Poster 131

Phase 3 trial comparing depot buprenorphine (CAM2038) to sublingual buprenorphine/naloxone for OUD treatment: Subanalysis among persons with heroin as the primary opioid of abuse

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ABSTRACT

Aims: To report subgroup analyses for participants identifying heroin as the primary opioid of abuse (n = 303) from a phase 3 trial comparing the extended-release depot injectable buprenorphine (CAM2038) to sublingual buprenorphine/naloxone (SL BPN/NX) in initiation and maintenance treatment of adults with moderate-to-severe Opioid Use Disorder (OUD) (n = 428).

Methods: This 24-week, randomized, double-blind, double-dummy, active-controlled, parallel group, multicenter study, designed to evaluate the non-inferiority of CAM2038 compared to an existing standard of care, SL BPN/NX, in initiation and maintenance treatment with buprenorphine. The prespecified primary endpoint was responder rate, with a responder defined as having no evidence of illicit opioid use at ≥8 of 10 pre-specified time points over Weeks 9–24; two must be at Week 12 and during Month 6 (weeks 21-24). The study involved four phases: Screening, Phase 1 (weekly visits), Phase 2 (monthly visits), and Follow-up. A post-hoc analysis was conducted (ITT population) to access efficacy of CAM2038 compared to SL BPN/NX in treating participants identifying heroin as the primary opioid of abuse at baseline.

Results: Primary analyses demonstrated that CAM2038 (17.4%) was noninferior to SL BPN/NX (14.4%) on the primary endpoint of responder rate. The responder rate among opioid dependent participants using heroin at baseline was higher in the CAM2038 group (15.8%) compared to SL BPN/NX group (4.6%), a difference of 11.2% (95% CI, 4.5%, 17.9%). The mean percentage of urine samples negative for illicit opioids supported by self-reports was higher in the CAM2038 group (28.2%) relative to SL BPN/NX group (13.2%), a 15.0% difference (95% CI, 7.8%, 22.1%; p <0.001). In both treatment groups, a majority of participants completed the study with retention rates of 56% for the CAM2038 group and 54% for the SL BPN/NX group.

Conclusions: Treatment with CAM2038 was shown to increase the likelihood of no illicit opioid-use compared to current standard treatment with SL BPN/NX in participants whose primary opioid of abuse was heroin.

INTRODUCTION

- In the United States, heroin is increasingly available in larger quantities and increasing purity, used by a greater number of people, and is causing an increasing number of deaths due to overdoses[1]
- In 2016, an estimated 15,446 people died from heroin-related overdoses, more than quadruple the number in 2010[2,4,6]
- Increased demand for, and use of, heroin is being driven by both increasing availability of heroin in the U.S. market and by prescription drug users turning to heroin, potentially as a result of reduction efforts involving the availability of prescription opioids[3,5,6]
- In 2014, the population using prescription pain relievers non-medically was approximately 10 times the size of the heroin user population; however, heroin-involved deaths were more than double than those reported for opioid analgesic-involved overdose deaths[5]
- Heroin use is associated with treatment attrition and opioid misuse during treatment for OUD[7]
- SL BPN/NX is known to be effective for the treatment of OUD, however treatment response is typically lower in people that use heroin[7]

