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Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult out-patients with opioid use disorder

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ABSTRACT

Aims To assess the long-term safety of subcutaneous buprenorphine (CAM2038) weekly and monthly depots. **Design** Phase 3, open-label, observational, multi-centre 48-week trial (ClinicalTrials.gov NCT02672111). **Setting** Twenty-six out-patient sites (United States, United Kingdom, Hungary, Denmark, Sweden, Germany, Australia) between 14 December 2015 and 12 April 2017. **Participants** Two hundred and twenty-eight adults with opioid use disorder; 227 received CAM2038 (37 initiated onto CAM2038 and 190 converted from sublingual buprenorphine). **Interventions** CAM2038 weekly (8, 16, 24 or 32 mg) or monthly (64, 96, 128 or 160 mg) with flexible dosing and individualized titration utilizing multiple CAM2038 weekly and monthly doses. **Measurements** Safety variables, urine toxicology samples and self-reported illicit opioid use were collected at each visit. Participants were administered a patient satisfaction survey at months 6 and 12, completed by 162 of 227 (71.4%) participants. **Findings** The study treatment period was completed by 167 of 227 (73.6%) participants. At least one treatment-emergent adverse event (TEAE) was reported by 143 of 227 (63.0%) participants, of whom 60 of 227 (26.4%) reported as being drug-related. Most of the TEAEs, reported by 128 of 227 (56.4%) of participants, were mild or moderate in intensity. Injection-site reactions were reported by 46 of 227 (20.3%) participants, with most [45 of 46 (97.8%)] reported as mild to moderate. Five participants (2.2%) discontinued the study drug due to a TEAE, two cases (0.9%) of which were injection-site-related. No serious adverse events were attributed to the study drug. At the end of the study, the percentage of opioid-negative urine tests combined with self-reports was 63.0% (17 of 37) in new-to-treatment participants and 82.8% (111 of 190) for participants converted from sublingual buprenorphine. Participants reported high levels of satisfaction with CAM2038. **Conclusions** Subcutaneous buprenorphine delivered weekly or monthly (CAM2038) was well tolerated, with a systemic safety profile consistent with the known profile of sublingual buprenorphine. CAM2038 weekly and monthly was associated with high retention rates and low levels of illicit opioid use throughout this study.

Keywords Buprenorphine, CAM2038, depot, long-term safety, opioid use disorder, Phase 3 trial.

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INTRODUCTION

Opioid use disorder (OUD) and opioid-related overdose deaths are escalating global health problems [1–3]. In 2015, approximately 35 million people globally used opioids for non-medical purposes [4]. Opioid use disorder is a chronic, relapsing disorder causing significant mental, physical and social problems, including transmission of infectious diseases, unintentional overdose and criminal activity [5–7]. Treatment with sublingual buprenorphine (SL BPN) is effective in treating moderate or severe OUD [5–7]; however, SL BPN is associated with significant limitations, including non-adherence to prescribed daily dosing schedule, burdens and stigma to patients and health-care providers, diversion and misuse of medication and accidental paediatric exposure [8–14]. Additionally, supervised administration of SL BPN, if applied, increases the cost and inconvenience of treatment for service providers and patients.

CAM2038, a weekly or monthly buprenorphine (BPN), is a ready-to-use, extended-release injection designed for flexible and individualized treatment of OUD from day 1 of treatment through long-term maintenance therapy. The injection depot is engineered to immediately and

spontaneously start to form a matrix for extended release of BPN upon exposure to the subcutaneous environment. Administration of CAM2038 is performed by health-care professionals, thereby effectively reducing risks of non-medical use or misuse, non-adherence and diversion.

In a 24-week randomized controlled study, compared with SL BPN, CAM2038 demonstrated non-inferiority for the proportion of participants with no evidence of illicit opioid use, and met superiority on the cumulative distribution function (CDF) for no illicit opioid use with comparable systemic safety [15]. This open-label, multi-centre, multinational study was conducted to assess the long-term safety of a flexible dosing regimen of weekly and monthly CAM2038 during a 48-week period in adult out-patients with OUD. Effectiveness (unsanctioned substance use, withdrawal and craving measures) and treatment retention were assessed as secondary outcomes.

METHODS

Study design

This Phase 3, open-label, multi-centre, 48-week study (ClinicalTrials.gov NCT02672111) was conducted at 26 sites in the United States, the United Kingdom, Hungary, Denmark, Sweden, Germany and Australia to assess the safety of CAM2038 weekly and monthly (Supporting information, Table S1). The study was approved by the Institutional Review Board in the United States or national equivalent at respective countries and conducted in compliance with Good Clinical Practice regulations and guidelines, the ethical principles originated from the Declaration of Helsinki, the International Council for Harmonisation guidance, and all applicable local regulations. Signed informed consent forms were obtained from each participant before undergoing any study procedure.

Participants

Males and females aged 18–65 years (inclusive) with a current diagnosis of moderate or severe OUD based on the Diagnostic and Statistical Manual of Mental Disorders, 5th edn (DSM-5) criteria [16] or a past medical history of dependence, currently treated with SL BPN, or seeking to initiate BPN treatment and had had no BPN treatment for ≥ 60 days were enrolled. Female participants of childbearing potential were required to use contraception throughout the study (screening to follow-up) and could not be breastfeeding. Key exclusion criteria comprised moderate-to-severe substance use disorder defined by DSM-5 for any substance other than opioids, caffeine or nicotine; chronic pain requiring opioid treatment; hypersensitivity or allergy to naloxone (NX; for participants receiving a SL BPN/NX test dose), BPN or excipients of CAM2038; exposure to any investigational drug 4 weeks prior to screening; acquired immune deficiency syndrome; and recent or current suicidal ideation or behaviour based on the Columbia Suicide Severity Rating Scale (C-SSRS). Additional exclusion criteria are provided in the Supporting information.

