Injectable Weekly and Monthly Buprenorphine in the Outpatient Treatment of Fentanyl Users with Opioid Use Disorder.

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BACKGROUND

- The introduction of the very high potency opioid analgesic fentanyl into the illicit heroin supply in the U.S. has compounded the opioid epidemic. Fentanyl and its high potency analogs now account for a majority of overdose deaths, and for the rise in overdose deaths.[1]
- Fentanyl is a fully synthetic opioid, which does not bear a structural resemblance to naturally occurring opiates (morphine, codeine), it is not detected by routine immunoassay urine drug testing typically used as first-line screening. [2]
- Few clinical studies conducted to date have utilized quantitative urine toxicology methods for fentanyl and norfentanyl, thus, data on the effectiveness of buprenorphine (BPN) among those with positive urine toxicology for fentanyl is limited.[3]
- CAM2038, weekly or monthly subcutaneous (SC) BPN, is a ready-to-use, extended-release injection, with multiple dosing options for the treatment of OUD that may allow flexibility and individualization from day 1 initiation through long-term maintenance therapy.[4]
- A 24-week randomized controlled study evaluated the efficacy of CAM2038 as compared to the standard of care, daily sublingual buprenorphine/naloxone (SL BPN/NX). Previous post-hoc analyses of this study demonstrated higher proportion of responders (based on analyses of urine toxicology) in the CAM2038 treated group compared to SL BPN/NX in both participants who were heroin users and in participants who used injection route of administration of illicit opioids. While heroin was the most common opioid in prior to randomization urine samples, a significant proportion of study participants were positive for fentanyl (25.9%).[4] This post-hoc analysis was conducted to determine the impact of positive fentanyl use on buprenorphine treatment and the comparisons between CAM2038 and SL BPN/NX in this subgroup.

METHODS

- A Phase 3, outpatient, double-blind, double-dummy, active-controlled, parallel group study was conducted at 35 centers throughout the US to evaluate the non-inferiority and superiority of CAM2038 compared with the standard of care, daily SL BPN/NX, starting from day 1 of BPN initiation through maintenance treatment.[4]
- Primary endpoint variable was urine toxicology, conducted using highly sensitive, quantitative liquid chromatography tandem mass spectrometry (LC-MS/MS) analytical techniques and included fentanyl and its metabolite, norfentanyl.[4]
- Participants were randomized to CAM2038 or SL BPN/NX on day 1 of treatment initiation. Phase 1 (first 12 weeks) required weekly visits with both daily dosing and weekly injections. Participants transitioned to monthly visits during Phase 2 (second 12 weeks) with both daily dosing and monthly injections. (daily dosing = either SL BPN/NX or matching placebo; weekly or monthly injections = either CAM2038 or matching placebo injections).[4]
- A post-hoc analysis was conducted (intent-to-treat [ITT] population) to assess efficacy of CAM2038 compared with SL BPN/NX in treating subgroup of participants who tested positive for fentanyl/norfentanyl by LC-MS/MS with a cutoff of 0.1 ng/mL for fentanyl and 0.2 ng/mL for norfentanyl prior to randomization.

RESULTS

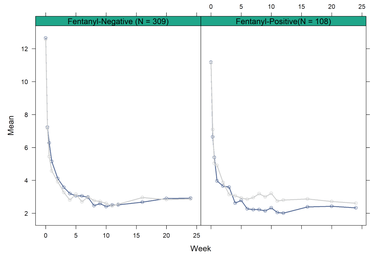
- Of the 428 randomized participants (enrolled mostly in 2016), a total of 111 (62 [29.1%] in the CAM2038 group and 49 [22.8%] in the SL BPN/NX group) provided positive urine toxicology results for fentanyl/ norfentanyl prior to randomization (65 men [58.6%] and 46 women [41.4%]; mean [SD] age, 39.1 [10.9] years).
  - Of the 317 subjects with no evidence of fentanyl use prior to randomization, 71 provided urine toxicology positive for fentanyl/ norfentanyl at any point during treatment phase (25 in the CAM2038 group and 46 in the SL BPN/NX group).
- The subgroup with baseline fentanyl exposure exhibited markers of greater severity of illness at baseline.
  - Most participants in the fentanyl-positive group (93 [83.8%]) identified heroin as their primary opioid of use, compared to (210 [66.2%]) in the fentanyl-negative group.
  - At baseline, the fentanyl-positive group provided higher mean percentage of positive urine toxicology results as compared to the fentanyl-negative group for cocaine (37.8% vs 20.2%) and benzodiazepines (21.6% vs 12.9%). (Table 1)
- There were no difference in IV route of use at baseline for both groups (54.1% vs 51.7% for fentanyl-positive and fentanyl-negative groups, respectively).
- In fentanyl-positive group, 40 out of 62 participants in the CAM2038 group completed the 24-week treatment period (64.5%); and 30 out of 49 participants in the SL BPN/NX group completed the 24-week treatment period (61.2%). Total (SL BPN/NX and CAM2038) retention rates were also similar for fentanyl-positive as compared to fentanyl-negative group (63.1% vs 65.0%).

