Effect of Subcutaneous Weekly and Monthly Buprenorphine (CAM2038) Dose on OUD Treatment Outcomes

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INTRODUCTION

- Opioid Use Disorder (OUD) is a chronic, relapsing disease with various pharmacologic treatment options[1]
- The safety and effectiveness of buprenorphine (BPN) in both sublingual (SL), injectable, and implantable, extended-release formulations for treatment of OUD has been established[2]
- Clinical guidelines recommend a target dose of 16mg of SL BPN, with a range from 4 to 24mg for daily maintenance, but encourage individualization of dosing to find the lowest dose that can meet treatment goals[3]
- Flexible dosing enables individualized treatment to address evolving patient needs and to ensure comfort (i.e., suppress opioid craving and withdrawal) over the course of the disease[4]
- CAM2038 is an extended-release injectable BPN developed in weekly and monthly formulations with multiple doses

METHODS

- A post-hoc analysis was conducted to evaluate the impact of CAM2038 dose on OUD treatment outcomes in a 48-week, open-label, flexible-dosing, multi-national Phase 3 study evaluating the long-term safety, tolerability and efficacy of CAM2038 in adults with OUD[5]
- Inclusion criteria: Moderate to severe OUD; age 18–65 years; currently treated with SL BPN or BPN/naloxone (NX) (converted from SL BPN/NX group) or seeking to initiate BPN treatment and with no BPN treatment for ≥60 days (new to treatment group)[5]
- Exclusion criteria: Moderate to severe substance use disorder defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, for any substance other than opioids, caffeine, or nicotine; chronic pain requiring opioid treatment; acquired immune deficiency syndrome; and recent or current suicidal ideation or behavior based on the Columbia Suicide Severity Rating Scale[5]
- New-to-treatment participants were initiated with CAM2038 (weekly)[5]
- Participants converted from SL BPN or SL BPN/NX treatment were transitioned to treatment with CAM2038 (weekly) or (monthly) at doses corresponding to their prior daily treatment (**Table 1**) [5]
- In alignment with clinical practice and in accordance with Treatment Improvement Protocol (TIP)-63 Clinical Practice Guidelines[3], the study included flexible CAM2038 doses and individualized dose adjustments and changes in visit frequency were permitted as per the investigator's clinical judgement, in consultation with the participant, at any time during the treatment phase[5]
- Urine samples were collected at weekly or monthly visits based on the frequency of CAM2038 injection[5]
- Outcomes were evaluated by patient for each dose received prior to the collection of the outcome. Therefore, the sample size is variable between doses, depending on the frequency of the dose administered. Supplemental BPN doses were not included and missing values were not imputed.

Table 1. Dose Conversion for Patients Converting from Sublingual Buprenorphine or Buprenorphine/Naloxone to CAM2038 (weekly) and (monthly)

SL BPN or SL BPN/NX	CAM2038 (weekly)[a]	CAM2038 (monthly)
≤6 mg	8 mg (0.16 mL)	N/A
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	N/A	160 mg (0.45 mL)

[a]Participants were allowed dose adjustments as needed at scheduled visits or with 8 mg CAM2038 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 2 supplemental injections of 8 mg CAM2038 per week; dose adjustments could be made at investigator discretion at scheduled visits.
N/A, not applicable; SL BPN, sublingual buprenorphine; NX, naloxone

RESULTS

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.

Table 2. Demographics and Clinical Characteristics at Baseline (overall safety population)

Category	Converted from SL BPN/NX N = 190	New to Treatment N = 37	Overall N = 227
Age, mean (SD), y	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/m², 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)
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	4 (1.8)
Substance abuse history			
Opioid Use Disorder (DSM-5) diagnosis	157 (82.6)[a]	37 (100)	194 (85.5)
Time from first opioid abuse, y, mean (SD)	14.7 (8.5)	15.7 (9.0)	14.8 (8.6)
Time from first diagnosis, y, mean (SD)	9.8 (7.6)	10.0 (8.6)	9.8 (7.8)
Heroin as primary opioid of use, n (%)	97 (51.1)	37 (100.0)	134 (59.0)
Injection as route of heroin abuse, n (%)	80 (42.1)	14 (37.8)	94 (41.4)
Baseline withdrawal and cravings, mean (SD)[b]			
COWS[c]	2.0 (2.7)	10.6 (3.7)	3.4 (4.3)
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 edition; 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).