Study treatment and participant care

Medications were supplied as prefilled syringes of CAM2038 weekly (50 mg/ml) and CAM2038 monthly (356 mg/ml) (Table 1). CAM2038 weekly was provided at dose strengths of 8, 16, 24 or 32 mg BPN base and CAM2038 monthly was provided at dose strengths of 64, 96, 128 or 160 mg BPN base. Investigators could titrate doses and adjust dosing intervals (weekly or monthly) as needed for each participant. Subcutaneous injections were administered to the buttock; re-injection in the same location was avoided for the duration of the study for CAM2038 monthly and for at least 8 weeks for CAM2038 weekly.

The study included screening (weeks −3 to −1), treatment (weeks 1–48) and follow-up (weeks 49–53) phases. Following screening, eligible participants initiated subcutaneous injections of CAM2038 weekly or monthly, based on their current treatment status. On study day 1, new-to-treatment participants in mild-to-moderate withdrawal received a 4-mg test dose of SL BPN/NX and were observed for at least 1 hour. Tolerability was confirmed by a lack of precipitated withdrawal symptoms, assessed clinically. Participants were then administered a single dose of 16-mg CAM2038 weekly and, if needed, received an additional 8-mg weekly dose titration on day 4. Based on the investigator's clinical judgement, participants could receive additional 8-mg weekly doses on days 5–7, up to a maximum dose of 40 mg during week 1. Participants who were not

Table 1 Dose conversion for participants converting from sublingual buprenorphine or sublingual buprenorphine/naloxone to CAM2038 weekly and monthly.

SL BPN or SL BPN/NX	*CAM2038 weekly*[a]	*CAM2038 monthly*[b]
≤ 6 mg	8 mg (0.16 ml)	NA
8–10 mg	16 mg (0.32 ml)	64 mg (0.18 ml)
12–16 mg	24 mg (0.48 ml)	96 mg (0.27 ml)
18–24 mg	32 mg (0.64 ml)	128 mg (0.36 ml)
26–32 mg	NA	160 mg (0.45 ml)

NA = not applicable; NX = naloxone; SC = subcutaneous; SL BPN = sublingual buprenorphine. [a]Participants were allowed dose adjustments as needed with CAM2038 weekly at scheduled visits or with 8 mg CAM2038 SC supplemental injections at unscheduled visits up to a maximum weekly dose of 40 mg per week. [b]Participants who needed additional temporary buprenorphine were allowed a maximum of two supplemental injections of 8 mg CAM2038 weekly per week; dose adjustments could be made at investigator discretion at scheduled visits.

new-to-treatment were converted directly to CAM2038 weekly or monthly at a dose corresponding to their current daily SL BPN or SL BPN/NX treatment (Table 1). Adjustments of CAM2038 dose, either increases or decreases, were permitted during the 48-week treatment period as indicated based on the investigator's clinical judgement. Temporary dose adjustments with supplemental 8-mg CAM2038 weekly were allowed as needed during both weekly and monthly dosing intervals (maximum weekly dose of 40 mg per week for participants on weekly dosing and maximum two supplemental doses per week for participants on monthly dosing). Transitions from CAM2038 weekly to CAM2038 monthly or vice versa were permitted as per the investigator's clinical judgement, in consultation with the participant, at any time during the treatment phase.

Psychosocial components of care including case management and counselling were provided at each site in accordance with local procedures. At the end of the treatment phase, participants were converted to usual care (SL BPN/NX) and followed for an additional 4 weeks (follow-up phase).

Outcome measures and participant assessments

The primary objective was to evaluate the safety and tolerability of CAM2038. Safety was assessed by treatment-emergent adverse event (TEAE) and serious AE (SAE) monitoring, injection-site examinations, clinical laboratory tests, vital signs, electrocardiogram (ECG), physical examinations, C-SSRS and pregnancy reporting. All AEs were collected throughout the study until 14 days after the follow-up visit (or 30 days after early termination). TEAEs and SAEs were followed until resolution or stabilization of the condition. AEs were coded by primary system organ class and preferred term, according to the Medical Dictionary for Regulatory Activities, version 18.0.

Injection-site examinations were performed during each scheduled visit by monitoring reactions—including erythema, swelling and pain—and by participant interview and investigator assessments. Level of injection-site pain was assessed using a numerical pain scale. The intensity of injection-site symptoms was graded as mild, moderate or severe; an injection-site reaction was defined as the presence of ≥ 1 moderate or severe symptom or ≥ 2 mild symptoms.

Laboratory tests including haematological, coagulation, biochemical and urinalysis profiles were performed at screening and the end-of-study visit. Vital signs were collected at scheduled visits following ≥ 3 minutes of rest. Twelve-lead ECGs were performed at screening, after the first CAM2038 administration, at time of increasing a CAM2038 dose, after taking QT-extending drugs or cytochrome P450 3A4 inhibitors and at the end of the study. Evaluations with the baseline/screening version of the C-SSRS were performed at screening and at all subsequent visits with the since-last-visit C-SSRS.