Table 1. Demographics and Baseline Clinical Characteristics by Treatment and Fentanyl Use at Baseline

DEMOGRAPHICS AND CHARACTERISTICS	FENTANYL POSITIVE			FENTANYL NEGATIVE		
	CAM2038 N = 62	SL BPN/NX N = 49	Total N=111	CAM2038 N = 151	SL BPN/NX N = 166	Total N=317
Age, mean (SD), y	39.9 (11.1)	38.0 (10.7)	39.1 (10.9)	38.3 (11.2)	38.0 (11)	38.1 (11.1)
Male, No. (%)	32 (51.6)	33 (67.3)	65 (58.6)	89 (58.9)	109 (65.7)	198 (62.5)
White, No. (%)	47 (75.8)	34 (69.4)	81 (73.0)	112 (74.2)	130 (78.3)	242 (76.3)
Employed full or part time, No. (%)	19 (30.6)	15 (30.6)	34 (30.6)	57 (37.7)	57 (34.3)	114 (36.0)
Positive history of any arrest, No. (%)	36 (58.1)	25 (51.0)	61 (55.0)	94 (62.3)	119 (71.7)	213 (67.2)
Duration since OUD diagnosis, mean (SD), y	10.6 (14.6)	3.4 (6.8)	7.5 (12.1)	2.9 (4.8)	4.9 (6.0)	3.7 (5.4)
Injection route of illicit opioid use, No. (%)	36(58.1)	24(49.0)	60 (54.1)	78(51.7)	86(51.8)	164 (51.7)
Heroin primary opioid of use, No. (%)	54 (87.1)	39 (79.6)	93 (83.8)	98 (64.9)	112(67.5)	210(66.2/3)
Nonopioid drug use at screening, No (%):	55 (88.7)	47 (95.9)	102 (91.9)	123 (81.4)	137 (82.5)	260 (82.0)
Methamphetamine	7 (11.3)	3 (6.1)	10 (9.0)	31 (20.5)	29 (17.5)	60 (18.9)
Benzodiazepine	13 (21.0)	11 (22.4)	24 (21.6)	17 (11.3)	24 (14.5)	41 (12.9)
Marijuana	12 (19.4)	14 (28.6)	26 (23.4)	45 (29.8)	50 (30.1)	95 (30.0)
Cocaine	23 (37.1)	19 (38.8)	42 (37.8)	30 (19.9)	34 (20.5)	64 (20.2)
Hep. C antibody positive at screening, No. (%)	33 53.2)	18 36.7)	51 (45.9)	53 (35.1)	63 (38.0)	116 (36.6)
COWS score, mean (SD)	11.2 (4.0)	11.1 (5.0)	11.2 (4.4)	12.6 (5.9)	12.6 (6.3)	12.6 (6.1)
SOWS score, mean (SD)	33.9 (14.6)	32.5 (15.8)	33.3 (15.1)	30.5 (15.7)	30.0 (16.1)	30.2 (15.9)
Opioid craving: desire-to-use VAS (SD)	78.9 (22.1)	73.7 (24.9)	76.7 (23.4)	76.5 (27.8)	77.6 (25.5)	77.0 (26.6)
Opioid craving: need-to-use VAS (SD)	77.4 (26.0)	75.8 (25.0)	76.7 (25.8)	76.2 (25.2)	75.5 (24.7)	75.9 (24.9)