METHODS

- A Phase 3 outpatient, double-blind, double-dummy, active-controlled, parallel group, multi-center study was conducted to evaluate the non-inferiority of CAM2038 compared with an existing standard of care, SL BPN/NX, in buprenorphine initiation and maintenance treatment
- A post-hoc analysis was conducted to assess the efficacy of CAM2038 compared with SL BPN/NX in treating participants for whom heroin was the primary opioid of abuse at baseline
- Participants randomized 1:1 to SL BPN/NX tablets + placebo SC injections or CAM2038 SC injections + SL placebo tablets
- The study involved four phases: screening, phase 1 (weekly visits), phase 2 (3 monthly visits plus 3 unscheduled urine sample visits), and follow-up
- Inclusion criteria: age 18 to 65 years, diagnosed with and seeking treatment for moderate-to-severe OUD, considered to be good candidates for buprenorphine treatment based on medical and psychosocial history, and willing to use reliable contraception
- Exclusion criteria: receiving pharmacotherapy for OUD within 60 days or any investigational drug within 4 weeks; AIDS; chronic pain requiring opioid therapy; pregnancy, lactation, or planned pregnancy; hypersensitivity or allergy to buprenorphine, other opioids, or excipients in CAM2038; use of strong cytochrome P450 3A4 inhibitors (azole antifungals, macrolide antibiotics, or protease inhibitors); recent or current suicidal ideation or behavior; risk for torsades de pointes (heart failure, hypokalemia, or family history of long QT syndrome); electrocardiogram with Fridericia formula QTc > 450 milliseconds in men and > 470 milliseconds in women; aspartate aminotransferase or alanine aminotransferase levels 3-fold higher than the upper limits of the reference range; total bilirubin or creatinine level 1.5-fold higher than the upper limits of the reference range; or pending legal action or other factors or conditions that could adversely affect participant safety and adequate adherence
- Assessments:
  - Urine samples collected at all scheduled visits (weekly during Phase 1 and monthly during Phase 2) plus 3 random unscheduled visits during phase 2; missing urine results were imputed as positive
    - Urine toxicology was conducted using quantitative methods (liquid chromatography-tandem mass spectrometry [LC/MS-MS])
  - Participant self-reports using a timeline follow-back interview at all visits
  - Other outcomes: time to first illicit opioid use, percentage of illicit opioid use by month, and cumulative percentage of negative urine results at 6 months; craving and withdrawal and safety, based on adverse event (AE) reporting
    - Self-reported opioid craving was measured with unipolar “desire-to-use” and “need-to-use” 100-mm visual analogue scales (VAS, range 0 [none] to 100 [strongest possible)
    - Opioid withdrawal was measured as screening, day 1, and at every visit by the Subjective Opioid Withdrawal Scale (SOWS) and Clinical Opioid Withdrawal Scale (COWS)
- Adverse events were coded by primary system organ class (SOC) and preferred term according to MedDRA version 18, and summarized by number and percent of subjects in each primary SOC and preferred term
- The prespecified primary endpoint was responder rate (RR), with a responder defined as having no evidence of illicit opioid use (negative urine test for opioids supported by self-report of no illicit use) at ≥8 of 10 pre-specified time points over weeks 9–24; 2 were required week 12 and during month 6 (weeks 21-24)
- Continuous data were summarized using descriptive statistics; categorical data were summarized as frequencies and percentages (chi-square for RR; analysis of variance (ANOVA) for mean urine toxicology; Wilcoxon for CDF)

RESULTS

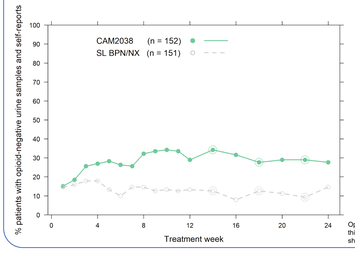
Table 1. Demographics and baseline clinical characteristics for participants identifying heroin as the primary opioid of abuse at baseline (n=303)

Category	CAM2038 N = 152	SL BPN/NX N = 151	Total N=303
Age, mean (SD), y	38.9 (11.2)	38.9 (11.4)	38.9 (11.3)
Male, No. (%)	86 (56.6)	105 (69.5)	191 (63.0)
White, No. (%)	101 (66.4)	105 (69.5)	206 (68.0)
Ethnicity			
Hispanic or Latino	19 (12.5)	19 (11.9)	37 (12.2)
Not Hispanic or Latino	133 (37.5)	133 (88.1)	266 (87.8)
BMI, mean (SD), kg/m²	25.2 (4.9)	25.5 (4.9)	25.3 (4.9)
Employed full or part time, No. (%)	42 (27.6)	41 (27.2)	83 (27.4)
Education status, No. (%)			
College or university degree (2 or 4 year)/ Graduate	11 (7.2)	18 (12.0)	29 (9.6)
Did not complete high school	28 (18.4)	33 (21.9)	61 (20.1)
High school diploma or GED	62 (40.8)	56 (37.1)	118 (38.9)
Some college or certificate program	51 (33.6)	43 (28.5)	94 (31.0)
History of any arrest, No. (%)	101 (66.4)	112 (74.2)	213 (70.3)
Duration since OUD diagnosis, mean (SD), y	4.03 (8.74)	3.19 (4.67)	3.72 (7.44)
Injection route of illicit opioid use, No. (%)	97 (63.8)	95 (62.9)	192 (63.4)
Utox positive for Fentanyl at screening, No. (%)	54 (35.5)	39 (25.8)	93 (30.7)
Nonopioid drug use at screening, No (%):			
Methamphetamine	27 (17.8)	25 (16.6)	52 (17.2)
Benzodiazepine	18 (11.8)	23 (15.2)	41 (13.5)
Marijuana	39 (25.7)	47 (31.1)	86 (28.4)
Cocaine	51 (33.6)	47 (31.1)	98 (32.3)
Hepatitis C antibody positive at screening, No. (%)	71 (46.7)	70 (46.4)	141 (46.5)
Medical history of depression, No. (%)	16 (10.5)	19 (12.6)	35 (11.6)
COWS, mean (SD)	11.74 (4.79)	11.86 (5.95)	11.80 (5.39)
SOWS, mean (SD)	32.0 (14.9)	31.4 (167)	31.7 (15.8)
Desire to use VAS (SD)	76.2 (26.7)	77.1 (24.6)	76.6 (25.8)
Need to use VAS (SD)	75.4 (26.3)	76.0 (25.7)	75.7 (26.0)