Measurement of illicit opioid and other substance use was based on urine toxicology, evaluated using immunoassay for opioids and other substances using reflex quantitative confirmation methods (liquid chromatography/mass spectrometry) for opioids and self-reported drug use. Urine toxicology samples were collected at each visit; specimen authenticity was ensured by temperature measurement or direct observation as needed. Treatment period completion was defined as participants who completed the day 337 visit.

Withdrawal symptoms were measured by participant self-assessment using the Subjective Opioid Withdrawal Scale (SOWS) and the clinician-administered Clinical Opioid Withdrawal Scale (COWS) [17]. Cravings, or desire and need to use, were assessed with a unipolar 100-mm visual analogue scale (VAS) ranging from 0 (no desire/need to use) to 100 mm (strongest possible desire/need to use) since the last visit [18,19].

At months 6 and 12, a subset of participants in both groups completed a patient-reported experience questionnaire rating seven characteristics of their BPN treatment (ease of travel, daily adherence, privacy, lack of need for daily medication or regular visits to pharmacy, accidental paediatric exposure, access by others to medications) on Likert scales (1 was 'not important'; 7 was 'extremely important'). Participants also rated their overall experience with CAM2038 compared with prior SL BPN treatment on a five-unit scale from 'much worse' to 'much better'. The subsample reflects participants recruited in the latter half of the recruitment period.

Statistics

The overall safety population included all participants who received ≥ 1 dose of CAM2038; the full exposure safety population included all participants treated with CAM2038 for 48 weeks. Efficacy was assessed in all participants who received ≥ 1 dose of CAM2038 and provided some post-baseline efficacy measurements. No imputation was provided for missing data. Data analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). Continuous data were summarized using descriptive statistics, and categorical data were presented using frequencies and percentages. Baseline was recorded as the last observed measurement before the first dose of CAM2038; if multiple observations were noted prior to the first dose, baseline was defined as the average of these observations.

Safety analyses required 100 participants with ≥ 48 weeks of CAM2038 exposure. Assuming a 50%

discontinuation rate, enrolment of approximately 228 participants was planned to ensure a sufficient number of participants with appropriate duration of CAM2038 exposure for safety assessments.

RESULTS

Participants and treatment exposure

Between 14 December 2015 and 12 April 2017, 228 participants were enrolled; one participant withdrew consent prior to the first dose of CAM2038, and 227 participants received ≥ 1 dose of CAM2038. Prior to study entry, a majority of participants (59.0%) used heroin as their primary illicit opioid (51.1% of participants converted from treatment with SL BPN/NX and 100% of new-to-treatment participants) (Table 2). Other drugs were prescription opioid analgesics, 'street' BPN and methadone. Most participants (84%; n = 190) were converted from treatment with SL BPN and 16% (n = 37) were new to treatment (Fig. 1). Individualization of treatment resulted in participants

Table 2 Demographics and baseline clinical characteristics (overall safety population).

Characteristic	*Converted from SL BPN treatment n = 190*	*New to BPN treatment n = 37*	*Overall N = 227*
Age, years, mean (SD)	41.3 (9.6)	41.8 (9.4)	41.4 (9.6)
Sex			
Male	119 (62.6)	24 (64.9)	143 (63.0)
Female	71 (37.4)	13 (35.1)	84 (37.0)
BMI, kg/m^2, mean (SD)	26.7 (5.8)	25.3 (5.3)	26.5 (5.8)
Region			
Australia	23 (12.1)	1 (2.7)	24 (10.6)
Europe	76 (40.0)	0	76 (33.5)
United States	91 (47.9)	36 (97.3)	127 (55.9)
Employment status			
Employed	106 (55.8)	13 (35.1)	119 (52.4)
Unemployed	77 (40.5)	23 (62.2)	100 (44.1)
Other	7 (3.7)	1 (2.7)	8 (3.5)
Marital status			
Married	59 (31.1)	6 (16.2)	65 (28.6)
Single	102 (53.7)	30 (81.1)	132 (58.1)
Other	29 (15.3)	1 (2.7)	30 (13.2)
Residential status			
Own	55 (28.9)	2 (5.4)	57 (25.1)
Rent	121 (63.7)	33 (89.2)	154 (67.8)
Other	14 (7.4)	2 (5.4)	16 (7.0)
Arrest and conviction history			
Previously arrested	48 (25.3)	10 (27.0)	58 (25.6)
Felony conviction	15 (7.9)	11 (29.7)	26 (11.5)
Misdemeanour conviction	18 (9.5)	5 (13.5)	23 (10.1)
None	108 (56.8)	11 (29.7)	119 (52.4)
Other	1 (0.5)	0	1 (0.4)
Substance use history			
Opioid use disorder (DSM-5) diagnosis	157 (82.6)[a]	37 (100.0)	194 (85.5)
Time to first opioid abuse, years, mean (SD)	14.7 (8.5)	15.7 (9.0)	14.8 (8.6)
Time to first diagnosis, years, mean (SD)	9.8 (7.6)	10.0 (8.6)	9.8 (7.8)
Heroin as primary opioid of use	97 (51.1)	37 (100.0)	134 (59.0)
Baseline withdrawal and craving scores, mean (SD)[b]			
Clinical Opioid Withdrawal Scale (COWS)[c]	2.0 (2.7)	10.6 (3.7)	3.4 (4.3)
Subjective Opioid Withdrawal Scale (SOWS)[d]	4.7 (8.1)	27.1 (15.3)	8.3 (12.7)
Opioid craving; desire-to-use VAS[e]	11.7 (24.2)	74.8 (24.8)	22.0 (33.7)
Opioid craving; need-to-use VAS[f]	11.7 (23.8)	76.3 (24.9)	22.3 (33.8)