Data presented as n (%) unless otherwise noted. Clinical opioid withdrawal scale (COWS);Standard deviation (SD); Sublingual buprenorphine/naloxone (SL BPN/NX); Subjective opioid withdrawal scale (SOWS); Visual analog scale (VAS)

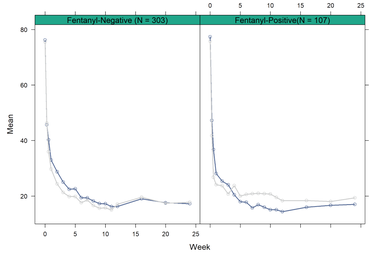
Figure 1. Mean Clinical Opioid Withdrawal Scale (COWS) Total Score Over Time in Fentanyl-Negative Group and Fentanyl-Positive Group



- For fentanyl-negative group, in both cohorts, opioid withdrawal, as evaluated by COWS, was suppressed from day 1 and throughout the study, including during transitions from weekly to monthly injections, without significant group differences.
- For fentanyl-positive group, opioid withdrawal was suppressed in both cohorts, however, COWS scores were lower for CAM2038 vs SL BPN/NX.

Sublingual buprenorphine/naloxone (SL BPN/NX)

Figure 2. Mean Craving Assessed by Need to Use VAS* by Treatment Week and Treatment Group in Fentanyl-Negative Group and Fentanyl-Positive Group

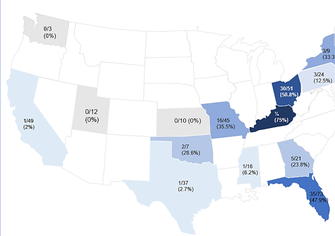


- For fentanyl-negative group, in both cohorts, ratings of opioid cravings were suppressed at treatment initiation on day 1 and throughout the study, including during transitions from weekly to monthly injections, without significant group differences.
- For fentanyl-positive group, ratings of opioid cravings were suppressed for both cohorts, however, ratings of opioid cravings were lower for CAM2038 vs SL BPN/NX.

*Need to Use (opioid cravings) were assessed using unipolar 100 mm VAS ("Since your last scheduled assessment visit, indicate your worst or strongest desire/need to use opioids, where 0 = No desire to use and 100 mm = Strongest possible desire, and from 0 = No need to use and 100 mm = Strongest possible need, respectively")

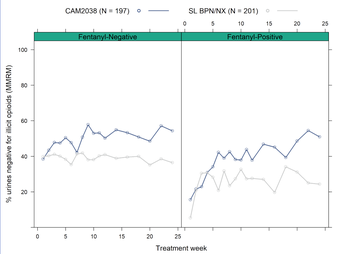
Sublingual buprenorphine/naloxone (SL BPN/NX)

Figure 3. Geographic Distribution and Proportion of Study Participants Who Tested Positive for Fentanyl/ Norfentanyl Prior to Randomization



- Most of the participants who tested positive for fentanyl and norfentanyl were concentrated in Ohio (30 [27%]), Missouri (16 [14.4%]), and Florida (35 [31.5%]). The rest were distributed throughout AL, CA, KY, MA, MS, NJ, NY, OK, PA and TX.
- The proportion of study participants who tested positive for fentanyl was highest in KY (75%), OH (58.8%), FL (47.9%), MO (35.5%), NY (33.3%), OK (28.6%), AL (23.8%) and NJ (20%).
- The proportion of participants with evidence of fentanyl use aligned with the growing prevalence of fentanyl use and fentanyl-related fatal overdoses observed in 2016.[6]

Figure 4. Weekly Percentage of Urine Samples Negative for Any Illicit Opioids by Treatment and Fentanyl Use at Screening/ Baseline (MMRM)

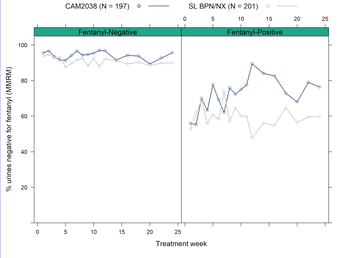


Sublingual buprenorphine/naloxone (SL BPN/NX)

