Long-term safety, tolerability and effectiveness of CAM2038 weekly and monthly buprenorphine depots for treatment of opioid dependence: A U.S., Australian and European Phase 3 study

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Background

While buprenorphine is an efficacious treatment for opioid use disorder (OUD), daily oral/transmucosal preparations may be associated with poor adherence and extra-medical use including diversion and misuse. Long acting preparations of opioid medications have the potential to improve adherence, reduce illicit opioid use, and decrease burdens of daily medication.

Research Question(s)

To demonstrate long-term safety and local tolerability and evaluate efficacy of the depot buprenorphine formulation CAM2038 in adults with current diagnosis or past medical history of moderate-to-severe opioid use disorder. Longer term safety monitoring (e.g. 48 weeks) is important given that most efficacy studies are of shorter duration, and may not identify safety concerns after extended drug exposure.

Methods

This multinational, open-label, flexible dosing study conducted in USA, Australia and Europe enrolled participants, either seeking or currently in OUD treatment with sublingual buprenorphine, to individualised outpatient treatment with CAM2038. The study included screening, 48 weeks of treatment and 4 weeks of follow-up. Safety and local tolerability, urinalysis of illicit opioids, self-report of drug use, craving, withdrawal and other outcome measures were collected.

Results

A total of 227 participants were enrolled and dosed with CAM2038 (baseline demographics and characteristics shown in **Table 1**). A total of 167 (73.6%) participants completed the study treatment period with 156 (68.4%) receiving the full 48 weeks of treatment. Treatment retention over time is shown in **Figure 1**.

TABLE 1. Demographics and baseline clinical characteristics (Overall Safety Population)

Characteristic	Transferred from SL BPN treatment N = 190	New to BPN treatment N = 37	Overall N = 227
Age, y, mean (SD)	41.3 (9.64)	41.8 (9.41)	41.4 (9.59)
Sex			
Male	119 (62.6)	24 (64.9)	143 (63.0)
Female	71 (37.4)	13 (35.1)	84 (37.0)
Race			
White	183 (96.3)	20 (54.1)	203 (89.4)
Black or African American	3 (1.6)	17 (45.9)	20 (8.8)
Other	4 (2.1)	0 (0)	4 (1.8)
BMI, kg/m2, mean (SD)	26.7 (5.84)	25.3 (5.33)	26.5 (5.77)
Region			
Australia	23 (12.1)	1 (2.7)	24 (10.6)
Europe	76 (40.0)	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)
Neither	108 (56.8)	11 (29.7)	119 (52.4)
Substance abuse history			
Time to first opioid abuse, y, mean (SD)	14.7 (8.48)	15.7 (8.98)	14.8 (8.55)
Time to first diagnosis, y, mean (SD)	9.8 (7.60)	10.0 (8.60)	9.8 (7.75)
Heroin as primary opioid of use	97 (51.1)	37 (100.0)	134 (59.0)
Baseline withdrawal and cravings, mean (SD)			
COWS at baseline	2.0 (2.7)	10.6 (3.7)	3.4 (4.3)
SOWS at baseline	4.7 (8.1)	27.1 (15.3)	8.3 (12.7)
Desire to use VAS at baseline	11.7 (24.2)	74.8 (24.8)	22.0 (33.7)
Need to use VAS at baseline	11.7 (23.8)	76.3 (24.9)	22.3 (33.8)

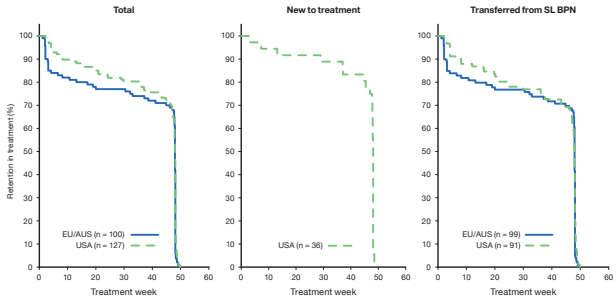
Unless otherwise noted, data presented as n (%).
BMI, body mass index; BPN, buprenorphine; COWS, clinical opioid withdrawal scale (0–48); SD, standard deviation; SL BPN, sublingual buprenorphine; SOWS, subjective opioid withdrawal scale (0–64); VAS, visual analogue scale (0–100 mm).

