severity. No injection site reactions were reported as severe intensity.

Table 13: Injection-Site Reactions in the Double-Blind Phase 3 Study: ≥ 2% of Patients Receiving BRIXADI

Preferred Term (PT)[a]	BRIXADI Total[b] (N=213) n(%)	SL BPN/NX[c] (N=215) n(%)
Administration site reactions[d]	**44 (20.7%)**	**49 (22.8%)**
Injection site pain	21 (9.9%)	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%)

Preferred Term (PT)[a]	BRIXADI Total[b] (N=213) n(%)	SL BPN/NX[c] (N=215) n(%)
Administration site reactions[d]	**44 (20.7%)**	**49 (22.8%)**
		(b) (4)

a = Injection site reactions (ISR) that occurred in ≥2% of patients receiving BRIXADI, in the controlled trial, HS-11-421. Patients are represented once per PT.
b = This group includes patients exposed to varying doses of both the BRIXADI weekly and monthly formulations.
c = SL BPN/NX denotes the active comparator: subjects assigned to daily buprenorphine with sham (placebo) injections. Patients randomized to this group could also receive a supplemental 'booster' injection of BRIXADI (weekly), 8 mg, per protocol.
d = The ISRs that occurred in ≥2% of the patients randomized to BRIXADI were reported under the HGLT of Administration site reactions. However, ISRs were also identified under the Bacterial infectious disorders HGLT (of which, there were three injection site related cellulitis reactions in the BRIXADI group and one in the SL BPN/NX group, respectively) but those numbers did not rise to level of reporting. Tabulation included all events coded as treatment-emergent and injection site reactions, regardless of treatment-emergent flags.
Source: Table 6, Physician Package Insert

Of note, in the Investigator Brochure, version 14 (data lock of February 19, 2020), results from study HS-17-585 were reported (the study was completed in the year prior). HS-17-585 was an Australian trial that compared efficacy, safety, treatment satisfaction, quality of life and health economics of CAM2038 to those of standard of care BPN treatment in 24 weeks of treatment. In the CAM2038 treatment group, the two most frequently occurring adverse drug reactions (in ≥5% of patients) were injection site pain (11 patients [18.3%]) and injection site mass (10 patients [16.7%]). Injection site mass was seen in three patients (1.4%) exposed to CAM2038 in Study 421.

Post-marketing data: Fourteen cases of ISRs coded as "injection site mass" were included in the updated safety information. This term was not commonly-reported in the clinical trials data and represents a new finding. Labeling should note that a palpable mass may be observed after dosing. Table 14 shows reported ISRs from post-marketing sources from July 31, 2019 through April 30, 2020.

Table 14: Injection- Site Reactions Received from Postmarketing Sources

MedDRA PT	Number of ISRs
Injection site mass	14
Injection site pain	14
Injection site erythema	10
Injection site swelling	7
Injection site inflammation	3
Injection site pruritus	3
Injection site bruising	2
Injection site discoloration	2
Injection site hematoma	2
Injection site nodule	2
Injection site rash	2
Injection site cyst	1
Injection site extravasation	1
Injection site haemorrhage[17]	1
Injection site induration	1
Injection site urticaria	1
Injection site warmth	1
Total	**67**

Adapted from Applicant-provided clinical information

A 15-day safety report submitted to IND 114082 on 5-19-2020 (outside of the data lock for the Applicant-provided materials for this review) revealed a case (reference number AU-CAM-20-00007) of "injection site necrosis" where the description included the formation of "skin necrosis with yellow top" over the skin where the injection site of Buvidal had been administered. The Australian adult male patient, of unknown age, "plucked the top off" with no pain and received an additional dose of Buvidal. No treatment was sought or recommended for the "necrosis" and no information was provided on the dose, formulation, or location of the injection. The report indicated that the injection placement could have been incorrect. Buvidal treatment was continued.

Other narratives related to injection site masses were reported by the Applicant in the Clinical Information Amendment under the subsection 'Concomitant use of gabapentinoids'. These included:

- AU-CAM-19-00089: "A patient developed a lump one day following first injection of Buvidal 96 mg to abdominal site. The lump was not painful, and treatment was not required. The lump disappeared after the fifth week post injection."

[17] On review, it appears that injection site hemorrhage and hematoma were related to case number FI-CAM-20-00057: A Finnish patient with medical history of asthma, sleep apnea, type-2 diabetes and morbid obesity who experienced several ISRs after receiving her first dose of Buvidal 96 mg monthly. These included bleeding, hematoma and puncture mark at the injection site, stinging pain, and a burning and itching feeling in the arm. In addition, a rash appeared after injection that extended to the neck and slightly over the elbow. The patient also had some difficulty breathing. Action taken and outcome were not reported.

- SE-CAM-20-00036: “A patient experienced 'bulges from previous injections' that became infected twice. The patient was treated with antibiotics.”

The pre-marketing findings taken together with the results received from post-marketing data sources, indicate that injection site mass might be reported after US marketing.

9.1.5. Hepatic

Premarketing data:
Hepatic adverse events are referenced in the Division’s agreed upon labeling language for sections 5, 8, and 12 (see listed language above in Clinical Pharmacology). One suspected case of hepatitis (case AU-CAM-19-00051) was reported from a single, investigator-initiated study (dBC2531) in Australia, which involved a 36-year-old subject who experienced hepatitis acute six days after initiating treatment with CAM2038. Treatment with CAM2038 was interrupted as a response to the event which resolved 9 days later. In a follow-up received by Camurus after the data lock date of the DSUR, the causality of this event was re-assessed to not related to CAM2038. Review of the extremely limited case information yielded no additional information.

Postmarketing data:
Two cases of serious hepatic adverse events were identified from post-marketing sources. One of the cases (NO-CAM-20-00056) is described above and was reported as a death. This was the 63-year-old male with a history of hepatitis C. The second case (FI-CAM-20-00042) occurred in Finland in a 44-year-old male who was hospitalized with shortness of breath, peripheral edema, and abdominal pain 3-weeks after receiving the 96 mg Monthly dose of Buvidal. Significant concurrent medical history included chronic viral hepatitis C, insomnia, depression, in addition to severe OUD. On exam, the patient had bile duct calculi and elevated liver enzymes. The symptoms resolved and the patient was discharged and continued Buvidal treatment.

From the data reviewed, nothing in DSUR or post-market reports require modification of the labeling agreed upon in previous review cycle.

9.1.6. Cardiac

Premarketing data:
In the pre-marketing program, clinically significant ECG abnormalities reported as an AE occurred in 10 patients treated with CAM2038 (studies 549, 478, 421, and 499), in addition to a few cases of mild to moderate QT prolongation. Data were reviewed by the QT-IRT team during the first review cycle.

Post-marketing data:
No adverse drug experiences of ECG abnormalities or serious cardiac events (of any severity) were reported in the ongoing clinical trials. However, one expedited 15-day safety report was submitted on 6-29-2020 to IND 114082 involving Buvidal administration in a 62-year-old

Norwegian male with OUD (reference number NO-CAM-20-00108) who experienced SVT and QTc prolongation and hospitalization after Buvidal dosing of 64 mg (formulation not provided). On review, the dosing of the drug was administered after document ECG changes and arrythmia the week prior. The patient recovered and action with the medication was unknown.

Since the time of the TA action, DAAP has undertaken a comprehensive review of all available information about the cardiac effects of buprenorphine, including mechanistic studies performed by the Division of Applied Regulatory Science. A review of all of the material considered, prepared by Dr. Daniel Foster, documents the overall conclusion that the observed QT prolongation with buprenorphine does not appear to be mediated by hERG channels and that buprenorphine is unlikely to be pro-arrhythmic when used alone. Acccordingly, new language was recommended for sections 5.15 (Warnings and Precautions) and 12.2 (Clinical Pharmacology) of the proposed drug label for this review cycle.

5.15 QTc Prolongation

Some studies demonstrate a modest QTc prolongation of uncertain clinical significance. This effect does not appear to be mediated by hERG channels and buprenorphine is unlikely to be pro-arrhythmic when used alone. The effect of combining buprenorphine with other QT-prolonging agents is not known *[see Clinical Pharmacology (12.2)]*.

12.2 Pharmacodynamics

…

Cardiac Electrophysiology

Thorough QT studies with buprenorphine products have demonstrated modest QT prolongation ≤15 msec. Two categorical analyses of cardiovascular-specific adverse events among patients exposed to buprenorphine demonstrated no proarrhythmic potential. One Holter monitoring study demonstrated no arrhythmia. An analysis of medical literature provided no evidence for causal association between buprenorphine and Torsades de Pointes.

9.1.7. CNS/Respiratory Depression

Pre-marketing data:

Symptoms such as somnolence and sedation were not commonly reported in the safety database. One patient (CAM3028 (weekly) 32 mg) discontinued study medication due to sedation. No TEAEs potentially associated with respiratory depression were reported in patients treated with CAM2038.

Post-marketing data:
Only one case of potential "overmedication" was reported and is listed above under Serious Adverse Events. This case was reported (b) (4) after the data lock.

These findings did not appear to change the overall safety profile of Brixadi.

9.1.8. Inadequate dosing

Of the 20 cases submitted for review with this application cycle, using the standardized MedDRA query "drug withdrawal reactions," 19 post-marketing reports involved patients complaining of withdrawal at or after 2-weeks following treatment initiation with Buvidal. In most cases, the event resolved with increasing doses of Buvidal. These cases did not describe the syndrome of precipitated withdrawal as much as they described sub-therapeutic dosing of Buvidal.

Notably, several cases reviewed mentioned the upper arm was used as the initial dosing site. Because of the multiple available doses, there may be some difficulty in selecting the correct dose for a given patient, and the requirement for two doses the first week when initiating the Weekly product may present difficulties for some patients.

In three cases, patients described product 'encapsulation'(N=2) or 'bump' (N=1) under the skin (unknown doses and formulations) and unspecified 'drug withdrawal' was reported, which was treated with additional CAM2038 doses to prevent 'cravings.'

These findings did not change the overall safety profile of Brixadi.

9.1.9. Medication errors

In the clinical development program, no studies were performed to evaluate whether lower doses of either formulation could be combined to yield exposures equivalent to the mathematical sum of the doses of CAM2038 (e.g., 2 x 16 mg Weekly formulation compared to 1 x 32 mg Weekly formulation). The proposed label cautions against combining doses in this fashion. Instances of investigators making such substitutions were recorded in the clinical trials submitted with the first review cycle and may be predicted to occur after marketing. However, review of post-marketing data submitted with this application cycle, did not reveal situations where providers reported combinations of doses to achieve a desired mathematical sum. Last, only one report of "package difficult to open" was reported and this did not result in a medication error.

One report of a significant medication error was identified in post-marketing sources. A patient was administered 128 mg CAM2038 Monthly (Buvidal) instead of 8 mg CAM2038 Weekly (Buvidal), as was prescribed. The event occurred in an Australian emergency department and was related to a serious AE in a patient (refer to section 9.2.4 below for clinical details). No details regarding the causality of the medication error were provided. This finding did not

change the overall safety profile of Brixadi but reflects the importance of cross-checking the order with the dispensed drug.

9.1.10. Common AEs

The systemic safety profile for CAM3038, when given by a HCP in clinical trials, was broadly consistent with the known safety profile of transmucosal buprenorphine. The indented text in Arial font below from the proposed labeling summarizes the findings from the clinical program.

> Adverse reactions commonly reported after BRIXADI administration (≥5%, regardless of dose and regimen) in the double-blind study, were injection site pain (9.9%), headache (7.5%), constipation (7.5%), nausea (7.0%), injection site erythema (6.6%), injection site pruritis (6.1%), Insomnia (5.6%), and urinary tract infection (5.2%).
>
> Table 15 shows the adverse reactions for BRIXADI compared with the active-control group (SL BPN/NX) in the double-blind study.

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Table 15: Adverse Reactions in the Phase 3 Double-Blind Study: ≥ 2% of Patients Receiving BRIXADI (Excluding Injection-Site Reactions)

System Organ Class (SOC) Preferred Term (PT)[a]	**BRIXADI Total[b]** (N=213) **n(%)**	**SL BPN/NX[c]** (N=215) **n(%)**
Cardiac disorders	**6 (2.8%)**	**9 (4.2%)**
Tachycardia	5 (2.3)	5 (2.3)
Gastrointestinal disorders	**43 (20.2%)**	**45 (20.9%)**
Constipation	16 (7.5)	16 (7.4)
Diarrhea	6 (2.8)	7 (3.3)
Nausea	15 (7.0)	17 (7.9)
Vomiting	9 (4.2)	8 (3.7)
Infections and infestations	**42 (19.7%)**	**50 (23.3%)**
Urinary tract infection	11 (5.2)	10 (4.7)
Upper respiratory tract infection	9 (4.2)	9 (4.2)
Musculoskeletal and connective tissue disorders	**20 (9.4%)**	**22 (10.2%)**
Arthralgia	7 (3.3)	3 (1.4)
Nervous system disorders	**27 (12.7%)**	**27 (12.6%)**
Headache	16 (7.5)	17 (7.9)
Psychiatric disorders	**20 (9.4%)**	**20 (9.3%)**
Anxiety	6 (2.8)	7 (3.3)
Insomnia	12 (5.6)	6 (2.8)

a = report of adverse reactions that occurred in ≥ 2% of the patients randomized to BRIXADI in Study HS-11-421. Patients are represented once per PT; b = This group includes all subjects exposed to varying doses of both the BRIXADI (weekly) and BRIXADI (monthly) formulations.; c = SL BPN/NX denotes the active comparator: patients assigned to daily buprenorphine with sham (placebo) injections. Patients randomized to this group could also receive a 'booster' injection of BRIXADI (weekly), 8 mg, per protocol.; All patients in Study 421 received a single test dose of 4 mg SL BPN/NX before randomization into either arm.
Source: Table 5, Physician Package Insert

9.2. Other Safety Concerns

Certain concerns not observed in the clinical trials were identified as areas of particular interest that might arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated in a patient still dependent on a full agonist.

9.2.1. Precipitated Withdrawal

Pre-marketing data:

Buprenorphine itself can precipitate withdrawal if initiated in patients who are not yet in significant opioid withdrawal. For this reason, initial dosing is generally cautious and typically begins with a sublingual dose of 2 mg- 4 mg. Some of the doses of CAM2038 contain a large amount of buprenorphine. In new entrants to treatment, the clinical trials included a test dose of 4 mg sublingual buprenorphine and then initiated treatment with a 16 mg weekly dose. Two

patients did not tolerate the test dose. The Applicant reported that no patient experienced precipitated withdrawal due to CAM2038.

Post-marketing data:
Of the 20 cases submitted for review from post-marketing reports with this application cycle, using the standardized MedDRA query "drug withdrawal" some patients appeared to experience precipitated withdrawal while others complained of effects consistent with dose inadequacy. These findings did not change the overall safety profile of CAM2038.

9.2.2. Consequences of Intravenous Injection

In the clinical development program, CAM2038 was administered in a supervised setting by HCPs. If a patient, household contact, or associate were to obtain access to CAM2038, the pre-filled syringe containing a Schedule III opioid might be an attractive target for abuse by the intravenous route. Therefore, given the route of administration of CAM2038, it is predicted that injection into a vessel could result in the formation of a gel or solid, with resulting occlusion and possibly tissue damage or embolus. Clinical review of the ongoing clinical trial adverse event data and provided post-marketing data revealed no cases involving intravenous injection of Buvidal.

9.2.3. Serotonin Syndrome

One post-marketing case report[18] of serotonin syndrome in a 41-year-old female from Australia with a history of OUD, insomnia, anxiety, and major depressive disorder was submitted to IND 114082 on 9-04-2020. The patient was transferred to Buvidal, 16 mg Weekly on (b) (6) from 12 mg daily dosing of Subutex. Concomitant medications included amitriptyline, escitalopram, and diazepam. The patient was titrated to Buvidal 24 mg Weekly on (b) (6) then titrated to 32 mg Weekly on (b) (6) then transferred to Buvidal 128 mg Monthly on (b) (6) at the same time amitriptyline dosing increased from 10 mg to 20 mg. Symptoms of hot and cold flushes, yawning, "sweating profusely", cannot concentrate", and "feeling foggy" were reported. Diazepam was discontinued, amitriptyline dosing was decreased and a physical exam on (b) (6) yielded normal vital signs, and 5 mm pupils that were reactive to light. The event was marked "resolved" on (b) (6) and the patient received her second dose of Buvidal 128 mg Monthly.

No reports of serotonin syndrome were identified in the clinical trials for CAM2038. In review of this case, it is possible that the presenting symptoms were related to Buvidal. Because serotonin syndrome is listed in (b) (4) the drug label (and in the drug labels of other buprenorphine products), this finding did not change the risk-benefit profile of Brixadi.

[18] Case reference number AU-CAM-20-00143 (2020BBN00021)

9.2.4. Seizure

One post-marketing case report of seizure[19], following Brixadi administration in the context of a medication error, was submitted to IND 114082 on 10-16-2020. A 50-year old Australian male with a history of alcohol use and chronic pain [treated with Norspan (buprenorphine patch, unknown dose)], presented to an emergency department acutely intoxicated. The sequence of events is unknown, but the patient was physically restrained in the emergency department in order to receive an 8 mg injection of Buvidal Weekly. However, 128 mg Buvidal Monthly was administered. The patient experienced a seizure and was transferred to ICU where naloxone was administered.

No reports of seizure were identified in the clinical trials for CAM2038. In review of this case, it is possible that the presenting symptoms were related to Buvidal in the context of alcohol intoxication. Additional details of the case are unknown. Although "seizure" is not listed in the Warnings and Precautions section of the drug label (or in the drug labels of other buprenorphine products), clinical studies have been published on the onset of seizures following buprenorphine overdose and are a risk factor in alcohol withdrawal. At this time and in the context of the event described, the finding does not change the risk-benefit profile of Brixadi.

10. Advisory Committee Meeting

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.[20] No additional Advisory Committee input was sought for the second or third cycle.

11. Pediatrics

Braeburn received a full waiver of the Pediatric Research Equity Act (PREA) requirements on the basis of infeasibility. The prevalence of OUD in the pre-adolescent population is very low, and this product would not be suitable for treating iatrogenic opioid dependence (i.e., physical dependence without meeting criteria for OUD). Prevalence in adolescents under age 17 is also too low for feasible study.

[19] Case reference number AU-CAM-20-00180 (2020BBN00032)

[20] A verbatim transcript of this meeting is available on the FDA website at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm535446.htm

12. Other Relevant Regulatory Issues

12.1. Exclusivity

In 2018, during the second application cycle, the administrative records related to the approval of NDAs 204442 and 209819 were reviewed and the Exclusivity Board determined that the 3-year exclusivity for Sublocade (NDA 209819) would block the approval of the Brixadi monthly depot product. The Board recommended that Brixadi's weekly depot product should not be blocked. At that time, Braeburn expressed that they were not willing to entertain separating the Weekly and Monthly Brixadi product formulations. Therefore, only a combined label was negotiated during the second review cycle and the tentative approval (TA) was issued applying to both formulations. Braeburn timed this resubmission of NDA 210136 to align with the expiration of Sublocade's 3-year exclusivity for Sublocade[21].

13. Labeling

The submitted proposed labeling is in Physician's Labeling Rule (PLR) format and in many respects is similar to the previously agreed-upon labeling from the second review cycle. Several revisions were made by Braeburn, informed by recent labeling changes to other buprenorphine products and class labeling changes for opioids. This included changes to Section 9 where descriptive text was added to reflect buprenorphine labeling changes[22]. CSS was consulted to review those changes, and found them acceptable.

As noted above, the Division also made revisions to the sections of labeling pertinent to cardiac conduction effects.

Additionally, the Applicant proposed (b) (4) No other changes to the presentation of safety or efficacy data were proposed, including no proposed changes to the post-marketing safety section.

[21] In April 2019, Braeburn filed an action with the federal district court for the District of Columbia, in an effort to overturn that 3-year exclusivity period (which blocked Brixadi from final approval for marketing). After a court hearing in July 2019, the Court's Chief Judge did not overturn FDA's decision. Braeburn was notified that they could resubmit their application in June 2020, to request final approval of Brixadi, because Sublocade's exclusivity expires in November 2020. Further, and in order to eliminate the risk of further exclusivity periods blocking Brixadi from marketing approval, Braeburn also filed a Citizen Petition in April 2019, That Citizen Petition requested that FDA review the orphan designation granted to Sublocade. FDA reviewed the conditions of the orphan designation and granted Braeburn's Citizen Petition. Thus, the risk of Brixadi being blocked from marketed approval through November 2024 was eliminated.

[22] Derived from the 2019 FDA Draft Guidance (Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products-Content and Format Guidance for Industry).

Below is a summary of changes and recommendations for Section 6 of the labeling:

The following adverse reactions have been identified during post-approval use of an identical buprenorphine extended-release injection for subcutaneous use outside of the United States and are not described elsewhere in the label. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Injection site mass:
Cases of injection site mass have been reported after treatment initiation.

Insufficient dosing:
Cases of drug withdrawal reactions consistent with insufficient drug dosing have been reported, often occurring on or after two weeks of treatment initiation and resolved upon dose increase.

14. Postmarketing Recommendations

14.1. Risk Evaluation and Mitigation Strategies (REMS)

With this submission, Braeburn agreed to keep the agreed-upon Risk Evaluation and Mitigation Strategy (REMS) from the second (2018) review cycle, which was reviewed by the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology. Consistent with the previous review cycle, DRISK has determined that a REMS with elements to assure safe use (ETASU) is needed to ensure the benefits of CAM2038 outweigh its risks. The REMS should include restricted distribution with CAM2038 being dispensed only in healthcare settings that are certified. The goal of the BRIXADI REMS is to mitigate the risk of serious harm or death that could result from intravenous self-administration by ensuring healthcare settings and pharmacies are certified and only dispense BRIXADI directly to a healthcare provider for administration by a healthcare professional.

The elements of the REMS are:

- Elements to assure safe use to ensure that health care settings and pharmacies that dispense BRIXADI are specially certified;
- An implementation system; and,
- A timetable for submission of assessments of the REMS.

Materials include:

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

The content of these materials was largely agreed upon during the initial review cycle and final materials were submitted during this cycle.

14.2. Postmarketing Requirements (PMRs) and Commitments (PMCs)

Two postmarketing trials will be required to evaluate whether Brixadi can safely be initiated (b) (4) This is expected to be of great interest to clinicians who see patients in Emergency Department settings where treatment could be expeditiously initiated.

The following non-clinical post-marketing studies were required at the time of the previous tentative approval action and are still outstanding:

1. Evaluate elemental impurity levels in at least three batches of drug product on stability at 12 and 24 months or provide adequate extraction data to characterize the elemental impurities that could be leached from the container closure system using suitable solvents (e.g., nitric acid for elementals from glass).

2. Conduct a study to confirm, using validated methods, the identity of the unspecified (b) (4) the unidentified compound with relative retention time (RRT) of (b) (4) minutes, the unknown compound containing (b) (4) with RRT of (b) (4) min, and the unknown compound with (b) (4) with RRT of (b) (4) min that were detected in your leachable studies above the safety concern threshold of 5 mcg/day and the levels of the identified leachables (b) (4) (b) (4) Evaluate at least three batches of your to-be-marketed drug product at multiple timepoints over the course of your stability studies to identify trends in leachable levels over time. Base the final safety assessment on the maximum predicted levels of leachables identified in individual batches to determine the safe level of exposure via the label-specified route of administration. Do not combine samples from different batches. Once chemical identification is confirmed for the unknown compounds, provide a toxicological risk assessment for each of these compounds and any other compounds detected at ≥5 mcg/day.

14.3. Associate Division Director Comments

The efficacy and safety of Brixadi (weekly) and Brixadi (monthly) were demonstrated in data submitted and reviewed in the previous review cycle. A tentative approval action was taken at that time, pending the expiration of exclusivity for another product. Review of the safety update included in this submission does not identify any new concerns that alter the overall assessment of the risk/benefit ratio for this product.

However, in the intervening time since the last action, new product quality issues have arisen that preclude approval at this time. In July 2020, contract manufacturing and testing facilities were inspected as part of a pre-approval inspection (PAI) for an NDA unrelated to this one, and significant Good Manufacturing Practice (GMP) deficiencies were identified. The company (Pii) made an internal decision to shut down those manufacturing facilities to address the deficiencies. This shut-down required a reinspection after resumption of operations. This inspection was prioritized by ORA due to the importance of this product, and was conducted in late October. This reinspection identified deficiencies (b) (4)

Responses to the Form 483 deficiencies were received from Pii and additional arguments were received from Braeburn providing reassurances that the observed deficiencies would not affect the manufacture of Brixadi. These responses did not mitigate the concerns, and OPMA made a recommendation to withhold approval. At this time it is not possible to determine whether a reinspection will be needed, but given the nature of the quality system deficiencies observed, it is likely that a follow-up inspection would be warranted. This could take place in the context of review of another application manufactured at the same site, or as part of review of a resubmission of this application. Neither a clock extension (not normally permitted for response to 483s) or a missed PDUFA date seem appropriate under these circumstances, because it is not clear how readily the manufacturing concerns can be addressed, and the time frame for resolving them is not known.

A Complete Response letter will be sent to Braeburn citing deficiencies at the manufacturing facility. At the same time, OPMA will send a Post-Action Letter to Pii.

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/

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CELIA J WINCHELL
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Cross-Discipline Team Leader Review
And
Summary Basis for Approval

Date	12/21/18
CDTL	Celia Winchell, M.D.
Division Director	Sharon Hertz, M.D.
NDA/BLA # and Supplement#	210136
Applicant	Braeburn Pharmaceuticals, Inc.
Date of Submission	6/26/18
PDUFA Goal Date	12/26/2018
Proprietary Name	Brixadi
Established or Proper Name	(buprenorphine extended-release) injection, for subcutaneous administration
Dosage Form(s)	Injection Weekly Formulation: 8mg, 16mg, 24mg, 32mg Monthly Formulation: 64mg, 96mg, 128mg
Applicant Proposed Indication(s)/Population(s)	For the treatment of moderate to severe opioid use disorder (b) (4) (b) (4)
Applicant Proposed Dosing Regimen(s)	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.
Recommendation on Regulatory Action	*Tentative Approval*
Recommended Indication(s)/Population(s) (if applicable)	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.
Recommended Dosing Regimen(s) (if applicable)	New Entrants to treatment: after test dose of sublingual buprenorphine, titrate to 24-32 mg Weekly in the first week then dose adjust. Adults stabilized on current buprenorphine product: transfer to appropriate Weekly or Monthly formulation.

Tables and Figures

1 Benefit-Risk Assessment

Benefit-Risk Assessment Framework

CAM2038 (buprenorphine extended-release) injection, for subcutaneous administration use is intended for the treatment of moderate to severe opioid use disorder; the Weekly formulation is for initiating treatment in patients who have tolerated a test dose of a transmucosal buprenorphine-containing product; the Monthly formulation is for patients already in established treatment with another buprenorphine-containing product (including the Weekly formulation).

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 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. 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. 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. 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. Similar to the recently-approved subcutaneous

depot formulation of buprenorphine, Sublocade, Brixadi has the potential to address several limitations of existing treatments.
The submitted clinical data show that the Brixadi weekly formulation, in doses of 24 mg and 32 mg, is able to block subjective effects of a clinically-relevant dose of opioid agonist, more completely after the second weekly dose. Based on PK-PD analysis, the plasma levels delivered by the corresponding monthly doses are predicted to produce similar blockade. In a non-inferiority comparison to sublingual buprenorphine/naltrexone treatment, the effect of this blockade was shown to translate to clinical efficacy for a regimen beginning with weekly doses and transitioning to monthly doses, based the proportion of subjects whose drug use assessments met a pre-specified responder definition.

The safety profile of buprenorphine is well-characterized, and the overall Brixadi safety profile appears similar. Analysis of dose-dependent adverse effects was hampered by the study design and the presentation of data. However, various explorations for dose-effects did not identify concerning dose-limiting adverse effects in the doses currently proposed for marketing.

Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated at doses higher than studied in the clinical trial (16 mg weekly x 1) in a patient still dependent on a full agonist. Additionally, there may be circumstances under which the rapid discontinuation or dose reduction of buprenorphine might be desirable for a given patient. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with Brixadi for a period of time. Possibilities for surgical removal have not been explored. Patients developing intolerance to buprenorphine will require long-term monitoring by a health care professional.

Moderate-to-severe opioid use disorder is a serious and life-threatening condition and the need for more treatment options and greater access to treatment is clear. Brixadi, as a HCP-administered long-acting depot providing a sustained effective plasma level of buprenorphine over a prolonged period, has the potential to address some of the limitations of available options.

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 by ensuring healthcare settings and pharmacies are certified and only dispense Brixadi directly to a health care provider for administration by a healthcare provider.

Approval is recommended. However, the Office of Regulatory Policy has concluded that this application falls within the scope of Sublocade's exclusivity. Therefore, a tentative approval action should be taken until the exclusivity for Sublocade expires.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Opioid use disorder or OUD, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), 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 over 2.1 million Americans aged 12 and over met criteria for either opioid abuse or dependence. - In 2015, the CDC reported that drug overdose was the leading cause of accidental death in the US, with 52,404 lethal drug overdoses in 2015. Of these, 20,101 overdose deaths were related to prescription pain relievers, and 12,990 overdose deaths were related to heroin. - 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 for years, or even indefinitely.	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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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). o Behavioral treatment alone (individual or group counseling, self-help groups) is not effective for many patients. o 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 overdoses in patients and in their household contacts, including children. o 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. o Depot buprenorphine (SUBLOCADE) o 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. o 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	An additional buprenorphine depot injection would be a desirable addition to the therapeutic armamentarium. - Convenience of weekly or monthly vs daily dosing - Provides consistent buprenorphine levels sufficient to block effects of exogenous opioids - Improves adherence - Reduces potential for diversion, misuse, abuse and accidental pediatric exposure - No surgical procedure needed
Benefit	Evidence: - The opioid blockade study, Study HS-13-478, demonstrated that after CAM2038 (weekly) injections of either 24 mg or 32 mg, on average, subjective effects of both 6 mg and 18 mg doses of hydromorphone were blocked in non-treatment-seeking subjects with OUD, although significant variation was seen across subjects.	CAM2038 24 mg *weekly* and CAM2038 32 mg *weekly* are capable of blocking the subjective effects of a clinically-relevant dose of opioid agonist, and this blockade becomes longer-lasting after two weekly doses.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Dose-response analysis showed a decreasing number of outliers (unblocked responses) with increasing plasma levels, with very few outliers above a plasma level of 4 ng/ml. - The pivotal efficacy trial, Study HS-11-421 (N=428) demonstrated that patients treated with a regimen of 12 weeks on individually-determined doses of CAM2038 (weekly), followed by 12 weeks on individually-determined doses of CAM2038 (monthly) had a response rate non-inferior to patients treated with sublingual buprenorphine/naltrexone tablets (and placebo injections). - CAM2038 is to 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. Uncertainties: - The design of the studies did not permit analyses by dose	The effect of this blockade was shown to translate to clinical efficacy as demonstrated by comparable outcomes in patients treated with a regimen of weekly followed by monthly CAM2038 compared with patients treated with sublingual buprenorphine/naloxone. Taken together, and considering the established efficacy of the reference product, Subutex, these studies provide substantial evidence of efficacy for CAM2038 in the treatment of moderate or severe OUD in patients who tolerate at least an initial test dose of buprenorphine. CAM2038 weekly is suitable for starting treatment, while CAM2038 (monthly) has been studied only in patients already in established treatment.
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. - 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 case was identified in the clinical development program - One death occurred in a CAM2038-treated patient, due to a car-vs-pedestrian traffic accident	The safety profile of buprenorphine is well-characterized, and the overall safety profile of CAM2038 seems similar. However, the presentation of data did not permit characterization of dose-dependent adverse effects and the size of the safety database is not sufficient to characterize the safety of all the studied doses. Even if the data concerns can be resolved, there is clearly insufficient data to support approval of the 160 mg monthly dose. Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated too quickly in a patient

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with CAM2038 for a period of time. Possibilities for surgical removal have not been explored. Patients developing intolerance to buprenorphine effects will require long-term monitoring by a health care professional. - Buprenorphine itself can precipitate withdrawal if initiated in patients who are not yet in significant opioid withdrawal. For this reason, initial dosing is generally cautious and typically begins with a dose of 2 mg- 4 mg. The starting dose of CAM2038 in the efficacy trial was divided over several visits in the first week of treatment. Clinicians may be interested in initiating CAM2038 more expeditiously, for example, administering a single 24 mg or 32 mg weekly injection at the first visit, or administering a monthly dose at the first visit. It is not known if this can be accomplished safely. - CAM2038 forms a gel when injected. If patients obtain direct access to the product, there is a risk they may choose to attempt to inject the product intravenously. Notably, the consequences of intravenous injection of the contents of the pre-filled syringe are not known, it is anticipated that there is a risk of occlusion, tissue damage, and emboli.	still dependent on a full agonist. Additionally, there may be circumstances under which the rapid discontinuation or dose reduction of buprenorphine might be desirable for a given patient. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with CAM2038 for a period of time. It is not known whether there are possibilities for surgical removal. Patients developing intolerance to buprenorphine effects will require long-term monitoring by a health care professional. A REMS is required to ensure that CAM2038 is not distributed directly to patients, and is administered by a health care professional, to mitigate the risk of serious consequences should the product be administered intravenously.

2 Introduction

This is the second review cycle for this application. The application was initially submitted in July, 2017 and received a Complete Response letter on January 19, 2018, citing significant manufacturing issues as well as concerns about the clinical datasets. This resubmission addresses the deficiencies.

The application for CAM2038 (aka BRIXADI) includes two modified-release formulations 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 for the treatment of moderate to severe opioid use disorder (OUD) in adults. According to Braeburn, this delivery technology results in a liquid-to-gel phase transition that occurs when the lipid-based FC system is exposed to the subcutaneous (SC) tissue. The phase transition from liquid to gel proceeds from the periphery of the FC injectable towards the center of the product by absorption of minute quantities of water. The injection of CAM2038 into SC tissue results in an immediate and spontaneous formation of a matrix providing release over the designated period in vivo. This product is available in weekly and monthly formulations, each of which contains different doses and excipients.

CAM2038 (weekly) formulations in the 24 mg/week and 32 mg/week provide sustained plasma levels of buprenorphine intended to block the effects of exogenous opioids over 7 days. Based on pharmacokinetic data, the CAM2038 (monthly) formulations are predicted to block exogenous opioids for at least 28 days. The weekly formulation is intended for the treatment of moderate to severe opioid use disorder (OUD) in patients who have tolerated at least a test dose of transmucosal buprenorphine, and the monthly product is envisioned for more stable patients transferring from established buprenorphine treatment. The products should be used as part of a complete treatment plan to include counselling and psychosocial support.