- 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)
- The doses utilized mimic clinical practice recommendation of 16 mg SL BPN target average dose, with some individuals requiring lower or higher doses
  - In participants converted from SL BPN, all available CAM2038 doses were utilized during the study, however, the majority received 24 or 32mg (weekly) CAM2038 (mean [SD]: 25.2mg [7.1]), and 96 or 128mg (monthly) CAM2038 (mean [SD]: 107.3mg [32.2]), corresponding to 16 to 24mg SL BPN
  - In new to treatment participants, the majority received 24mg of CAM2038 (weekly) (mean [SD] 23.4mg [4.4]), and 96mg (monthly) CAM2038 (mean[SD]: 85.3mg [15.8]), corresponding to 16mg SL BPN

Table 3. Highest CAM2038 Dose Reached by Regimen (overall safety population)

Regimen	CAM2038 dose (mg)	Converted from SL BPN/NX N=190 n (%)	New to Treatment N=37 n (%)	Total CAM2038 N=227 n (%)
Weekly	8	5 (4.3)	0	5 (3.2)
	16	21 (17.9)	7 (18.9)	28 (18.2)
	24	44 (37.6)	26 (70.3)	70 (45.5)
	32	45 (38.5)	4 (10.8)	49 (31.8)
	40[a]	2 (1.7)	0	2 (1.3)
Monthly	64	32 (23.0)	4 (33.3)	36 (23.8)
	96	48 (34.5)	8 (66.7)	56 (37.1)
	128	37 (26.6)	0	37 (24.5)
	160	22 (15.8)	0	22 (14.6)

[a]Dose achieved by the administration of supplemental doses of CAM2038 (weekly) 8mg in addition to the available CAM2038 (weekly) doses

- For participants converted from SL BPN/NX, the mean percentage urine samples negative for illicit opioids was similar across CAM2038 (weekly) 16mg, 24mg, and 32mg doses (range 76.5 to 80.9% urine samples negative for illicit opioids) and all monthly doses (range 83.2 to 88.6%). CAM2038 (weekly) 8mg and 40mg dose had 91.5% and 100% urine samples negative for illicit opioids, respectively, possibly reflecting the small sample size (n=31 and n=2). **(Table 4)**
- For participants new to treatment, the mean percentage urine samples negative for illicit opioids was similar across CAM2038 (weekly) 16mg, 24mg, and 32mg doses (range 25.5 to 37.6% urine samples negative for illicit opioids) and all monthly doses (range 67.5 to 79.2%). The ranges were wider as compared to the participants converted from SL BPN/NX, possibly reflecting the small sample size. **(Table 4)**

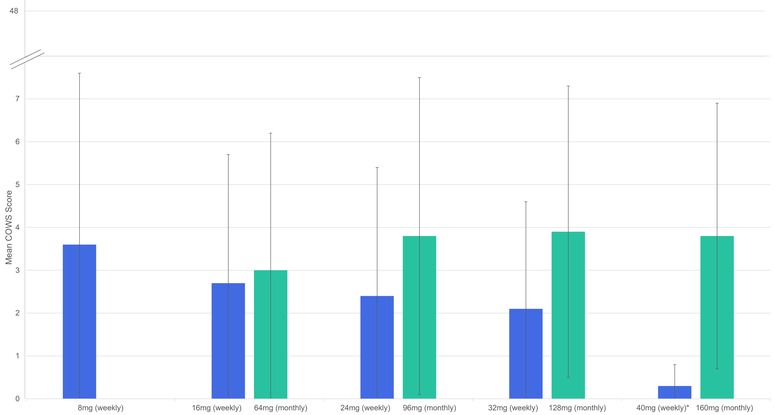
Table 4. Mean Percent of Urine Samples Negative for Illicit Opioids by Patient by Dose