Unless otherwise noted, data presented as n (%). BMI = body mass index; BPN = buprenorphine; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edn; OUD = opioid use disorder; SD = standard deviation; SL BPN = sublingual buprenorphine; VAS = visual analogue scale. [a]33 participants had a history of OUD; [b]efficacy population; [c]scores range from 0 (no withdrawal) to 48 (severe withdrawal); [d]scores range from 0 (no withdrawal) to 64 (severe withdrawal); [e]scores range from 0 (no desire to use) to 100 mm (maximum desire to use since the last visit); and [f]scores range from 0 (no need to use) to 100 mm (maximum need to use since the last visit).

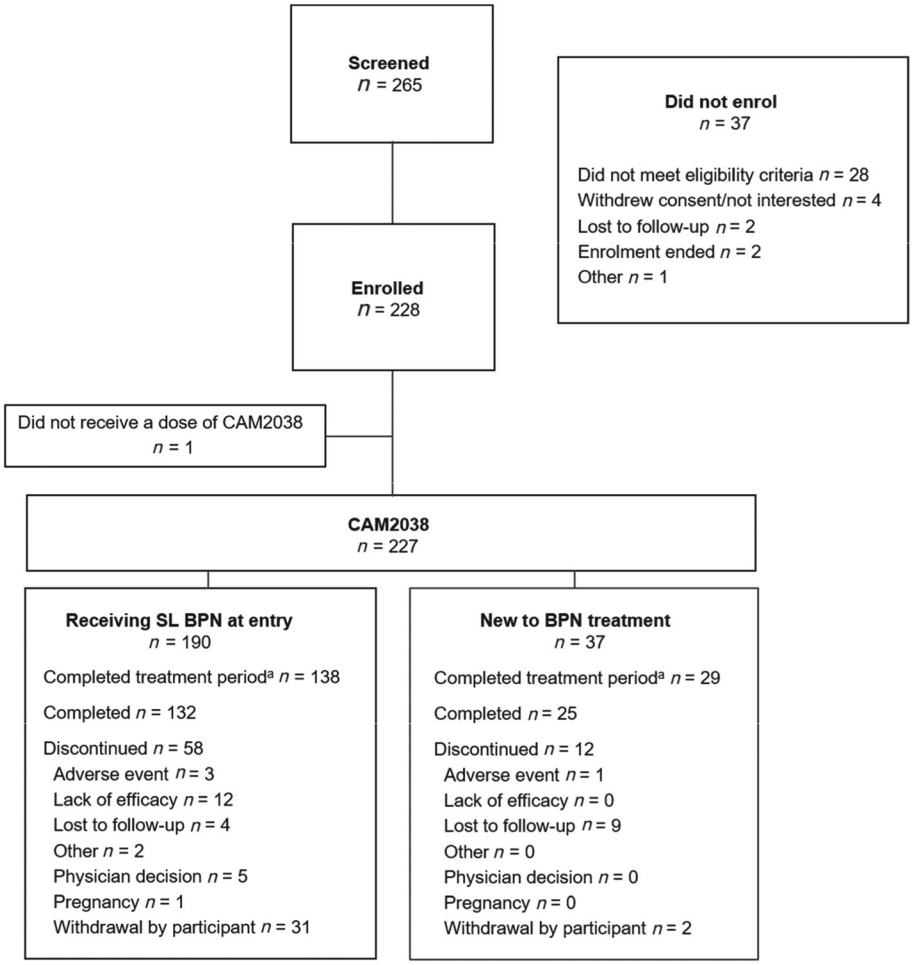


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram. [a]Participants who completed the treatment period were those who completed a day 337 visit. BPN = buprenorphine; SL BPN = sublingual buprenorphine

receiving either weekly or monthly CAM2038 doses ranging from 8 to 40 mg weekly and 64 to 160 mg monthly (Table 3).

Table 3 Highest CAM2038 dose reached by regimen.

Regimen	*CAM2038 dose (mg)*	*Total CAM2038 N = 227 n (%)*
Weekly, *n* = 154	8	5 (3.2)
	16	28 (18.2)
	24	70 (45.5)
	32	49 (31.8)
	40[a]	2 (1.3)
Monthly, *n* = 151	64	36 (23.8)
	96	56 (37.1)
	128	37 (24.5)
	160	22 (14.6)

[a]Maximum dose for participants receiving CAM2038 weekly was 40 mg per week.

Overall, the mean [standard deviation (SD)] duration of CAM2038 exposure was 39.1 (16.2) weeks (range = 1.1–49.9 weeks). A total of 5196 CAM2038 injections were administered with a mean of 22.9 injections per participant over the course of the study, corresponding to 170.2 participant-exposure years.