Because of the potential for a depot product to mitigate risks of abuse, diversion, and accidental pediatric exposure associated with oral transmucosal buprenorphine, the application was granted a priority review when originally submitted in July, 2017. There were no monthly depot formulations approved at the time this application was submitted. A monthly depot formulation, Sublocade (NDA 209819) was approved in November, 2017.

To ensure that the amount of buprenorphine provided and the proposed dosing interval were suitable to support the proposed indication, the Applicant was required to support a finding of efficacy for this product with two adequate and well-controlled clinical trials or one adequate and well-controlled clinical trial and a human behavioral pharmacology study demonstrating the ability of the product to block the effects of exogenous opioids (blockade study). In this submission, the Applicant has provided efficacy data from a blockade study, and from a single, double-blind, active-controlled trial in patients newly-entering buprenorphine treatment demonstrating that the blockade effect translates to an effect on illicit drug use. Additionally, safety experience from an open-label trial and from the Phase 1 program was provided.

The Applicant's submission included safety data from 729 subjects who were exposed to at least one injection of either CAM2038 (weekly) or CAM2038 (monthly). The safety analysis population comprised 594 patients with OUD, of whom 531 received at least one injection of CAM2038 (weekly) and 346 received at least one injection of CAM2038 (monthly). The Sponsor tabulates that 68 patients were exposed to the weekly formulation for 24 weeks or longer, 116 were exposed to the monthly formulation for 24 weeks or longer, and 299 patients had a cumulative exposure of a combination of the two formulations that was at least 24 weeks in duration. The number of patients with at least 48 weeks of exposure was 132 (combination of formulations), with 42 exposed to the weekly formulation and 45 exposed to the monthly formulation for at least 48 weeks. Exposure by dose is illustrated in Table 17 and Table 18, which highlight that the number of patients with at least 48 weeks exposure is limited. Taken together with the established systemic safety profile of buprenorphine, the pooled exposure is sufficient to characterize the overall safety for each formulation, with the exception of the 160 mg monthly dose.

The steady-state exposure associated with some of the doses/formulations exceeds that associated with the maximum recommended dose of Subutex, 24 mg/day. Labeled risks of oral transmucosal buprenorphine for opioid dependence include hepatic effects, possible effects on cardiac conduction, and allergic reactions, as well as the possibility of overdose particularly when combined with other depressants. The overall safety experience with all doses/formulations of CAM2038 pooled is consistent with the known safety profile of buprenorphine. The experience of patients exposed to the higher doses would be of particular interest, but the submitted data did not facilitate examination of the safety experience by dose.

One risk associated with CAM2038 that differentiates it from the transmucosal formulations is the concern that serious consequences could ensue if the product were injected intravenously. A Risk Mitigation and Evaluation Strategy (REMS) is proposed to ensure that the product is administered appropriately.

3 Background

Buprenorphine is a partial agonist at the μ-opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain, and two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence[1]. Three other transmucosal formulations and a six-month, surgically-placed implant have subsequently been approved for opioid dependence, as well as two transdermal products and one transmucosal product for pain. 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 film during 2016. Primary care physicians accounted for 39% of dispensed prescriptions, followed by psychiatrists (21%), osteopaths (14%), emergency physicians (4%) and anesthesiologists (4%). Recently, the authority to prescribe

[1] Subutex, buprenorphine sublingual tablets (Reckitt Benckiser (now Indivior) NDA 20732) and Suboxone, buprenorphine/naloxone sublingual tablets (Reckitt Benckiser (now Indivior) 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.

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.

Buprenorphine 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. First, buprenorphine had been shown to have a ceiling effect for respiratory depression, suggesting that it would be "impossible to overdose" on buprenorphine. Second, initial clinical evaluations of buprenorphine's ability to produce physical dependence led to the conclusion that physical dependence to buprenorphine, if it developed, was associated with a mild withdrawal syndrome. Third, it was expected to have limited attractiveness as a drug of abuse relative to full agonists.[2]

Buprenorphine was expected to have limited abuse potential for two reasons. First, due to its partial agonist properties, the euphorigenic effects of buprenorphine were 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. Second, 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 buprenorphine. These features were expected to limit its attractiveness as a drug of abuse for patients and for illicit use.

In addition to the improved safety profile, at sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, deterring abuse of opioids by buprenorphine-maintained patients.

Unfortunately, despite these features, buprenorphine 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 a number of cases of accidental poisonings of small children. Therefore, a depot injection which would be difficult to divert or abuse, and would be less likely to be accidentally ingested by small 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 in order to experience the effects of their opioids of choice.

Comparison of exposures after CAM2038 doses to exposures after sublingual buprenorphine demonstrate that, at steady-state (4th injection), CAM2038 (weekly) and monthly deliver plasma concentrations ($C_{avg,ss}$) that are higher than the corresponding dose of sublingual buprenorphine in Braeburn's proposed conversion scheme. (See
Table 4 Summary of steady-state PK parameters of buprenorphine after subcutaneous buttock injections of CAM2038 (weekly) (q1w) and CAM2038 (monthly) (q4w) and SL

[2] Many of these beliefs have subsequently been found to have been erroneous, or at least overstated, but these were the generally-held views about buprenorphine's pharmacology at the time it was being developed.

administration of SUBUTEX,) Based on plasma levels, the efficacy would be anticipated to be at least non-inferior to, if not superior to, the corresponding doses.

3.1 Clinical Development of CAM2038

The clinical development of CAM20388 was undertaken with advice from the Division. At pre-IND and advice meetings, options for populations (e.g., new entrants to treatment vs. established, stable patients) were discussed, along with the type and number of studies needed to support approval. Braeburn elected to undertake a program that they hoped would provide support for multiple doses of two different formulations, in patients both new to buprenorphine treatment and in patients already in established treatment. They combined doses, formulations, and patient populations in an open-label study, and conducted a controlled study in patients new to treatment. We agreed that, though not optimal, with sufficiently persuasive results, a claim for treatment of opioid use disorder could be supported by a study showing that the product yielded a plasma level sufficient to completely block (not just attenuate) the effects of a clinically-relevant dose of an opioid agonist, taken together with a controlled study demonstrating that the blockade effect translated to a clinically-relevant change in drug-use behavior over a six-month treatment period.

The blockade of subjective response to opioids is one of the ways in which buprenorphine treatment exerts its effect, through the behavioral principle of extinction. When a behavior is not reinforced, it is less likely to occur. Illicit opioid use is reinforced by the subjective effects of the drug. Blockade is particularly important early in treatment when a "slip" (isolated incident of illicit use) could turn into a "relapse" (return to out-of-control use). By preventing the reinforcing effects of the "slip," a treatment that provides a blockade effect can help the patient discontinue the drug self-administration behavior. Some stable patients or highly-motivated patients may not require the blockade effect for effective treatment long-term.

Although the Application rests in part on cross-referenced data on the efficacy of Subutex, the nature of the product is sufficiently different from Subutex that two studies were needed to support approval. The blockade study was accepted in lieu of a second efficacy study[3]. Both the blockade study and the controlled efficacy trial are considered necessary for approval.

3.1.1 Background Related to Efficacy Endpoints and Study Design

There is currently no standard approach to clinical trials in this therapeutic area; the first Guidances on drug development for OUD were issued in 2018.

Previously-approved products were supported by a variety of studies with treatment as long as 40 weeks, and various analytic approaches were applied in evaluating the results. All focused the assessment of efficacy on the patterns of on-treatment drug use, primarily through frequent collection of urine toxicology samples.

[3] As originally envisioned, the blockade study was to have preceded the clinical efficacy study and should have been used to select doses for the clinical efficacy study.

Drug use patterns are a convenient surrogate, but many patients, families, and clinicians may be interested in study designs that establish whether a treatment has an impact on other aspects of opioid use disorder and its effects on how patients feel, function, or survive. Historically, direct clinical measures have always been welcome, but prove challenging to incorporate into clinical trials. For example, although mortality and viral seroconversion are outcomes of interest, both occur at very low rates in clinical trials and would require much larger sample sizes to detect an effect than studies with drug use patterns as the primary endpoint. A patient-reported outcome assessment could be developed using appropriate methods, with input from patients and family members to determine the most concerning symptoms/experiences associated with OUD, but such an instrument does not currently exist. Retention in treatment, *per se*, is not recommended as a stand-alone endpoint. Many features of study design can produce incentives to remain "in treatment" without accruing significant clinical improvement.

For lack of available direct clinical measures, analysis of the pattern of drug use remains the primary approach to assessing treatment response. The Division has taken the position that analyses focused on group means (such as mean percent negative urine tests), which have been used in some prior studies, are not the most clinically meaningful approach because they do not reflect the experience of individual patients, who might range from complete responders to complete non-responders. In discussing how individual response should be assessed, there has been considerable debate over whether endpoints focused on patients attaining complete abstinence from illicit drug use are realistic, and whether they are necessary to ensure that the drug yields clinical benefit. As described below, the responder definition used in this study is not an "abstinence" endpoint.

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 illicit drug use episodes. These include:

- Less frequent urine toxicology tests

  Historically, studies of opioid dependence treatment have incorporated thrice-weekly urine sampling. This frequency was identified as providing the best balance between detecting all use and avoiding false-positive tests due to "carry-over" positives, based on the time window of detection for heroin, which was the most commonly-used opioid in populations being studied when this approach was established. Additionally, this approach was not considered unduly burdensome because the treatments being evaluated were agonists that were administered in-clinic on a daily basis.

  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. 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.

  Braeburn's clinical efficacy study employed weekly, *scheduled*, urine testing during the first 12 weeks of treatment. It is understood that weekly sampling may miss some occasions of use, and that scheduled testing may allow patients to deliberately avoid

detection of use through timing their episodes of drug use. The second 12 weeks, during which patients received monthly injections, employed only monthly scheduled urine testing. To augment this, the protocol also required the patients be called in for random urine testing on three occasions, yielding only six assessments in the final 12 weeks of the study. Thus, even if the definition of response is 100% negative samples, patients who are continue to have some episodes of use may be adjudicated as successful, because some use will not be detected. We accept this for reasons of feasibility.

- A responder definition that allows a few missing or positive samples

  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. Braeburn's responder definition required patients to meet separate response definitions in phase 1 *and* phase 2, which together required only 8 negative samples.

  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 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

- The incorporation of a "grace period" (assessments at the beginning of treatment which are not considered in the analysis) because patients may not respond immediately. Braeburn's responder definition included grace periods in each phase of the study.

- The use of a "continuous responder" analysis.

  One approach that the Division has proposed is to perform an analysis that considers the full range of responder definitions, from use detected at zero visits to use detected at all visits, but to emphasize the effect of the drug on promoting a higher proportion of negative assessments. This approach, the continuous responder curve, or the cumulative distribution function (CDF) of drug use assessments, was employed in this program. The continuous responder curve gives an overall picture of the drug's effect on drug use behavior. Pairing this analysis with a responder rate comparison ensures that the effect is of a magnitude that has clinical meaningfulness.

In Braeburn's study, there were weekly, scheduled, samples collected over the first twelve weeks (at injection visits), and monthly, scheduled samples at injection visits over the second twelve weeks. Three additional random visits for urine testing were to occur during the latter phase. The primary analysis was a responder analysis, and CDF of patient responses was analyzed as secondary endpoint. The responder definition agreed to, described above, was

simply a pragmatic choice, based on a definition used in published literature. The responder definition was intended to allow for independent assessment of response to both the weekly and monthly phases of treatment, and to strike a balance between patient burden (to minimize missing data) and the ability to detect episodes of use. Clearly, given the schedule of sampling, patients classified as responders may have a number of undetected occasions 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.

There is also no standard approach to studies intended to demonstrate that a product can block the effects of exogenously-administered opioids. The ability of buprenorphine to attenuate the reinforcing effects of other opioids has been studied in various ways over the past decades, but at the time this development program was initiated, studies in the literature did not support a consistent conclusion about the relationship between plasma buprenorphine levels, opioid receptor occupancy, and blockade of clinically relevant doses of opioids of abuse. Heterogeneity in the challenge doses used, the interpretation of the term "blockade" (to mean either any detectable attenuation of agonist effect, or complete prevention of agonist effect), and in the doses, route, and timing of the buprenorphine administration complicated interpretation of literature findings. However, the Division's review of the literature suggested that clinically-relevant doses of opioids of abuse may require fairly high doses of buprenorphine (and by extension, plasma levels) for full blockade, and that 85% receptor occupancy or better would be a reasonable target, to allow room for inter-individual variation, given that the shape of the curve relating plasma level to receptor occupancy in published studies at that time was exponential. Our recommendation was to target exposure of approximately 3 ng/ml, and to establish in a behavioral pharmacology trial that the selected dose was capable of blocking the reinforcing effects of a clinically-relevant dose of a full agonist.

The design of the blockade study was based on designs used to evaluate human abuse liability, and was developed with input from the Controlled Substances Staff and supporting biostatistical reviewers. A broadly similar design was used to support approval of Vivitrol (depot naltrexone, Alkermes NDA 21-897) for treatment of opioid dependence and to support approval of Sublocade (depot buprenorphine, Indivior NDA 209819).

3.2 Safety Concerns Related to Formulation

The injection of CAM2038 into SC tissue results in an immediate and spontaneous formation of a gel matrix providing release over the designated period in vivo. Individuals with OUD are known to use a variety of opioids by unintended routes, sometimes with severe consequences. There are limited data to inform what could occur should someone attempt to misuse the CAM2038 intravenously. In a nonGLP rat intravenous toxicity study in three males, administration of the drug to the tail vein resulted in occlusion of the vessel to the base of the tail with no clear evidence of distribution to other tissues. Lungs, however, could not be evaluated as the animals were sacrificed via CO_2 which results in lung pathology itself. The data suggest that if the drug product were to be administered intravenously, it will either gel rapidly and potentially block the injected vessel as it apparently did in the rat tail vein, or if the injected vein is larger and the product does not gel quickly enough, it could likely result in a lung emboli or eventually be lodged in other small capillaries. This raised a safety concern

about the possible consequences of this type of misuse, which could involve occlusion, tissue damage, or possibly embolus.

3.3 Legal and Regulatory Issues Constraining Buprenorphine Treatment

Buprenorphine is a Schedule III Controlled Substance and physicians prescribing buprenorphine must comply with the relevant aspects of the Controlled Substances Act. In addition, the provision of agonist treatment of opioid addiction is governed by certain legal requirements. Unlike methadone, buprenorphine may be prescribed by physicians meeting certain requirements.

Methadone treatment of opioid addiction is delivered in a closed distribution system (opioid treatment programs, OTPs) that originally required special licensing by both Federal and State authorities, under the Narcotic Addict Treatment Act of 1974. The current regulatory system is accreditation-based, but OTPs must still comply with specific regulations that pertain to the way clinics are run, the credentials of staff, and the delivery of care. To receive methadone maintenance, patients are required to attend an OTP, usually on a daily basis, with the possibility of earning the privilege of taking home doses as their treatment stability increases. Buprenorphine may also be administered to patients at OTPs.

Buprenorphine treatment is covered in Title XXXV of the Children's Health Act of 2000 (P.L. 106-310), which provides a "Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment of Opioid-Dependent Patients." This part of the law is known as the Drug Addiction Treatment Act of 2000 (DATA 2000). Under the provisions of DATA 2000, qualifying physicians may obtain a waiver from the special registration requirements in the Narcotic Addict Treatment Act of 1974, and its enabling regulations, to treat opioid addiction with Schedule III, IV, and V opioid medications that have been specifically approved by FDA for that indication, and to prescribe and/or dispense these medications in treatment settings other than licensed OTPs, including in office-based settings. The Comprehensive Addiction and Recovery Act (CARA) of 2016 (P.L. 114-198) extended the privilege of prescribing buprenorphine in office-based settings to qualifying nurse practitioners (NPs) and physician assistants (PAs) until Oct. 1, 2021. At present, the only products covered by DATA 2000 (i.e., Schedule III-IV, approved for the indication) are buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets and films.

To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of opioid addiction or have certain other qualifications defined in the legislation (e.g., clinical research experience with the treatment medication, certification in addiction medicine) and must attest that they can provide or refer patients to necessary, concurrent psychosocial services. The 8-hour training courses are provided by various physician organizations (e.g. APA) and delivered in-person, in web-based formats, or through other mechanisms. Physicians who obtain DATA 2000 waivers may treat opioid addiction with products covered by the law in any appropriate clinical settings in which they are credentialed to practice medicine. Specific requirements for non-physician HCPs are stipulated in the CARA legislation. Under the DATA 2000, the number of patients a provider may treat with buprenorphine is capped at an "applicable number," initially 30 and then

increasing as the provider gains experience. The text of the legislation also notes that "The Secretary may exclude from the applicable number patients to whom such drugs or combinations of drugs are directly administered by the qualifying practitioner in the office setting." This implies that the Secretary could determine that the number of patients a given provider may treat with CAM2038 is not limited.

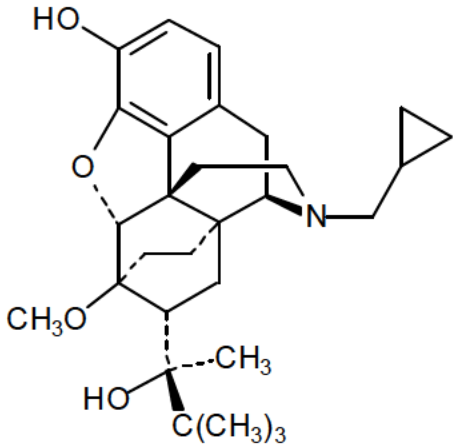
The Applicant has been advised by DEA that both the physician who prescribes CAM 2038 must be DATA-waived, or practicing in an OTP where DATA waivers are not required.

4 Product Quality

The CAM2038 FluidCrystal subcutaneous injection depot drug product is a yellowish to yellow clear liquid which is [redacted] (b) (4) 1 mL long clear glass syringes with grey plungers. It is a lipid-based parenteral (subcutaneous injection) extended-release product (once weekly or once monthly dosing) based on the proprietary FluidCrystal (hereinafter denoted FC) injection depot technology.

The active ingredient in CAM 2038 is buprenorphine free base, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist.

The molecular weight of buprenorphine free base is 467.6, and its molecular formula is $C_{29}H_{41}NO_4$. Chemically, buprenorphine is (2S)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol. The structural formula is:



The CAM2038 q1w (weekly) solution consists of 50 mg buprenorphine base (BUP)/mL, 10% w/w ethanol (EtOH) and Soybean Phosphatidylcholine (SPC)/Glycerol Dioleate (GDO) in the weight ratio 50/50 to final volume. The CAM2038 q4w Monthly solution consists of 356 mg buprenorphine base (BUP)/mL, 30% w/w N-methyl-2-pyrrolidone (NMP), and SPC/GDO in the weight ratio 40/60 to the final volume. The injection products utilizing the lipid-based formulations are low viscosity liquids. When the product is injected into the subcutaneous tissue, the formulation absorbs interstitial aqueous body fluid and transforms the liquid to a

highly viscous gel. According to the applicant, [redacted] (b) (4) CAM2038 q1w and CAM2038 q4w drug product.

The compositions are shown in the tables below.

Table 1 Composition of CAM2038 q1w Drug Product (50 mg/mL)

Component	Standard	Function	Composition (mg) per dose			
			8 mg/ 0.16 mL	16 mg/ 0.32 mL	24 mg/ 0.48 mL	32 mg/ 0.64 mL
Buprenorphine Base (BUP)	Ph. Eur.	Active ingredient	8	16	24	32
Ethanol Anhydrous (Dehydrated alcohol) (EtOH)	USP	[redacted] (b) (4)	[redacted] (b) (4)			
Soybean Phosphatidylcholine (SPC)	In-house					
Glycerol Dioleate (GDO)	In-house					
Total weight (mg) for all components per dose	Not Applicable	Not Applicable				

Table 2 Composition of CAM2038 q4w Drug Product (356 mg/mL)

Component	Standard	Function	Composition (mg) per dose		
			64 mg/ 0.18 mL	96 mg/ 0.27 mL	128 mg/ 0.36 mL
Buprenorphine Base (BUP)	Ph. Eur.	Active ingredient	64	96	128
N-Methyl-2-Pyrrolidone (NMP)	USP	[redacted] (b) (4)			
Soybean Phosphatidylcholine (SPC)	In-house				
Glycerol Dioleate (GDO)	In-house				

Total weight (mg) for all components per dose	Not Applicable	Not Applicable	(b) (4)

CAM2038 weekly and monthly formulations are drug/device combination products as defined under 21 CFR 3.2(e)(1) and produced as single entities, i.e., a pre-filled syringe, presented in a sterile pre-filled syringe assembly and a pre-packaged sterile needle for injection.

Figure 1 Brixadi Pre-Filled Syringe

No issues were identified in the manufacturing of the drug substance. However, in the first review cycle, concerns were noted in many aspects of the manufacture of the finished drug product. These included concerns about sterility, concerns about a lack of specification for factors affecting dissolution, and significant concerns based on inspectional findings at the site responsible for testing of the drug product.

Acceptable method and method validation data have been provided for the method to detect (b) (4)
The sponsor provided (b) (4) data for several batches of product as well as data (b) (4) has been added to the drug product specification for both q1w and q4w product.

Methods validated to measure (b) (4) have been provided and these will be measured at release and tracked on stability.

An analytical measurement to monitor changes in the performance of the excipients over the shelf-life of the product has been provided.

The sponsor has provided adequate data to show that the Uniformity of Dosage Units (UDU) by weight variation method is representative of the dose delivered to the patient. A comparison of delivered dose by HPLC content uniformity and UDU by weight variation

showed that results are within (b)(4)% range. The HPLC results are (b) (4) (b) (4) calculated (b) (4)

The sponsor has adequately explained that ethanol content within the (b) (4)% w/w range does not pose any safety or efficacy concerns. They have tightened the release spec to (b) (4)% w/w to ensure that no product falls below (b)(4)% w/w on stability.

The sponsor provided an adequate study that showed results within specification for formulations that will be approved and marketed. (b) (4)

Data were provided validating the dissolution method.

The stability data submitted supports a shelf-life of (b)(4) months for the CAM2038 q1w and CAM2038 q4w drug product when stored at controlled room temperature, 25°C with excursions permitted from 15°C to 30°C in the commercial container/closure system.

Follow-up PAI was performed for the manufacturing ((b) (4) FEI 3006503102) and laboratory operations (b) (4) FEI 1000513101) for this NDA; and results supported that facilities are capable and considered adequate to perform their functions for this application.

5 Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review was conducted by Gary Bond, Ph.D., Jaime D'Agostino, Ph.D., and Elizabeth Bolan, Ph.D. The review focuses on the safety of the CAM2038 formulations, and the two novel excipients, N-methyl-pyrrolidone (NMP), found in the monthly product, and glycerol dioleate (GDO), a diglyceride, found in both products. In the first cycle, the review team noted that inadequate information had been provided to justify the safety of the container closure system, The components of the container closure system that contact the drug product primarily include a (b) (4) glass syringe with a (b) (4) rubber plunger stopper. Importantly, the drug products include (b) (4)

The submitted extraction studies with the container closure system were not performed appropriately to fully characterize the potential leachables profile of the container closure system.

In the second cycle, the Applicant submitted new extractable and leachable data to address the deficiencies identified in the first cycle. However, the review team noted three remaining concerns:

- the Applicant did not conduct new extractable/leachable testing for inorganic compounds
- there were at least four unidentified compounds above the safety concern threshold of 5 mcg
- two identified compounds were detected above 5 mcg/day but validated methods to confirm the levels were not employed.

The pharmacology-toxicology team recommends that these be addressed as a post marketing requirement, noting that the majority of the identified leachables were adequately qualified, and the levels of the unidentified compounds in the formulations were predicted to be low (≤ (b) (4) mcg/dose), and levels of inorganic compounds were within acceptable levels in the drug product and (b) (4) are not expected to significantly increase over time. These mitigating factors, taken together with the potential public health benefit of the product, argue that these deficiencies should not preclude approval.
Two other key review issues pertained to the excipients, NMP and GDO. Braeburn submitted studies with GDO addressing pre-clinical requirements and establishing acceptable NOAELs.

Standard reproductive and developmental toxicology study requirements were addressed by a combination of published literature testing diacyl glycerol (DAG) oil containing significant levels of GDO (fertility and early embryonic development and embryofetal development studies in the rat) and a Braeburn-conducted pre- and post-natal study on GDO. Adequate NOAELs were established to support safety.

Braeburn also cited published carcinogenicity studies with DAG oil to address the requirement for carcinogenicity of GDO. They leveraged the published analytical data and provided a risk assessment based on the probability of the DAGs in the DAG oil to contain two oleic acid residues. The basis of this assessment and the calculations to estimate the GDO content were reviewed and considered adequate. The studies for DAG oil also suggested significant safety margins for the predicted levels of GDO. As such, the collective data to support the safety of the novel excipient GDO has been provided and deemed adequate.

To support the safety of NMP, Braeburn submitted a 9-month dog study that contained NMP in the formulation tested, and a literature review. Based on PK studies in humans following administration of CAM2038 q4w, the NMP in this formulation appears to be cleared from plasma within 24 hours of drug product injection. NMP has been tested in several published subchronic toxicology studies using the oral or inhalation route of administration and although some adverse effects (mostly hepatocellular hypertrophy) were reported in these studies, NOAELs that established reasonable safety margins were demonstrated for this product suggesting limited concern. NMP was deemed overall negative in terms of genotoxic potential.

Published carcinogenicity studies with NMP suggest the potential for NMP-induced liver tumors in mice. In this cycle, Braeburn was required to submit mode of action assessment to address whether this finding is relevant to humans. The data suggested limited concern in human, but the review team noted that the assessment lacked key data points to be conclusive. The pharmacology/toxicology review team recommends that these findings be included in

labeling, but given the exposure margins for this product, further studies would not be required. Should Braeburn seek to have this information removed from labeling, they would need to submit a revised MOA assessment with additional data to bolster the weight of evidence to argue that the tumorigenesis is driven by a PPAR alpha-mediated pathway.
The Applicant submitted published and unpublished reproductive and developmental studies with NMP in lieu of new studies. These studies did not include data on administration by the intended route and did not support definitive conclusions. In the first review cycle, definitive studies via the SC route were considered warranted. These studies have not been conducted. In the second cycle submission, oral pharmacokinetic data were provided in the rat which suggest adverse effects in males occurred only at doses that are greater than 108 times the human maximum daily dose of NMP based on AUC. The review team noted that data are still not available on all standard female and early embryonic development endpoints. However, given the exposure margins estimated to date, they recommend that a definitive fertility and early embryonic development study can completed as a post-marketing requirement.

The published and unpublished embryofetal development data (EFD) for NMP submitted by the Applicant and identified by the Agency suggested the potential for adverse effects of NMP on embryofetal development in the rat that includes preimplantation losses, delayed ossification, and decreased fetal weight at doses 8.4 times the maximum daily dose (MDD) via this product based on body surface area. An embryofetal development study in rabbits was also submitted in draft in the first cycle. The final report was submitted in the second cycle and was deemed acceptable. In addition, the Applicant submitted new rat and rabbit oral pharmacokinetic data to bridge to the referenced published oral reproductive and developmental toxicology studies. These data suggest significantly larger exposures margins than predicted by the body surface area comparisons. Collectively, the submitted studies and bridging PK data were deemed adequate to address the embryo-fetal development study requirements for NMP for this drug product. No further EFD studies for NMP are necessary.

Finally, several published reports on the impact of NMP on pre- and postnatal development (PPND) were reviewed in support of the original application. The data suggested that NMP can result in decreased pup survival at doses 12.9 times the MDD and developmental delays at 7.6 times the MDD based on body surface area. A NOAEL was not determined in this study. The oral PK data submitted in the second cycle suggest adverse effects occurred at 242 times the MDD of NMP based on AUC. Given the lack of a NOAEL, the review team recommends that a definitive study be completed as a post-marketing requirement.

Finally, in this cycle, additional calculations were provided that permitted the review team to determine exposure margins for use in labeling.

6 Clinical Pharmacology

The following summary of clinical pharmacology is based on the Clinical Pharmacology review by Suresh Narahansetti, PhD, and language from the Division's proposed labeling. In the text below, the weekly formulation is sometimes referred to as CAM2038 q1w, and the monthly formulation as CAM2038 q4w. Much of the general text about buprenorphine is

identical to language in the Subutex label. Text specific to CAM2038 is based on Braeburn's development program.

The pharmacokinetics of buprenorphine following SC injection of CAM2038 was investigated in five clinical studies, including two studies in healthy volunteers under naltrexone (NTX) blockade and 3 studies in patients with opioid dependence as described in Table 3.

Table 3 Overview clinical pharmacology studies of CAM2038 q1w and CAM2038 q4w

Study	Study Description	Population (No. of subjects)	q1w (SC)	q4w (SC)
HS-11-426	Open-label, randomized, PK, BA, and safety study assessing 3 different SC doses of q1w versus IV and SL BPN	Healthy, N=56	- 8 mg (single dose) - 16 mg (single dose) - 32 mg (single dose)	NA
HS-13-487	Randomized, open-label, single- and repeated-dose PK, BA, and safety study with q1w and q4w versus IV and SL BPN	Healthy, N=79	- 16 mg (4 repeated doses)	- 64 mg (single dose) - 96 mg (single dose) - 128 mg (single dose) - 192 mg (single dose)
HS-07-307[$]	Single-dose, dose-escalation PK, PD and safety study investigating 4 different doses of q1w	Patients with OUD, N=41	- 7.5 mg (single dose) - 15 mg (single dose) - 22.5 mg (single dose) - 30 mg (single dose)	NA
HS-15-549	Open-label, partially randomized PK, efficacy and safety study	Patients with OUD and a history of moderate to severe chronic non-cancer pain, N=65	- 32 mg (7 repeated doses) 3 weekly doses in the buttock followed by 4 weekly doses in the buttock, abdomen, thigh, and back of upper arm. Also, open-label safety extension including 6 additional weekly SC injections of 32 mg q1w in the buttock.	- 128 mg (4 repeated doses in the buttock) - 160 mg (4 repeated doses in the buttock)
HS-13-478*	Randomized, double-blind, repeated-dose, PK, efficacy and safety study	Patients with OUD, N=47	- 24 mg (2 repeated doses) - 32 mg (2 repeated doses)	NA

[$] In study HS-07-307, the dose used for CAM2038 q1w (7.5 mg, 15 mg, 22.5 mg and 30 mg) were not intended clinical dose of CAM2038 q1w. Hence this study was not reviewed.

Note that not all of the proposed doses have been studied in both single-dose and steady-state conditions. Although Braeburn used population PK for deriving the PK parameters of CAM2038 q1w, CAM2038 q4w, and SL Subutex, the Clinical Pharmacology review team reviewed PK data from clinical pharmacology studies for most of the doses of these products for comparison of PK parameters between CAM2038 and SL Subutex (especially for the

highest doses). Some cross-study comparisons were required to develop a full picture of the relative exposures. Cross-study comparisons are typically considered less reliable than within-study comparisons, but the program did not include all the necessary within-study comparisons.

A study conducted to determine whether PK differed when the weekly formulation (32 mg) was injected into different anatomical locations (thigh, buttock, abdomen, or arm) was conducted after the clinical efficacy studies had already been initiated using a variety of sites.

No studies were performed to evaluate whether lower doses of either formulation could be combined to yield exposures equivalent to the mathematical sum of the doses (e.g., 2 x 16 mg weekly formulation compared to 1 x 32 mg weekly formulation). At present, the label cautions against combining doses in this fashion. Instances of investigators making such substitutions were recorded in the clinical trials and may be predicted to occur after marketing.

The text in Arial font below is based on the Division's recommended labeling language, with additional information/comments in Times New Roman:

Absorption

BRIXADI is an extended-release formulation of buprenorphine designed for subcutaneous administration. BRIXADI is available in two regimens: weekly and monthly. Following single of doses of BRIXADI (weekly) or BRIXADI Monthly, the buprenorphine Cmax and AUCinf increase dose-proportionally.

The steady-state pharmacokinetics (PK) of buprenorphine following BRIXADI (weekly), BRIXADI Monthly and their comparison to sublingual SUBUTEX across three studies are shown in

Table 4. In these studies, BRIXADI (weekly) was administered for 4 or 4 to 7 weekly doses, BRIXADI Monthly was administered for 4 monthly doses, and SUBUTEX was administered for 7 daily doses.

After BRIXADI subcutaneous injection, the buprenorphine plasma concentration increases with a median time to maximum plasma concentration (tmax) of about 24 hours for the weekly BRIXADI and 10-246-10 hours for monthly BRIXADI. Based on trough levels after each dose, steady-state exposure is reached at just prior to administration of the fourth weekly or monthly dose.

After four repeated doses of BRIXADI (weekly) (16 mg) AUC_{tau} (0-7d), Cmax and Ctrough values are ~40% higher exposure compared to the first dose. Based on cross-study comparisons, four repeated doses of BRIXADI Monthly (128 mg) results in 68%, 65%, and 124% higher AUC_{tau} (0-28d), Cmax and Ctrough values, respectively compared to the first dose.

Table 4 Summary of steady-state PK parameters of buprenorphine after subcutaneous buttock injections of CAM2038 (weekly) (q1w) and CAM2038 (monthly) (q4w) and SL administration of SUBUTEX

Drug product dose			Cav (ng/mL)			Cmax,ss (ng/mL)			Ctrough[a] (ng/mL)		
SL BPN	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly	SL BPN *	Brixadi Weekly	Brixadi Monthly
8 mg	16 mg	64 mg	1.2	2.1	2.0 $	4.7	4.3	4.0 $	0.7	0.8	1.3 $
16 mg	24 mg	96 mg	1.8	2.9 $	2.9 $	6.5	5.5 $	6.0 $	1.0	1.4 $	2.0 $
24 mg	32 mg	128 mg	2.5	4.2	3.9	8.2	6.9	11.1	1.4	2.6	2.1

* Average value of two studies

$ Simulated

[a] C168h for BRIXADI (weekly), C28d for BRIXADI Monthly and C24h for Subutex

Injection Site Effect on PK of BRIXADI

After multiple dose subcutaneous injections of 32 mg BRIXADI weekly product at different injection sites (abdomen, thigh, buttock or upper arm), a comparable PK exposure was observed. However, injection in the arm site was associated with approximately 10% lower plasma levels than other sites.

In the first review cycle, he clinical pharmacology review team conducted a bioequivalence assessment (geometric mean ratios and 90% CI) between different injection sites using buttocks as a reference. Of the three sites, compared to the buttock, the trough levels from upper arm site (1.3.6a) was lower and it also failed to meet the bioequivalence criteria for 80 to 125%. Although Cmax and AUC between different injection sites are important, the trough levels are considered more important for the efficacy of this product because the trough concentration is associated with the lowest percentage of mu-receptor occupancy during the entire dosing interval. Hence, the upper arm is not recommended as an injection site for this product.

In this resubmission, the Applicant argued that there were no differences in efficacy between patients receiving injections in the arm and patients receiving injections in other sites, but the design of the study did not allow any conclusions to be drawn. However, the Clinical Pharmacology review team noted 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); [and] 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. To facilitate the 8-week rotation of injections required for the weekly formulation, the Clinical Pharmacology team felt it would be acceptable to allow injection in the arm site.