Regimen	CAM2038 Dose (mg)	Converted from SL BPN/NX N=190 Mean %(SD)	New to Treatment N=37 Mean %(SD)	Total CAM2038 N=227 Mean %(SD)
Weekly	8	91.5 (24.9)	-	91.5 (24.9)
	16	77.4 (37.4)	25.5 (36.3)	66.6 (42.6)
	24	80.9 (34.8)	37.6 (35.9)	69.0 (40.0)
	32	76.5 (37.3)	27.2 (37.5)	72.0 (39.5)
	40[a]	100 (0)	-	100 (0)
Monthly	64	83.2 (33.8)	67.5 (39.5)	82.2 (34.0)
	96	84.5 (30.0)	79.2 (39.6)	84.0 (30.7)
	128	88.6 (26.5)	-	88.6 (26.5)
	160	85.6 (32.3)	-	85.6 (32.3)

SD; Standard Deviation; [a]Dose achieved by the administration of supplemental doses of CAM2038 (weekly) 8mg in addition to the available CAM2038 (weekly) doses

- Across all doses, opioid withdrawal was similar and well-controlled, with no mean Clinical Opioid Withdrawal Scale (COWS) score greater than 4 (range 0.33-3.89), indicative of no withdrawal. Overall, lower scores were not observed with increasing doses (**Figure 1**)

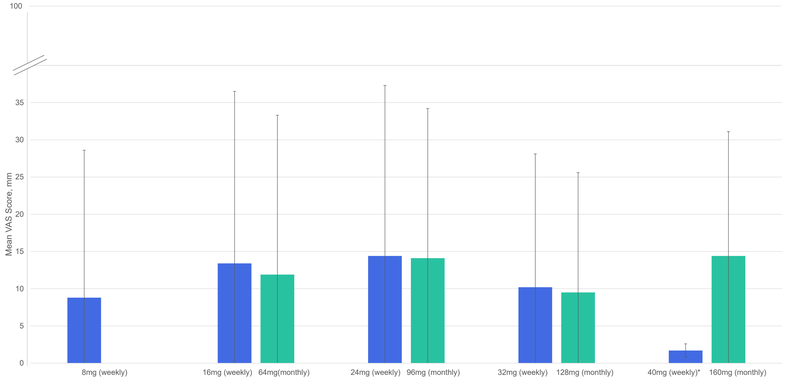
Figure 1. Clinical Opioid Withdrawal Scale (COWS) (N=227)



*Dose achieved by the administration of supplemental doses of CAM2038 (weekly) 8mg in addition to the available CAM2038 (weekly) doses

- Opioid cravings were controlled across all doses (range 1.67-14.45). Lower scores were not observed with increasing doses (**Figure 2**)
  - Assessed with a unipolar 100-mm Visual Analog Scale (VAS) ranging from 0 (no need to use) to 100 mm (strongest possible need to use) since the last visit

Figure 2. Opioid Craving: Need-To-Use Opioids (N=227)



*Dose achieved by the administration of supplemental doses of CAM2038 (weekly) 8mg in addition to the available CAM2038 (weekly) doses

- 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. With the exception of injection site adverse events, the long-term safety profile observed with CAM2038 was consistent with the known safety profile of SL BPN; no unexpected adverse events were observed. No deaths were reported. The overall incidence of TEAEs was higher in participants converted from SL BPN relative to new to treatment, the reason for the relatively low number of TEAEs in the new to treatment group is unknown. (**Table 5**)

Table 5. Overall Summary of Adverse Events (overall safety population)

Category	Converted from SL BPN N=190 n(%)	New to Treatment N=37 n(%)	Total N=227 n(%)
≥ 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)
≥ 1 SAE	10 (5.3)	2 (5.4)	12 (5.3)
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)

TEAE, treatment-emergent adverse event; SA, serious adverse event

CONCLUSIONS

- Treatment with CAM2038 individualized to lowest effective dose based on clinical response resulted in similar treatment outcomes in participants new to BPN treatment and converted from SL BPN/NX, independent of dose
- New to treatment and converted from SL BPN/NX participants responded to all doses of CAM2038. Treatment outcomes were similar for CAM2038 (weekly) and (monthly) formulations at comparable doses.
  - CAM2038 was effective in suppressing opioid cravings and withdrawal at all doses in participants that were new to treatment and converted from SL BPN/NX
  - The mean percentage urine samples negative for illicit opioids was similar across doses of CAM2038 in participants that were new to treatment and converted from SL BPN/NX
- CAM2038 was well-tolerated, with a safety profile consistent with the known profile of BPN
- As these are post-hoc analyses, and, in some cases the sample size is limited, more research is needed to evaluate the impact of CAM2038 dose on treatment outcomes

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