A total of 75 of 227 (33.0%) participants were treated exclusively with CAM2038 weekly throughout the study, 77 of 227 (33.9%) were treated exclusively with CAM2038 monthly and 75 of 227 (33.0%) started weekly and transitioned later to monthly doses. Of 190 participants receiving SL BPN at enrolment, 50 (26.3%) converted to, and remained on, CAM2038 weekly; 63 (33.2%) converted to CAM2038 weekly and subsequently transitioned to CAM2038 monthly; and 77 (40.5%) converted to CAM2038 monthly. Of the 37 new-to-treatment participants, 25 (67.6%) commenced and remained on CAM2038 weekly, while 12 (32.4%) transitioned from CAM2038 weekly to CAM2038 monthly.

Temporary dose adjustments with supplemental 8-mg weekly CAM2038 accounted for 301 (5.8%) of the total

number of injections throughout the 48 weeks of treatment. The majority of participants who required dose adjustments received ≤ 3 temporary dose adjustments throughout the 48 weeks of treatment.

Safety

In the overall safety population, 143 of 227 (63.0%) participants experienced ≥ 1 TEAE, with 60 of 227 (26.4%) participants experiencing an AE considered as being related to study medication (Table 4). Rates of TEAEs were similar between participants in the full exposure safety population (n = 156) and the overall safety population (n = 227). The most common TEAEs occurring in ≥ 5% of participants were pain, swelling or erythema at the injection site; nasopharyngitis; headache; nausea; urinary tract infection; and vomiting. The overall incidence of TEAEs was higher in participants converted from SL BPN (68.9%) compared with new-to-treatment participants (32.4%); this also included a numerical difference in the incidence of injection-site TEAEs (23.2 versus 5.4%). A total of 12 of 227 (5.3%) participants experienced ≥ 1 treatment-emergent SAE; none occurred at the injection site or in association with an injection-site reaction, and none were determined to be related to study drug. No deaths occurred during the study.

Most TEAEs were mild or moderate in intensity [reported by 128 of 227 (56.4%) of participants]; 15 of 227 (6.6%) participants had a TEAE of severe intensity. Injection-site reactions were reported for 46 of 227 (20.3%) participants, with most [45 of 46 (97.8%)] reported as mild to moderate. One (0.4%) participant experienced a single instance of a severe injection-site reaction of transient pain considered to be related to treatment; the event occurred on day 1 of treatment and was resolved the same day with no change in study drug. No other TEAEs of severe intensity were related to the injection site or to the study drug.

Laboratory-related TEAEs were reported for four (1.8%) participants. None were serious or severe in intensity, related to the study drug or led to discontinuation of the study drug. No vital signs or C-SSRS results indicated clinically meaningful concerns. In total, three (1.9%) participants had ECG-related TEAEs not considered related to the study drug; these included QRS complex abnormal and moderate QT prolonged (n = 1), myocardial ischaemia (n = 1) and ventricular tachycardia (n = 1).

A total of 5 (2.2%) participants discontinued the study drug due to TEAEs. Two (0.9%) participants discontinued due to mild injection-site TEAEs related to medication (pain and swelling in one participant and erythema, swelling and pruritus in one participant). One (0.4%) participant discontinued due to multiple non-injection-site TEAEs, including two SAEs (road traffic accident and multiple injuries) considered unrelated to treatment. An additional two participants discontinued due to TEAEs of pain in extremity (n = 1) and abnormal QRS complex and prolonged QT on ECG (n = 1).

Three pregnancies occurred during the study; two participants elected to terminate the pregnancy and remain in the study. One participant withdrew from the study and carried the pregnancy to term. The infant was born with

Table 4 Summary of treatment-emergent adverse events (overall safety population).

Category	*Converted from SL BPN n = 190*	*New to BPN treatment n = 37*	*Overall N = 227*
≥ 1 TEAE	131 (68.9)	12 (32.4)	143 (63.0)
≥ 1 drug-related TEAE	58 (30.5)	2 (5.4)	60 (26.4)
Injection-site TEAE	43 (22.6)	2 (5.4)	45 (19.8)
Non-injection-site TEAE	23 (12.1)	1 (2.7)	24 (10.6)
≥ 1 severe TEAE	13 (6.8)	2 (5.4)	15 (6.6)
Deaths	0	0	0
≥ 1 SAE	10 (5.3)	2 (5.4)	12 (5.3)
≥ 1 drug-related SAE	0	0	0
Hospitalizations	9 (4.7)	1 (2.7)	10 (4.4)
TEAEs leading to discontinuations	4 (2.1)	1 (2.7)	5 (2.2)
TEAEs in ≥ 5% of participants			
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)
Headache	18 (9.5)	0	18 (7.9)
Nasopharyngitis	17 (8.9)	1 (2.7)	18 (7.9)
Nausea	16 (8.4)	0	16 (7.0)
Urinary tract infection	9 (4.7)	3 (8.1)	12 (5.3)
Vomiting	12 (6.3)	0	12 (5.3)

Data presented as n (%). BPN = buprenorphine; SL BPN = sublingual buprenorphine; TEAE = treatment-emergent adverse event; SAE = serious adverse event.

neonatal opioid abstinence syndrome (NAS), attributed to BPN use during the pregnancy (CAM2038 during the first 5 weeks and subsequently SL BPN prescribed for 8 months prior to birth). The infant was treated with morphine for 12 days starting day 3 after delivery; NAS was considered resolved 17 days after delivery.

Retention

Rates of treatment retention were high; 188 of 227 (82.8%) participants completed 24 weeks of treatment and 167 of 227 (73.6%) completed the treatment period (Fig. 2a). The mean (SD) and median duration of overall treatment was 39.1 (16.2) and 48 weeks, respectively.