Noting that there are no data showing trough levels after injection of the 24 mg weekly dose (which was used by about half the patients), 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. This recommendation has been incorporated into the Dosing and Administration section of labeling.

Distribution
Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Elimination
Buprenorphine is metabolized and eliminated in urine and feces. The apparent terminal plasma half-life of buprenorphine following subcutaneous injection of BRIXADI ranged between 3 to 5 days for BRIXADI weekly and 19 to 26 days for BRIXADI monthly as a result of the slow release of buprenorphine from the subcutaneous depot.

OCP investigated the buprenorphine PK profile after the last injection of CAM2038 at steady-state. Simulations were conducted to generate a PK profile following the final dose of CAM2038 at steady-state for the maximum proposed dose level for the CAM2038 (weekly) formulation (32 mg once weekly) as well as the CAM2038 (monthly) formulation (128 mg once monthly). The PK simulations indicate that the buprenorphine plasma concentrations remain above the LLOQ (0.025 ng/mL) for up to 6 weeks for 32 mg once weekly and for up to 6 months following 128 mg once monthly. However, the correlation between plasma concentrations of buprenorphine and those detectable in urine is not known.

Metabolism
Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity. Norbuprenorphine steady-state plasma concentrations in humans after subcutaneous injection of BRIXADI are low compared to buprenorphine (AUC norbuprenorphine/buprenorphine ratio of 0.35 to 0.53).

Excretion
A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of the buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Drug-Drug Interactions
The effects of co-administered CYP3A4 inhibitors and inducers on buprenorphine exposure in subjects treated with BRIXADI have not been studied; however, such

interactions have been established in studies using transmucosal buprenorphine. The effects of buprenorphine may be dependent on the route of administration. Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when BRIXADI is given concurrently with agents that affect CYP3A4 activity. The effects of co-administered CYP3A4 inducers or inhibitors have been established in studies using transmucosal buprenorphine. Patients who transfer to BRIXADI treatment from a regimen for transmucosal buprenorphine used concomitantly with CYP3A4 inhibitors (e.g., ketoconazole, macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors, or CYP3A4 inducer (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) should be monitored to ensure that the plasma buprenorphine level provided by BRIXADI is adequate and not excessive.

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in in vitro studies employing human liver microsomes. However, plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic BRIXADI doses are not expected to significantly affect the metabolism (systemic exposure) of other concomitantly administered medications.

The labeling will note the possibility of drug-drug interactions.

Specific Populations

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of BRIXADI has not been studied.

In a pharmacokinetic study, the disposition of buprenorphine was determined after administering a 2.0/0.5 mg Suboxone (buprenorphine/naloxone) sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine in patients with hepatic impairment was compared to disposition in subjects with normal hepatic function.

In subjects with mild hepatic impairment, the changes in mean Cmax, AUC0-last, and half-life values of buprenorphine were not clinically significant. For subjects with moderate and severe hepatic impairment, mean Cmax, AUC0-last, and half-life values of buprenorphine were increased.

Because buprenorphine levels cannot be rapidly adjusted during CAM2038 treatment, patients with pre-existing moderate to severe hepatic impairment are not candidates for treatment with CAM2038, and patients who develop moderate-to-severe hepatic impairment while being treated with CAM 2038 will need to be monitored for signs and symptoms of toxicity or overdose.

Removal of the CAM2038 depot is unlikely to be feasible; there is no experience with removing the depot. Moreover, residual plasma levels from prior injections would still be present.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of BRIXADI has not been studied. Clinical studies of BRIXADI did not include subjects with severe renal impairment. Less than 1% is excreted as unchanged buprenorphine in urine following IV buprenorphine administration. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine.
Population PK analyses indicated no notable relationship between creatinine clearance and steady-state buprenorphine plasma concentrations.

Q-T evaluation

5.15 Use in Patients at Risk for Arrhythmia

Buprenorphine has been observed to prolong the QTc interval in some patients participating in clinical trials. Consider these observations in clinical decisions when prescribing buprenorphine to patients with hypokalemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Periodic electrocardiographic (ECG) monitoring is recommended in these patients. Avoid the use of buprenorphine in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval.

A particular issue of concern in this development program was the evaluation of buprenorphine's effects on cardiac conduction. Careful evaluation of the effects of buprenorphine on cardiac conduction was not performed during the development programs for Suboxone or Subutex. Based on *in vitro* binding studies, buprenorphine was not expected to have cardiac conduction effects.

However, a thorough QT (TQT) study was performed in a more-recent development program for a transdermal buprenorphine product used for analgesia. This study identified a signal for QT prolongation that was considered to meet the threshold for regulatory concern, but that was not of clear clinical significance. The dose studied was significantly lower than the labeled dose used for sublingual buprenorphine products for treating drug addiction, which is, in turn, lower than the many of the CAM2038 doses.

In view of the fact that Subutex and Suboxone had been marketed for several years before the signal was identified, letters requiring post-marketing studies of Q-T effects were issued to marketing application holders for buprenorphine products used for treatment of OUD. However, significant technical difficulties in designing these studies prevented them from being conducted according to the planned schedule. Therefore, Braeburn was informed that data on the Q-T effects of CAM2038 would be needed to support approval.

Rather than performing a specific QT study, Braeburn provided data collected in their clinical trial program for CAM2038. These included studies of volunteers under naltrexone blockade, which may not be informative, and ECGs collected during efficacy studies that did not include PK assessments. Braeburn also submitted in vitro studies of cardiac channel effects. The data submitted were deemed sufficient for filing by the interdisciplinary review team responsible for cardiac conduction study reviews (QT-IRT). Details of their evaluation of the data may be found in the QT-IRT review by Dr. Gopichand Gottipati; excerpts are also found in the CDTL/Division Director memo from the first cycle. In summary, the QT-IRT review team concluded:

> Overall, the data reviewed in this submission shows an absence of large mean increases in the QTc interval compared to a baseline where patients have been taking buprenorphine. In addition, the data shows that buprenorphine and its metabolite norbuprenorphine are unlikely to interact with any of the major cardiac ionic currents (I_{kr}, I_{ks}, $I_{Na,Peak}$, $I_{Na,Late}$ and I_{Ca}). However, as the data do not permit excluding changes in the QTc interval from a drug-free baseline, we suggest that the sponsor includes similar language in the label as is included for other buprenorphine products.
>
> To understand the safety of buprenorphine, the FDA requested the sponsor conduct *in vitro* pharmacology studies of buprenorphine, its major metabolite norbuprenorphine, and naltrexone on five cardiac ionic currents that underlie the ventricular action potentials. To fulfill this request, the sponsor submitted two preclinical study reports (TO-17-589 and TO-17-594). The five ionic currents are hERG and KVLQT1/minK currents that repolarize the action potential, peak Na+ current that generates action potential upstroke, and late Na+ and L-type Ca2+ currents that mediate action potential plateau or duration… Review of the data showed that although buprenorphine inhibited all five ionic currents, it blocked inward (L-type Ca2+ and late Na+ current) and outward (hERG current) currents with similar potencies. Of note, the IC_{50} values needed to block cardiac ion channels directly were in the micromolar ranges, far above the subnanomolar free C_{max} for buprenorphine associated with QTc prolongation in vivo. These findings suggest that QTc prolongation with buprenorphine is not mediated via inhibition of the cardiac ionic currents studied.

To explore the changes in QTc as it relates to exposure, the QT-IRT reviewer evaluated the data from Study HS-15-549, A Phase 2, Open-label, Partially Randomized, Three Treatment Groups, Multi-Site Study Assessing Pharmacokinetics after Administration of the Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) at Different Injection Sites in Opioid-Dependent Subjects with Chronic Pain.

The reviewer noted that the baseline collected was not a true baseline as the patients were on buprenorphine prior to study initiation and as such traditional change from baseline analysis is not appropriate. The reviewer therefore compared the buprenorphine concentrations and QTc values at "baseline" with the median group T_{max}, and observed the following:

- At the baseline visit the mean buprenorphine levels were ~2 ng/mL for the 32 mg q1w and 128 q4w dose groups and ~4.3 ng/mL for the 160 mg q4w group. The concentrations at T_{max} were ~2.7 to ~4-fold as high (up to ~14 ng/mL).
- No QTc values greater than 480 or 500 ms were observed at the T_{max} time-point in any dose group and there were no ΔQTcF values >30 ms. Additionally, no trend towards an increase in the median QTcF values were observed.
- These observations do not suggest the presence of a concentration-dependent increase in QTc (between 2 and 14 ng/mL). However, this does not support concluding an absence of QTc prolongation, as no drug-free baseline was available.

Labeling similar to that used for the buprenorphine products approved for pain is recommended, suggesting caution in patients at risk for QT prolongation.

7 Clinical Microbiology

N/A

8 Clinical/Statistical- Efficacy

The review of efficacy of CAM2038 focused on the findings from an inpatient opioid blockade study (HS-13-478) and a randomized, double-blind, double-dummy, active-control efficacy study (HS-11-421).

8.1 Blockade study (HS-13-478)

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 by CSS Medical Officer, Dr. Alan Trachtenberg, and Biostatistics Reviewer, Wei Liu, during the initial review cycle. No additional information was submitted in this review cycle and their findings from the original review are summarized below.

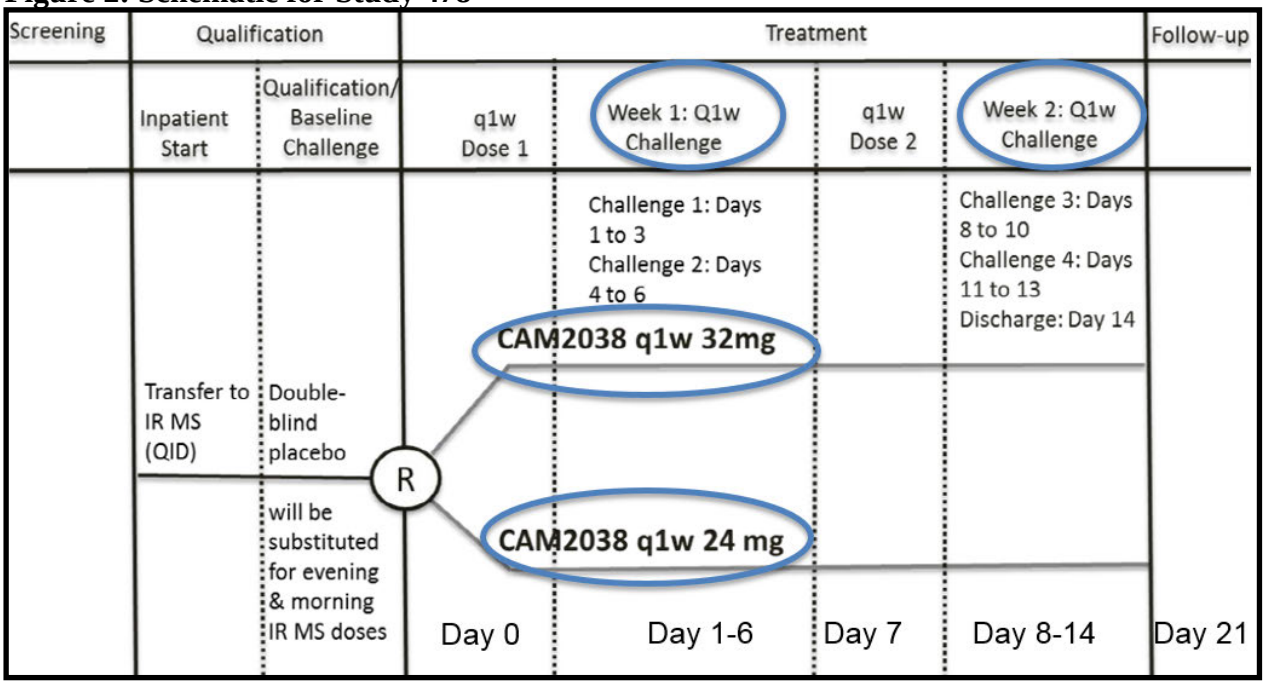
8.1.1 Design and Endpoints

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.

Forty-seven, non-treatment seeking patients with moderate-severe OUD diagnosis were enrolled while physically dependent and self-reported a minimum of 21 days of IV or insufflated opioid-use in the 30-days preceeding 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 (Figure 2). 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 to7 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 seven weeks. The testing portion of the study was two weeks.

Figure 2: 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 2)

The study was primarily intended to demonstrate that, following injections of either 24 mg or 32 mg CAM2038 (weekly), that "Drug Liking" scores measured after challenge with 6 mg or 18 mg of IM HM (a C-II narcotic full μ-opioid agonist) were non-inferior to (not liked better than) those measured after challenge with an IM placebo injection. 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. Under a full blockade of subjective opioid effects by BUP treatment, there should be no significant subjective differences between placebo injections and HM injections.

8.1.2 Population

To be eligible, participants had to meet criteria in the qualification phase:

- Maximum effect (Emax) in response to IM hydromorphone 6 mg greater than that of placebo on Drug Liking bipolar VAS (response to hydromorphone 6 mg greater than 55 mm in the VAS and a difference of at least 15 mm between placebo and hydromorphone 6 mg) and acceptable overall responses to hydromorphone 6 mg and placebo on the subjective measures, as judged by the Investigator or designee.
- Emax in response to IM hydromorphone 18 mg greater than that of placebo on Drug Liking bipolar VAS (greater than 60 mm and a difference of at least 20 mm between placebo and hydromorphone 18 mg) and Emax score of at least 20 points, and acceptable overall responses to hydromorphone 18 mg and placebo on the subjective measures, as judged by the Investigator or designee.
- Acceptable placebo response based on Drug Liking bipolar VAS (score between 40 and 60 mm, inclusive).
- Patient was able to tolerate IM hydromorphone 6 mg and 18 mg, as judged by the Investigator, including ability to complete most efficacy assessments administered within 5 hours post-dose.

A total of 47 subjects passed the Qualification Phase and were randomized into the Treatment Phase study with 22 subjects in the group of CAM2038 24 mg q1w (less than the planned 24) and 25 in the group of CAM2038 32 mg q1w. There were 22 completers in the CAM2038 24 mg q1w group and 24 in the CAM2038 32 mg q1w group (with one dropout subject due to adverse event).

Baseline characteristics are listed in Table 5 and were comparable between groups. Baseline characteristics were also similar to the patient characteristics of Study 421.

Table 5 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.**

8.1.3 Results

The peak (E_{max}) effect of "Drug Liking" (DL) visual analogue scale (VAS) was measured following the once-daily IM injections of 0, 6, and 18 mg hydromorphone (HM). The placebo-corrected (PC) VASDL E_{max} score was computed by subtracting the VASDL E_{max} during 0 mg HM challenge from the VASDL E_{max} during the 6 mg and 18 mg HM challenges acquired within the same session. Blockade of positive subjective effects for 6 mg HM or 18 mg HM was claimed if the largest difference between active hydromorphone doses and placebo (0 mg HM) was less than 11 mm (non-inferiority margin)[4] with confidence following CAM2038 injection.

[4] 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.

The responses of subjects to the same hydromorphone dose decreased significantly after CAM2038 (weekly) exposure at either 24 mg or 32 mg doses as compared to that before the CAM2038 injection. These significant changes between pre- and post-CAM exposure are also seen in the secondary endpoints (High, Good drug effect, Bad drug effect.) Blockade of subjective effects of 6 mg HM was, on average, achieved during all 4 HM challenge sessions for both the 24 mg and 32 mg CAM2038 (weekly) arms.

The PC-VASDL E_{max} scores for each of the 5 hydromorphone challenge sessions are shown in the figures below, generated by Dr. Michael Bewernitz of the Office of Clinical Pharmacology, illustrating the maximum drug liking scores at each challenge. In the figure, vertical lines indicate the time of SC injections of CAM2038. The light grey and dark grey squares represent the 25th percentile, 50th percentile (median) and 75th percentile Emax drug-liking scores, placebo-corrected (VAS drug liking for that week's 0 mg dose subtracted) during the hydromorphone challenge of 6 mg. The placebo-corrected Emax distribution is shown by test session time period. The horizontal line at 11 mm delineates the non-inferiority margin for opioid blockade. Outliers are presented by open circles.

The x-axis shows how much time has elapsed following injection #1 for each placebo-corrected Emax drug-liking score. The number appearing at the bottom of the figure below each boxplot is the number of patients which provided placebo-corrected VASDL Emax measurement for the 6 mg HM challenge in the 24 mg CAM2038 (weekly) arm and the 32 mg CAM2038 (weekly) arm at the particular time point.

Figure 3 Placebo-Corrected Drug Liking Scores By Weekly CAM2038 Dose Level and Test Session Time Period for 6 mg Hydromorphone Dose Level

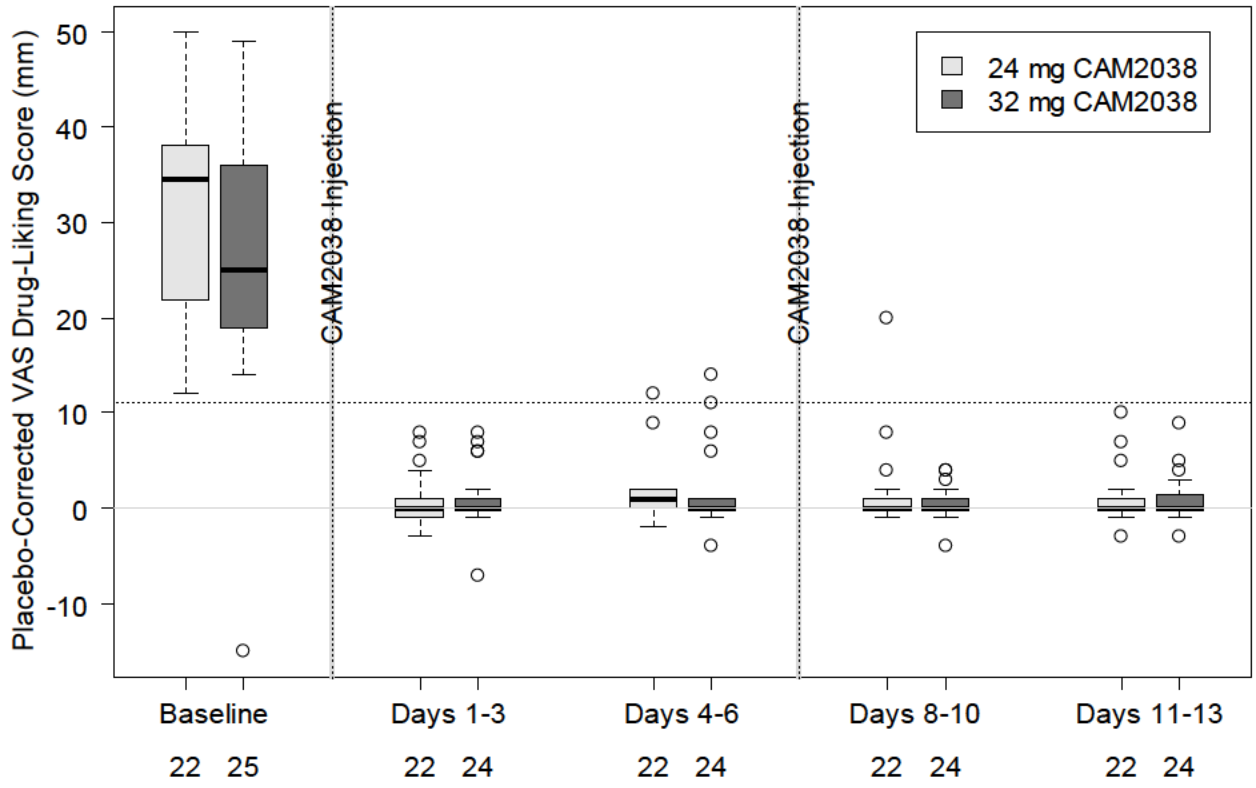
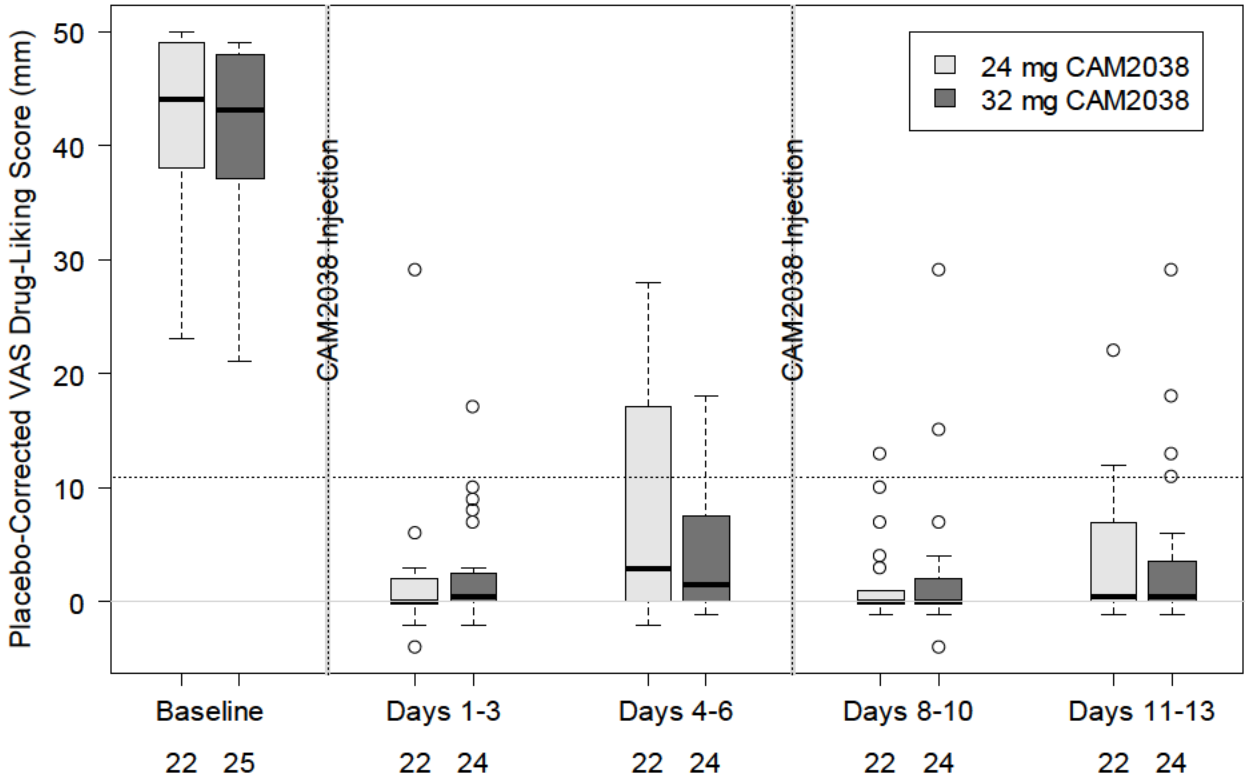


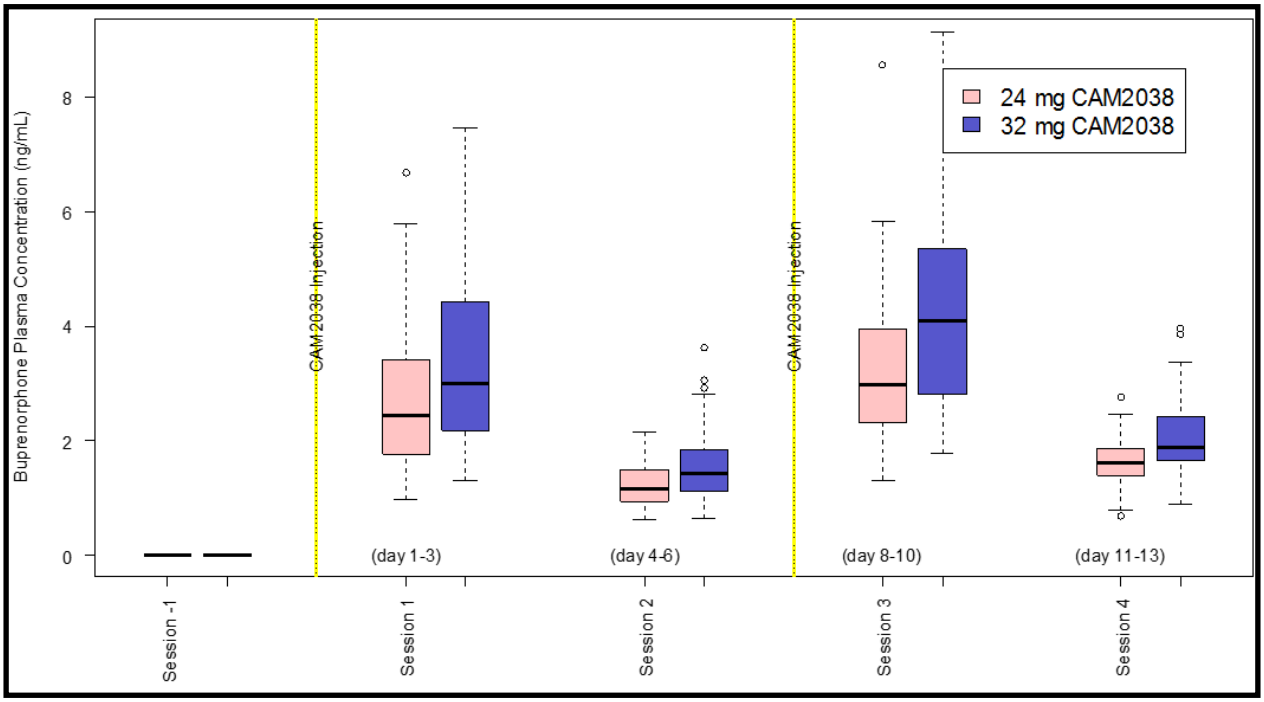
Figure 4 Placebo-Corrected Drug Liking Scores By CAM2038 (weekly) Dose Level and Test Session Time Period for 18 mg Hydromorphone Dose Level



More effective blockade of "drug liking" for the 6 mg hydromorphone dose level than for 18 mg was noted. Additionally, blockade was more effective after the second CAM2038 administration, likely due to greater buprenorphine concentrations achieved during this period. However, the figure also illustrates the substantial inter-individual variability in response, with outliers at each time point who did not, apparently, experience a blockade of hydromorphone effects.

Dr. Bewernitz also analyzed the dose-response relationships in this study. The figures below show the buprenorphine concentration by time, and then the relationship between drug liking scores and buprenorphine concentration.

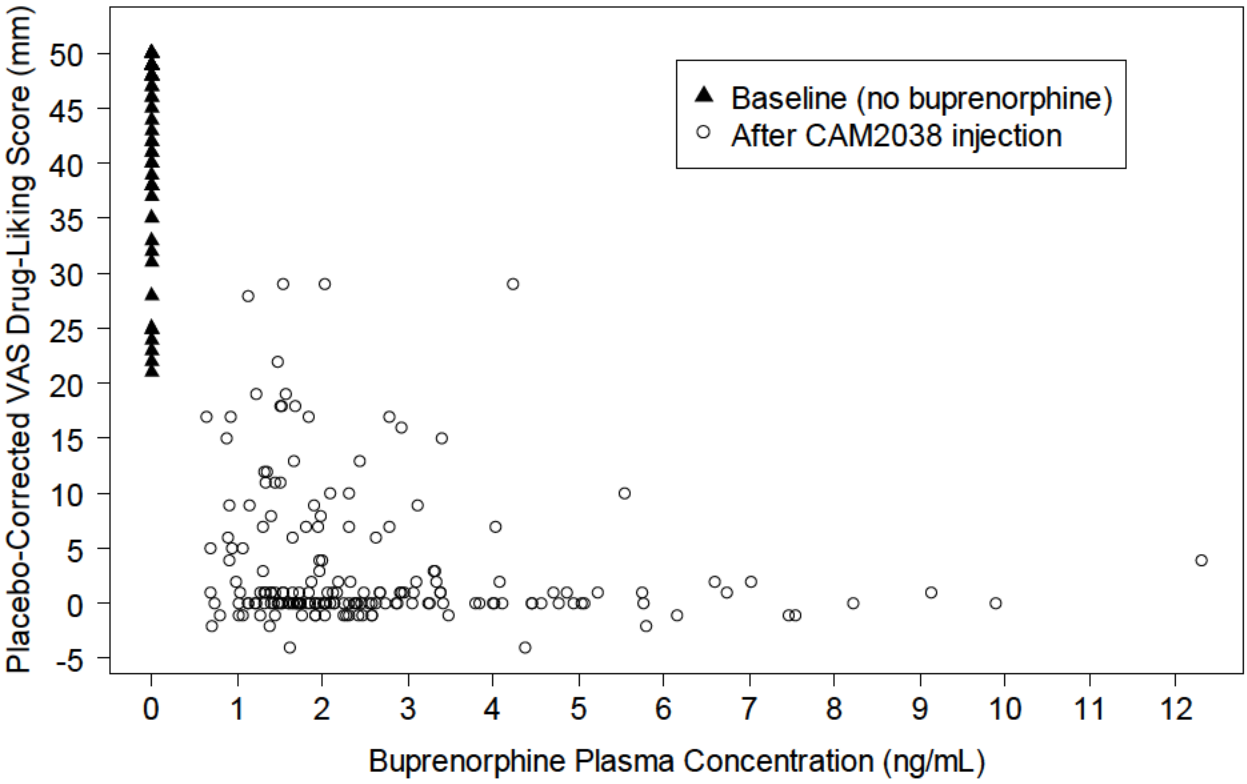
Figure 5 Buprenorphine concentration by time in Study 478



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 6 Plot of Drug-liking relative to plasma BPN levels after a hydromorphone challenge in Study 478Figure 6 illustrates the relationship between buprenorphine plasma level and drug liking after an 18 mg hydromorphone dosing challenge. Data from the CAM2038 (weekly) 24 mg dosing arm is pooled with data from the CAM2038 (weekly) 32 mg dosing arm to show the relationship between drug liking effect (VAS) and plasma levels of BPN. 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.

Figure 6 Plot of Drug-liking relative to plasma BPN levels after a hydromorphone challenge in Study 478



Source: Pharmacometrics Reviewer

Overall, the available PK and PD data provide supportive evidence of opioid blockade. There is an overall trend of increasing response (that is, reduced drug-liking) with increasing buprenorphine exposure. As expected, higher buprenorphine exposures are required to reduce the drug-liking following an 18 mg hydromorphone challenge compared to a 6 mg hydromorphone challenge.

However, these plots also demonstrate that the dispersion in drug-liking scores is wider at the lower buprenorphine exposures compared to higher buprenorphine exposures. The dispersion in the drug-liking scores was further investigated to explore and potentially uncover a reason for the wide range of drug-liking scores observed at lower buprenorphine exposures. When looking at the individual time course of buprenorphine concentration alongside the time course of drug-liking scores, approximately one-quarter of the subjects appeared to present substantial changes in the drug-liking scores from one dosing interval to the next despite having comparable exposures. These observations suggest that, in addition to buprenorphine concentration, other factors which are currently unknown, are likely influencing the drug liking scores.

8.2 Efficacy Study (HS-11-421)

In the initial review cycle, the clinical and statistical review teams identified a number of discrepancies in the submitted datasets, including what appeared to be duplicate entries and errors. Additionally, some data fields necessary for analyses such as dose-response were not included. Braeburn was asked to audit the data to find the cause of duplicate entries and discrepancies, and to submit datasets with the needed fields.

Braeburn conducted a thorough audit and root cause analysis to identify and correct any issues with the data. The audit report states that the primary root cause of 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 report states that the "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." These issues did not affect data from any other studies because these systems were not in use in other studies.

The resubmitted data was reanalyzed by the Dr. Gioia Guerrieri (clinical) and Dr. James Travis (statistical). Dr. Travis' review contains a detailed tabulation of data discrepancies and their resolution.

Their safety and efficacy findings based on analysis of the resubmitted datasets are summarized below.

8.2.1 Study Design and Endpoints

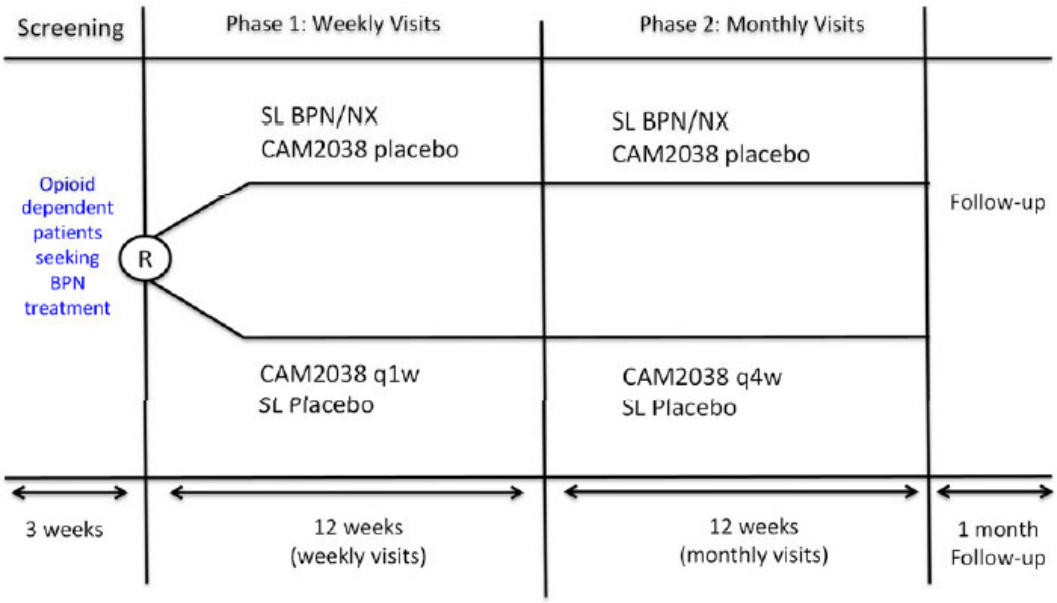
Study HS-11-421 was a randomized, double-blind, double-dummy, active-controlled study designed to evaluate the efficacy and safety of CAM2038 compared to sublingual buprenorphine/naloxone (SL BPN/NX) in patients with opioid use disorder who are new entrants to treatment. Patients were eligible for inclusion in the study if they met the following requirements:

- Male or female, 18-65 years of age, inclusive.
- Diagnosis of moderate or severe opioid use disorder as described in the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V).
- Voluntarily sought treatment for opioid use disorder.
- Had not received medication-assisted treatment for opioid use disorder within 60 days prior to randomization.
- Considered by the investigator to be a good candidate for buprenorphine treatment, based on medical and psychosocial history.
- Must not have a current diagnosis of chronic pain requiring opioids for treatment.
- Must not have a current DSM-V diagnosis of moderate to severe substance use disorder on any other psychoactive substance other than opioids, caffeine, or nicotine.