Percent Urine Samples Negative for Any Illicit Opioids by Fentanyl Use at Screening/Baseline (weeks 1-24; not imputed)

Group	Treatment	Mean (%)	95% CI	p-value (ANOVA)
Fentanyl-Negative	CAM2038 (N=139)	48.7	0.2, 18.6	0.05
	SL BPN/NX (N=156)	39.3		
Fentanyl-Positive	CAM2038 (N=58)	34.8	-3.3, 24.6	0.13
	SL BPN/NX (N=45)	24.2		

Figure 5. Weekly Percentage of Urine Samples Negative for Fentanyl/ Norfentanyl by Treatment and Fentanyl Use at Screening/ Baseline (MMRM)



Sublingual buprenorphine/naloxone (SL BPN/NX)

Percent Urine Samples Negative for a) Fentanyl and b) Norfentanyl by Fentanyl Use at Screening/ Baseline (weeks 1-24; not imputed)

A

Group	Treatment	Mean (%)	95% CI	p-value (ANOVA)
Fentanyl-Negative	CAM2038 (N=139)	94.2	-2.5, 8.1	0.30
	SL BPN/NX (N=156)	91.4		
Fentanyl-Positive	CAM2038 (N=58)	69.9	2.0, 20.1	0.01
	SL BPN/NX (N=45)	58.9		

B

Group	Treatment	Mean (%)	95% CI	p-value (ANOVA)
Fentanyl-Negative	CAM2038 (N=139)	91.0	-0.9, 11.9	0.09
	SL BPN/NX (N=156)	85.5		
Fentanyl-Positive	CAM2038 (N=58)	56.0	2.9, 24.6	0.01
	SL BPN/NX (N=45)	42.2		

Table 2. Highest Dose Achieved Week 1

Group	Dose*	CAM2038 (N=213)		SL BPN/NX (N=215)	
		n (N=151)	%	n (N=166)	%
Fentanyl-Negative (N=317)	8mg	1	0.7	3	1.8
	16mg	93	61.6	110	66.3
	24mg	40	26.5	40	24.1
	Other	17**	11.2	13***	7.8
		n (N=62)	%	n (N=49)	%
Fentanyl-Positive (N=111)	8mg	1	1.6	1	2.0
	16mg	41	66.1	34	69.4
	24mg	14	22.6	10	20.4
	Other***	6	9.7	4	8.2

*CAM2038 doses were converted to SL BPN/NX dose equivalents based on the following conversions: CAM2038 weekly 16, 24, and 32mg was converted to SL BPN/NX daily doses of 8, 16, and 24mg, respectively.
**One participant achieved a dose of CAM2038 8mg weekly and 16 participants were not dosed
***Not dosed

Table 3. Highest Dose Achieved

Group	Dose* (SL BPN dose equivalents)	CAM2038 (N=213) n (N=151)	%	SL BPN/NX (N=215) n (N=166)	%
Fentanyl-Negative	8mg	20	13.2	15	9.0
	16mg	75	49.7	83	50
	24mg	50	33.1	60	36.1
	32mg	6	4.0	8	4.8
		n (N=62)	%	n (N=49)	%
Fentanyl-Positive	8mg	7	11.3	4	8.2
	16mg	28	45.2	24	49.0
	24mg	24	38.7	20	40.8
	32mg	3	4.8	1	2.0

*CAM2038 doses were converted to SL BPN/NX dose equivalents based on the following conversions: CAM2038 weekly 16, 24, 32mg and CAM2038 monthly 64, 96 and 128mg were converted to SL BPN/NX daily doses of 8, 16, and 24mg, respectively. CAM2038 monthly 160mg was converted to SL BPN/NX 32mg daily.