Substance use, withdrawal and cravings

All new-to-treatment participants were positive for illicit opioids at baseline; the percentage of the composite of illicit opioid-negative urine samples and self-reports at last study visit increased to 63.0% (17 of 37) at the end of the treatment period. For participants converted from SL BPN, the percentage of participants negative for illicit opioids increased from 78.4% on day 1 to 82.8% (111 of 190) at the end of the treatment period (Fig. 2b). Participant self-reports of no illicit opioid use increased from 0% on day 1 to 81.5% at the end of the treatment period for new-to-treatment participants and was high on day 1 for participants converted from SL BPN (92.1%), and remained high through the end of treatment period (93.2%). The percentage of participants with positive samples for other drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol and phencyclidine, remained low and generally stable from baseline to the end of the treatment.

Mean COWS and SOWS scores decreased from baseline to the end of the treatment for both converted and new-to-treatment participants (Fig. 2c, Table 5). Craving, measured by both mean 'need to use' and 'desire to use' VAS scores, also decreased from baseline to the end of the treatment for converted and new-to-treatment participants (Fig. 2d, Table 5).

Patient-reported experience measures

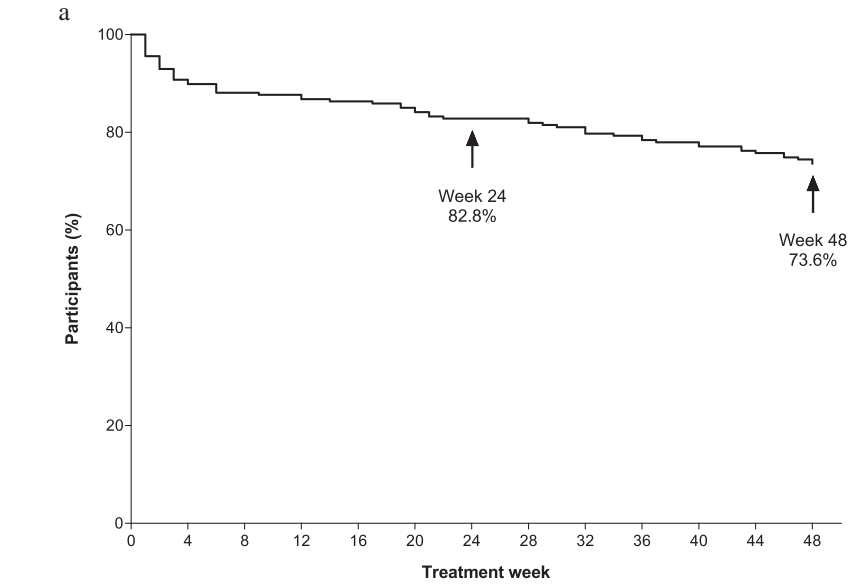
A total of 110 (48.4%) participants completed surveys at month 6 (34 participants new to treatment and 76 converted from SL BPN); 162 of 227 (71.4%) participants completed surveys rating the importance of various characteristics regarding BPN treatment and participant satisfaction with CAM2038 relative to previous treatment with SL BPN at 12 months (29 participants new to treatment and 133 converted from SL BPN). In both groups, for all items on the survey, for the importance of various characteristics regarding treatment with BPN including ease of travel, daily adherence, privacy, lack of need for daily medication or regular trips to pharmacy, accidental paediatric exposure and access by others to medications, median scores for patient satisfaction with CAM2038 treatment at 6 and 12 months were 7.0 ('extremely important'), except for a median score of 6.5 for 'prevents other access to my medication' at month 6 for new-to-treatment participants (Supporting information, Table S1). Results were similar for participants converted from SL BPN and those new to treatment. For participant satisfaction, 91 of 133 (68.4%) participants converted from SL BPN responded that CAM2038 was 'much better' than their previous treatment with SL BPN, while four participants (3.0%) responded that CAM2038 was 'much worse' than their previous treatment.

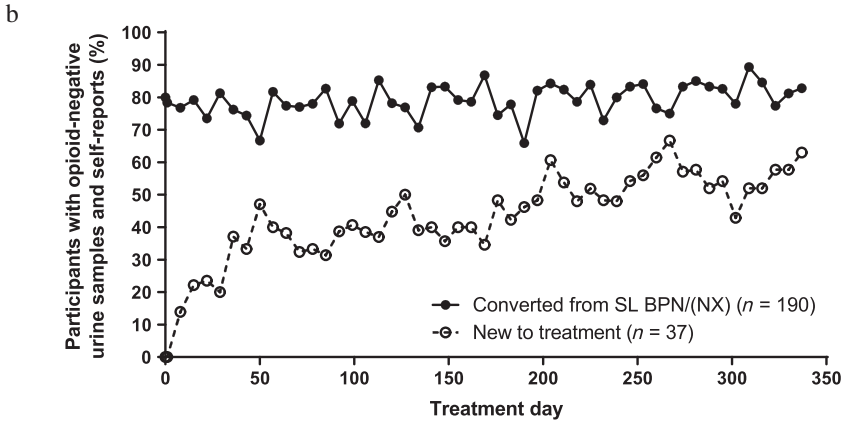
DISCUSSION

CAM2038 weekly and monthly was well tolerated in this Phase 3, open-label, multi-centre, 48-week safety study and demonstrated a safety profile consistent with the known profile of BPN [20]. The majority of TEAEs were mild or moderate in intensity. There were few injection-site TEAEs leading to discontinuations, and the majority of injection-site TEAEs, occurring in 20% of participants, were mild or moderate pain, swelling and erythema. There were no unexpected safety findings or drug-related SAEs. The overall incidence of TEAEs was numerically and statistically higher in participants converted from SL BPN relative to new to treatment ($P = 0.0001$). However, no difference was seen in severe TEAEs, SAEs, hospitalizations or discontinuation. The reason for the relatively low number of TEAEs in the new to treatment group is unknown.