Eligible patients were randomized in a 1:1 ratio to receive either CAM2038 injections with placebo sublingual tablets, or placebo injections with sublingual SL BPN/NX tablets. The schedule of the study is illustrated below in Figure 7. Of note, there were three scheduled

visits during the first week of the study, followed by weekly visits through the rest of the first phase of the study.

Figure 7 Study Schema for HS-11-421



Abbreviations: BPN/NX, buprenorphine/naloxone; q1w, once weekly; q4w, once monthly; R = randomization; SL = sublingual
Source: Figure 1, Applicant's Study Report

On the first day of treatment patients received an open-label 4 mg test dose of sublingual buprenorphine. Patients who tolerated the test dose were randomized and given a 16 mg injection of CAM2038 or matched placebo. During the next six days patients were allowed up to two further 8 mg injections as needed. Patients received an injection of 16, 24, or 32 mg on Day 8 matched to the dose they received in the previous seven days. Patients received injections weekly for twelve weeks total and then transitioned to what was intended to be an equivalent dose of the monthly formulation for the remaining twelve weeks. Dose adjustments and supplemental 8 mg injections were permitted for the duration of the study. Supplemental 8 mg doses of CAM2038 (weekly) were allowed during the study in both treatment arms. The sublingual buprenorphine 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.

Because the study was intended to provide efficacy information about both the weekly and monthly products, 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 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.

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 and SL BPN/NX was greater than the pre-specified non-inferiority margin of 10%. As described in Section 3.1.1, both the responder definition and the NI margin were chosen pragmatically. The NI margin was arrived at after some discussion; the Division expressed a preference for a smaller margin but acknowledged that an impractically-large sample size might then be needed.

The secondary endpoint was the cumulative distribution function (CDF) of the percentage of assessments negative for illicit opioids between week 5 and 25, allowing a several-week grace period. This analysis could not be used as the primary outcome because it would not be possible to determine whether patients might have responded to only one of the two formulations. The percentage negative assessments was computed for each patient as the number of weeks of negative assessments divided by 15. The 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.

8.2.2 Demographics and Disposition

A total of 428 subjects were randomized, 213 to CAM2038 and 215 to groups BPN/NX. The demographic and baseline characteristics were comparable across treatment groups (Table 6: 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: Dr. Guerrieri's Table 11 ;

Table 7 Other Relevant Baseline Characteristics--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: Table 6, Section 2.7.3 of Resubmission

). The majority of the subjects were male (~60%) and white (76%). Overall, about 52% of the subjects had history of injectable opioid use.

Table 6: 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: Dr. Guerrieri's Table 11

Table 7 Other Relevant Baseline Characteristics--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)
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Positive for Any Opioid at Screening, n (%)	200 (93.0)	193 (90.6)
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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: Table 6, Section 2.7.3 of Resubmission

Table 8 Substance Use History in randomized population of HS-11-421

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

Source: Table 7, Applicant's Study Report, original submission

The disposition for the randomized patients is shown in Table 9 Disposition in Study 421

	CAM2038 N= 213	**SL BPN/NX N=215**	**TOTAL (N=428)**
Completed	121 (56.8%)	126 (58.6%)	247 (57.7%)
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: From Dr. Guerrieri's Table 29r. 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.

constructed by Dr. Guerrieri. The completion rates are similar for the two treatment arms (56.8% vs 58.6%) and there do not appear to be any substantial differences between the two arms in the reasons for study discontinuation. The most common reasons for discontinuation in both groups were "lost to follow up" and "withdrawal by patient." Dr. Guerrieri identified a small number of patients who should have been classified as withdrawing due to AEs and the table below reflects this reclassification.

Table 9 Disposition in Study 421

	CAM2038 N= 213	SL BPN/NX N=215	TOTAL (N=428)
Completed	121 (56.8%)	126 (58.6%)	247 (57.7%)
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: From Dr. Guerrieri's Table 29r. 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.

8.2.3 Dosing

Dose adjustments were permitted for the duration of the study. Supplemental 8 mg (weekly) injections were allowed during the second phase of the study and were also used in the active-controlled group. Overall, supplemental 8 mg injections were given to 14 patients (6.6%) in the CAM2038 arm and 17 patients (7.9%) in the SL BPN/NX arm. Table 10 shows the doses of CAM2038 (weekly) administered following the initial titration period and at the final visit before transition to the monthly formulation. Table 13 shows the first and final monthly dose administered to each patient.

Table 10 Number of patients receiving each BRIXADI weekly dose at selected time points

BRIXADI (Weekly) Dose	Following Titration Period	End of Weekly Phase
16 mg	2	6
24 mg	128	84
32 mg	54	64

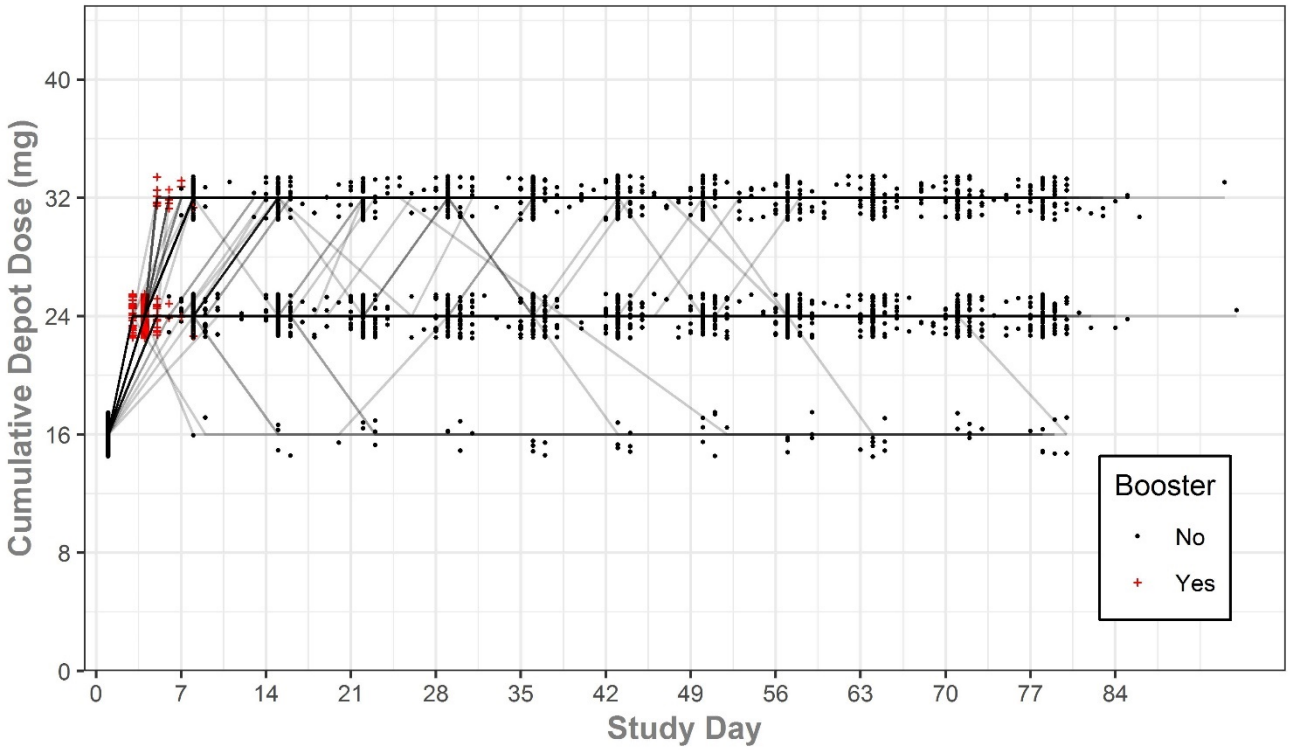
Table 11 Number of patients receiving each BRIXADI Monthly dose at selected time points

BRIXADI Monthly Dose	First BRIXADI Monthly dose	Final BRIXADI Monthly dose
64 mg	8	11
96 mg	84	83
128 mg	66	56
160 mg	0	8

Source: generated by Dr. Travis for use in PI

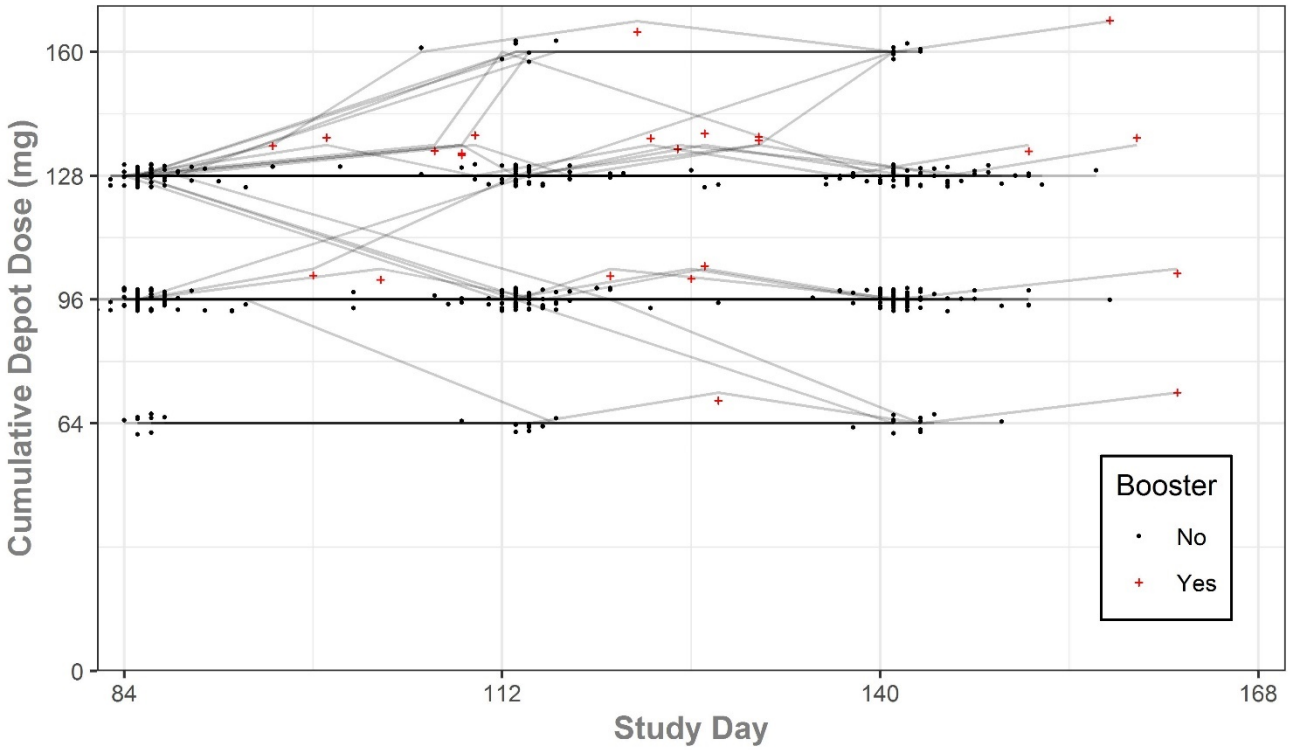
Complicating any interpretation of results by dose, the protocol allowed dose adjustments and booster doses without providing protocol-specified criteria for either. As illustrated in the figures below, prepared by Dr. Travis, dose adjustments, both upward and downward, were very common.

Figure 8: CAM2038 Dose for Phase 1 (Months 1-3)



Source: Dr. Travis' Figure 6

Figure 9: CAM2038 Dose for Phase 2 (Months 4-6)



Source: Dr Travis' Figure 7

8.2.4 Results and Conclusions

Using the resubmitted data, Dr. Travis was able to reproduce the analyses performed by the sponsor and the overall conclusions did not change. Dr. Travis' replication of the applicant's primary analysis is shown in Table 12. In all 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) who were classified as responders in the applicant's primary analysis but who did not appear to meet the applicant's responder definition. These patients were classified as non-responders in Dr. Travis' analyses.

The applicant concluded CAM2038 was noninferior 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 pre-specified −10% NI margin. However, as the 95% confidence interval of the difference contained zero, CAM2038 was not demonstrated to be superior to the SL BPN/NX.

Table 12 Applicant's Primary Analysis: Responder Rate (ITT Population)

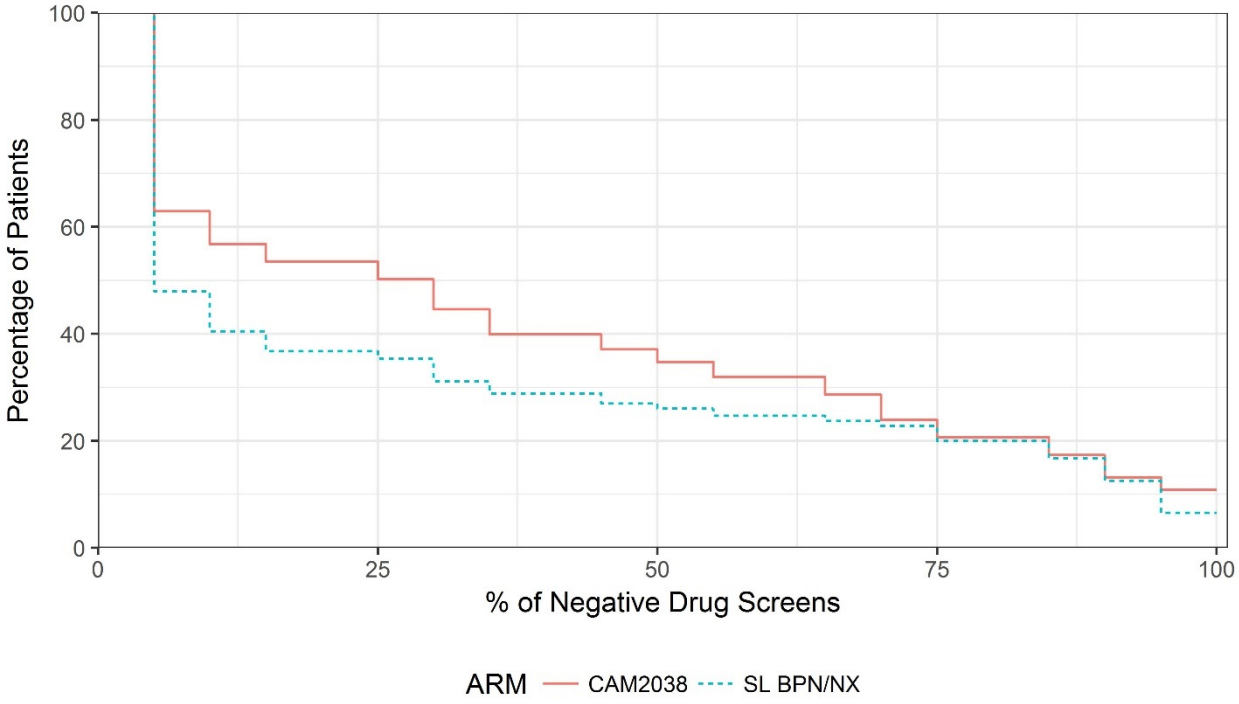
Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)	Non-Inferiority P-value 2-sided
Responder, n (%)	36 (16.9%)	30 (13.9%)	2.9% (−3.9%, 9.8%)	< 0.001
Non-Responder, n (%)	177 (83.1%)	185 (86.0%)		

Source: Statistics Review, Table 5
Abbreviations: CI, Confidence interval; ITT, intent to treat; SL BPN/NX, sublingual buprenorphine/naloxone

Dr. Travis also performed sensitivity analyses reclassifying "indeterminate" lab tests as positive, which provided similar results.

The results of the applicant's analysis of the CDF are illustrated in Figure 10. The corresponding values plotted in the figure are shown in Table 13. 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. 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. Dr. Travis' sensitivity analysis yielded similar results.

Figure 10 Cumulative Distribution Function (CDF) of Percentage of Negative Opioid Use Assessments over Weeks 5-25



Source: Statistics Review

Table 13 Cumulative Distribution Function (CDF) of Percentage of Urine Samples Negative for Illicit Opioids Supported by Self-Reported Illicit Opioid Use over Weeks 5-25

% Self-Reports Negative for Illicit Opioid Use	Number (%) of Patients	
	CAM2038 N=213	SL BPN/NX N=215
≥ 0%	213 (100)	215 (100)
≥ 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)
≥ 60%	68 (31.9)	53 (24.7)
≥ 70%	51 (23.9)	49 (22.8)
≥ 80%	44 (20.7)	43 (20)
≥ 90%	28 (13.1)	27 (12.6)
≥ 100%	23 (10.8)	14 (6.5)

Source: Statistics Review

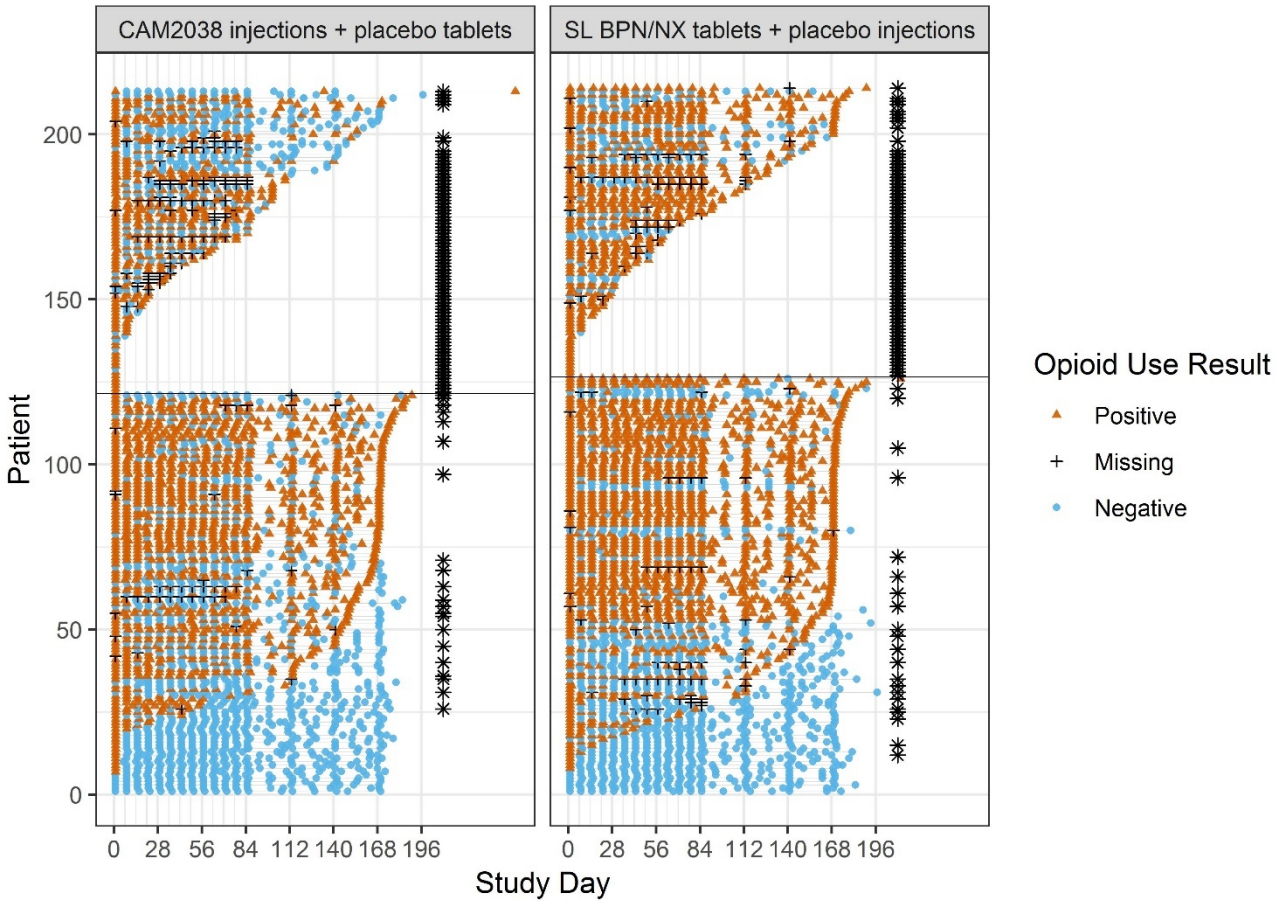
The overall percent of negative tests does not differentiate between, for example, a patient who is abstinent for half the study and then relapses to daily illicit drug use, a patient who continues to use illicit drugs daily for half the study and then stops completely, and a patient who uses intermittently, half of the days throughout the study. All of these patients might have 50% of their tests negative. This also illustrates the reason that the overall CDF was not an appropriate endpoint to examine response to the weekly formulation in phase 1 and to the monthly formulation in phase 2. To allow an appreciation of the temporal sequence of patients' test results, the graphic depictions below show the results of each urine test for each patient. They also distinguish between tests that were imputed as positive in the analyses because they were intermittent missing, or because a patient self-reported drug use, and actual positive tests. Patients with missed random tests are indicated by a star on the right side of the figure.

In these patient-level presentations, each individual patient is represented along the y-axis. On the x-axis are the time points during which urine samples were collected. (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 orange data points, particularly along the right-hand side of the x-axis which represents longer periods of time on treatment. The data points that appear as black '+' symbols in these presentations denote intermittent missing urine data. 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 and are sorted based on time in the study. Assessments after the last dot in the row were missing and were imputed as positive for the purposes of analysis. Completers are shown in the bottom of each display, arranged by time to last positive sample.

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 by the applicant. Dr. Travis re-classified these patients.

Using the corrected datasets, Dr. Travis generated updated plots of the opioid use assessment results. For Figure 11 partially inconclusive results are classified according to the status of the remaining results, that is if there were any positive results then the result was positive, otherwise the assessment was classified as negative. If all panels are inclusive, then test was classified as missing and treated as positive.

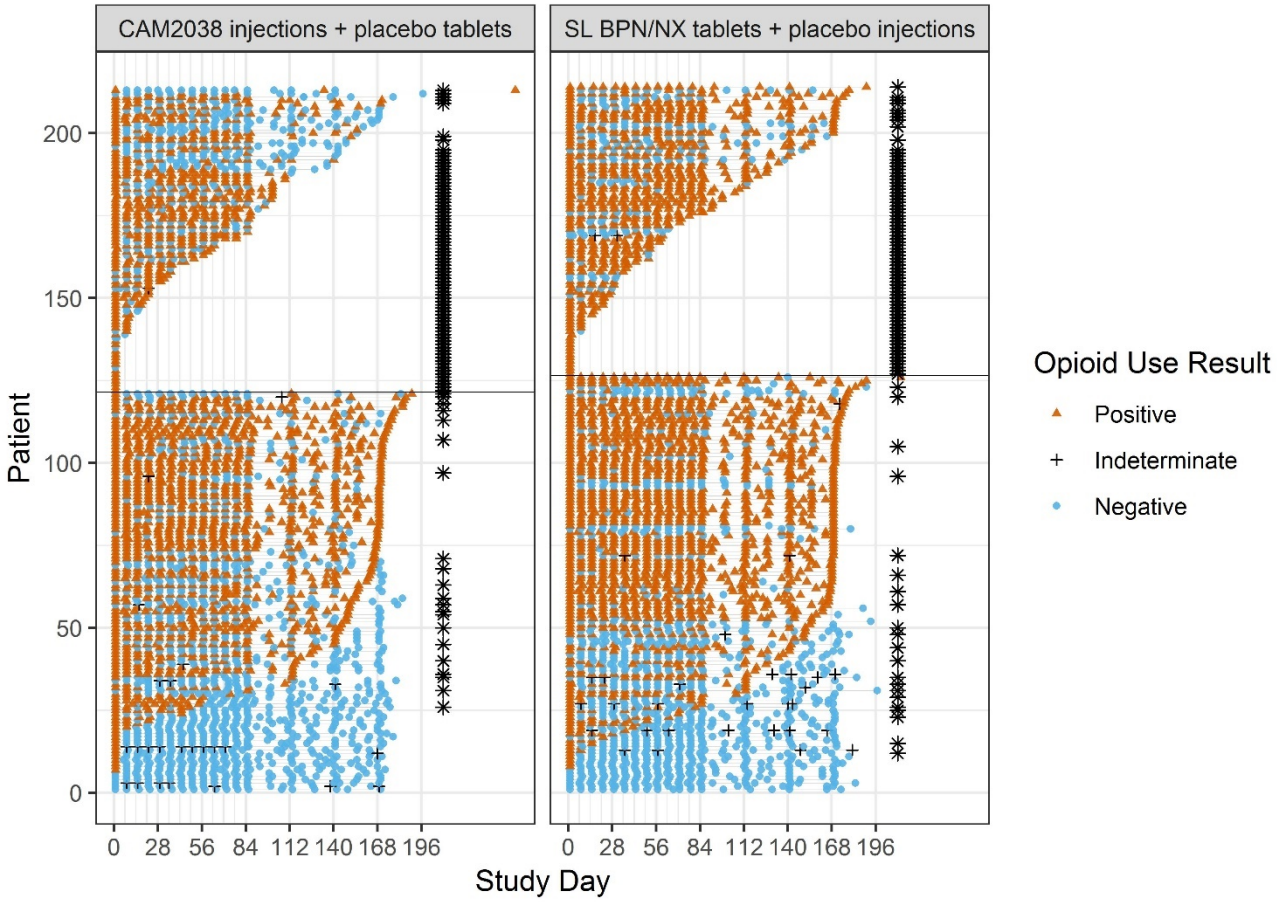
Figure 11: Plot of the Opioid Use Assessment Results



Source: Statistical Reviewer
Note: Patients with missed random tests are indicated by a star on the right-hand side of the plot. Patients above the horizontal line were classified as early dropouts.

In Figure 12, missing results are now classified as positive and any partially indeterminate results are indicated as such.

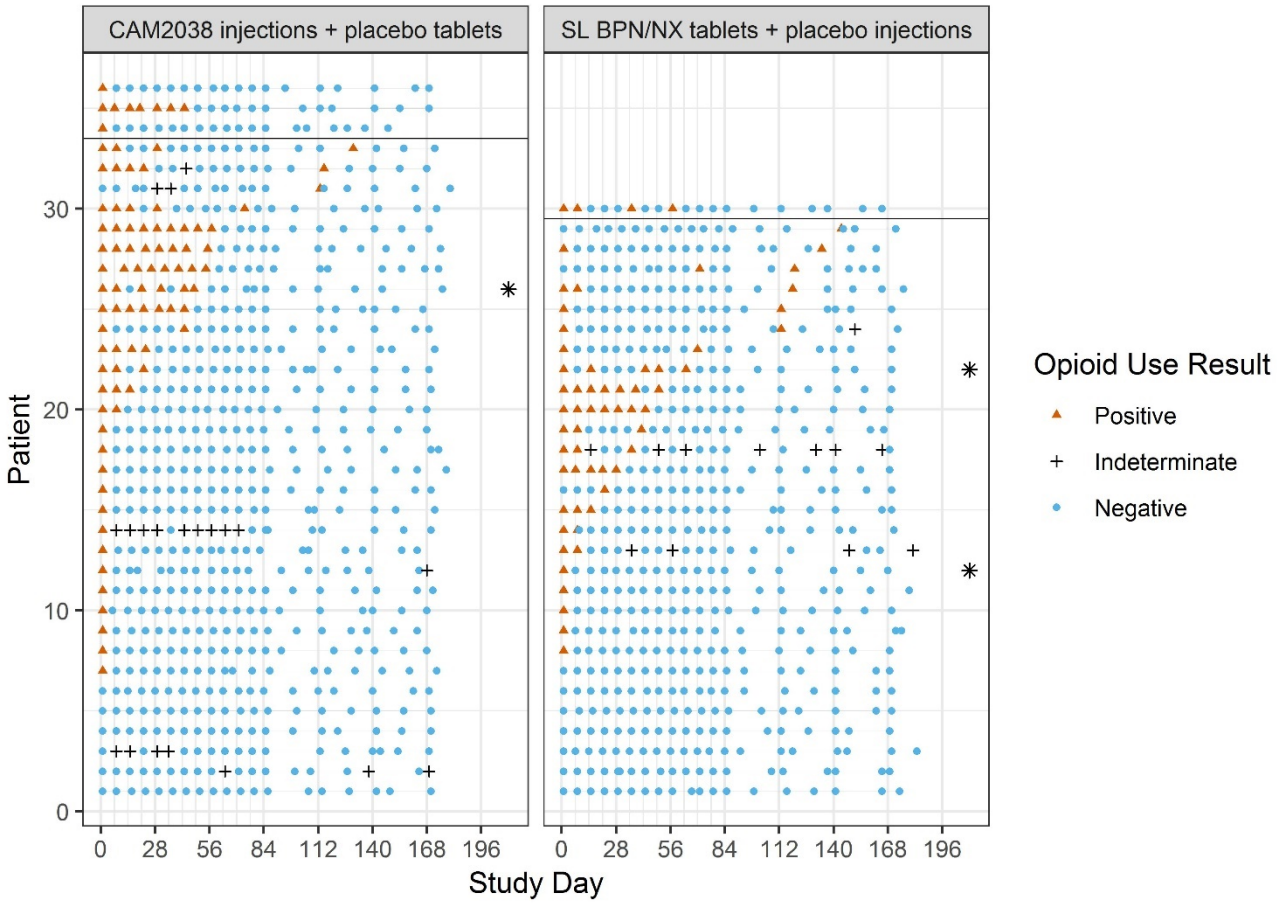
Figure 12: Plot of the Urinalysis Results with Missing Counted as Positive and Indeterminate Results Indicated



Source: Statistics Reviewer
Note: Patients with missed random tests are indicated by a star on the right-hand side of the plot.

Finally, Figure 13 shows the urinalysis results for patients classified as responders.

Figure 13: Plot of the Urinalysis results for Responders



Source: Statistical Reviewer
Note: Patients with missed random tests are indicated by a star on the right-hand side of the plot.

8.2.4.1 Subgroup Analyses

In the analyses by sex, race, and age, females responded at a higher rate than males in the study in both treatment groups, but broadly similarly across treatments. 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.

Analysis based on history of opioid use was also performed by Dr. Travis. 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 was used to divide the 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 14 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%)	8/11 (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: Statistics review

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 [redacted] (b) (4) Notably, the same post-hoc analysis suggests that CAM2038 confers no benefit (other than possible patient preference/convenience) for patients whose primary opioid at initiation is a prescription analgesic.

8.3 Data Quality Concerns

Dr. Travis' review provides an overview of the data issues that were identified by either the Agency or the applicant during the initial review cycle and were corrected in the current submission. Errors noted included duplicated records of administered doses and site visits and incorrect dosing records. Of SDTM domains where errors were identified and corrected, only the lab results domain is utilized in the analysis of the primary endpoint. There were no modifications in this listing which would affect the analysis of the primary endpoints.

8.4 Discussion

When dosing data were received, [redacted] (b) (4) This was communicated as a deficiency in the first cycle [redacted] (b) (4)

The non-inferiority margin, which was agreed upon for largely pragmatic reasons, does not appear to be well-justified, because the response rate for the sublingual buprenorphine treatment arm was only 14% and so the study would only rule out a response rate of less than 4%. It is reasonable to assume that the placebo response rate is quite low (although not zero) in this population. Future studies should employ NI margins that are more data-supported.

The graphic displays of patient response allow us to appreciate that even some fully-compliant patients being treated with doses of buprenorphine that yield adequate steady-state blood levels—expected to block the reinforcing effects of opioids—will continue to use illicit opioids despite treatment. Ensuring compliance, via depot administration, does not ensure treatment response. There is little evidence that CAM2038 offers advantages over SL BPN in terms of efficacy, particularly in patients who are not using heroin or other drugs by injection; however, the paradigm in which it is to be used (depot medication initiated after a single observed test-dose of transmucosal buprenorphine; no take-home medication) does offer advantages in terms of the potential for abuse, misuse, and accidental overdose. For patients using prescription opioids by non-injection routes, there is a suggestion that the depot may be less effective than sublingual buprenorphine. However, the dosage form may offer advantages that are of importance to patients.

9 Safety

Safety data derive from Phase 1 PK studies, the blockade study and efficacy study described above, and a 24-week, Phase 3 open-label study which enrolled patients who could be new to treatment ("new entrants") or already in established treatment with transmucosal buprenorphine ("transfer") (Study 499). This study was initiated prior to the efficacy study, and dosing was entirely at investigator's discretion, employing any combination of doses and formulations for a given patient.

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.

In the resubmitted data, the number of injections given of either formulation totaled 8697, 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 15: Overall Patient Exposure to CAM2038 in the Clinical Program 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 15: 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: Dr. Guerrieri's review 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.

The safety review focused on the Phase 3 studies, involving 440 exposed patients (who received 7917 injections, with a mean of 18 injections per patient).

The number of patients exposed to the varying doses of the CAM2038 weekly and monthly formulations the pivotal Phase 3 Study (421) based on the resubmitted audited data is shown in Table 17. The control arm received placebo injections. An active 8 mg dose was used as a "booster" in both treatment arms. In total, thirteen patients in the CAM2038 group and 17 in the SL BPN group received booster injections in Study 421.

Table 16: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: Clinical Reviewer

Table 17 and Table 19**Error! Reference source not found.**, provided by Braeburn in the prior review cycle, illustrate in more detail the extent of cumulative exposure to the doses in each formulation of CAM2038 in the pooled Phase 3 studies. 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 17: 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 18: 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.

Although neither CAM2038 formulation contains a drug substance that is a new molecular entity, both contain novel excipients. The systemic safety of CAM2038 is supported, in part, by previous Agency findings for systemic safety of buprenorphine in the referenced drug, Subutex. Ideally, Braeburn would have provided a safety database at least 300 patients exposed for 12 months and 100 patients exposed for at least 6 months at the highest proposed dose *for each formulation* to characterize the safety. However, there is clearly a lack of long-term experience with both formulations, particularly the monthly formulation. (b) (4)

The resubmitted manufacturing and pharmacology/toxicology data provide reassurance of the safety of the excipients not available in the first review cycle.

It has been challenging to interpret the safety data to determine effects of dose, formulation, or time. Doses were changed frequently, patients were exposed to both the weekly and monthly formulations over the course of treatment, and supplemental 8 mg doses were administered throughout the studies at investigator discretion. Dr. Guerrieri's review includes several graphic displays, constructed by Braeburn, that illustrate 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.

Most subjects in the study were white males with an average age in the early 40's. Almost all of the 190 "transfer" patients in the OL study were white.

9.1 Deaths

One death was reported in the clinical program, in a patient treated with CAM2038 in Study 421. A 41-year-old female with no other reported medical history was hit by a car and died on Study Day 147. There were no factors suggesting a causal link to the study drug. No additional deaths were identified in the data audit or safety updates.

9.2 Serious Adverse Events

A total of 20 SAEs (including the fatality described above) occurred among 17 subjects of the 729 exposed to CAM2038 across the OUD treatment clinical program. None were related to injection site reactions. In Study 421, SAEs were reported in five (2.3%) of the CAM2038 group and in 13 (6%) of the SL BPN group. Accidental overdoses (3) were reported in the SL BPN group but not the CAM2038 group. One event (vomiting) was deemed plausibly related to study drug.