TABLE 2. Summary of treatment-emergent adverse events

Category	Overall Safety Population: Transferred from SL BPN N = 190	New to BPN treatment N = 37	Overall N = 227
A least 1 TEAE	131 (68.9)	12 (32.4)	143 (63.0)
At least 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)
At least 1 severe TEAE	13 (6.8)	2 (5.4)	15 (6.6)
Deaths	0 (0)	0 (0)	0 (0)
At least 1 SAE	10 (5.3)	2 (5.4)	12 (5.3)
At least 1 drug-related SAE	0 (0)	0 (0)	0 (0)
Hospitalisations	9 (4.7)	1 (2.7)	10 (4.4)
TEAEs leading to discontinuations	3 (1.6)	0 (0)	3 (1.3)
TEAEs in ≥5% of participants			
Nasopharyngitis	17 (8.9)	1 (2.7)	18 (7.9)
Urinary tract infection	9 (4.7)	3 (8.1)	12 (5.3)
Nausea	16 (8.4)	0 (0)	16 (7.0)
Vomiting	12 (6.3)	0 (0)	12 (5.3)
Headache	18 (9.5)	0 (0)	18 (7.9)
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)

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

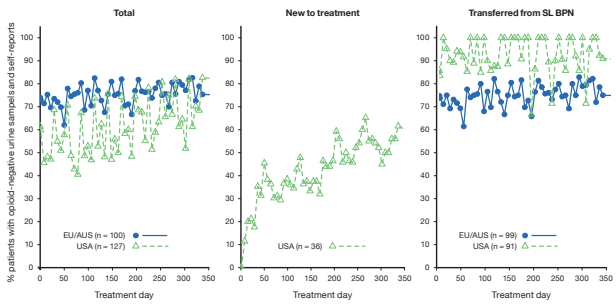
FIGURE 1. Retention in treatment by region with EU and AUS combined



Overall, 63.0% experienced any treatment-emergent adverse event (TEAE), with 26.4% being drug-related (**Table 2**). Serious TEAEs (5.3%) were considered not related to study drug. The safety profile of CAM2038 was generally consistent with the known safety profile of buprenorphine, except for injection site reactions (19.8%), of which 80% were of mild intensity.

Efficacy was generally well maintained over the study with a pronounced increase in the percentage of new to treatment patients with no illicit opioid use over time (**Figure 2**). Across the study, 76% of participant assessments (urine samples supported by self-reports) showed no evidence of illicit opioid use. Cravings and withdrawal were well controlled with mean need and desire to use VAS scores<10, SOWS<5 and COWS<2 after the first two months and until the end of treatment.

FIGURE 2. Percentage of patients with no illicit opioid use by time point and region (EU and AUS combined)



Data combines patients on weekly and monthly visit schedules. Missing values not imputed.

Conclusions

Individualised treatment with CAM2038 weekly and monthly depots demonstrated long-term safety and therapeutic effectiveness across 48 weeks and may be an interesting option for treatment of opioid dependence. The long acting duration combined with administration by healthcare professionals may reduce concerns about diversion, misuse, and accidental pediatric exposure.

John Strang (JS) is a clinician and researcher and has worked extensively with agencies in the addiction treatment fields and addiction-related charities and with government departments and has contributed to clinical guidelines on treatment types and provision. JS's employer (King's College London) has received, connected to his work, project grant support and/or honoraria and/or consultancy payments from Department of Health, NTA (National Treatment Agency), PHE (Public Health England), Home Office, NICE (National Institute for Health and Clinical Excellence), and EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) as well as research grants from (last 3 years) NIHR (National Institute on Health Research), MRC (Medical Research Council) and Pilgrim Trust. He has also worked with WHO (World Health Organization), UNODC (United Nations Office on Drugs and Crime), EMCDDA, FDA (US Food and Drug Administration) and NIDA (US National Institute on Drug Abuse) and also other international government agencies. JS's employer (King's College London) has also received, connected to his work, research grant support and/or payment of honoraria, consultancy payments and expenses from pharmaceutical companies (including, past 3 years, Martindale, Indivior, MundiPharma, Braeburn/Camurus) and trial medication supply from iGen and Braeburn. JS's employer (King's College London) has registered intellectual property on an innovative buccal naloxone with which JS is involved, and JS has been named in a patent registration by a Pharma company as inventor of a potential concentrated naloxone nasal spray. For updated information see: http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx

Adrian Dunlop, Michael Frost, Nicholas Lintzeris, Edward Nunes, Genie Bailey, Jakob Billeskov Jansen, Lars Chemnitz Frey and Bernd Weber were investigators in the study sponsored by Braeburn Pharmaceuticals. Sonnie Kim is an employee of Braeburn Pharmaceuticals and Fredrik Tiberg is an employee of Camurus AB.