Approximately equal numbers of participants started the study with weekly and monthly CAM2038, depending on treatment status at baseline. Additionally, investigators were able to treat with only weekly injections, only monthly injections, weekly then transitioning to monthly or monthly transitioning to weekly. As CAM2038 was available in multiple doses, this allowed the flexibility to individualize treatment based on clinical response. Temporary dose adjustments with 8-mg CAM2038, while allowed, were infrequent, occurring as only 5.8% of the total number of CAM2038 injections given. New-to-treatment participants were retained in treatment at least as well as those converted from SL BPN, suggesting that CAM2038 is suitable for new-to-treatment patients as well as those converting from SL BPN.

For the secondary end-point of effectiveness, measures of opioid withdrawal and cravings were well controlled following initiation of CAM2038. Composite self-report and urine toxicology measures of illicit opioid use were 63.0% at the end of the treatment for participants new to treatment and 82.8% for participants converted from SL





Treatment day	1	29	57	85	113	141	169	197	225	253	281	309	337
Converted from SL BPN/(NX), n	190	166	142	133	129	118	114	117	112	107	107	103	134
New to treatment, n	37	35	35	35	27	25	26	29	27	25	26	25	27

Figure 2 Efficacy measures, including (a) treatment period completion (participants who had day 337 visit); (b) percentage of urine samples and self-reports negative for illicit opioid use (*n* = participants who provided a urine sample); (c) scores for withdrawal, based on clinical opioid withdrawal scale scores; and (d) need to use visual analogue scale scores. COWS = clinical opioid withdrawal scale; SL BPN/NX = sublingual buprenorphine/naloxone; VAS = visual analogue scale

BPN. The majority of participants converted from SL BPN indicated that CAM2038 was 'much better' than their previous treatment.

Rates of treatment retention were high, with 167 of 227 (73.6%) total enrolled participants completing the 48-week treatment period. Our findings are favourable compared with other recent studies of long-term daily BPN. One large-scale randomized study reported retention rates of 46% after 6 months, with illicit opioid-negative urine samples in approximately 60% of participants [21]. In another recent 24-week extension study of daily BPN, the retention rate was 44%, and 76% of participants provided illicit opioid-negative urine samples at the end of the study [22]. Other studies reported treatment retention of approximately ≤ 60% at 6 months with daily BPN [23,24]. As demonstrated in this study, CAM2038 weekly and monthly may provide additional treatment retention benefits, as demonstrated by high retention rates at 24 and 48 weeks of treatment. This long-term study also reinforces previous safety and efficacy findings from earlier studies of CAM2038 [15].

Strengths of the study include a naturalistic, open-label design with flexible dosing and visit frequency, conducted across multiple geographies, and in patients initiating BPN treatment as well as converted from daily BPN. Baseline characteristics were representative of the population of participants with moderate or severe OUD. Additionally, the protocol allowed clinicians and participants