In the resubmission, Braeburn included an SAE that occurred in their development program using CAM2038 as an analgesic. This event occurred (b) (4) (b) (4) and was reported (b) (4) and should have been included in the original NDA submission. The case involved a woman who presented to the ER one day after her first injection of 8 mg CAM2038 with "acute onset altered mental status, rhabdomyolysis, acute renal failure, and markedly elevated liver transaminases leading to acute liver failure." The patient eventually recovered. Hepatic effects are known to be associated with buprenorphine.

9.3 Dropouts and/or Dose Reductions Due to Adverse Effects

In the initial submission, very few patients (2-3% of CAM3028-treated) were classified as discontinuing study drug due to AE. However, as illustrated 21% of each arm in Study 421 were classified as "withdrawal by patient."

At the Division's request, Braeburn pursued additional information on these patients. This information was submitted on September 13, 2018[5], 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. Dr. Guerrieri determined that the total number of discontinuations was unchanged, but that additional patients whose reason for discontinuation appeared to be related to an adverse event were identified. For some of these, the link between study drug and the reason for discontinuation (e.g., "injection site ulcer") was fairly clear. Braeburn reclassified several patients as discontinuing for AEs and Dr. Guerrieri added four additional patients. The tables below contain recalculated reasons for discontinuation based on the audited data. Dr. Guerrieri's review tabulates the patient numbers and circumstances of discontinuation for re-adjudicated patients in Section 13.2.

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

Table 19: Reviewer-reported Discontinuations in Study 421 after September 2018 Data Audit

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: Clinical 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.

Table 20: 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: Clinical Reviewer. Derived from Applicant Table 14.1.1.2, Study 421 - Section 14 tables resubmitted 5/23/2018

Because of the design of the studies, which permitted dose adjustments up or down at investigator discretion, information relating to adverse events leading to dose reductions were not well-captured in the clinical trials.

9.4 Significant Adverse Effects

9.4.1 Hepatic

Hepatic effects are a known risk of buprenorphine. Hepatic effects were reviewed through laboratory assessments and adverse events. Mild hepatic enzyme abnormalities were fairly common; some cases of more extreme elevations were reported, but had alternative explanations such as viral hepatitis. Thus, no cases meeting Hy's Law criteria were reported. In Study 421, a shift from normal-to-high in LFTs 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). This does not provide support for an advantage of CAM2038 over sublingual dosing in hepatic safety attributable to avoidance of first-pass metabolism. However, I note that the most extreme elevations occurred only in the SL BPN arm in Study 421, and not in the CAM2038 arm of that study or in the OL study.

9.4.2 Cardiac

A few cases of mild to moderate QT prolongation were reported in CAM2038-treated patients. Additionally, clinically significant ECG abnormalities reported as an AEs occurred in 10 patients treated with CAM2038 in Studies 549, 478, 421, and 499. One SAE was reported, in a patient[6] transferring from SL BPN to CAM2038 in study 599 experienced a serious TEAE of tachycardia on Day 313, which resulted in hospitalization. CAM2038 was not discontinued. The patient had reported drinking three to five 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.

These findings are consistent with the EKG findings from the QT-IRT team.

9.4.3 Injection Site Reactions

In this resubmission, Dr. Guerrieri identified a number of injection site reactions (ISRs) that were not coded as treatment-emergent, potentially due to being out of the time window prespecified in the protocol. For the purposes of these analyses, however, she considered any complaint at a previous site of study drug injection to be treatment-emergent and study drug related.

The applicant attempted to explore for a pattern of ISRs by site of injection, but this analysis linked any reported AE to the site of injection at the immediate prior visit, while the complaint might have been related to an injection at a site used at a different prior visit. Thus, it was not possible to determine the rate of ISRs by injection location.

[6] Subject (b) (6)

The same limitation applies to explorations of ISRs by dose. However, because dose remained the same over several injections for most patients, it may be possible to discern a pattern even with delayed reports. Exploration of ISRs by dose suggest that the frequency of ISRs is related to volume, rather than to dose.

Table 21 shows the distribution of ISRs in the controlled study. The results from the open-label study were similar.

Table 21: 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 hemorrhage	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: Clinical 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.

9.4.4 CNS/Respiratory Depression

Symptoms such as somnolence and sedation were not commonly reported in the safety database. One patient (CAM3028 (weekly) 32 mg) discontinued study medication due to sedation.

No TEAEs potentially associated with respiratory depression were reported in patients treated with CAM2038.

9.5 Common AEs

The systemic safety profile for CAM3038, when given by a HCP in clinical trials, was broadly consistent with the known safety profile of transmucosal buprenorphine. Common AEs included administration site reactions, infection, gastrointestinal symptoms, and nervous system disorders (headache).

Table 22 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 shown in tables below.

Table 22: 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 defecation 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	6 (<2%)
Road traffic accident	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	13 (3.0%)
Back pain	11 (2.5%)
Nervous system disorders	
Headaches	**40 (9.1%)**
Headache	34 (7.7%)
Migraine	9 (2%)
Neurological disorders NEC	**23 (5.2%)**
Hypoesthesia	7 (<2%)
Dizziness	6 (<2%)
Psychiatric disorders	
Anxiety disorders and symptoms	**15 (3.4%)**
Anxiety	13 (3.0%)
Depressed mood disorders and disturbances	**16 (3.6%)**
Depression	12 (2.7%)
Depressed mood	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	5 (<2%)
Rhinorrhea	2 (<2%)
Skin and subcutaneous tissue disorders	
Epidermal and dermal conditions	**18 (4.1%)**
Rash	5 (<2%)
Erythema	3 (<2%)

Source: Clinical 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.

Table 23: 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%)**
Hypoesthesia	4 (1.9%)	0 (<1%)
Dizziness	3 (1.4%)	2 (<1%)
Paresthesia	2 (<1%)	2 (<1%)
Sedation	2 (<1%)	1 (<1%)
Somnolence	2 (<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: Clinical 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 performed several explorations of the data to elucidate any dose-response signals. Using data from the Study HS-11-421 (*Module 2.7.4/ Section 2.1.1.5*), they reported the incidence of subjects with at least one 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.

In this review cycle, Braeburn provided additional analyses of the Study 421 safety dataset in which patients were divided into three groups according to the total buprenorphine dose received over the study. On review, these analyses did not reveal any patterns of AEs that differed from the known effects of buprenorphine products or from previous analyses.

Study 499

Common adverse events in Study 499 are listed in the Applicant-provided Table 24. 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 24: 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)
Diarrhea	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

9.6 Safety Analyses by Demographic Subgroups

No notable differences between male and female patients were observed. No other demographic analyses were undertaken.

9.7 Other Safety Concerns

Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated in a patient still dependent on a full agonist.

9.7.1 Precipitated Withdrawal

Buprenorphine itself can precipitate withdrawal if initiated in patients who are not yet in significant opioid withdrawal. For this reason, initial dosing is generally cautious and typically begins with a sublingual dose of 2 mg- 4 mg. Some of the doses of CAM2038 contain a large amount of buprenorphine. In new entrants to treatment, the clinical trials included a test dose of 4 mg sublingual buprenorphine and then initiated treatment with a 16 mg weekly dose. Two patients did not tolerate the test dose. 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.

9.7.2 Consequences of Intravenous Injection

CAM 2038 was administered in a supervised setting by HCPs in the clinical development program. If a patient, household contact, or associate were to obtain access to CAM2038, the pre-filled syringe containing a Schedule III opioid might be an attractive target for abuse by the intravenous route. As noted above, it is predicted that injection into a vessel could result in the formation of a gel or solid, with resulting occlusion and possibly tissue damage or embolus.

10 Advisory Committee Meeting

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.[7] No additional Advisory Committee input was sought for this cycle. The majority of the committee members agreed that safety data supported some of the proposed doses (b) (4)
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. The majority recommended approval with the REMS as proposed to ensure that the product is administered by healthcare providers.

[7] A verbatim transcript of this meeting is available on the FDA website at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm535446.htm

11 Pediatrics

Braeburn received a full waiver of the Pediatric Research Equity Act (PREA) requirements on the basis of infeasibility. The prevalence of OUD in the pre-adolescent population is very low, and this product would not be suitable for treating iatrogenic opioid dependence (i.e., physical dependence without meeting criteria for OUD). Prevalence in adolescents under age 17 is also too low for feasible study.

12 Other Relevant Regulatory Issues

12.1 Financial Disclosures

Review of financial disclosures revealed no concerns.

12.2 Bioresearch Monitoring Inspections

OSI conducted inspection of the Applicant (Braeburn Pharmaceuticals Inc.) and four clinical investigators. These inspections were performed as a routine data audit for the original submission and all sites were classified NAI or VAI.

12.3 Exclusivity

Upon review of the administrative records related to the approval of NDAs 204442 and 209819, the Exclusivity Board recommended that 3-year exclusivity for Sublocade should block the approval of Brixadi with regard to its monthly depot product. The Board recommended that Brixadi's weekly depot product should not be blocked.

In anticipation of this possibility, while deliberations were underway, the Division suggested that Braeburn consider submitting labeling that for the products separately. Had this option been acceptable to Braeburn, we could theoretically have taken an approval action for the weekly product only, and allowed launch of that product. A tentative approval action for the monthly product (and for labeling describing either the monthly by itself or the two products under one label) could have been taken.

Braeburn expressed that they were not willing to entertain separating the products. Therefore, only a combined label was negotiated and the tentative approval will apply to both formulations.

13 Labeling

The submitted proposed labeling is in Physician's Labeling Rule (PLR) format. The approved labeling for Suboxone/Subutex tablets forms the foundation for CAM2038 labeling, with new information, related to the delivery system and the clinical trials, included throughout in relevant sections. A number of revisions have been made by Braeburn since the first cycle, informed by labeling changes to other buprenorphine products in the time since the original submission.

The following are recommendations for the labeling.

Throughout the label, a convention has been employed of referring to the weekly formulation as "BRIXADI (weekly)" and the monthly formulation as "BRIXADI (monthly)." The Division approached Braeburn and asked them to consider proposing separate proprietary names for the two products (hypothetically, BRIXADI WEEKLY and BRIXADI MONTHLY), but Braeburn declined to entertain this possibility. Where the label reads only "BRIXADI," this refers to both formulations.

INDICATION AND USAGE
Braeburn proposed the following language:

BRIXADI is (b) (4) indicated for the treatment of moderate to severe opioid use disorder.

- (b) (4)
- (b) (4)

BRIXADI should be used as part of a complete treatment plan to include counseling and psychosocial support.

The agreed-upon wording at the time of this review adds the highlighted language:

> BRIXADI is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine.
>
> BRIXADI should be used as part of a complete treatment plan to include counseling and psychosocial support.

(b) (4)

DOSAGE AND ADMINISTRATION

The section has been reorganized to provide dosing recommendations for patients beginning treatment (including test transmucosal dose and titration with BRIXADI (weekly), and for patients switching from other products (a dose conversion table with both formulations).

A recommendation to avoid the arm site until after steady state is reached is included because of the lower bioavailability at the arm site.

WARNINGS AND PRECAUTIONS
The Warnings and Precautions generally align with this section for other buprenorphine products. A note about latex allergy is added to 5.10, Hypersensitivity Reactions, because of a latex-derived needle cap.

CLINICAL TRIALS EXPERIENCE

During label negotiations, the Division proposed including Dr. Guerrieri's **Error! Reference source not found.**, which groups AEs by HLGT in order to identify events which may have been divided up among multiple similar PTs and therefore fallen below the usual 2% threshold for inclusion. However, Braeburn proposed to replace this with a table listing PTs occurring at 2% and the clinical team determined that the most important events were still described in this table. Therefore, Braeburn's table was substituted. A separate table of ISRs was added.

USE IN SPECIFIC POPULATIONS:
The Pharmacology/Toxicology review team updated the text to reflect appropriate exposure margins.

PHARMACODYNAMICS;
A revised description of the blockade study and revised figures, similar to those described in this review, have been included.

NONCLINICAL TOXICOLOGY
This section has been updated and revised based on the pharmacology/toxicology review.

CLINICAL STUDIES
The clinical studies section has been revised to present the blockade study data as described in the review, above. The description of the efficacy trial was revised (b) (4) (b) (4) to be consistent with current labeling guidelines. A claim that the CDF analysis showed superiority to SL BPN was caveated with this language:

> Based on the CDF of the percentage of negative opioid assessments, superiority was demonstrated with BRIXADI with statistical significance compared with SL BPN/NX. However, on the right hand side of the curves where patients were reporting mostly negative urines (80% or greater) there was little to no difference between BRIXADI and SL BPN/NX.

14 Postmarketing Recommendations

14.1 Risk Evaluation and Mitigation Strategies (REMS)

Braeburn did not submit a proposed Risk Evaluation and Mitigation Strategy with the original NDA submission. However, during the initial review cycle, Braeburn proposed a REMS that was reviewed by the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology. DRISK has determined that a REMS with elements to assure safe use (ETASU) is needed to ensure the benefits of CAM2038 outweigh its risks. The REMS should include restricted distribution with CAM2038 being dispensed only in healthcare settings that are certified.

The goal of the BRIXADI REMS is to mitigate the risk of serious harm or death that could result from intravenous self-administration by:

• Ensuring healthcare settings and pharmacies are certified and only dispense BRIXADI directly to a healthcare provider for administration by a healthcare professional.

The elements of the REMS are:

- Elements to assure safe use to ensure that health care settings and pharmacies that dispense BRIXADI are specially certified;
- An implementation system; and,
- A timetable for submission of assessments of the REMS.

Materials include:

Healthcare Setting and Pharmacy Enrollment Form

Communication Materials

- Dear Healthcare Provider REMS Letter
- Fact Sheet

Other Materials

- REMS Program Website

The content of these materials were largely agreed upon during the initial review cycle and final materials were submitted during this cycle.

14.2 Postmarketing Requirements (PMRs) and Commitments (PMCs)

A postmarketing trial will be required to evaluate whether Brixadi can safely be initiated at a full blocking dose (e.g., 24-32 mg weekly) without titration over the initial week of treatment. This is expected to be of great interest to clinicians who see patients in Emergency Department settings where treatment could be expeditiously initiated.

The following non-clinical post-marketing studies will also be required:

1. Conduct a study to evaluate elemental impurity levels in at least three batches of drug product on stability at 12 and 24 months or provide adequate extraction data to characterize the elemental impurities that could be leached from the container closure system using suitable solvents (e.g., nitric acid for elementals from glass).

2. Conduct a study to confirm, using validated methods, the identity of the unspecified (b) (4), the unidentified compound with relative retention time (RRT) of (b) (4) minutes, the unknown compound containing (b) (4) with RRT of (b) (4) min, and the unknown compound with (b) (4) with RRT of (b) (4) min that were detected in your leachable studies above the safety concern threshold of 5 mcg/day and the levels of the identified leachables (b) (4) (b) (4) Evaluate at least three batches of your to-be-marketed drug product at multiple timepoints over the course of your stability studies to identify trends in leachable levels over time. Base the final safety assessment on the

maximum predicted levels of leachables identified in individual batches to determine the safe level of exposure via the label-specified route of administration. Do not combine samples from different batches. Once chemical identification is confirmed for the unknown compounds, provide a toxicological risk assessment for each of these compounds and any other compounds detected at ≥5 mcg/day.

3. Conduct a fertility and early embryonic development study in female rats testing NMP administered via the subcutaneous route.

4. Conduct a pre- and post-natal development study in rats testing NMP administered via the subcutaneous route.

The following comment is intended as an additional nonclinical recommendation regardless of whether the NDA is approved or given a complete response action.

Your assessment to establish a mode of action for the NMP-induced tumorigenesis observed in the 18-month study in B6C3F1 mice did not include adequate information to clearly demonstrate that the findings are not human relevant. The information submitted was inadequate for us to conclude that the NMP-induced effects are potentially attributed entirely to a PPAR alpha-mediated mechanism as proposed. However, because a NOEL was established in the mouse study that provided an 8x safety margin, we acknowledge that the risk to humans may not be significant. Therefore, no additional data will be required, but the findings must be included in labeling. If you want to remove the language from labeling, you must submit a revised MOA assessment with additional data to bolster the weight of evidence to argue that the tumorigenesis is driven by a PPAR alpha-mediated pathway. Refer to Klaunig et al., PPAR alpha Agonist-Induced Rodent Tumors: Modes of Action and Human Relevance. Critical Reviews In toxicology 33(6): 655-780. 2003.

14.3 Division Director Comments

The review team has conducted a thorough review and analysis of the data submitted in support of this application over the original and second review cycles. While there are currently multiple sublingual buprenorphine products and two approved products that provide longer release of buprenorphine, one by insertion and one by injection, the importance of multiple options for the management of opioid use disorder cannot be underestimated. Individual differences in response to pharmacological therapy is common across the spectrum of human disease. As a chronic disease that requires long-term management, and potentially lifelong treatment, the availability of many options permits clinicians and patients to work together to determine the product or products that are most likely to achieve therapeutic success.

I concur with the data analyses conducted by the review team and with Dr. Winchell's analysis and conclusions.

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/

CELIA J WINCHELL
12/21/2018

SHARON H HERTZ
12/21/2018

Cross-Discipline Team Leader Review
And
Summary Basis for Approval

Date	1/18/2017
CDTL	Celia Winchell, M.D.
Division Director	Sharon Hertz, M.D.
NDA/BLA # and Supplement#	210136
Applicant	Braeburn Pharmaceuticals, Inc.
Date of Submission	7/19/2017
PDUFA Goal Date	1/19/2018
Proprietary Name	Brixadi (proposed)
Established or Proper Name	(buprenorphine extended-release) injection, for subcutaneous administration
Dosage Form(s)	Injection
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Applicant Proposed Dosing Regimen(s)	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.
Recommendation on Regulatory Action	*Complete Response*
Recommended Indication(s)/Population(s) (if applicable)	N/A
Recommended Dosing Regimen(s) (if applicable)	N/A

1 Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
CAM2038 (buprenorphine extended-release) injection, for subcutaneous administration use is intended for the treatment of moderate to severe opioid use disorder; the Weekly formulation is for initiating treatment in patients who have tolerated a test dose of a transmucosal buprenorphine-containing product; the Monthly formulation is for patients already in established treatment with another buprenorphine-containing product (including the Weekly formulation). Because of significant deficiencies in the chemistry, manufacturing, and controls portion of the application and the non-clinical toxicology portion of the application, and data quality concerns in the clinical portion of the application, the action will be a Complete Response. 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 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. 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. 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. 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. Similar to the recently-approved subcutaneous depot formulation of buprenorphine, Sublocade, CAM2038 has the potential to address several limitations of existing treatments.

The submitted clinical data show that the CAM2038 weekly formulation, in doses of 24 mg and 32 mg, is able to block subjective effects of a clinically-relevant dose of opioid agonist, more completely after the second weekly dose. Based on PK-PD analysis, the plasma levels delivered by the corresponding monthly doses are predicted to produce similar blockade. In a non-inferiority comparison to sublingual buprenorphine/naltrexone treatment, the effect of this blockade was shown to translate to clinical efficacy for a regimen beginning with weekly doses and transitioning to monthly doses, based the proportion of subjects whose drug use assessments met a pre-specified responder definition.

The safety profile of buprenorphine is well-characterized, and the overall CAM2038 safety profile appears similar. Analysis of dose-dependent adverse effects was hampered by the study design and the presentation of data. The size of the safety database for individual doses was limited (b) (4) (b) (4)

Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated in a patient still dependent on a full agonist at doses higher than studied in the clinical trial (16 mg weekly x 1). Additionally, there may be circumstances under which the rapid discontinuation or dose reduction of buprenorphine might be desirable for a given patient. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with CAM2038 for a period of time. Possibilities for surgical removal have not been explored. Patients developing intolerance to buprenorphine will require long-term monitoring by a health care professional.

Moderate-to-severe opioid use disorder is a serious and life-threatening condition and the need for more treatment options and greater access to treatment is clear. CAM2038, as a HCP-administered long-acting depot providing a sustained effective plasma level of buprenorphine over a prolonged period, has the potential to address some of the limitations of available options. However, product quality information is inadequate, and certain non-clinical safety issues remain to be addressed. The clinical experience with these formulations is

insufficient to assuage concerns, and, at present, the clinical conclusions are tentative pending confirmation with a corrected dataset.

If the application is approved on a subsequent review cycle, 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 by ensuring healthcare settings and pharmacies are certified and only dispense CAM2038 directly to a health care provider for administration by a healthcare provider.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Opioid use disorder or OUD, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), 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 over 2.1 million Americans aged 12 and over met criteria for either opioid abuse or dependence. - In 2015, the CDC reported that drug overdose was the leading cause of accidental death in the US, with 52,404 lethal drug overdoses in 2015. Of these, 20,101 overdose deaths were related to prescription pain relievers, and 12,990 overdose deaths were related to heroin. - 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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). o Behavioral treatment alone (individual or group counseling, self-help groups) is not effective for many patients. o 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 overdoses in patients and in their household contacts, including children. o 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. o 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. o 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	Buprenorphine depot injection would be a desirable addition to the therapeutic armamentarium. - Convenience of weekly or monthly vs daily dosing - Provides consistent buprenorphine levels sufficient to block effects of exogenous opioids - Improves adherence - Reduces potential for diversion, misuse, abuse and accidental pediatric exposure - No surgical procedure needed
Benefit	Evidence: - The opioid blockade study, Study HS-13-478,, demonstrated that after CAM2038 *weekly* injections of either 24 mg or 32 mg,, on average, subjective effects of both 6 mg and 18 mg doses of hydromorphone were blocked in non-treatment-seeking subjects with OUD, although significant variation was seen across subjects.	CAM2038 24 mg *weekly* and CAM2038 32 mg *weekly* are capable of blocking the subjective effects of a clinically-relevant dose of opioid agonist, and this blockade becomes longer-lasting after two weekly doses.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Dose-response analysis showed a decreasing number of outliers (unblocked responses) with increasing plasma levels, with very few outliers above a plasma level of 4 ng/ml. - The pivotal efficacy trial, Study HS-11-421 (N=428) demonstrated that patients treated with a regimen of 12 weeks on individually-determined doses of CAM2038 weekly, followed by 12 weeks on individually-determined doses of CAM2038 monthly had a response rate non-inferior to patients treated with sublingual buprenorphine/naltrexone tablets (and placebo injections). - CAM2038 is to 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. Uncertainties: - Significant concerns have been identified by multiple review disciplines during this review cycle which cast doubt on the ability to rely on these conclusions. Manufacturing issues call into question whether the product can be reliably manufactured, and whether the clinical trial supplies were themselves reliably manufactured. - The clinical datasets submitted did not include dose information and did not permit analyses by dose; moreover, these datasets were found to contain numerous errors which the Applicant has attributed to a problem with cross-check between to data collection systems. This can be resolved but the clinical analyses need to be verified with re-submitted data. - Exposure to some of the doses proposed for marketing is quite limited, and there is limited long-term experience with any dose or formulation. The formulations contain novel excipients and some deliver buprenorphine plasma levels exceeding that of the reference product. The clinical data is insufficient to fully characterize the safety of all of the proposed doses.	The effect of this blockade was shown to translate to clinical efficacy as demonstrated by comparable outcomes in patients treated with a regimen of weekly followed by monthly CAM2038 compared with patients treated with sublingual buprenorphine/naloxone. Taken together, and considering the established efficacy of the reference product, Subutex, these studies could provide substantial evidence of efficacy for CAM2038 in the treatment of moderate or severe OUD in patients who tolerate at least an initial test dose of buprenorphine. CAM2038 weekly is suitable for starting treatment, while CAM2038 monthly has been studied only in patients already in established treatment. However, these conclusions are tentative, pending the resolution of a variety of concerns about the manufacture of the products, as well as confirmation of the findings in a corrected clinical dataset.
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.	The safety profile of buprenorphine is well-characterized, and the overall safety profile of CAM2038 seems similar. However, the presentation of data did not permit characterization of dose-dependent adverse effects and the size of the safety database is not sufficient to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- 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 case was identified in the clinical development program - One death occurred in a CAM2038-treated patient, due to a car-vs-pedestrian traffic accident - Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with CAM2038 for a period of time. Possibilities for surgical removal have not been explored. Patients developing intolerance to buprenorphine effects will require long-term monitoring by a health care professional. - Buprenorphine itself can precipitate withdrawal if initiated in patients who are not yet in significant opioid withdrawal. For this reason, initial dosing is generally cautious and typically begins with a dose of 2 mg- 4 mg. The starting dose of CAM2038 in the efficacy trial was divided over several visits in the first week of treatment. Clinicians may be interested in initiating CAM2038 more expeditiously, for example, administering a single 24 mg or 32 mg weekly injection at the first visit, or administering a monthly dose at the first visit. It is not known if this can be accomplished safely. - CAM2038 forms a gel when injected. If patients obtain direct access to the product, there is a risk they may choose to attempt to inject the product intravenously. Notably, the consequences of intravenous injection of the contents of the pre-filled syringe are not known, it is anticipated that there is a risk of occlusion, tissue damage, and emboli.	characterize the safety of all the studied doses. Even if the data concerns can be resolved, there is clearly insufficient data to support approval of the 160 mg monthly dose. Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated too quickly in a patient still dependent on a full agonist. Additionally, there may be circumstances under which the rapid discontinuation or dose reduction of buprenorphine might be desirable for a given patient. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with CAM2038 for a period of time. It is not known whether there are possibilities for surgical removal. Patients developing intolerance to buprenorphine effects will require long-term monitoring by a health care professional. A REMS is required to ensure that CAM2038 is not distributed directly to patients, and is administered by a health care professional, to mitigate the risk of serious consequences should the product by administered intravenously.

2 Introduction

The application for CAM2038 includes two modified-release formulations 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 for the treatment of moderate to severe opioid use disorder (OUD) in adults. According to Braeburn, this delivery technology results in a liquid-to-gel phase transition that occurs when the lipid-based FC system is exposed to the subcutaneous (SC) tissue. The phase transition from liquid to gel proceeds from the periphery of the FC injectable towards the center of the product by absorption of minute quantities of water. The injection of CAM2038 into SC tissue results in an immediate and spontaneous formation of a matrix providing release over the designated period in vivo. This product is available in weekly and monthly formulations, each of which contains different doses and excipients.

CAM2038 weekly formulations in the 24 mg/week and 32 mg/week provide sustained plasma levels of buprenorphine intended to block the effects of exogenous opioids over 7 days. Based on pharmacokinetic data, the CAM2038 monthly formulations are predicted to block exogenous opioids for at least 28 days. The weekly formulation is intended for the treatment of moderate to severe opioid use disorder (OUD) in patients who have tolerated at least a test dose of transmucosal buprenorphine, and the monthly product is envisioned for more stable patients transferring from established buprenorphine treatment. The products should be used as part of a complete treatment plan to include counselling and psychosocial support.

Because of the potential for a depot product to mitigate risks of abuse, diversion, and accidental pediatric exposure associated with oral transmucosal buprenorphine, the application was granted a priority review.

Although buprenorphine products have been approved for the treatment of opioid dependence, there were no monthly depot formulations approved at the time this application was submitted. To ensure that the amount of buprenorphine provided and the proposed dosing interval were suitable to support the proposed indication, the Applicant was required to support a finding of efficacy for this product with two adequate and well-controlled clinical trials or one adequate and well-controlled clinical trial and a human behavioral pharmacology study demonstrating the ability of the product to block the effects of exogenous opioids (blockade study). In this submission, the Applicant has provided efficacy data from a blockade study, and from a single, double-blind, active-controlled trial in patients newly-entering buprenorphine treatment demonstrating that the blockade effect translates to an effect on illicit drug use. Additionally, safety experience from an open-label trial and from the Phase 1 program was provided.

The Applicant's submission included safety data from 729 subjects who were exposed to at least one injection of either CAM2038 weekly or CAM2038 monthly. The safety analysis population comprised 594 patients with OUD, of whom 531 received at least one injection of CAM2038 weekly and 346 received at least one injection of CAM2038 monthly. The Sponsor tabulates that 68 patients were exposed to the weekly formulation for 24 weeks or longer, 116

were exposed to the monthly formulation for 24 weeks or longer, and 299 patients had a cumulative exposure of a combination of the two formulations that was at least 24 weeks in duration. The number of patients with at least 48 weeks of exposure was 132 (combination of formulations), with 42 exposed to the weekly formulation and 45 exposed to the monthly formulation for at least 48 weeks. Exposure by dose is illustrated in Table 14 and Table 15, which highlight that the number of patients with at least 48 weeks exposure is <10 for every individual dose, and limited to a single patient for three of the proposed doses.

The steady-state exposure associated with some of the doses/formulations exceeds that associated with the maximum recommended dose of Subutex, 24 mg/day. Labeled risks of oral transmucosal buprenorphine for opioid dependence include hepatic effects, possible effects on cardiac conduction, and allergic reactions, as well as the possibility of overdose particularly when combined with other depressants. The overall safety experience with all doses/formulations of CAM2038 pooled is consistent with the known safety profile of buprenorphine. The experience of patients exposed to these higher doses would be of particular interest, but the submitted data did not facilitate examination of the safety experience by dose.

One risk associated with CAM2038 that differentiates it from the transmucosal formulations is the concern that serious consequences could ensue if the product were injected intravenously. A Risk Mitigation and Evaluation Strategy (REMS) is proposed to ensure that the product is administered appropriately.

A number of deficiencies have been identified by the review team which preclude approval. These include a number of product quality issues, described below. In addition, during the course of the review, the clinical and statistical review teams discovered issues calling into question the reliability of the submitted analytic datasets..

3 Background

Buprenorphine is a partial agonist at the μ-opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain, and two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence[1]. Three other transmucosal formulations and a six-month, surgically-placed implant have subsequently been approved for opioid dependence, as well as two transdermal products and one transmucosal product for pain. 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 film during 2016. Primary care physicians accounted for 39% of dispensed prescriptions, followed by psychiatrists (21%), osteopaths (14%), emergency physicians (4%) and anesthesiologists (4%). Recently, the authority to prescribe buprenorphine for office-based treatment of OUD was expanded to include Nurse Practitioners

[1] Subutex, buprenorphine sublingual tablets (Reckitt Benckiser (now Indivior) NDA 20732) and Suboxone, buprenorphine/naloxone sublingual tablets (Reckitt Benckiser (now Indivior) 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.

and Physician's Assistants, so the distribution of specialties may be expected to change in the future.

Buprenorphine 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. First, buprenorphine had been shown to have a ceiling effect for respiratory depression, suggesting that it would be "impossible to overdose" on buprenorphine. Second, initial clinical evaluations of buprenorphine's ability to produce physical dependence led to the conclusion that physical dependence to buprenorphine, if it developed, was associated with a mild withdrawal syndrome. Third, it was expected to have limited attractiveness as a drug of abuse relative to full agonists.[2]

Buprenorphine was expected to have limited abuse potential for two reasons. First, due to its partial agonist properties, the euphorigenic effects of buprenorphine were 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. Second, 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 buprenorphine. These features were expected to limit its attractiveness as a drug of abuse for patients and for illicit use.

In addition to the improved safety profile, at sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, deterring abuse of opioids by buprenorphine-maintained patients.

Unfortunately, despite these features, buprenorphine 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 a number of cases of accidental poisonings of small children. Therefore, a depot injection which would be difficult to divert or abuse, and would be less likely to be accidentally ingested by small 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 in order to experience the effects of their opioids of choice.

Comparison of exposures after CAM2038 doses to exposures after sublingual buprenorphine demonstrate that, at steady-state (4th injection), CAM2038 weekly and monthly deliver plasma concentrations ($C_{avg,ss}$) that are higher than the corresponding dose of sublingual buprenorphine in Braeburn's proposed conversion scheme.. (SeeTable 4 Summary of steady-state PK parameters of buprenorphine after subcutaneous buttock injections of CAM2038 weekly (q1w) and CAM2038 monthly (q4w) and SL administration of SUBUTEX, page 29.))

[2] Many of these beliefs have subsequently been found to have been erroneous, or at least overstated, but these were the generally-held views about buprenorphine's pharmacology at the time it was being developed.

3.1 Clinical Development of CAM2038

The clinical development of CAM20388 was undertaken with advice from the Division. At pre-IND and advice meetings, options for populations (e.g., new entrants to treatment vs. established, stable patients) were discussed, along with the type and number of studies needed to support approval. Braeburn elected to undertake a program that they hoped would provide support for multiple doses of two different formulations, in patients both new to buprenorphine treatment and in patients already in established treatment. They combined doses, formulations, and patient populations in an open-label study, and conducted a controlled study in patients new to treatment. We agreed that, though not optimal, with sufficiently persuasive results, a claim for treatment of opioid use disorder could be supported by a study showing that the product yielded a plasma level sufficient to completely block (not just attenuate) the effects of a clinically-relevant dose of an opioid agonist, taken together with a controlled study demonstrating that the blockade effect translated to a clinically-relevant change in drug-use behavior over a six-month treatment period.

The blockade of subjective response to opioids is one of the ways in which buprenorphine treatment exerts its effect, through the behavioral principle of extinction. When a behavior is not reinforced, it is less likely to occur. Illicit opioid use is reinforced by the subjective effects of the drug. Blockade is particularly important early in treatment when a "slip" (isolated incident of illicit use) could turn into a "relapse" (return to out-of-control use). By preventing the reinforcing effects of the "slip," a treatment that provides a blockade effect can help the patient discontinue the drug self-administration behavior. Some stable patients or highly-motivated patients may not require the blockade effect for effective treatment long-term.

Although the Application rests in part on cross-referenced data on the efficacy of Subutex, the nature of the product is sufficiently different from Subutex that two studies were needed to support approval. The blockade study was accepted in lieu of a second efficacy study[3]. Both the blockade study and the controlled efficacy trial are considered necessary for approval.

3.1.1 Background Related to Efficacy Endpoints and Study Design

There is currently no standard approach to clinical trials in this therapeutic area.

Previously-approved products were supported by a variety of studies with treatment as long as 40 weeks, and various analytic approaches were applied in evaluating the results. All focused the assessment of efficacy on the patterns of on-treatment drug use, primarily through frequent collection of urine toxicology samples.

Drug use patterns are a convenient surrogate, but many patients, families, and clinicians may be interested in study designs that establish whether a treatment has an impact on other aspects of opioid use disorder and its effects on how patients feel, function, or survive. Historically, direct clinical measures have always been welcome, but prove challenging to incorporate into clinical trials. For example, although mortality and viral seroconversion are outcomes of interest, both occur at very low rates in clinical trials and would require much larger sample

[3] As originally envisioned, the blockade study was to have preceded the clinical efficacy study and should have been used to select doses for the clinical efficacy study.

sizes to detect an effect than studies with drug use patterns as the primary endpoint. A patient-reported outcome assessment could be developed using appropriate methods, with input from patients and family members to determine the most concerning symptoms/experiences associated with OUD, but such an instrument does not currently exist. Retention in treatment, *per se*, is not recommended as a stand-alone endpoint. Many features of study design can produce incentives to remain "in treatment" without accruing significant clinical improvement.