Table 4. Summary of Treatment-Emergent Adverse Events (AEs)

Adverse Event Characteristic	FENTANYL-POSITIVE SL BPN/NX N = 49	FENTANYL-POSITIVE CAM2038 N = 62	FENTANYL-POSITIVE Total N=111	FENTANYL-NEGATIVE SL BPN/NX N = 166	FENTANYL-NEGATIVE CAM2038 N = 151	FENTANYL-NEGATIVE Total N=317
Participants with any TEAEs	25 (51.0)	32 (51.6)	57 (51.3)	94 (56.6)	96 (63.6)	190 (59.9)
Number of TEAEs	155	147	302	407	326	733
Participants with serious AEs	3 (6.1)	0	3 (2.7)	10 (6.0)	5 (3.3)	15 (4.7)
Participants with AEs that led to drug discontinuation	0	0	0	3 (1.8)	7 (4.6)	10 (3.1)
Participants with suspected to be drug-related AEs	16 (32.7)	21 (33.9)	37 (33.3)	48 (28.9)	49 (32.5)	97 (30.6)
Participants with AEs that resulted in death	0	0	0	0	1 (0.7)*	1 (0.3)
Occurred in ≥5% of study participants	22 (44.9)	25 (40.3)	47 (42.34)	70 (42.2)	66 (43.7)	136 (42.9)
Injection-site pain	3 (6.1)	4 (8.2)	7 (6.3)	14 (9.3)	15 (9.9)	29 (9.1)
Headache	1 (2.0)	3 (6.1)	4 (3.6)	16 (10.6)	13 (8.6)	29 (9.1)
Constipation	6 (12.2)	5 (10.2)	11 (9.9)	10 (6.6)	11 (7.3)	21 (6.6)
Nausea	5 (10.2)	7 (14.3)	12 (10.8)	12 (7.9)	8 (5.3)	20 (6.3)
Injection-site pruritus	4 (8.2)	3 (6.1)	7 (6.3)	9 (6.0)	10 (6.6)	19 (6.0)
Injection-site erythema	3 (6.1)	3 (6.1)	6 (5.4)	9 (6.0)	9 (6.0)	18 (5.7)

*Participant was hit by a car and died; the death was assessed as unlikely related to the study drug

- Three non-fatal accidental overdoses involving heroin were reported, all occurred in the fentanyl-negative SL BPN/NX group; 1 overdose occurred in the context of withdrawal after being jailed without study medication.
- There were no clinically meaningful differences between the treatments for SAEs; however, all SAEs in the Infections and Infestations System Organ Class occurred in the SL BPN/NX group, suggesting ongoing IV drug use. For fentanyl-negative group, this included acute hepatitis C (n = 1), cellulitis (n = 1), osteomyelitis (n = 1), pneumonia (n = 1), and sepsis (n = 1). For fentanyl-positive group, this included abscess (n = 1, limb; n = 1 subcutaneous), and localized infection (n = 1).
- With the exception of injection site AEs, the safety profile observed with CAM2038 was consistent with the known safety profile of SL BPN with no unexpected AEs observed.

CONCLUSIONS

- The proportion of participants with evidence of fentanyl use aligned with the growing prevalence of fentanyl use and fentanyl-related fatal overdoses observed in 2016.[6]
- In this diverse sample of participants seeking treatment for OUD, the subgroup with exposure to fentanyl at screening or day 1 exhibited markers of greater severity of illness at baseline (more heroin use, more co-occurring cocaine use), took longer to stabilize, and produced fewer opioid negative urine results during treatment.
- The fentanyl-positive group did not require higher BPN doses; and cravings and withdrawal, as measured by COWS and VAS, were comparable to fentanyl-negative group.
- Consistent with previous post-hoc analyses of subgroups reporting heroin or intravenous drug use at baseline, [4, 5] treatment with CAM2038 resulted in a greater percentage of urine samples negative for illicit opioids in participants with evidence of fentanyl use prior to randomization vs SL BPN/NX. These findings are consistent with the primary and secondary endpoints of the total study population from this Phase 3 study. [4]
- The long-acting weekly and monthly injectable BPN, CAM2038, may have an advantage over SL BPN/NX on illicit opioid use outcome among difficult-to-treat patient population, including those who test positive for fentanyl at treatment initiation.
- As these are post-hoc analyses from a randomized study, results should be interpreted with caution as further studies are needed to confirm the improved effectiveness of CAM2038 in these subgroups.

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