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

- Of the 428 participants randomized, 303 (70.8%) identified heroin as the primary opioid of abuse at baseline
- Demographics and clinical characteristics were similar between treatment groups for participants identifying heroin as the primary opioid of abuse at baseline
- Responder rate was higher in the CAM2038 group (15.8%) compared to SL BPN/NX group (4.6%), a difference of 11.2% (95% CI, 4.5%, 17.9%; p<0.001) for participants identifying heroin as the primary opioid of abuse at baseline (Chi-square)

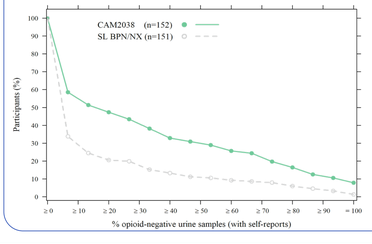
Figure 1. Mean percentage of participants with urine toxicology results negative for illicit opioids supported by self-reports over time (ITT population) for participants identifying heroin as the primary opioid of abuse at baseline (n=303)



- The mean percentage of urine samples negative for illicit opioids supported by self-reports was higher in the CAM2038 group (28.2%) relative to SL BPN/NX group (13.2%), a 15.0% difference (95% CI, 7.8%, 22.1%; p<0.001; superiority [ANOVA])

Open circles denote random samples. The random samples are the first, second, and third random sample, respectively, and these could occur in another period than shown. Sublingual buprenorphine/naloxone (SL BPN/NX)

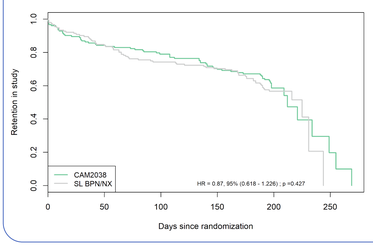
Figure 2. Cumulative distribution function (CDF) of percentage of opioid-negative urine samples supported by self-report for treatment weeks 4 to 24 for participants identifying heroin as the primary opioid of abuse at baseline (n=303)



- p<0.001 (Wilcoxon; superiority)
- Median (weeks 4 to 24)
  - CAM2038: 13.3%
  - SL BPN/NX: 0
- LS Mean (weeks 4 to 24)
  - CAM2038: 29.9%
  - SL BPN/NX: 12.7%

Sublingual buprenorphine/naloxone (SL BPN/NX)

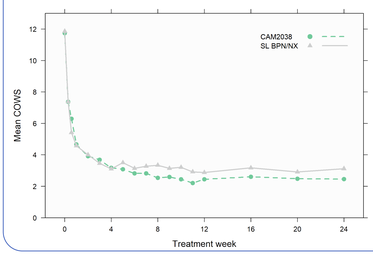
Figure 3: Retention in study for participants identifying heroin as the primary opioid of abuse at baseline (n=303)



- Majority of participants in both groups completed the study
- Retention rates were 56% for participants treated with CAM2038 and 54% for participants treated with SL BPN/NX

Last day in study used as censoring.
Hazard ratio (HR); Sublingual buprenorphine/naloxone (SL BPN/NX)

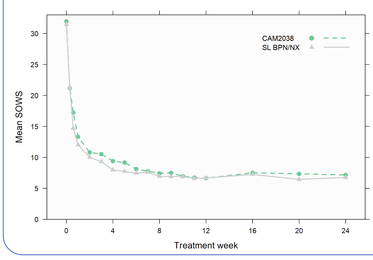
Figure 4. Mean Clinical Opioid Withdrawal Scale (COWS) total score over time for participants identifying heroin as the primary opioid of abuse at baseline (n=303)



- In both groups, 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

Sublingual buprenorphine/naloxone (SL BPN/NX)

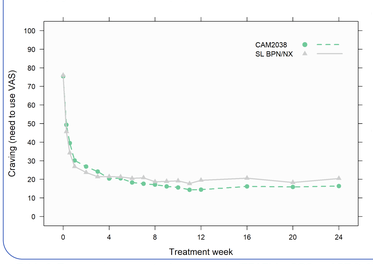
Figure 5. Mean Subjective Opioid Withdrawal Scale (SOWS) total score over time for participants identifying heroin as the primary opioid of abuse at baseline (n=303)