For lack of available direct clinical measures, analysis of the pattern of drug use remains the primary approach to assessing treatment response. The Division has taken the position that analyses focused on group means (such as mean percent negative urine tests), which have been used in some prior studies, are not the most clinically meaningful approach because they do not reflect the experience of individual patients, who might range from complete responders to complete non-responders. In discussing how individual response should be assessed, there has been considerable debate over whether endpoints focused on patients attaining complete abstinence from illicit drug use are realistic, and whether they are necessary to ensure that the drug yields clinical benefit. As described below, the responder definition used in this study is not an "abstinence" endpoint.

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 illicit drug use episodes. These include:

- Less frequent urine toxicology tests

  Historically, studies of opioid dependence treatment have incorporated thrice-weekly urine sampling. This frequency was identified as providing the best balance between detecting all use and avoiding false-positive tests due to "carry-over" positives, based on the time window of detection for heroin, which was the most commonly-used opioid in populations being studied when this approach was established. Additionally, this approach was not considered unduly burdensome because the treatments being evaluated were agonists that were administered in-clinic on a daily basis.

  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. 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.

  Braeburn's clinical efficacy study employed weekly, *scheduled*, urine testing during the first 12 weeks of treatment. It is understood that weekly sampling may miss some occasions of use, and that scheduled testing may allow patients to deliberately avoid detection of use through timing their episodes of drug use. The second 12 weeks, during which patients received monthly injections, employed only monthly scheduled urine testing. To augment this, the protocol also required the patients be called in for random urine testing on three occasions, yielding only six assessments in the final 12 weeks of the study. Thus, even if the definition of response is 100% negative samples, patients who are

continue to have some episodes of use may be adjudicated as successful, because some use will not be detected. We accept this for reasons of feasibility.

- A responder definition that allows a few missing or positive samples

  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. Braeburn's responder definition required patients to meet separate response definitions in phase 1 *and* phase 2, which together required only 8 negative samples.

  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 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

- The incorporation of a "grace period" (assessments at the beginning of treatment which are not considered in the analysis) because patients may not respond immediately. Braeburn's responder definition included grace periods in each phase of the study.

- The use of a "continuous responder" analysis.

  One approach that the Division has proposed is to perform an analysis that considers the full range of responder definitions, from use detected at zero visits to use detected at all visits, but to emphasize the effect of the drug on promoting a higher proportion of negative assessments. This approach, the continuous responder curve, or the cumulative distribution function (CDF) of drug use assessments, was employed in this program. The continuous responder curve gives an overall picture of the drug's effect on drug use behavior. Pairing this analysis with a responder rate comparison ensures that the effect is of a magnitude that has clinical meaningfulness.

In Braeburn's study, there were weekly, scheduled, samples collected over the first twelve weeks (at injection visits), and monthly, scheduled samples at injection visits over the second twelve weeks. Three additional random visits for urine testing were to occur during the latter phase. The primary analysis was a responder analysis, and CDF of patient responses was analyzed as secondary endpoint. The responder definition agreed to, described above, was simply a pragmatic choice, based on a definition used in published literature. The responder definition was intended to allow for independent assessment of response to both the weekly and monthly phases of treatment, and to strike a balance between patient burden (to minimize missing data) and the ability to detect episodes of use. Clearly, given the schedule of sampling, patients classified as responders may have a number of undetected occasions 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.

There is also no standard approach to studies intended to demonstrate that a product can block the effects of exogenously-administered opioids. The ability of buprenorphine to attenuate the reinforcing effects of other opioids has been studied in various ways over the past decades, but at the time this development program was initiated, studies in the literature did not support a consistent conclusion about the relationship between plasma buprenorphine levels, opioid receptor occupancy, and blockade of clinically relevant doses of opioids of abuse. Heterogeneity in the challenge doses used, the interpretation of the term "blockade" (to mean either any detectable attenuation of agonist effect, or complete prevention of agonist effect), and in the doses, route, and timing of the buprenorphine administration complicated interpretation of literature findings. However, the Division's review of the literature suggested that clinically-relevant doses of opioids of abuse may require fairly high doses of buprenorphine (and by extension, plasma levels) for full blockade, and that 85% receptor occupancy or better would be a reasonable target, to allow room for inter-individual variation, given that the shape of the curve relating plasma level to receptor occupancy in published studies at that time was exponential. Our recommendation was to target exposure of approximately 3 ng/ml, and to establish in a behavioral pharmacology trial that the selected dose was capable of blocking the reinforcing effects of a clinically-relevant dose of a full agonist.

The design of the blockade study was based on designs used to evaluate human abuse liability, and was developed with input from the Controlled Substances Staff and supporting biostatistical reviewers. A broadly similar design was used to support approval of Vivitrol (depot naltrexone, Alkermes NDA 21-897) for treatment of opioid dependence.

3.2 Safety Concerns Related to Formulation

The injection of CAM2038 into SC tissue results in an immediate and spontaneous formation of a gel matrix providing release over the designated period in vivo. Individuals with OUD are known to use a variety of opioids by unintended routes, sometimes with severe consequences. There are limited data to inform what could occur should someone attempt to misuse the CAM2038 intravenously. In a nonGLP rat intravenous toxicity study in three males, administration of the drug to the tail vein resulted in occlusion of the vessel to the base of the tail with no clear evidence of distribution to other tissues. Lungs, however, could not be evaluated as the animals were sacrificed via CO_2 which results in lung pathology itself. The data suggest that if the drug product were to be administered intravenously, it will either gel rapidly and potentially block the injected vessel as it apparently did in the rat tail vein, or if the injected vein is larger and the product does not gel quickly enough, it could likely result in a lung emboli or eventually be lodged in other small capillaries. This raised a safety concern about the possible consequences of this type of misuse, which could involve occlusion, tissue damage, or possibly embolus.

3.3 Legal and Regulatory Issues Constraining Buprenorphine Treatment

Buprenorphine is a Schedule III Controlled Substance and physicians prescribing buprenorphine must comply with the relevant aspects of the Controlled Substances Act. In

addition, the provision of agonist treatment of opioid addiction is governed by certain legal requirements. Unlike methadone, buprenorphine may be prescribed by physicians meeting certain requirements.

Methadone treatment of opioid addiction is delivered in a closed distribution system (opioid treatment programs, OTPs) that originally required special licensing by both Federal and State authorities, under the Narcotic Addict Treatment Act of 1974. The current regulatory system is accreditation-based, but OTPs must still comply with specific regulations that pertain to the way clinics are run, the credentials of staff, and the delivery of care. To receive methadone maintenance, patients are required to attend an OTP, usually on a daily basis, with the possibility of earning the privilege of taking home doses as their treatment stability increases. Buprenorphine may also be administered to patients at OTPs.

Buprenorphine treatment is covered in Title XXXV of the Children's Health Act of 2000 (P.L. 106-310), which provides a "Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment of Opioid-Dependent Patients." This part of the law is known as the Drug Addiction Treatment Act of 2000 (DATA 2000). Under the provisions of DATA 2000, qualifying physicians may obtain a waiver from the special registration requirements in the Narcotic Addict Treatment Act of 1974, and its enabling regulations, to treat opioid addiction with Schedule III, IV, and V opioid medications that have been specifically approved by FDA for that indication, and to prescribe and/or dispense these medications in treatment settings other than licensed OTPs, including in office-based settings. The Comprehensive Addiction and Recovery Act (CARA) of 2016 (P.L. 114-198) extended the privilege of prescribing buprenorphine in office-based settings to qualifying nurse practitioners (NPs) and physician assistants (PAs) until Oct. 1, 2021. At present, the only products covered by DATA 2000 (i.e., Schedule III-IV, approved for the indication) are buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets and films.

To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of opioid addiction or have certain other qualifications defined in the legislation (e.g., clinical research experience with the treatment medication, certification in addiction medicine) and must attest that they can provide or refer patients to necessary, concurrent psychosocial services. The 8-hour training courses are provided by various physician organizations (e.g. APA) and delivered in-person, in web-based formats, or through other mechanisms. Physicians who obtain DATA 2000 waivers may treat opioid addiction with products covered by the law in any appropriate clinical settings in which they are credentialed to practice medicine. Specific requirements for non-physician HCPs are stipulated in the CARA legislation. Under the DATA 2000, the number of patients a provider may treat with buprenorphine is capped at an "applicable number," initially 30 and then increasing as the provider gains experience. The text of the legislation also notes that "The Secretary may exclude from the applicable number patients to whom such drugs or combinations of drugs are directly administered by the qualifying practitioner in the office setting." This implies that the Secretary could determine that the number of patients a given provider may treat with CAM2038 is not limited.

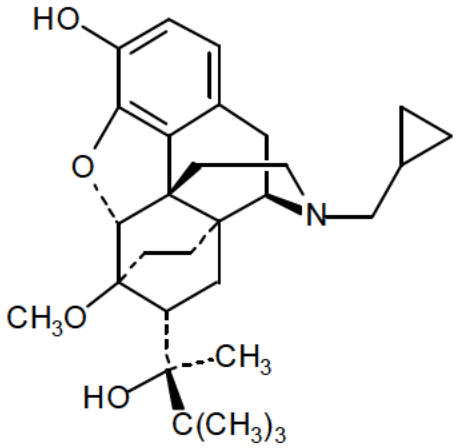
The Applicant has been advised by DEA that both the physician who prescribes CAM 2038 must be DATA-waived, or practicing in an OTP where DATA waivers are not required.

4 Product Quality

The CAM2038 FluidCrystal subcutaneous injection depot drug product is a yellowish to yellow clear liquid which is [redacted] (b) (4) 1 mL long clear glass syringes with grey plungers. It is a lipid-based parenteral (subcutaneous injection) extended-release product (once weekly or once monthly dosing) based on the proprietary FluidCrystal (hereinafter denoted FC) injection depot technology.

The active ingredient in CAM 2038 is buprenorphine free base, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist.

The molecular weight of buprenorphine free base is 467.6, and its molecular formula is $C_{29}H_{41}NO_4$. Chemically, buprenorphine is (2S)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol. The structural formula is:



The CAM2038 q1w (weekly) solution consists of 50 mg buprenorphine base (BUP)/mL, 10% w/w ethanol (EtOH) and Soybean Phosphatidylcholine (SPC)/Glycerol Dioleate (GDO) in the weight ratio 50/50 to final volume. The CAM2038 q4w (monthly) solution consists of 356 mg buprenorphine base (BUP)/mL, 30% w/w N-methyl-2-pyrrolidone (NMP), and SPC/GDO in the weight ratio 40/60 to the final volume. The injection products utilizing the lipid-based formulations are low viscosity liquids. When the product is injected into the subcutaneous tissue, the formulation absorbs interstitial aqueous body fluid and transforms the liquid to a highly viscous gel. The compositions are shown in the tables below.

Table 1 Composition of CAM2038 q1w Drug Product (50 mg/mL)

Component	Standard	Function	Composition (mg) per dose			
			8 mg/ 0.16	16 mg/ 0.32	24 mg/ 0.48	32 mg/ 0.64 mL
Buprenorphine Base (BUP)	Ph. Eur.	Active ingredient	8	16	24	32
Ethanol Anhydrous (Dehydrated alcohol) (EtOH)	USP	(b) (4	(b) (4			
Soybean Phosphatidylcholine (SPC)	In-house					
Glycerol Dioleate (GDO)	In-house					
Total weight (mg) for all components per dose	Not Applicable	Not Applicable				

Table 2 Composition of CAM2038 q4w Drug Product (356 mg/mL)

Component	Standard	Function	Composition (mg) per dose			
			64 mg/ 0.18 mL	96 mg/ 0.27 mL	128 mg/ 0.36 mL	(b) (4)
Buprenorphine Base (BUP)	Ph. Eur.	Active ingredient	64	96	128	
N-Methyl-2-Pyrrolidone (NMP)	USP	(b) (4				
Soybean Phosphatidylcholine (SPC)	In-house					
Glycerol Dioleate (GDO)	In-house					
Total weight (mg) for all components per dose	Not Applicable	Not Applicable				

CAM2038 Weekly and Monthly formulations are drug/device combination products as defined under 21 CFR 3.2(e)(1) and produced as single entities, i.e., a pre-filled syringe,

presented in a sterile pre-filled syringe assembly and a pre-packaged sterile needle for injection.

Figure 1

No issues were identified in the manufacturing of the drug substance. However, concerns were noted in many aspects of the manufacture of the finished drug product. These included concerns about sterility, concerns about a lack of specification for factors affecting dissolution, and significant concerns based on inspectional findings at the site responsible for testing of the drug product, calling into question the validity of the data supporting the application. Excerpts from Dr. Ciby Abraham's executive summary are shown below and the proposed deficiency language from the CMC review team are included in an Appendix, Section 15.

Regarding sterility:

(b) (4) Without additional information on the testing procedure or an alternative test method, the microbiology group cannot assess the assurance of sterility of the product throughout its shelf life.

Regarding specifications to ensure consistent drug delivery on release and stability:

According to the applicant, (b) (4) CAM2038 q1w and CAM2038 q4w drug product. The applicant provides release and stability data for the low viscous liquid but only performs dissolution testing for the high viscous gel. Though the applicant clearly mentions that the (b) (4) the applicant does not provide an assay or any controls (b) (4) for release or stability. The applicant references DMF# (b) (4) but the DMF is currently deficient for this application. The biopharmaceutics team reviewed the dissolution method and found the method and

results to be adequate to support the release of the 1 week and 4 week formulations. This assessment by the biopharmaceutics group of the dissolution method and results is critical for CMC (b) (4)

Regarding analytical testing facility issues:

In a recent inspection on 11/6/2017 of Pharmaceutics International, Inc. (Pii), FEI# 1000513101, the Office of Regulatory Affairs (ORA) investigators inspected the testing laboratory of the drug product and issued a 483 and recommended a withhold to the site for this application. The withhold recommendation from ORA was confirmed by the Office of Process and Facilities. One of the most concerning observations that were found at the site directly related to the dissolution method and results. A summary of the facility findings for the dissolution method and results are summarized below by the facility reviewer, Dr. Derek Smith:

(b) (4)

With these unresolved issues for the dissolution method and results, the biopharmaceutics and facilities group cannot recommend approval until Pii resolves their issues. Other issues were observed at the testing site which is documented in Dr. Derek Smith's facility review. The resolution of these issues and re-inspection of the site will be necessary to recommend approval. In addition, CDRH-OC recommends withhold of the firm for not complying with 21 CFR 820 to meet the requirements of 21 CFR Part 4. Their review was placed in DARRTS on 12/22/2017.

Additional concerns:

Other CMC deficiencies have been identified. The applicant did not provide an adequate extractables and leachables study report. The applicant has not provided freeze/thaw data for the drug product and no stability data on the upright and inverted storage conditions of the product. It is also not clear if the dose delivered testing is representative of the dose

delivered to the patient. The specification for the ethanol content for the weekly formulation is wide and needs to be tightened.

CMC recommends a complete response until all deficiencies are resolved.

5 Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review was conducted by Gary Bond, Ph.D., and Elizabeth Bolan, Ph.D. The text below is largely excerpted from their review.

From a nonclinical pharmacology toxicology perspective, there are inadequate data to support an approval recommendation at this time. Specifically, the Applicant has not provided an adequate extractable leachable evaluation of the container closure system (see below).

There are no safety concerns with the drug substance or drug product specifications.

In terms of general toxicity, the Applicant is relying upon the Agency previous finding of safety of Subutex to address general toxicity of buprenorphine. As noted in the clinical pharmacology review, the 128 mg and 160 mg doses (b) (4) result in exposures to buprenorphine that exceed the referenced drug product Subutex. In general, this would require general toxicity studies in two species (b) (4) The 9-month dog study with the clinical formulation discussed below does provide general toxicity data for buprenorphine in the nonrodent species. The Applicant did not provide a chronic rat toxicology study for buprenorphine. The Applicant cited the fact that the referenced drug product Subutex contains long-term carcinogenicity data in mice and rats. The Division has concluded that, for doses for which there are adequate clinical data, general toxicity in two species are not necessary (b) (4)

As with any depot formulation, the Applicant was required to address the fate of the injected materials. Collectively the data suggest that the depot can last up to 30 days or longer and local tissue reactions are consistent with a foreign body reaction and evidence that the body is attempting to clear the material from the injection site. Injection site reactions included swelling and thickening of the skin with both drug products and drug product vehicles. The swelling was the result of both the remaining depot material as well as the expected local tissue response to the depot (inflammatory cell infiltrates).

The pharmacology/toxicology review also focused on the data submitted to support the novel excipients, NMP and GDO. Braeburn submitted PK studies in the rat that demonstrated that SC injection of GDO resulted in no detectable levels of GDO in the plasma over background levels. They also submitted a chronic toxicology study in the rat testing GDO and leveraged the findings in the 9-month dog study with CAM2038 q4w to address chronic toxicity. The results suggest expected local tissue reactions and evidence of systemic inflammation, also not unexpected for a lipid. Adequate NOAELs were established to support safety. The Applicant conducted the full genetic toxicology battery of studies with GDO which indicated no risk for genotoxicity.

To address the standard reproductive and developmental toxicology study requirements, Braeburn submitted published literature testing diacyl glycerol (DAG) oil containing significant levels of GDO to address fertility and early embryonic development and embryofetal development studies in the rat and conducted a pre- and post-natal study on GDO. No embryofetal development studies in the rabbit were completed or submitted. Adequate NOAELs were established to support safety. Finally, the Applicant cited published carcinogenicity studies with DAG oil to address the requirement for carcinogenicity of GDO. These data suggest that the risk of carcinogenicity of DAG is no different than the risk of triglycerides. However, Braeburn had been advised that the literature data described above would be adequate to support the new excipient only if data could be provided document that the DAG oil studies contained adequate levels of GDO in the material tested, and provided adequate coverage for the safety of the GDO administered, these data. Braeburn did not specifically address this requirement. Further, no rabbit embryo-fetal development (EFD) data, as required in the FDA guidance for new excipient safety testing, were submitted. An EFD study in the rabbit is required unless the Applicant can provide adequate justification that systemic levels of GDO and metabolites are not elevated over baseline in humans.

Regarding the excipient NMP, the Applicant submitted a 9-month dog study that contained NMP in the formulation tested, along with a literature review to support the safety of NMP in this drug product formulation. NOAELs that established reasonable safety margins were demonstrated for this product suggesting limited concern. NMP was deemed overall negative in terms of genotoxic potential. Published carcinogenicity studies with NMP do suggest the potential for NMP-induced liver tumors in mice which may not be relevant to human risk assessment; however, a mode of action assessment was not provided to permit dismissal of the findings in the study as not relevant to human risk assessment. These findings should be included in labeling, unless demonstrated to be irrelevant to human risk via a mode of action assessment.

The Applicant submitted published and unpublished reproductive and developmental studies with NMP in lieu of new studies. The published studies employed the oral (gavage/dietary) or inhalation routes and did not test the clinical route of administration. These studies indicate that NMP can have adverse effects on male and female fertility and fetal development. The pharmacology-toxicology team noted that definitive studies via the SC route are warranted..

Deficiencies precluding approval

Importantly, inadequate information was provided to justify the safety of the container closure system, The components of the container closure system that contact the drug product primarily include a (b) (4) glass syringe with a (b) (4) rubber plunger stopper. Importantly, the drug products include (b) (4)

The submitted extraction studies with the container closure system were not performed appropriately to fully characterize the potential leachables profile of the container closure system. Specifically,

At the time of filing, the pharmacology/toxicology review team communicated concerns about the extractables and leachables evaluations, and Braeburn proposed to conduct new extractables and leachables studies and provide these data during the review cycle. New (b) (4) extraction data and leachables data from drug product on stability for 24 months were submitted on 12/14/2017. However, the additional (b) (4) extraction data and leachables data from interim stability samples have not yet been submitted, and some of these data are not expected until at least February of 2018. Based on the data submitted in the NDA, the lack of adequate data on the container closure system precludes approval of the application.

6 Clinical Pharmacology

The following summary of clinical pharmacology is based on the Clinical Pharmacology review by Suresh Narahansetti, PhD, and language from the Division's proposed labeling. In the text below, the weekly formulation is sometimes referred to as CAM2038 q1w, and the monthly formulation as CAM2038 q4w. Much of the general text about buprenorphine is identical to language in the Subutex label. Text specific to CAM2038 is based on Indivior's development program.

The pharmacokinetics of buprenorphine following SC injection of CAM2038 was investigated in 5 clinical studies, including 2 studies in healthy volunteers under naltrexone (NTX) blockade and 3 studies in patients with opioid dependence as described in Table 3.

Table 3 Overview clinical pharmacology studies of CAM2038 q1w and CAM2038 q4w

Study	Study Description	Population (No. of subjects)	q1w (SC)	q4w (SC)
HS-11-426	Open-label, randomized, PK, BA, and safety study assessing 3 different SC doses of q1w versus IV and SL BPN	Healthy, N=56	- 8 mg (single dose) - 16 mg (single dose) - 32 mg (single dose)	NA
HS-13-487	Randomized, open-label, single- and repeated-dose PK, BA, and safety study with q1w and q4w versus IV and SL BPN	Healthy, N=79	- 16 mg (4 repeated doses)	- 64 mg (single dose) - 96 mg (single dose) - 128 mg (single dose) - 192 mg (single dose)
HS-07-307[$]	Single-dose, dose-escalation PK, PD and safety study investigating 4 different doses of q1w	Patients with OUD, N=41	- 7.5 mg (single dose) - 15 mg (single dose) - 22.5 mg (single dose) - 30 mg (single dose)	NA
HS-15-549	Open-label, partially randomized PK, efficacy and safety study	Patients with OUD and a history of moderate to severe chronic non-cancer pain, N=65	- 32 mg (7 repeated doses) 3 weekly doses in the buttock followed by 4 weekly doses in the buttock, abdomen, thigh, and back of upper arm. Also, open-label safety extension including 6 additional weekly SC injections of 32 mg q1w in the buttock.	- 128 mg (4 repeated doses in the buttock) - 160 mg (4 repeated doses in the buttock)
HS-13-478*	Randomized, double-blind, repeated-dose, PK, efficacy and safety study	Patients with OUD, N=47	- 24 mg (2 repeated doses) - 32 mg (2 repeated doses)	NA

[$] In study HS-07-307, the dose used for CAM2038 q1w (7.5 mg, 15 mg, 22.5 mg and 30 mg) were not intended clinical dose of CAM2038 q1w. Hence this study was not reviewed.

Note that not all of the proposed doses have been studied in both single-dose and steady-state conditions. Although Braeburn used population PK for deriving the PK parameters of CAM2038 q1w, CAM2038 q4w, and SL Subutex, the Clinical Pharmacology review team reviewed PK data from clinical pharmacology studies for most of the doses of these products for comparison of PK parameters between CAM2038 and SL Subutex (especially for the highest doses). Some cross-study comparisons were required to develop a full picture of the relative exposures. Cross-study comparisons are typically considered less reliable than within-study comparisons, but the program did not include all the necessary within-study comparisons.

A study conducted to determine whether PK differed when the product was injected into different anatomical locations (thigh, buttock, abdomen, or arm) was conducted after the

clinical efficacy studies had already been initiated using a variety of sites. This study supported the use of the thigh, buttock, and abdomen, but not the arm. No PK sampling was included in the clinical efficacy study.

No studies were performed to evaluate whether lower doses of either formulation could be combined to yield exposures equivalent to the mathematical sum of the doses (e.g., 2 x 16 mg weekly formulation compared to 1 x 32 mg weekly formulation). At present, the label cautions against combining doses in this fashion. Instances of investigators making such substitutions were recorded in the clinical trials and may be predicted to occur after marketing.

The text in Arial font below is based on the Division's recommended labeling language, with additional information/comments in Times New Roman:

Absorption

Following single doses, the buprenorphine Cmax and AUCinf increase dose-proportionally for CAM2038 weekly and CAM2038 monthly.

The steady-state pharmacokinetics (PK) of buprenorphine following CAM2038 weekly, CAM2038 monthly, and their comparison to sublingual Subutex across three studies are shown in Table 4. In these studies, CAM2038 weekly was administered for 4 to 7 weekly doses, CAM2038 monthly was administered for 4 monthly doses, and SUBUTEX was administered for 7 daily doses.

After CAM2038 subcutaneous injections, the buprenorphine plasma concentration increases with a median time to maximum plasma concentration (T_{max}) of about 24 hours for the weekly product and 10-24 hours for the monthly product. Based on trough levels after each dose, steady-state exposure is reached at the fourth weekly or monthly dose.

After four repeated doses of CAM2038 weekly (16 mg) AUC_{τ} (0-7d), Cmax and Ctrough values are ~40% higher compared to the first dose. Based on cross-study comparisons, four repeated doses of CAM2038 monthly (128 mg) results in 68%, 65%, and 124% higher AUC_{τ} (0-28d), Cmax and Ctrough values, respectively compared to the first dose.

Table 4 Summary of steady-state PK parameters of buprenorphine after subcutaneous buttock injections of CAM2038 weekly (q1w) and CAM2038 monthly (q4w) and SL administration of SUBUTEX

Drug product dose			Cav (ng/mL)			Cmax,ss (ng/mL)			Ctrougha (ng/mL)		
SL BPN	q1w	q4w	SL BPN *	q1w	q4w	SL BPN *	q1w	q4w	SL BPN *	q1w	q4w
8 mg	16 mg	64 mg	1.2	2.1	2.0 $	4.7	4.3	4.0 $	0.7	0.8	1.3 $
16 mg	24 mg	96 mg	1.8	2.9 $	2.9 $	6.5	5.5 $	6.0 $	1.0	1.4 $	2.0 $
24 mg	32 mg	128 mg	2.5	4.2	3.9	8.2	6.9	11.1	1.4	2.6	2.1

* Average value of two studies
$ Simulated
a C168h for CAM2038 q1w, C28d for CAM2038 q4w and C24h for Subutex

Injection Site Effect on PK of CAM2038

Following multiple dose subcutaneous injections of 32 mg CAM2038 weekly at different injection sites, injections into abdomen, thigh, and buttock result in comparable PK exposure.

The clinical pharmacology review team conducted a bioequivalence assessment (geometric mean ratios and 90% CI) between different injection sites using buttocks as a reference. Of the three sites, compared to the buttock, the trough levels from upper arm site (1.3.6a) was lower and it also failed to meet the bioequivalence criteria for 80 to 125%. Although Cmax and AUC between different injection sites are important, the trough levels are considered more important for the efficacy of this product because the trough concentration is associated with the lowest percentage of mu-receptor occupancy during the entire dosing interval. Hence, the upper arm is not recommended as an injection site for this product.

Starting Dose Proposed in Sponsor's Labeling

Although the clinical studies were performed with an initial dose of 16 mg CAM2038 weekly, with 1-2 additional 8 mg doses at subsequent visits over the first week, Braeburn proposed that treatment could be initiated with a single 24 mg weekly dose at the first visit. The Clinical Pharmacology team modeled the concentration-time profiles of these two regimens for comparison. The exposure (AUC) and duration of exposure of the split doses (16 mg weekly given on Day 1 followed by 8 mg weekly given on Day 4; total 24 mg) appears higher compared to the single 24 mg weekly dose. Because this higher initial exposure could increase the risk of precipitated withdrawal, (b) (4) (b) (4) further clinical data are provided to support the safety.

Distribution

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Elimination

Buprenorphine is metabolized and eliminated in urine and feces. The apparent terminal plasma half-life of buprenorphine following subcutaneous injection of CAM2038 ranged between 3 to 5 days for CAM2038 weekly and 19 to 26 days for CAM2038 monthly as a result of the slow release of buprenorphine from the subcutaneous depot.

OCP investigated the buprenorphine PK profile after the last injection of CAM2038 at steady-state. Simulations were conducted to generate a PK profile following the final dose of CAM2038 at steady-state for the maximum proposed dose level for the CAM2038 weekly formulation (32 mg once weekly) as well as the CAM2038 monthly formulation (128 mg once monthly). The PK simulations indicate that the buprenorphine plasma concentrations remain above the LLOQ (0.025 ng/mL) for up to 6 weeks for 32 mg once weekly and for up to 6 months following 128 mg once monthly. However, the correlation between plasma concentrations of buprenorphine and those detectable in urine is not known.

Metabolism

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity. Norbuprenorphine steady-state plasma concentrations in humans after subcutaneous injection of CAM2038 are low compared to buprenorphine (AUC norbuprenorphine/buprenorphine ratio of 0.35 to 0.53).

Excretion

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of the buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Drug-Drug Interactions

The effects of co-administered CYP3A4 inhibitors and inducers on buprenorphine exposure in subjects treated with CAM2038 have not been studied; however, such interactions have been established in studies using transmucosal buprenorphine. The effects of buprenorphine may be dependent on the route of administration. Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when CAM2038 is given concurrently with agents that affect CYP3A4 activity. The effects of co-administered CYP3A4 inducers or inhibitors have been established in studies using transmucosal buprenorphine

The labeling will note the possibility of drug-drug interactions.

Specific Populations

Hepatic Impairment

The referenced label describes a study of the effect of hepatic impairment on the PK of buprenorphine in a study using 2 mg/0.5 mg buprenorphine/naloxone sublingual tablet in subjects with various degrees of hepatic impairment as indicated by Child-Pugh criteria. While no clinically relevant changes were observed in subjects with mild hepatic impairment, buprenorphine plasma exposure was increased by 64% and 181% in subjects with moderate and severe hepatic impairment, respectively, compared to healthy subjects

In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean C_{max}, $AUC_{0\text{-}last}$, and half-life values of buprenorphine were not clinically significant in comparison to healthy subjects without HCV infection.

This information will be included in labeling, noting that the effect of hepatic impairment on the PK of CAM 2038 has not been studied. Because buprenorphine levels cannot be rapidly adjusted during CAM2038 treatment, patients with pre-existing moderate to severe hepatic impairment are not candidates for treatment with CAM2038, and patients who develop moderate-to-severe hepatic impairment while being treated with CAM 2038 will need to be monitored for signs and symptoms of toxicity or overdose.

Removal of the CAM2038 depot is unlikely to be feasible; there is no experience with removing the depot. Moreover, residual plasma levels from prior injections would still be present.

Renal Impairment

Previous studies showed that less than 1% of buprenorphine is excreted unchanged in urine following IV administration. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine.

The effect of renal impairment on the pharmacokinetics of CAM2038 has not been studied. Clinical studies of CAM2038 did not include subjects with severe renal impairment.

Q-T evaluation

A particular issue of concern in this development program was the evaluation of buprenorphine's effects on cardiac conduction. Careful evaluation of the effects of buprenorphine on cardiac conduction was not performed during the development programs for Suboxone or Subutex. Based on *in vitro* binding studies, buprenorphine was not expected to have cardiac conduction effects.

However, a thorough QT (TQT) study was performed in a more-recent development program for a transdermal buprenorphine product used for analgesia. This study identified a signal for

QT prolongation that was considered to meet the threshold for regulatory concern, but that was not of clear clinical significance. The dose studied was significantly lower than the labeled dose used for sublingual buprenorphine products for treating drug addiction, which is, in turn, lower than the many of the CAM2038 doses.

In view of the fact that Subutex and Suboxone had been marketed for several years before the signal was identified, letters requiring post-marketing studies of Q-T effects were issued to marketing application holders for buprenorphine products used for treatment of OUD. However, significant technical difficulties in designing these studies prevented them from being conducted according to the planned schedule. Therefore, Braeburn was informed that data on the Q-T effects of CAM2038 would be needed to support approval.

Rather than performing a specific QT study, Braeburn provided data collected in their clinical trial program for CAM2038. These included studies of volunteers under naltrexone blockade, which may not be informative, and ECGs collected during efficacy studies that did not include PK assessments. Braeburn also submitted in vitro studies of cardiac channel effects. The data submitted were deemed sufficient for filing by the interdisciplinary review team responsible for cardiac conduction study reviews (QT-IRT). The following assessment of the data is excerpted from the QT-IRT review by Dr. Gopichand Gottipati.

> The provided information in this application supports an absence of large mean (i.e., 20 ms) increases in the QTc interval for buprenorphine (b) (4) at the time of expected maximum buprenorphine exposure (b) (4) compared to a baseline where patients had been taking buprenorphine (with low systemic exposure).
>
> To assess the effects of buprenorphine on the QT/QTc interval in NDA 210136, the sponsor collected time-matched ECG and PK samples in two healthy volunteer studies under naltrexone blockade and in a phase 2 study in patients as well as carried out a comprehensive preclinical assessment of buprenorphine, norbuprenorphine and naltrexone. The comprehensive preclinical assessment included assessment of the major cardiac ionic currents (hERG, peak sodium, late sodium, L-type calcium and KVLQT1/minK).
>
> The comprehensive preclinical assessment indicated that at concentrations in the micromolar range that buprenorphine and norbuprenorphine inhibits all the currents studied. However, these concentrations are well above the clinically relevant concentrations (subnanomolar range), and it therefore seems unlikely that buprenorphine or norbuprenorphine would cause QT prolongation via interaction with any of the cardiac ionic currents studied. In addition, the results also suggested that naltrexone does not block any of the cardiac ionic currents studied.
>
> The clinical evaluation of buprenorphine under naltrexone blockade did not reveal a concentration-dependent relationship, which contradicts our experience from other healthy volunteer studies that did not include naltrexone. It is not clear why there is a difference as the preclinical results reviewed in this submission suggest that buprenorphine, norbuprenorphine and naltrexone do

not interact with any of the major cardiac ionic currents. The sponsor also conducted clinical evaluation of the effects of buprenorphine on the ECG in a phase 2 study in patients. Few QTc outliers were observed in this study and no apparent concentration-dependent QTc prolongation between 2 and 14 ng/mL was observed.

Overall, the data reviewed in this submission shows an absence of large mean increases in the QTc interval compared to a baseline where patients have been taking buprenorphine. In addition, the data shows that buprenorphine and its metabolite norbuprenorphine are unlikely to interact with any of the major cardiac ionic currents (I_{kr}, I_{ks}, $I_{Na,Peak}$, $I_{Na,Late}$ and I_{Ca}). However, as the data do not permit excluding changes in the QTc interval from a drug-free baseline, we suggest that the sponsor includes similar language in the label as is included for other buprenorphine products.

To understand the safety of buprenorphine, the FDA requested the sponsor conduct *in vitro* pharmacology studies of buprenorphine, its major metabolite norbuprenorphine, and naltrexone on five cardiac ionic currents that underlie the ventricular action potentials. To fulfill this request, the sponsor submitted two preclinical study reports (TO-17-589 and TO-17-594). The five ionic currents are hERG and KVLQT1/minK currents that repolarize the action potential, peak Na+ current that generates action potential upstroke, and late Na+ and L-type Ca2+ currents that mediate action potential plateau or duration…Review of the data showed that although buprenorphine inhibited all five ionic currents, it blocked inward (L-type Ca2+ and late Na+ current) and outward (hERG current) currents with similar potencies. Of note, the IC_{50} values needed to block cardiac ion channels directly were in the micromolar ranges, far above the subnanomolar free C_{max} for buprenorphine associated with QTc prolongation in vivo. These findings suggest that QTc prolongation with buprenorphine is not mediated via inhibition of the cardiac ionic currents studied.