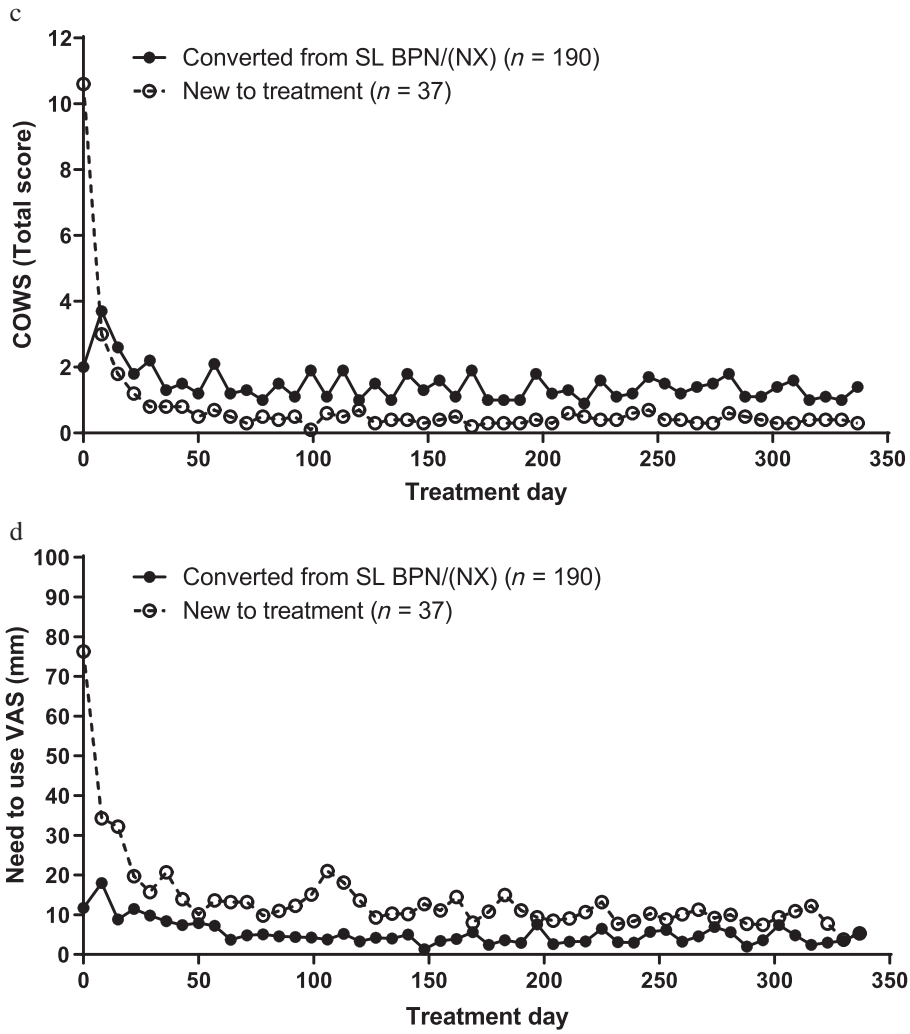


Figure 2 Continued

Table 5 Change in mean scores for withdrawal and craving from baseline to end of treatment.

	Converted from SL BPN		*New to BPN treatment*	
	Baseline	*End of treatment*	*Baseline*	*End of treatment*
COWS[a]	2.0 (2.7)	1.4 (2.3)	10.6 (3.7)	0.3 (0.5)
SOWS[b]	4.7 (8.1)	3.3 (6.3)	27.1 (15.3)	3.9 (8.0)
Desire to use VAS[c]	11.7 (24.2)	6.4 (16.5)	74.8 (24.8)	2.8 (6.2)
Need to use VAS[c]	11.7 (23.8)	5.4 (14.3)	76.3 (24.9)	5.3 (15.9)

Data presented as mean (SD). BPN = buprenorphine; COWS = Clinical Opioid Withdrawal Scale; SD = standard deviation; SL BPN = sublingual buprenorphine; SOWS = Subjective Opioid Withdrawal Scale; VAS = visual analogue scale. [a]Score ranges from 0 to 48. [b]Score ranges from 0 to 64. [c]100-mm scale.

considerable autonomy in dosing and treatment conditions, reflecting real-world conditions. Limitations include a lack of explicit directions concerning dosage increases for administration of supplemental BPN. Because the main purpose of this study was to examine the safety and acceptability of long-term treatment with CAM2038, the design did not include a control group. Some outcomes were collected by self-report to clinicians. No data were collected on broader psychosocial or quality-of-life outcomes.

CONCLUSION

In this study, CAM2038 was well tolerated, retained participants in treatment for the 48-week study and

had a systemic safety profile consistent with the known profile of BPN. CAM2038 weekly and monthly were effective in reducing and maintaining low opioid withdrawal and cravings scores, and the treatment was associated with a high percentage of illicit opioid-free urine samples and self-reports from treatment initiation throughout maintenance. Participant retention and abstinence appeared similar or compared favourably with recent studies of daily SL BPN, suggesting that this long-acting injectable BPN may be a useful addition to the armamentarium for treatment of OUD. Future research should examine types of patients who may particularly benefit from a long-acting injection. Patients having difficulty adhering to daily sublingual dosing would be promising candidates.

Declaration of interests

This study was sponsored by Braeburn. M.F. has received consulting fees from BioDelivery Sciences International, Braeburn Inc., Camurus and Knight Therapeutics; and served as an adviser for Kaleo, Indivior and US Worldmeds. G.B.'s institution has received grant support from the National Institutes of Drug Abuse, Braeburn Inc. and Reckitt-Benckiser/Indivior; G.B. reports consulting fees from Alkermes and Braeburn; served as an adviser to Alkermes, Otsuka, Titan Pharmaceuticals and Braeburn Inc.; and is on the speaker bureau for Alkermes. N.L. has received funding from Braeburn and Indivior to conduct clinical studies with buprenorphine products; and has served on advisory boards for Indivior and Mundipharma. J.S. reports consultancy fees to his institution from Martindale Pharma, Indivior, Mundipharma, Molteni Farma and Braeburn/Camurus AB; and grants from Martindale Pharma, Indivior, Mundipharma, and Camurus AB. A.D. reports grants from Braeburn/Camurus AB to Hunter New England Health, which employs A.D., during the conduct of the study. E.V.N. has consulted without compensation for Alkermes Inc., Braeburn/Camurus AB and Pear Therapeutics; and has been an investigator on National Institutes of Health-funded studies that received medication from Reckitt/Indivior and Alkermes. J.B.J. reports personal fees from Medpace Inc. during the conduct of the study and non-financial support from Camurus AB, outside the submitted work. L.C.F. reports non-financial support from Camurus AB, outside the submitted work. B.W. has received funding from Braeburn, Abbvie, Gilead, Mundipharma and Indivior to conduct clinical studies, and has served on advisory boards for Gilead, Abbvie and Merck for unrelated products. P.H. has served on advisory boards for Gilead and Merck for unrelated products. S.K. is an employee of and holds equity in Braeburn. S.O. was an employee of and holds equity in Braeburn. F.T. is an employee of and shareholder in Camurus AB.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Summary of participant satisfaction scale scores by item at end of study.