- In both groups, opioid withdrawal, as evaluated by SOWS, was suppressed from day 1 and throughout the study, including during transitions from weekly to monthly injections, without significant group differences

Sublingual buprenorphine/naloxone (SL BPN/NX)

Figure 6. Mean craving assessed by need to use VAS by treatment week and treatment group among participants identifying heroin as the primary opioid of abuse at baseline (n=303)



- 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”)
- In both groups, opioid cravings (need-to-use VAS item) were suppressed from day 1 and throughout the study, including during transitions from weekly to monthly injections without significant group differences

Sublingual buprenorphine/naloxone (SL BPN/NX)

Table 2. Treatment emergent adverse events (TEAE) by SOC and PT (≥ 2% in either CAM2038 or SL BPN/NX for participants identifying heroin as the primary opioid of abuse at baseline, Safety Population)

System Organ Class/Preferred Term	CAM2038 N=152 n (%)	SL BPN/NX N=151 n (%)	Total N=303 n (%)
Cardiac disorders			
Tachycardia	5 (3.3%)	5 (3.3%)	10 (3.3%)
Gastrointestinal disorders			
Constipation	10 (6.6%)	6 (4.0%)	16 (5.3%)
Diarrhea	4 (2.6%)	5 (3.3%)	9 (3.0%)
Nausea	9 (5.9%)	4 (2.6%)	13 (4.3%)
Toothache	2 (1.3%)	6 (4.0%)	8 (2.6%)
General disorders and administration site conditions			
Injection site erythema	5 (3.3%)	5 (3.3%)	10 (3.3%)
Injection site induration	2 (1.3%)	5 (3.3%)	7 (2.3%)
Injection site inflammation	2 (1.3%)	7 (4.6%)	9 (3.0%)
Injection site pain	9 (5.9%)	8 (5.3%)	17 (5.6%)
Injection site pruritus	7 (4.6%)	7 (4.6%)	14 (4.6%)
Injection site reaction	4 (2.6%)	3 (2.0%)	7 (2.3%)
Injection site swelling	4 (2.6%)	4 (2.6%)	8 (2.6%)
Infections and infestations			
Cellulitis	0 (0.0%)	6 (4.0%)	6 (2.0%)
Nasopharyngitis	4 (2.6%)	2 (1.3%)	6 (2.0%)
Upper respiratory tract infection	8 (5.3%)	5 (3.3%)	13 (4.3%)
Urinary tract infection	6 (3.9%)	8 (5.3%)	14 (4.6%)
Injury, poisoning and procedural complications			
Accidental overdose	0 (0.0%)	4 (2.6%)	4 (1.3%)
Investigations			
Alanine aminotransferase increased	4 (2.6%)	4 (2.6%)	8 (2.6%)
Aspartate aminotransferase increased	4 (2.6%)	4 (2.6%)	8 (2.6%)
Musculoskeletal and connective tissue disorders			
Back pain	2 (1.3%)	5 (3.3%)	7 (2.3%)
Nervous system disorders			
Headache	10 (6.6%)	3 (2.0%)	13 (4.3%)
Hypoaesthesia	4 (2.6%)	0 (0.0%)	4 (1.3%)
Psychiatric disorders			
Insomnia	7 (4.6%)	4 (2.6%)	11 (3.6%)

Sublingual buprenorphine/naloxone (SL BPN/NX); System organ class (SOC)

- All four participants with accidental overdose were in the SL BPN/NX group (3 involving heroin and 1 involving clonazepam); 1 overdose occurred in the context of withdrawal after being jailed without study medication
- With the exception of injection site treatment-emergent adverse events, the safety profile observed with CAM2038 was consistent with the known safety profile of SL BPN; no unexpected adverse events were observed

CONCLUSIONS

- Treatment with CAM2038 increased the likelihood of no illicit opioid-use compared with current standard treatment with SL BPN/NX in participants whose primary opioid of abuse at baseline was heroin
- CAM2038 was effective in treating heroin dependent individuals, showing sustained opioid withdrawal and craving suppression from treatment initiation through maintenance, including during transition from weekly to monthly injections with a safety profile comparable to that of SL BPN/NX with the exception of injection site reactions
- Weekly and monthly dosing options allow treatment providers the ability to individualize dosing based on evolving patient needs as done in current clinical practice

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DISCLOSURES

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