Ventricular myocytes do not express μ-opioid receptors (Peng et al., 2012; The Human Protein Atlas). However, these receptors are found on the cardiac parasympathetic, sympathetic, and sensory neurons (Mousa et al., 2010). Buprenorphine mediated QTc prolongation may thus reflect this drug's effect on the neuromodulatory tone onto the heart that indirectly alters cardiac ion channel activity or binding to auxiliary ion channel proteins or signaling cascades that are not expressed by cell lines. Further details may be found in a review by the Division of Applied Regulatory Science.

To explore the changes in QTc as it relates to exposure, the QT-IRT reviewer evaluated the data from Study HS-15-549, A Phase II, Open-label, Partially Randomized, Three Treatment Groups, Multi-Site Study Assessing Pharmacokinetics after Administration of the Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) at Different Injection Sites in Opioid-Dependent Subjects with Chronic Pain.

The reviewer noted that the baseline collected was not a true baseline as the patients were on buprenorphine prior to study initiation and as such traditional change from baseline analysis is not appropriate. The reviewer therefore compared the buprenorphine concentrations and QTc values at "baseline" with the median group T_{max} , and observed the following:

- At the baseline visit the mean buprenorphine levels were ~2 ng/mL for the 32 mg q1w and 128 q4w dose groups and ~4.3 ng/mL for the 160 mg q4w group. The concentrations at T_{max} were ~2.7 to ~4-fold as high (up to ~14 ng/mL).
- No QTc values greater than 480 or 500 ms were observed at the T_{max} time-point in any dose group and there were no ΔQTcF values >30 ms. Additionally, no trend towards an increase in the median QTcF values were observed.
- These observations do not suggest the presence of a concentration-dependent increase in QTc (between 2 and 14 ng/mL). However, this does not support concluding an absence of QTc prolongation, as no drug-free baseline was available.

Labeling similar to that used for the buprenorphine products approved for pain is recommended, suggesting caution in patients at risk for QT prolongation.

7 Clinical Microbiology

N/A

8 Clinical/Statistical- Efficacy

The review of efficacy of CAM2038 focused on the findings from an inpatient opioid blockade study (HS-13-478) and a randomized, double-blind, double-dummy, active-control efficacy study (HS-11-421).

8.1 Blockade study (HS-13-478)

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 by CSS Medical Officer, Dr. Alan Trachtenberg, and Biostatistics Reviewer, Wei Liu.

8.1.1 Design and Endpoints

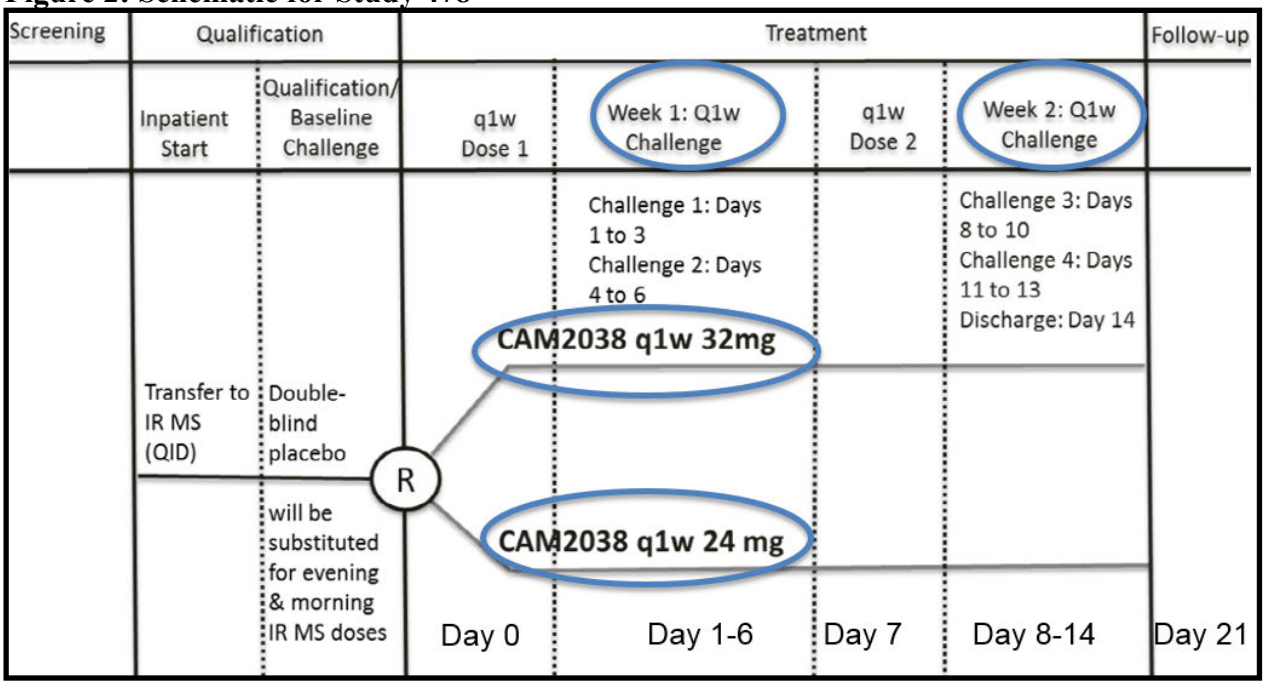
Study HS-13-478 (Study 428) was a Phase 2, randomized (1:1) multiple-dose, within-patient comparison study of an opioid challenge, to assess the blockade of subjective opioid effects CAM2038 24 mg and 32 mg Weekly formulation, compared with placebo.

The CAM2038 Monthly formulation was not evaluated in this Study.

Forty-seven, non-treatment seeking patients with moderate-severe OUD diagnosis were enrolled while physically dependent and self-reported a minimum of 21 days of IV or

insufflated opioid-use in the 30-days preceeding 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 (Figure 2). 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 to7 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 seven weeks. The testing portion of the study was two weeks.

Figure 2: 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 2)

The study was primarily intended to demonstrate that, following injections of either 24 mg or 32 mg CAM2038 Weekly, that "Drug Liking" scores measured after challenge with 6 mg or 18 mg of IM HM (a C-II narcotic full μ-opioid agonist) were non-inferior to (not liked better than) those measured after challenge with an IM placebo injection. 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. Under a full blockade of subjective opioid effects by BUP treatment, there should be no significant subjective differences between placebo injections and HM injections.

8.1.2 Population

To be eligible, participants had to meet criteria in the qualification phase:

- Maximum effect (Emax) in response to IM hydromorphone 6 mg greater than that of placebo on Drug Liking bipolar VAS (response to hydromorphone 6 mg greater than 55 mm in the VAS and a difference of at least 15 mm between placebo and hydromorphone 6 mg) and acceptable overall responses to hydromorphone 6 mg and placebo on the subjective measures, as judged by the Investigator or designee.
- Emax in response to IM hydromorphone 18 mg greater than that of placebo on Drug Liking bipolar VAS (greater than 60 mm and a difference of at least 20 mm between placebo and hydromorphone 18 mg) and Emax score of at least 20 points, and acceptable overall responses to hydromorphone 18 mg and placebo on the subjective measures, as judged by the Investigator or designee.
- Acceptable placebo response based on Drug Liking bipolar VAS (score between 40 and 60 mm, inclusive).
- Patient was able to tolerate IM hydromorphone 6 mg and 18 mg, as judged by the Investigator, including ability to complete most efficacy assessments administered within 5 hours post-dose.

A total of 47 subjects passed the Qualification Phase and were randomized into the Treatment Phase study with 22 subjects in the group of CAM2038 24 mg q1w (less than the planned 24) and 25 in the group of CAM2038 32 mg q1w. There were 22 completers in the CAM2038 24 mg q1w group and 24 in the CAM2038 32 mg q1w group (with one dropout subject due to adverse event).

Baseline characteristics are listed in Table 5 and were comparable between groups. Baseline characteristics were also similar to the patient characteristics of Study 421.

Table 5 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.**

8.1.3 Results

The peak (E_{max}) effect of "Drug Liking" (DL) visual analogue scale (VAS) was measured following the once-daily IM injections of 0, 6, and 18 mg hydromorphone (HM). The placebo-corrected (PC) VASDL E_{max} score was computed by subtracting the VASDL E_{max} during 0 mg HM challenge from the VASDL E_{max} during the 6 mg and 18 mg HM challenges acquired within the same session. Blockade of positive subjective effects for 6 mg HM or 18 mg HM was claimed if the largest difference between active hydromorphone doses and placebo (0 mg HM) was less than 11 mm (non-inferiority margin)[4] with confidence following CAM2038 injection.

The responses of subjects to the same hydromorphone dose decreased significantly after CAM2038 Weekly exposure at either 24 mg or 32 mg doses as compared to that before the

[4] 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.

CAM2038 injection. These significant changes between pre- and post-CAM exposure are also seen in the secondary endpoints (High, Good drug effect, Bad drug effect.) Blockade of subjective effects of 6 mg HM was, on average, achieved during all 4 HM challenge sessions for both the 24 mg and 32 mg CAM2038 Weekly arms.

The PC-VASDL E_{max} scores for each of the 5 hydromorphone challenge sessions are shown in the figures below, generated by Dr. Michael Bewernitz of the Office of Clinical Pharmacology, illustrating the maximum drug liking scores at each challenge. In the figure, vertical lines indicate the time of SC injections of CAM2038. The light grey and dark grey squares represent the 25th percentile, 50th percentile (median) and 75th percentile Emax drug-liking scores, placebo-corrected (VAS drug liking for that week's 0 mg dose subtracted) during the hydromorphone challenge of 6 mg. The placebo-corrected Emax distribution is shown by test session time period. The horizontal line at 11 mm delineates the non-inferiority margin for opioid blockade. Outliers are presented by open circles.

The x-axis shows how much time has elapsed following injection #1 for each placebo-corrected Emax drug-liking score. The number appearing at the bottom of the figure below each boxplot is the number of patients which provided placebo-corrected VASDL Emax measurement for the 6 mg HM challenge in the 24 mg CAM2038 Weekly arm and the 32 mg CAM2038 Weekly arm at the particular time point.

Figure 3 Placebo-Corrected Drug Liking Scores By Weekly CAM2038 Dose Level and Test Session Time Period for 6 mg Hydromorphone Dose Level

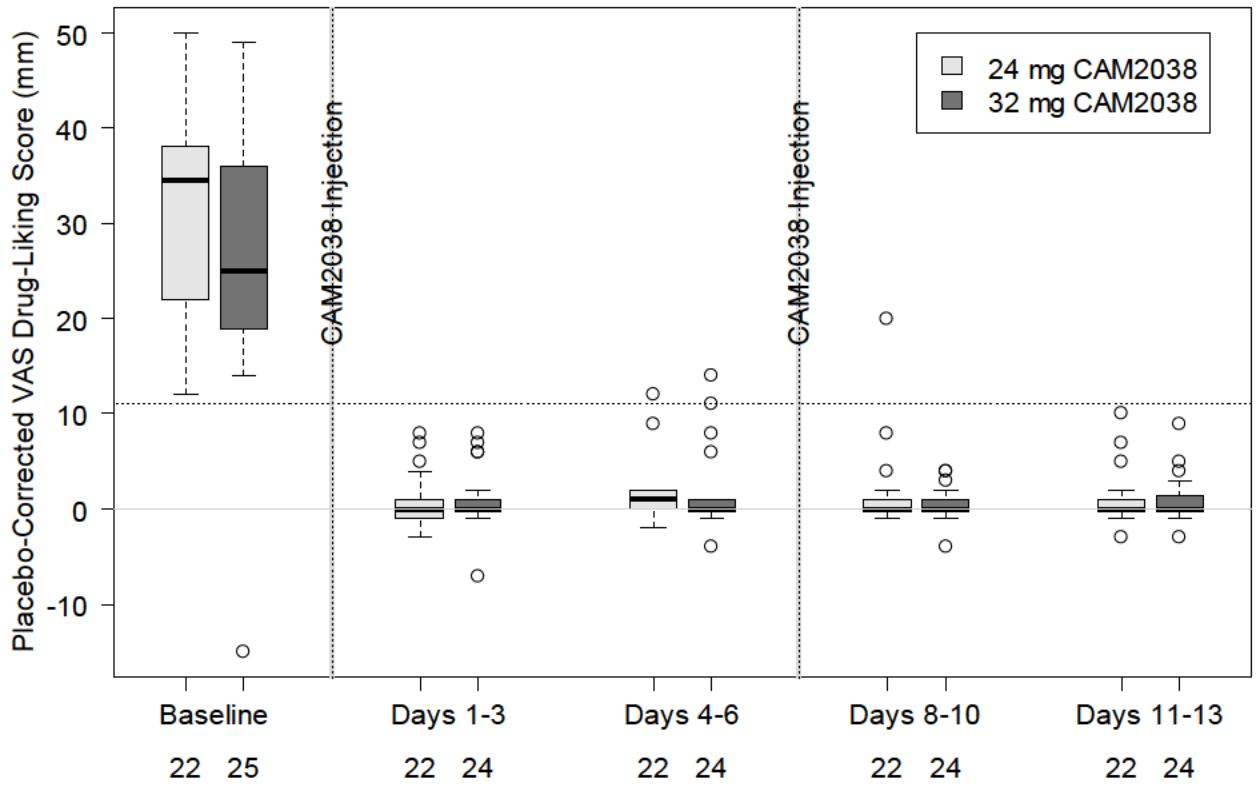
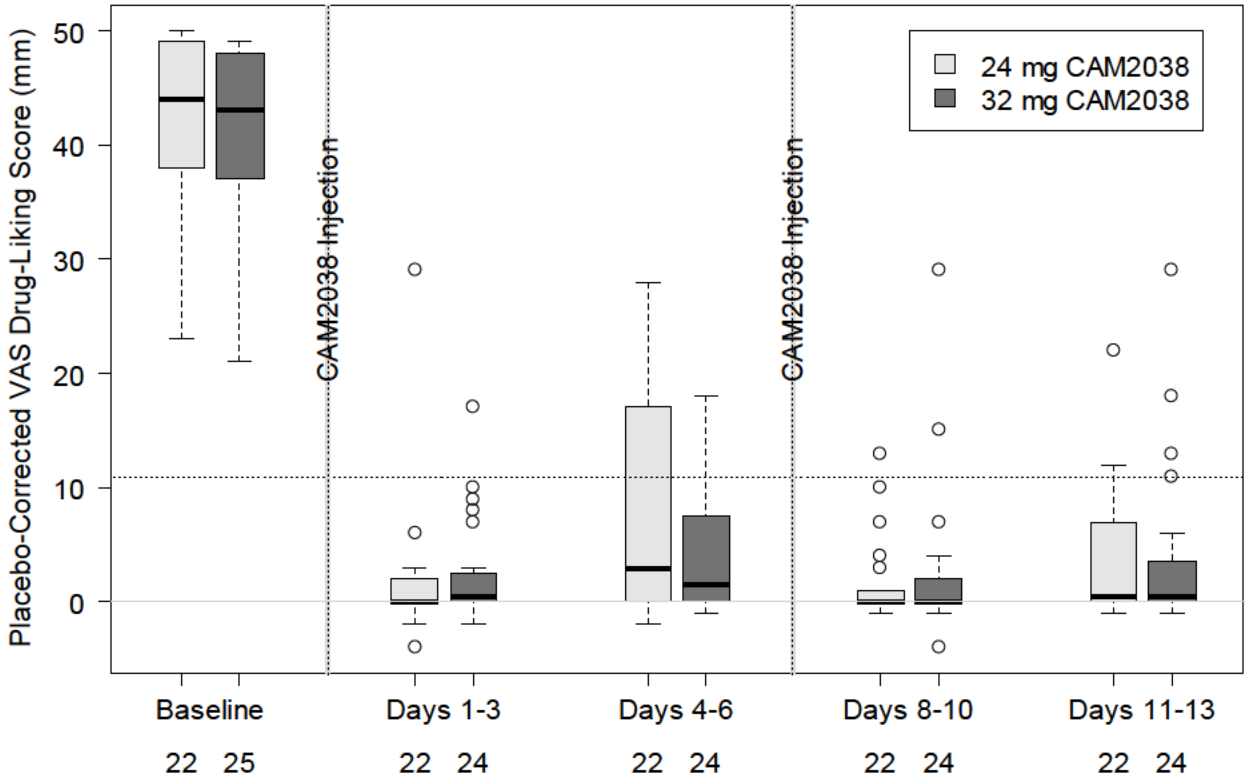


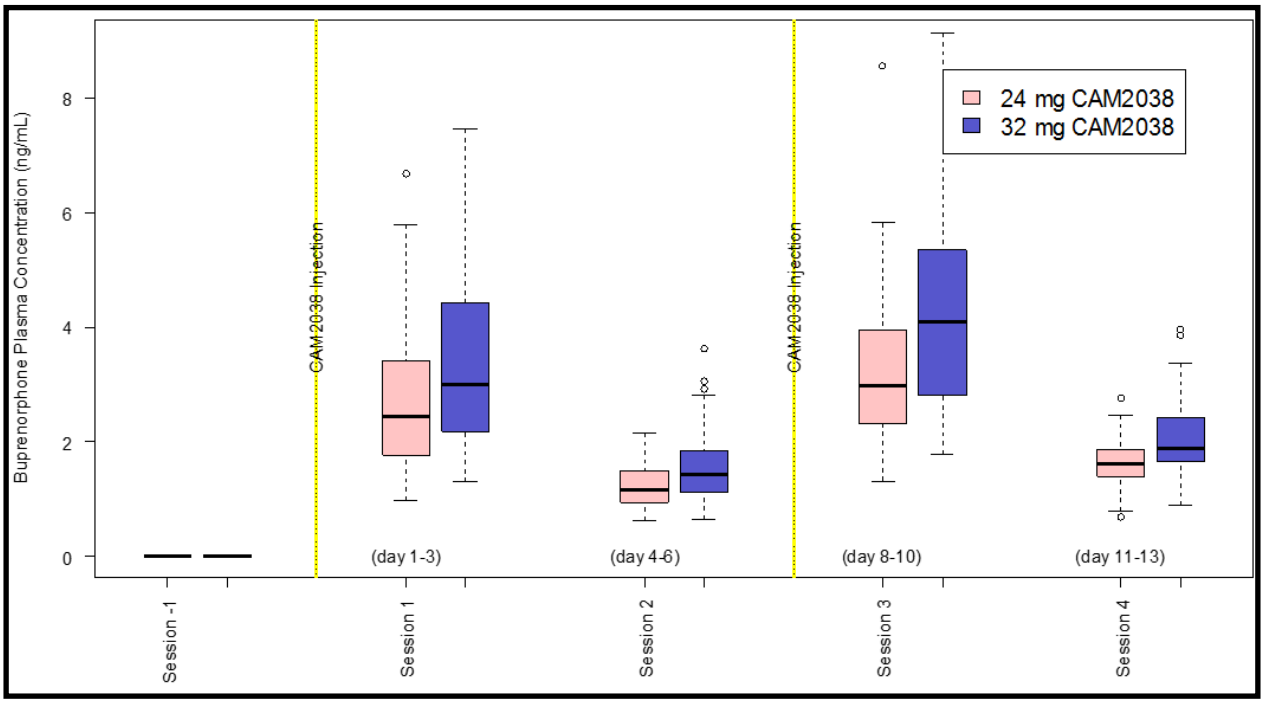
Figure 4 Placebo-Corrected Drug Liking Scores By CAM2038 WEEKLY Dose Level and Test Session Time Period for 18 mg Hydromorphone Dose Level



More effective blockade of "drug liking" for the 6 mg hydromorphone dose level than for 18 mg was noted. Additionally, blockade was more effective after the second CAM2038 administration, likely due to greater buprenorphine concentrations achieved during this period. However, the figure also illustrates the substantial inter-individual variability in response, with outliers at each time point who did not, apparently, experience a blockade of hydromorphone effects.

Dr. Bewernitz also analyzed the dose-response relationships in this study. The figures below show the buprenorphine concentration by time, and then the relationship between drug liking scores and buprenorphine concentration.

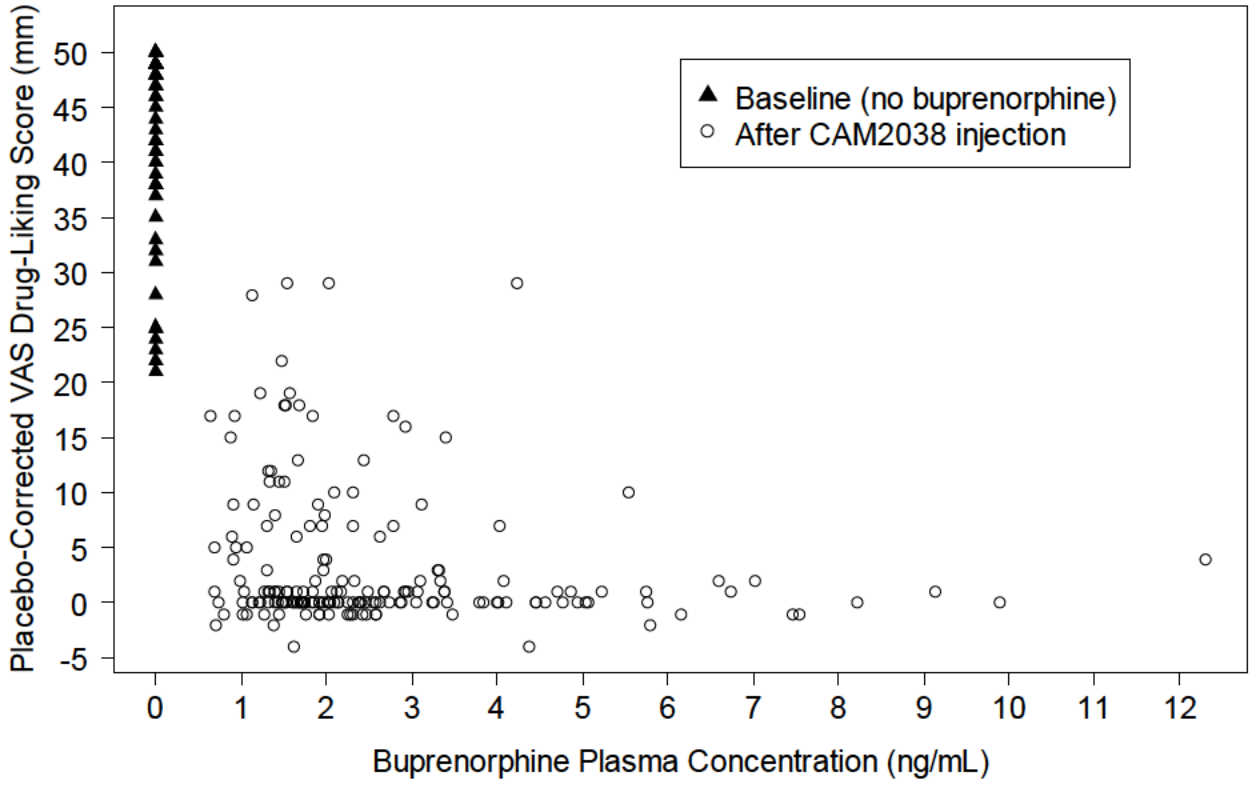
Figure 5 Buprenorphine concentration by time in Study 478



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 6 Plot of Drug-liking relative to plasma BPN levels after a hydromorphone challenge in Study 478Figure 6 illustrates the relationship between buprenorphine plasma level and drug liking after an 18 mg hydromorphone dosing challenge. Data from the CAM2038 Weekly 24 mg dosing arm is pooled with data from the CAM2038 Weekly 32 mg dosing arm to show the relationship between drug liking effect (VAS) and plasma levels of BPN. 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.

Figure 6 Plot of Drug-liking relative to plasma BPN levels after a hydromorphone challenge in Study 478



Source: Pharmacometrics Reviewer

Overall, the available PK and PD data provide supportive evidence of opioid blockade. There is an overall trend of increasing response (that is, reduced drug-liking) with increasing buprenorphine exposure. As expected, higher buprenorphine exposures are required to reduce the drug-liking following an 18 mg hydromorphone challenge compared to a 6 mg hydromorphone challenge.

However, these plots also demonstrate that the dispersion in drug-liking scores is wider at the lower buprenorphine exposures compared to higher buprenorphine exposures. The dispersion in the drug-liking scores was further investigated to explore and potentially uncover a reason for the wide range of drug-liking scores observed at lower buprenorphine exposures. When looking at the individual time course of buprenorphine concentration alongside the time course of drug-liking scores, approximately one-quarter of the subjects appeared to present substantial changes in the drug-liking scores from one dosing interval to the next despite having comparable exposures. These observations suggest that, in addition to buprenorphine concentration, other factors which are currently unknown, are likely influencing the drug liking scores.

8.2 Efficacy Study (HS-11-421)

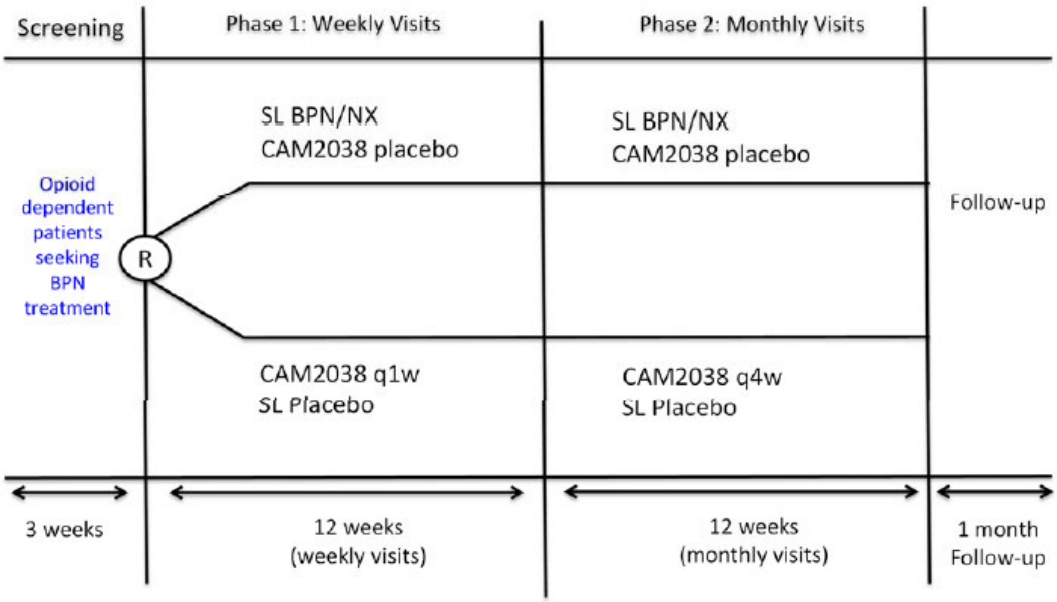
8.2.1 Study Design and Endpoints

Study HS-11-421 was a randomized, double-blind, double-dummy, active-controlled study designed to evaluate the efficacy and safety of CAM2038 compared to sublingual buprenorphine/naloxone (SL BPN/NX) in patients with opioid use disorder who are new entrants to treatment. Patients were eligible for inclusion in the study if they met the following requirements:

- Male or female, 18-65 years of age, inclusive.
- Diagnosis of moderate or severe opioid use disorder as described in the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V).
- Voluntarily sought treatment for opioid use disorder.
- Had not received medication-assisted treatment for opioid use disorder within 60 days prior to randomization.
- Considered by the investigator to be a good candidate for buprenorphine treatment, based on medical and psychosocial history.
- Must not have a current diagnosis of chronic pain requiring opioids for treatment.
- Must not have a current DSM-V diagnosis of moderate to severe substance use disorder on any other psychoactive substance other than opioids, caffeine, or nicotine.

Eligible patients were randomized in a 1:1 ratio to receive either CAM2038 injections with placebo sublingual tablets, or placebo injections with sublingual SL BPN/NX tablets. The schedule of the study is illustrated below in Figure 6. Of note, there were three scheduled visits during the first week of the study, followed by weekly visits through the rest of the first phase of the study.

Figure 6 Study Schema for HS-11-421



Abbreviations: BPN/NX, buprenorphine/naloxone; q1w, once weekly; q4w, once monthly; R = randomization; SL = sublingual

Source: Figure 1, Applicant's Study Report

On the first day of treatment patients received an open-label 4 mg test dose of sublingual buprenorphine. Patients who tolerated the test dose were randomized and given a 16 mg injection of CAM2038 or matched placebo. During the next six days patients were allowed up to two further 8 mg injections as needed. Patients received an injection of 16, 24, or 32 mg on Day 8 matched to the dose they received in the previous seven days. Patients received injections weekly for twelve weeks total and then transitioned to what was intended to be an equivalent dose of the monthly formulation for the remaining twelve weeks. Dose adjustments and supplemental 8 mg injections were permitted for the duration of the study. Supplemental 8 mg doses of CAM2038 weekly were allowed during the study in both treatment arms. The sublingual buprenorphine 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.

Because the study was intended to provide efficacy information about both the weekly and monthly products, 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 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.

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 and SL BPN/NX was greater than the pre-specified non-inferiority margin of 10%. As described in Section 3.1.1, both the responder definition and the NI margin were chosen pragmatically. The NI margin was arrived at after some discussion; the Division expressed a preference for a smaller margin but acknowledged that an impractically-large sample size might then be needed.

The secondary endpoint was the cumulative distribution function (CDF) of the percentage of assessments negative for illicit opioids between week 5 and 25, allowing a several-week grace period. This analysis could not be used as the primary outcome because it would not be possible to determine whether patients might have responded to only one of the two formulations. The percentage negative assessments was computed for each patient as the number of weeks of negative assessments divided by 15. The 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.

8.2.2 Demographics and Disposition

A total of 428 subjects were randomized, 213 to CAM2038 and 215 to groups BPN/NX. The demographic and baseline characteristics were comparable across treatment groups (Table 6;

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Table 7). The majority of the subjects were male (~60%) and white (76%). Overall, about 52% of the subjects had history of injectable opioid use.

Table 6 Demographics of randomization patients in HS-11-421

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

Source: Table 6, Applicant's Study Report

Table 7 Substance Use History in randomized population of HS-11-421

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

Source: Table 7, Applicant's Study Report
Abbreviations: SL BPN/NX, sublingual buprenorphine/naloxone.

The disposition for the randomized patients is shown in Table 8. The completion rates are similar for the two treatment arms (56.8% vs 58.6%) and there do not appear to be any substantial differences between the two arms in the reasons for study discontinuation. The most common reasons for discontinuation in both groups were "lost to follow up" and "withdrawal by patient."

Table 8: Patient Disposition in HS-11-421

	CAM2038 N=213 n (%)	SL BPN/NX N=215 n (%)	Total N=428 n (%)
Completed	**121 (56.8%)**	**126 (58.6%)**	**247 (57.7%)**
Discontinued	**92 (43.2%)**	**89 (41.4%)**	**181 (42.3%)**
Primary Reason for Early Discontinuation			
Adverse Event	**6 (2.8%)**	**1 (0.5%)**	**7 (1.6%)**
Death	**1 (0.5%)**	**0 (0.0%)**	**1 (0.2%)**
Lost to Follow	**27 (12.7%)**	**29 (13.5%)**	**56 (13.1%)**
Physician Decision	**8 (3.8%)**	**4 (1.9%)**	**12 (2.8%)**
Pregnancy	**0 (0.0%)**	**1 (0.5%)**	**1 (0.2%)**
Withdrawal by Patient	**44 (20.7%)**	**46 (21.4%)**	**90 (21.0%)**
Other	**6 (2.8%)**	**8 (3.7%)**	**14 (3.3%)**

Source: Table 6, Applicant's Study Report

8.2.3 Results and Conclusions

Note: As discussed elsewhere, there are concerns about the quality of the dataset submitted. Numerous errors and discrepancies were identified by the reviewers. The results presented in this section reflect the issues and corrections to the source data that have been identified, but the results must still be viewed as subject to confirmation when revised datasets are reviewed.

Dr. Travis' replication of the applicant's primary analysis is shown in Table 9. In all 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 Dr. Travis' analyses.

The applicant concluded CAM2038 was noninferior 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 pre-specified −10% NI margin. However, as the 95% confidence interval of the difference contained zero, CAM2038 was not demonstrated to be superior to the SL BPN/NX.

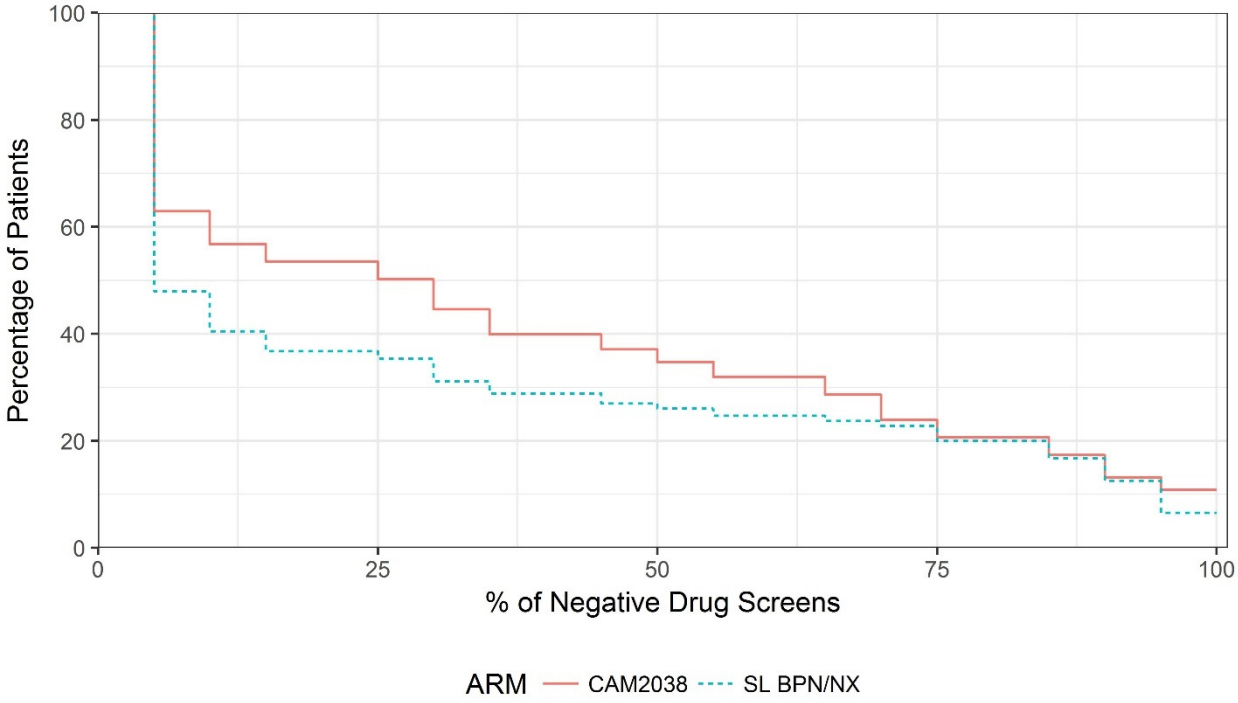
Table 9 Applicant's Primary Analysis: Responder Rate (ITT Population)

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: Statistics Review, Table 6
Abbreviations: CI, Confidence interval; ITT, intent to treat; SL BPN/NX, sublingual buprenorphine/naloxone

The results of the applicant's analysis of the CDF are illustrated in Figure 7. The corresponding values plotted in the figure are shown in Table 10. 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. 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 7 Cumulative Distribution Function (CDF) of Percentage of Negative Opioid Use Assessments over Weeks 5-25



Source: Statistics Review

Table 10 Cumulative Distribution Function (CDF) of Percentage of Urine Samples Negative for Illicit Opioids Supported by Self-Reported Illicit Opioid Use over Weeks 5-25

% Self-Reports Negative for Illicit Opioid Use	Number (%) of Patients	
	CAM2038 N=213	SL BPN/NX N=215
≥ 0%	213 (100)	215 (100)
≥ 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)
≥ 60%	68 (31.9)	53 (24.7)
≥ 70%	51 (23.9)	49 (22.8)
≥ 80%	44 (20.7)	43 (20)
≥ 90%	28 (13.1)	27 (12.6)
≥ 100%	23 (10.8)	14 (6.5)

Source: Statistics Review

The overall percent of negative tests does 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 of the days throughout the study. All of these patients might have 50% of

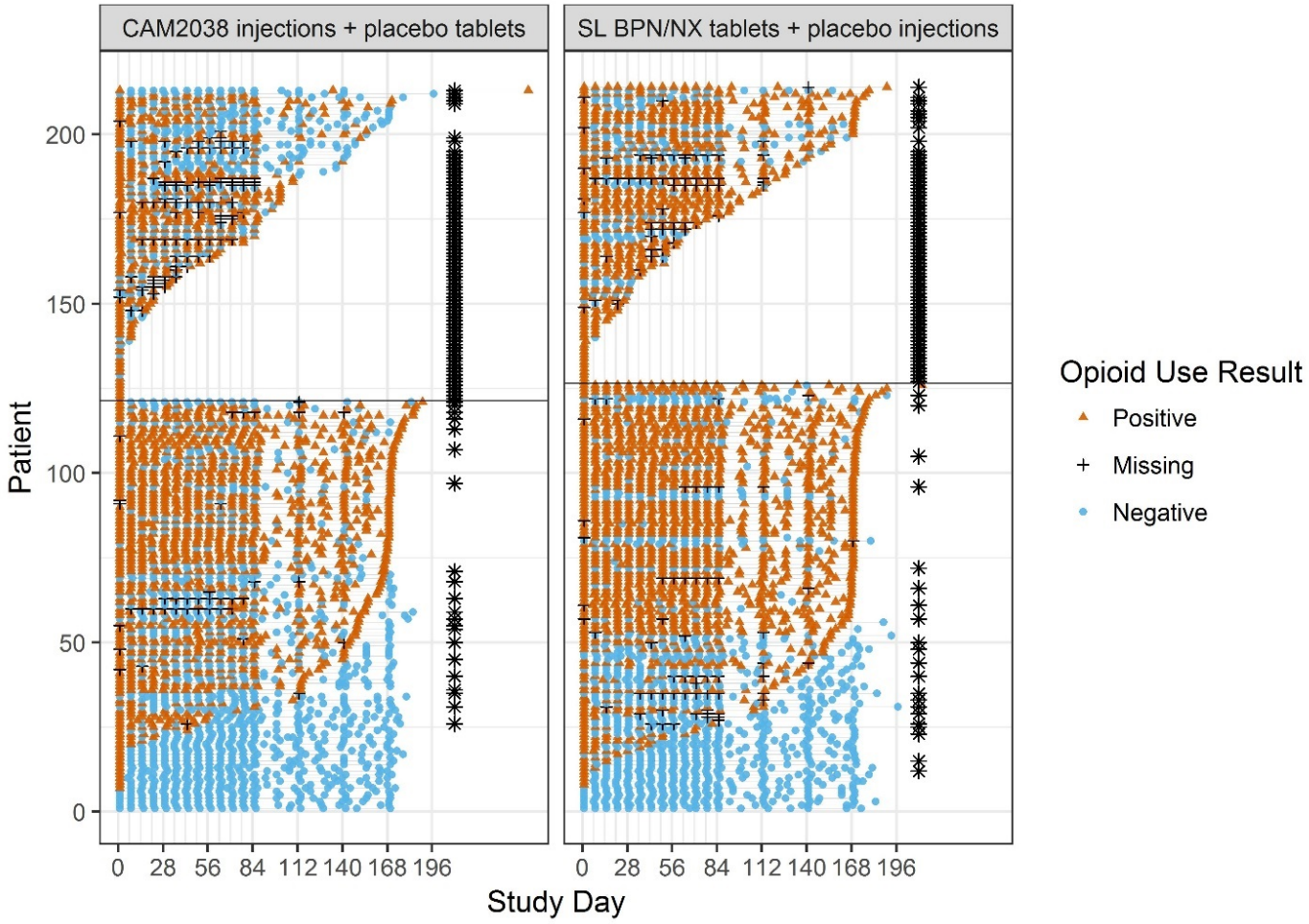
their tests negative. This also illustrates the reason that the overall CDF was not an appropriate endpoint to examine response to the weekly formulation in phase 1 and to the monthly formulation in phase 2. To allow an appreciation of the temporal sequence of patients' test results, the graphic depictions below show the results of each urine test for each patient. They also distinguish between tests that were imputed as positive in the analyses because they were intermittent missing, or because a patient self-reported drug use, and actual positive tests. Patients with missed random tests are indicated by a star on the right side of the figure.

In these patient-level presentations, each individual patient is represented along the y-axis. On the x-axis are the time points during which urine samples were collected. (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 orange data points, particularly along the right-hand side of the x-axis which represents longer periods of time on treatment. The data points that appear as black '+' symbols in these presentations denote intermittent missing urine data. 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 and are sorted based on time in the study. Assessments after the last dot in the row were missing and were imputed as positive for the purposes of analysis. Completers are shown in the bottom of each display, arranged by time to last positive sample.

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.

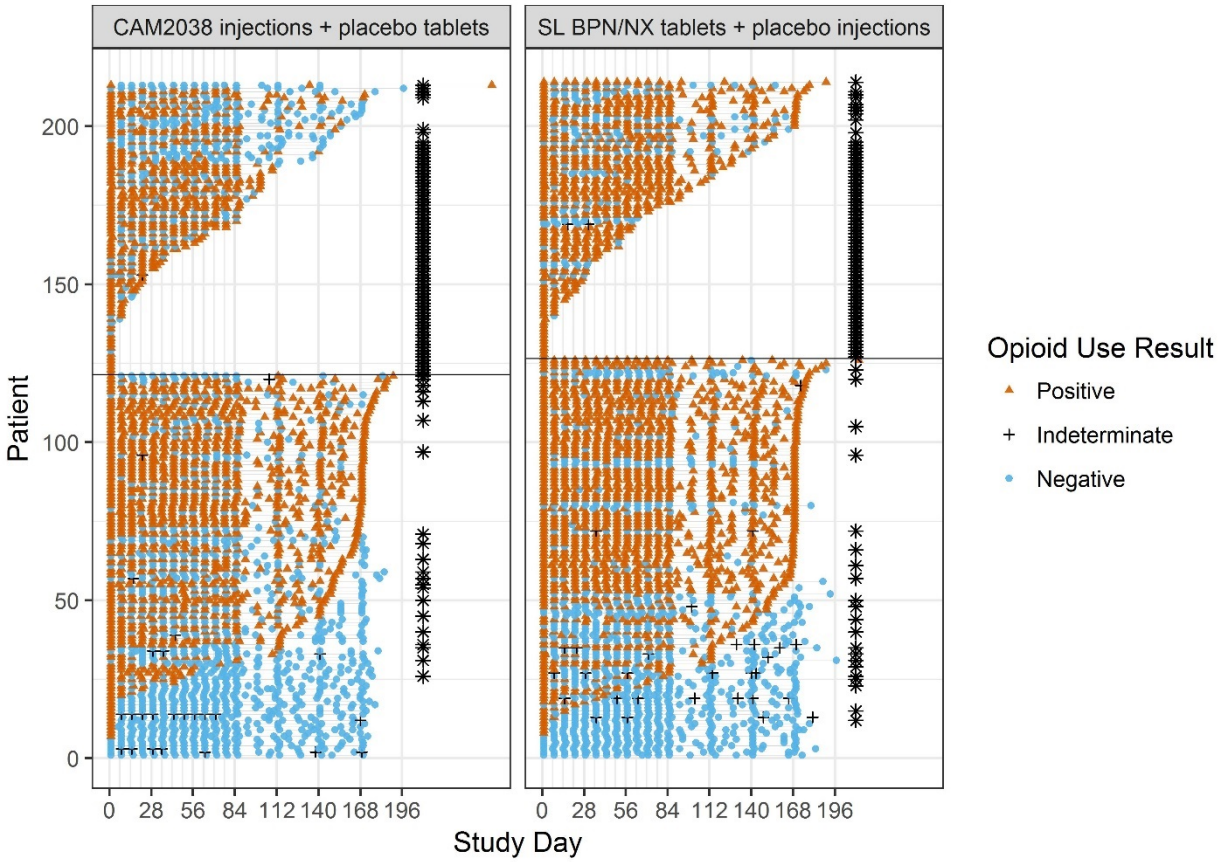
There were also several opioid use assessments where the results for some of the panels within the opioid urine test were reported as indeterminate by the applicant. If no illicit opioids were detected, then these samples were considered to be negative in the applicant's primary analysis.

Figure 8 Plot of the Opioid Use Assessment Results



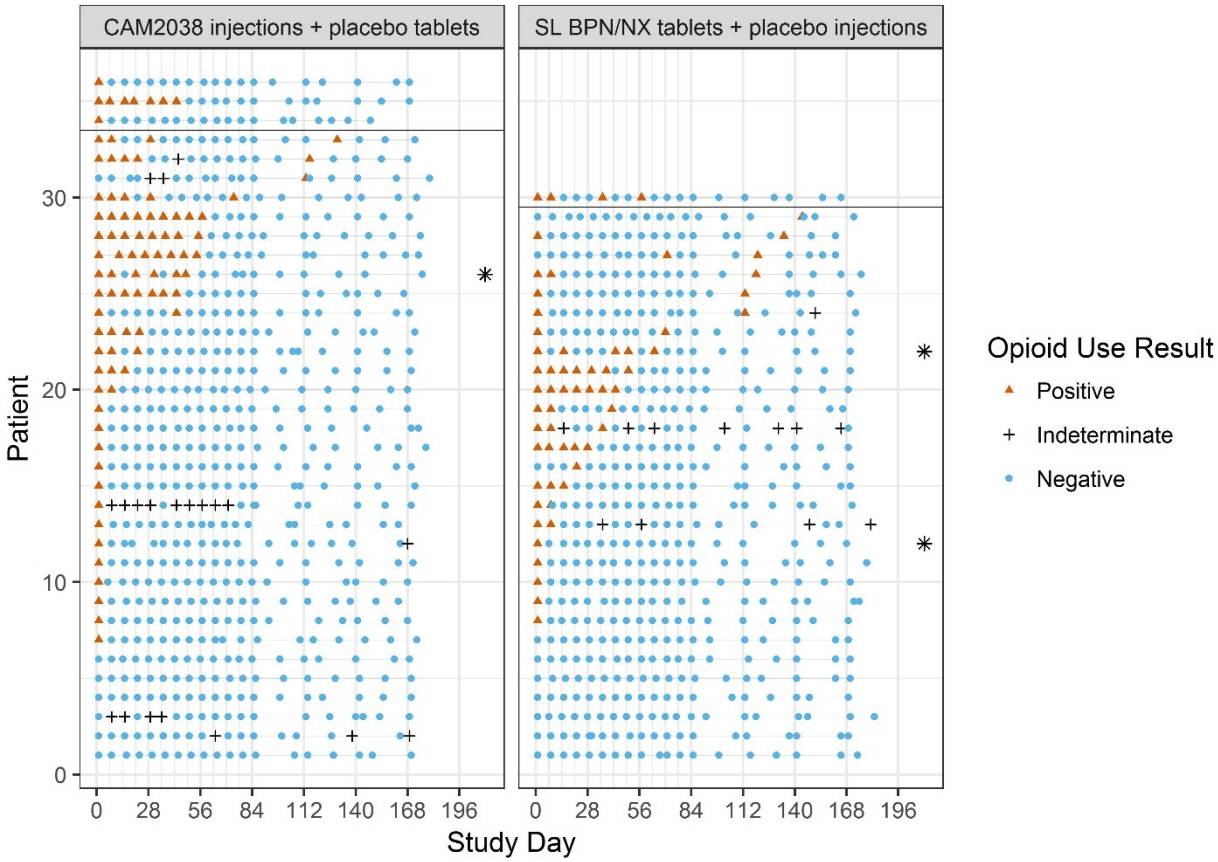
Source: Statistical Review
Note: Patients with missed random tests are indicated by a star on the right-hand side of the plot.

Figure 9 Plot of the Urinalysis Results with Missing Counted as Positive and Indeterminate Results Indicated



Source: Statistical Review
Note: Patients with missed random tests are indicated by a star on the right-hand side of the plot.

Figure 10: Plot of the Urinalysis results for Responders



Source: Statistical Review
Note: Patients with missed random tests are indicated by a star on the right-hand side of the plot.

A sensitivity analysis was performed in which indeterminate opioid use assessments were imputed as positive. As expected, the responder rates in both treatment arms are slightly lower than seen in the primary analysis; however, the lower bound of the 95% confidence interval for the difference is less than 10%, thus NI would still be concluded.

8.2.3.1 Subgroup Analyses

In the Applicant's analysis by sex, race, and age, females responded at a higher rate than males in the study in both treatment groups, but broadly similarly across treatments. 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.

Analysis based on history of opioid use was also performed. 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 was used to divide the 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 11 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%)	8/11 (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: Statistics review

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)

8.3 Data Quality Concerns

The Clinical Study Report for this study did not include any attempts to elucidate the efficacy of the individual formulations separately, or to explore any dose-response relationships. Patients were combined into two arms, CAM2038 and SL BPN, no matter the dose received. The originally-submitted datasets did not include fields for dose received, and this information had to be derived by the reviewers from subsequently-requested data.

The review team, seeking to conduct their own explorations of the dosing patterns, identified a number of unexpected findings concerning dosing, but the Applicant's response to requests for clarification or explanation typically indicated that a "data error" had occurred and that the dosing had, in fact, occurred per protocol. Over time, it became increasingly apparent that a large number of "data errors" existed.

Dr. Travis summarizes as follows:

The presence of these errors brings into doubt the accuracy of the submitted data. These data entry errors include delivery of dosing kits of study medication on days when the patient didn't have a site visit, duplicated injection entries, duplicated sublingual tablet dispensing records with the same kit number, mismatches between the recorded dose and the actual doses, multiple scheduled site visits listed on the same day, and dose units for injections were mislabeled. Many of these errors either contradict the prespecified conduct of protocol or fall outside the range of plausible outcomes. To me these errors were obvious and should have been easily caught in the applicant's audit of the data. This information was conveyed to the applicant in a telephone call on December 14, 2017. In response, the applicant is conducting a thorough audit of all data submitted to the Agency. In a communication received on December 19, 2017 the applicant stated that they had identified inconsistences between the interactive voice response database and the submitted clinical database that were caused by limited quality control checks between the two systems.

The table below, from Dr. Travis' review, lists some of the issues identified. It is not believed to be all-inclusive, and it is not yet known whether the data entry errors also affected the safety datasets.

Table 12: Summary of Data Quality Issues Identified by Review Team

Issue	Explanation Provided by the Applicant	Number of Patients Affected	Treatment Arm Affected
Patients received a starting dose of 8 mg instead of the protocol specified 16 mg	This was confirmed by the applicant to be a data entry error	5	Both
Multiple injections reported at on the same day	Several of the duplicated entries were uncorrected data entry errors. Others were actual duplicated doses.	11	Both
Patient listed as having received a 32 mg CAM2038 dose on day 3 of study	The patient did not visit the site on this day and the applicant confirmed with the site that no injection was given.	1	SL/BPN
Multiple entries referencing the same sublingual tablet kit ID were reported	The applicant attributes these to data entry errors by the site that were missed during the cleaning process.	22	Both
A patient was reported as having received 32 mg CAM2038 with a dose frequency of every 4 weeks.	The applicant reported that this was a mistake by the site and that a 128 mg injection was administered	1	CAM2038
Multiple scheduled visits occurred on the same day	The applicant reported that these were data entry errors	2	Both
Dose units for injections were listed as mL instead of mg	This was not confirmed with the applicant	4	CAM2038

Source: Statistical Reviewer

8.4 Discussion

The overall quality and integrity of the datasets submitted in this application are in question, which precludes any definitive conclusion about the study results.

Additionally, it is not clear that the study will be able to support any conclusions about the dose-response for efficacy. The design of the study allowed for dose adjustments, but the frequency with which doses were changed (both up and down) and the use of "booster doses" exceeded expectations and resulted in an inability to reliably interpret the efficacy (or the safety) of the individual doses, or determine if the CAM2038 arm was compared to truly comparable doses in the SL BPN arm.

When dosing data were received, it was revealed that only 14 injections of the 160 mg dose were administered (to 9 patients), giving inadequate information about either safety or incremental efficacy of this dose, which exceeds currently approved transmucosal exposures.

The non-inferiority margin, which was agreed upon for largely pragmatic reasons, does not appear to be well-justified, because the response rate for the sublingual buprenorphine treatment arm was only 14% and so the study would only rule out a response rate of less than 4%. It is reasonable to assume that the placebo response rate is quite low (although not zero) in this population. Future studies should employ NI margins that are more data-supported.

The graphic displays of patient response allow us to appreciate that even some fully-compliant patients being treated with doses of buprenorphine that yield adequate steady-state blood levels—expected to block the reinforcing effects of opioids—will continue to use illicit opioids despite treatment. Ensuring compliance, via depot administration, does not ensure treatment response. There is little evidence that CAM2038 offers advantages over SL BPN in terms of efficacy; however, the paradigm in which it is to be used (depot medication initiated after a single observed test-dose of transmucosal buprenorphine; no take-home medication) does offer advantages in terms of the potential for abuse, misuse, and accidental overdose.

If Braeburn can successfully provide a more reliable dataset and the findings are confirmed, the results of the blockade study and the efficacy study, taken together with the Agency's previous finding of efficacy for Subutex, could support a conclusion of efficacy.

9 Safety

Safety data derive from Phase 1 PK studies, the blockade study and efficacy study described above, and a 24-week, Phase 3 open-label study which enrolled patients who could be new to treatment ("new entrants") or already in established treatment with transmucosal buprenorphine ("transfer") (Study 499). This study was initiated prior to the efficacy study, and dosing was entirely at investigator's discretion, employing any combination of doses and formulations for a given patient.

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=594Table 13).

Table 13: 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%)**

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 14 and Table 15, 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. 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 14: 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 15: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.

Although neither CAM2038 formulation contains a drug substance that is a new molecular entity, both contain novel excipients. The systemic safety of CAM2038 is supported, in part, by previous Agency findings for systemic safety of buprenorphine in the referenced drug, Subutex. Ideally, Braeburn would have provided a safety database at least 300 patients exposed for 12 months and 100 patients exposed for at least 6 months at the highest proposed dose *for each formulation* to characterize the safety. However, there is clearly a lack of long-term experience with both formulations, particularly the monthly formulation. (b) (4) The extent of exposure, nature and frequency of safety monitoring were not adequate to characterize the safety profile for all doses and formulations. This lack of clinical experience lends additional importance to the identified manufacturing and non-clinical safety concerns, because the clinical data are not adequate to provide reassurance.

Moreover, it has been challenging to interpret the safety data to determine effects of dose, formulation, or time. Doses were changed frequently, patients were exposed to both the weekly and monthly formulations over the course of treatment, and supplemental 8 mg doses were administered throughout the studies at investigator discretion. Dr. Guerrieri's review includes several graphic displays, constructed by Braeburn, that illustrate 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.

Most subjects in the study were white males with an average age in the early 40's. Almost all of the 190 "transfer" patients in the OL study were white.

9.1 Deaths

One death was reported in the clinical program, in a patient treated with CAM2038 in Study 421. A 41-year-old female with no other reported medical history was hit by a car and died on Study Day 147. There were no factors suggesting a causal link to the study drug.

9.2 Serious Adverse Events

A total of 20 SAEs (including the fatality described above) occurred among 17 subjects of the 729 exposed to CAM2038 across the clinical program. None were related to injection site reactions. In Study 421, SAEs were reported in five (2.3%) of the CAM2038 group and in 13 (6%) of the SL BPN group. Accidental overdoses (3) were reported in the SL BPN group but not the CAM2038 group. One event (vomiting) was deemed plausibly related to study drug.

9.3 Dropouts and/or Dose Reductions Due to Adverse Effects

Error! Reference source not found., from the Applicant's ISS, illustrates that very few patients (2-3% of CAM3028-treated) were classified as discontinuing study drug due to AE. However, as illustrated in Table 8, 21% of each arm in Study 421 were classified as "withdrawal by patient."

Review of narratives suggests that only injection site related AEs, GI symptoms, and sedation seem plausibly related to study drug.

Table 16 AEs leading to treatment withdrawal by study, treatment group and PT in Phase 3 studies (safety population)

Preferred Term	HS-11-421		HS-14-499	TOTAL
	CAM2038 (N=213)	SL BPN (N=215)	CAM2038 (N=227)	CAM2038 (N=440)
	n (%)	n (%)	n (%)	n (%)
Any AE leading to drug withdrawal	7 (3.3%)	3 (1.4%)	3 (1.3%)	10 (2.3%)
Injection site pain	2 (0.9%)	0	1 (0.4%)	3 (0.7%)
Injection site swelling	1 (0.5%)	0	2 (0.9%)	3 (0.7%)
Injection site erythema	1 (0.5%)	0	1 (0.4%)	2 (0.5%)
Injection site pruritus	1 (0.5%)	1 (0.5%)	1 (0.4%)	2 (0.5%)
Injection site reaction	2 (0.9%)	1 (0.5%)	0	2 (0.5%)
Vomiting	2 (0.9%)	0	0	2 (0.5%)
Dehydration	1 (0.5%)	0	0	1 (0.2%)
Facial bones fracture	0	0	1 (0.4%)	1 (0.2%)
Intervertebral disc injury	0	0	1 (0.4%)	1 (0.2%)
Lower limb fracture	0	0	1 (0.4%)	1 (0.2%)
Multiple injuries	0	0	1 (0.4%)	1 (0.2%)
Nausea	1 (0.5%)	0	0	1 (0.2%)
Non-cardiac chest pain	1 (0.5%)	0	0	1 (0.2%)
Esophageal rupture	1 (0.5%)	0	0	1 (0.2%)
Pharyngeal injury	0	0	1 (0.4%)	1 (0.2%)
Road traffic accident	0	0	1 (0.4%)	1 (0.2%)
Sedation	1 (0.5%)	0	0	1 (0.2%)
Skull fractured base	0	0	1 (0.4%)	1 (0.2%)
Spinal fracture	0	0	1 (0.4%)	1 (0.2%)
Ulcer	1 (0.5%)	0	0	1 (0.2%)
Upper limb fracture	0	0	1 (0.4%)	1 (0.2%)
Drug withdrawal syndrome	0	1 (0.5%)	0	0
Sepsis	0	1 (0.5%)	0	0

Applicant's ISS Table 27
Source: Extracted from Table 7.2.1 in Module 5.3.5.3
N.B., numbers do not match the patient disposition table for Study 421 because of four patients (two per group) who discontinued study medication due to AE but did not discontinue the *study* due to AE.

Because of the design of the studies, which permitted dose adjustments up or down at investigator discretion, information relating to adverse events leading to dose reductions were not well-captured in the clinical trials.

9.4 Significant Adverse Effects

9.4.1 Hepatic

Hepatic effects are a known risk of buprenorphine. Hepatic effects were reviewed through laboratory assessments and adverse events. Mild hepatic enzyme abnormalities were fairly common; some cases of more extreme elevations were reported, but had alternative explanations such as viral hepatitis. Thus, no cases meeting Hy's Law criteria were reported. In Study 421, a shift from normal-to-high in LFTs 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). This does not provide support for an advantage of CAM2038 over sublingual dosing in hepatic safety attributable to avoidance of first-pass metabolism. However, I note that the most extreme elevations occurred only in the SL BPN arm in Study 421, and not in the CAM2038 arm of that study or in the OL study.

9.4.2 Cardiac

A few cases of mild to moderate QT prolongation were reported in CAM2038-treated patients. Additionally, clinically significant ECG abnormalities reported as an AEs occurred in 10 patients treated with CAM2038 in Studies 549, 478, 421, and 499. One SAE was reported, in a patient[5] transferring from SL BPN to CAM2038 in study 599 experienced a serious TEAE of tachycardia on Day 313, which resulted in hospitalization. CAM2038 was not discontinued. The patient had reported 3 to 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.

These findings are consistent with the EKG findings from the QT-IRT team.

9.4.3 Injection Site

The percentage of subjects with any injection site AE was 14.6% for CAM2038 weekly and 9.3% for CAM2038 monthly. There was a trend of increasing number of injection site AEs with increasing dose for both CAM2038 weekly (from 2.7% at 8 mg to 18.3% at 32 mg) and CAM2038 weekly (from 4.5% at 64 mg to 11.1% at 160 mg). Overall, the percentage of subjects reporting any unsolicited injection site AE increased with increasing volume, from 2.9% after injection volumes of <0.27 mL to 13.7% after injection volumes of 0.45-0.64 mL.

[5] Subject (b) (6)

Most injection site reactions were of mild to moderate severity, with moderate events more likely in patients receiving the active injection than the placebo injection (mild: CAM2038 70.9% vs SL BPN/NX: 85.2%; moderate: CAM2038 29.1% vs SL BPN/NX 14.8%). One event was severe (CAM2038). None of the injection site reactions were serious. Five subjects (0.7%) receiving CAM2038 withdrew from treatment due to an injection site AE.

9.4.4 CNS/Respiratory Depression

Symptoms such as somnolence and sedation were not commonly reported in the safety database. One patient (CAM3028 weekly 32 mg) discontinued study medication due to sedation.

No TEAEs potentially associated with respiratory depression were reported in patients treated with CAM2038.

9.5 Common AEs

The systemic safety profile for CAM3038, when given by a HCP in clinical trials, was broadly consistent with the known safety profile of transmucosal buprenorphine. Common adverse reactions in CAM2038-treated patients included nausea (7%), constipation (8%), vomiting (4%), diarrhea (3%), injection site reactions(~17%), insomnia (6%) and headache (8%) Dose-relationships could not be explored due to the way the studies were conducted and the way the findings were reported.

The Sponsor's table below lists preferred terms occurring in at least 5% of CAM-treated patients in the pooled Phase 3 studies.

Table 17: Common Treatment-Emergent Adverse Events (≥ 5%) in the CAM2038 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).

9.6 Safety Analyses by Demographic Subgroups

No notable differences between male and female patients were observed. No other demographic analyses were undertaken.

9.7 Other Safety Concerns

Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated in a patient still dependent on a full agonist.

9.7.1 Precipitated Withdrawal

Buprenorphine itself can precipitate withdrawal if initiated in patients who are not yet in significant opioid withdrawal. For this reason, initial dosing is generally cautious and typically begins with a sublingual dose of 2 mg- 4 mg. Some of the doses of CAM2038 contain a large amount of buprenorphine. In new entrants to treatment, the clinical trials included a test dose of 4 mg sublingual buprenorphine and then initiated treatment with a 16 mg weekly dose. It is not known whether CAM2038 could precipitate withdrawal if initiated in patients who have not had a test dose of sublingual buprenorphine, or if initiated at higher doses.

9.7.2 Consequences of Intravenous Injection

CAM 2038 was administered in a supervised setting by HCPs in the clinical development program. If a patient, household contact, or associate were to obtain access to CAM2038, the pre-filled syringe containing a Schedule III opioid might be an attractive target for abuse by the i.v. route. As noted above, it is predicted that injection into a vessel could result in the formation of a gel or solid, with resulting occlusion and possibly tissue damage or embolus.

10 Advisory Committee Meeting

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[6] 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.

[6] A verbatim transcript of this meeting is available on the FDA website at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm535446.htm

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)

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) *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.* (b) (4)

The Committee also noted that clinical data of surgical removal of the RBP-6000 in case of medical emergency was lacking. They wanted to know how long the buprenorphine level will be detectable after the last injection of RBP-6000. The Committee recommended that the instructions for surgical removal of RBP-6000 should be addressed in the labeling.

11 Pediatrics

Braeburn received a full waiver of Pediatric Research Equity Act.
(PREA) requirements on the basis of infeasibility. The prevalence of OUD in the pre-adolescent population is very low, and this product would not be suitable for treating iatrogenic opioid dependence (i.e., physical dependence without meeting criteria for OUD). Prevalence in adolescents under age 17 is also too low for feasible study.

12 Other Relevant Regulatory Issues

12.1 Financial Disclosures

Review of financial disclosures revealed no concerns.

12.2 Bioresearch Monitoring Inspections

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 18.

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Table 18: 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. Dr. Green also related certain irregularities, such as investigators collecting "random" samples on the same day as scheduled study visits, which were technically not in violation of the protocol due to lack of clear wording. The final OSI report is pending.

13 Labeling

Final labeling recommendations were not made because of issues precluding approval. The submitted proposed labeling is in Physician's Labeling Rule (PLR) format. The approved labeling for Suboxone/Subutex tablets forms the foundation for CAM2038 labeling, with new information related to the novel delivery system and the clinical trials, included throughout in relevant sections.

The following are recommendations for the labeling.

INDICATION AND USAGE

Braeburn proposed the following indication statement:

(b) (4)

The Division recommends modifying the language to clearly identify the different uses of the Weekly and Monthly Products, and to limit use to treating moderate to severe opioid use disorder.

DOSAGE AND ADMINISTRATION

The Division recommends reorganizing the proposed labeling to clearly identify the uses of the Weekly and Monthly Products and the approach to dose conversion. The starting dose should be revised from the Sponsor's proposed (b) (4) to the regimen studied in the clinical trials (16 mg weekly, followed by additional 8 mg weekly at subsequent visits later the same week).

The recommended injection sites should be limited to the abdomen, buttock, and thigh because the arm site did not yield BE results.

WARNINGS AND PRECAUTIONS
The Division recommends adding labeling highlighting the difference between the formulations

CLINICAL TRIALS EXPERIENCE
(b) (4) The Division recommends that the data be separated to show dose-effects and formulation effects, and to list all events occurring at a minimum frequency in the CAM arms.

CLINICAL STUDIES
The clinical studies section should be revised to present the blockade study data as described in the review, above. The description of the efficacy trial should be revised (b) (4) (b) (4) be consistent with current labeling guidelines.

14 Postmarketing Recommendations

14.1 Risk Evaluation and Mitigation Strategies (REMS)

Although Braeburn did not initially propose a Risk Evaluation and Mitigation Strategy, during the review cycle the Applicant proposed a REMS that was reviewed by the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology. DRISK has determined that a REMS with elements to assure safe use (ETASU) is needed to ensure the

(b) (4)

benefits of CAM2038 outweigh its risks. The REMS should include restricted distribution with CAM2038 being dispensed only in healthcare settings that are certified.

Currently, all buprenorphine products indicated for MAT of OUD are approved with REMS (Suboxone/Subutex REMS, the shared system Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS, the Probuphine REMS, and the Sublocade REMS). As an injectable depot, CAM2038 differs significantly from the oral transmucosal formulations of buprenorphine. Those products are self-administered by patients in their homes and the REMS are designed to mitigate risks associated with accidental overdose, particularly in children as well as misuse, and abuse. This is in contrast to CAM2038 which is intended to be administered by a HCP; CAM2038's risks are similar to those of Sublocade. Probuphine was similarly designed to be administered by HCP, but carries different risks as it is an implant device.

The REMS for transmucosal buprenorphine products for MAT consist of a Medication Guide and ETASU (i.e., safe use conditions and monitoring) which are not linked to distribution and therefore is not a restrictive program. The REMS for these products were required to address an increase in accidental exposures to children, increased misuse and abuse, as well as to improve prescribing practices of these products.

The goal of the Probuphine REMS is to mitigate the risk of complications of migration, protrusion, expulsion and nerve damage associated with insertion and removal of Probuphine and the risks of accidental overdose, misuse and abuse if the implant comes out of the skin. The Probuphine REMS consists of a Medication Guide and the ETASU that are comprised requirements that are restrictive and include healthcare provider (HCP) certification (e.g., HCP that prescribes and/or inserts Probuphine must be certified) and patient monitoring for removal of Probuphine. There are corresponding REMS materials for HCP education, enrollment, logging of insertion and removal procedures and patient education. The training with this REMS is linked to the ability to prescriber, insert and remove Probuphine. The goal of the recently-approved REMS for Sublocade 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 Sublocade directly to a health care provider for administration by a healthcare provider. Because CAM2038 has similar risks, a similar REMS would be appropriate.

The REMS ETASU and materials described below are necessary to support the goal.

DRISK conducted several interviews with healthcare providers and administrators in various health care settings to gain insight into the diversity of systems and approaches. DRISK noted that in some healthcare settings there is a centralized pharmacy for inpatient and outpatient and other systems may have use a separate pathway for procurement of drugs for outpatient pharmacies. The Agency has determined that all sites receiving product from the distributor should be certified and enrolled to ensure that in each case, in the various healthcare settings, there will be processes and procedures in place to ensure that dispensing staff are aware CAM2038 should be administered by a HCP and cannot be given directly to patients.

To assist health care providers with understanding the requirements of the REMS, the Agency is requiring a Fact Sheet that explains how to obtain CAM2038 for their patients, enrollment forms, and letters to healthcare professionals.

The following materials are recommended as part of the CAM2038 REMS**:**

Healthcare Setting and Pharmacy Enrollment Form

Communication Materials

- Dear Healthcare Provider REMS Letter
- Fact Sheet

Other Materials

- REMS Program Website

14.2 Postmarketing Requirements (PMRs) and Commitments (PMCs)

Not yet addressed because approval of the application is not recommended.

14.3 Division Director Comments

I concur with the data analyses conducted by the review team and with Dr. Winchell's analysis and conclusions.

15 Appendix: CMC Deficiencies

(b) (4)

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CELIA J WINCHELL
01/19/2018

SHARON H HERTZ
01/19/2018