Injectable Buprenorphine (CAM2038) vs. Sublingual Buprenorphine/Naloxone (SL-BPN/NX): Subpopulation Analyses Among Primary Heroin Users and Opioid Injectors

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BACKGROUND

- Daily sublingual buprenorphine/ naloxone (SL BPN/NX) is known to be effective for the treatment of opioid use disorder (OUD)
- Ongoing heroin and injection drug use during OUD treatment are not uncommon and some data suggest heroin use (versus prescription opioid use) and injection opioid use (versus non-injection opioid use) are associated with worse retention and more illicit opioid misuse while on SL BPN/NX OUD treatment[1]
- People who inject drugs (PWID) are susceptible to serious health hazards including blood-borne diseases and bacterial skin, soft tissue, and blood infections, with up to 32% of PWID affected by cellulitis and skin or soft tissue abscesses at a given time[2,3]
- An estimated 72.7% of PWID are people that mainly inject opioids (PWIO)[4]
- In the United States, heroin is increasingly available in larger quantities and increasing purity often tainted with fentanyl, used by a greater number of people, and is causing an increasing number of overdose deaths, with an estimated 15,958 deaths from heroin-related overdoses in 2017[5,6]

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, daily SL BPN/NX, in BPN initiation and maintenance treatment[7]
- 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 at week 12 and during month 6 (weeks 21-24)
  - Phase 1 (12 weekly visits), phase 2 (3 monthly visits plus 3 unscheduled urine sample visits), and follow-up
- Urine toxicology conducted using quantitative methods (liquid chromatography-tandem mass spectrometry [LC/MS-MS])
- A post-hoc analysis was conducted (intent-to-treat [ITT] population) to assess efficacy of CAM2038 compared with SL BPN/NX in treating subgroups of participants whom heroin was the primary opioid of abuse at baseline and PWIO

RESULTS

- Of the 428 participants randomized, 303 (70.8%) identified heroin as the primary opioid of abuse; 224 (52.33%) identified injection as the preferred route of illicit opioid use (PWIO) at baseline
- In participants identifying heroin as the primary opioid of abuse:
  - Responder rate (RR) was higher for CAM2038 (15.8%) vs. SL BPN/NX (4.6%), a difference of 11.2% (95% CI, 4.5%, 17.9%; p<0.001; Chi-square)
  - Retention was 56% for CAM2038 and 54% for SL BPN/NX
- In PWIO
  - RR was higher for CAM2038 (15.8%) vs. SL-BPN/NX (7.3%), a difference of 8.5% (95% CI 0.2%, 16.8%; p=0.047; Chi-square)
  - Retention was 55% for CAM2038 group compared to 49% for the SL BPN/NX

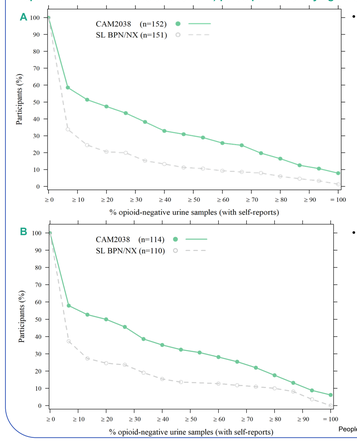
Table 1. Demographics and baseline clinical characteristics for participants identifying heroin as the primary opioid of abuse and PWIO

Demographics and Characteristics	Heroin CAM2038 N = 152	Heroin SL BPN/NX N = 151	Heroin Total N=303	PWIO CAM2038 N = 114	PWIO SL BPN/NX N = 110	PWIO Total N=224
Age, mean (SD), y	38.9 (11.2)	38.9 (11.4)	38.9 (11.3)	37.32 (11.65)	37.15 (11.54)	37.24 (11.57)
Male, No. (%)	86 (56.6)	105 (69.5)	191 (63.0)	62 (54.4)	73 (66.4)	135 (60.3)
White, No. (%)	101 (66.4)	105 (69.5)	206 (68.0)	90 (78.9)	91 (82.7)	181 (80.8)
Employed full or part time, No. (%)	42 (27.6)	41 (27.2)	83 (27.4)	34 (29.8)	28 (25.5)	62 (27.7)
History of any arrest, No. (%)	101 (66.4)	112 (74.2)	213 (70.3)	80 (70.2)	86 (78.2)	166 (74.1)
Duration since OUD diagnosis, mean (SD), y	4 (8.74)	3.19 (4.67)	3.72 (7.44)	3.06 (5.29)	2.76 (3.54)	2.95 (4.66)
Injection route of illicit opioid use, No. (%)	97 (63.8)	95 (62.9)	192 (63.4)	114 (100)	110 (100)	224 (100)
Heroin primary opioid of use, No. (%)	152 (100)	151 (100)	303 (100)	97 (85.1)	95 (86.4)	192 (85.7)
Utox Fentanyl positive at screening, No. (%)	54 (35.5)	39 (25.8)	93 (30.7)	36 (31.6)	24 (21.8)	60 (26.8)
Nonopioid drug use at screening, No (%):	135 (88.8)	142 (94)	277 (91.4)	95 (83.3)	101 (91.8)	196 (87.5)
Methamphetamine	27 (17.8)	25 (16.6)	52 (17.2)	21 (18.4)	23 (20.9)	44 (19.6)
Benzodiazepine	18 (11.8)	23 (15.2)	41 (13.5)	12 (10.5)	13 (11.8)	25 (11.2)
Marijuana	39 (25.7)	47 (31.1)	86 (28.4)	28 (24.6)	32 (29.1)	60 (26.8)
Cocaine	51 (33.6)	47 (31.1)	98 (32.3)	34 (29.8)	33 (30.0)	67 (29.9)
Hep. C antibody positive at screening, No. (%)	71 (46.7)	70 (46.4)	141 (46.5)	72 (63.2)	73 (66.4)	145 (64.7)
Medical history of depression, No. (%)	16 (10.5)	19 (12.6)	35 (11.6)	14 (12.3)	17 (15.5)	31 (13.8)
Baseline COWS score, mean (SD)	11.7 (4.79)	11.9 (5.95)	11.8 (5.39)	11.81 (5.27)	12.06 (6.58)	11.93 (5.94)
Baseline SOWS score, mean (SD)	32.0 (14.9)	31.4 (167)	31.7 (15.8)	30.54 (14.53)	31.23 (17.28)	30.88 (15.91)
Baseline desire-to-use VAS (SD)	76.2 (26.7)	77.1 (24.6)	76.6 (25.8)	76.78 (25.48)	77.71 (25.76)	77.24 (25.57)
Baseline need-to-use VAS (SD)	75.4 (26.3)	76.0 (25.7)	75.7 (26.0)	74.38 (26.92)	76.43 (25.90)	75.39 (26.38)

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)

Demographics and clinical characteristics were similar between treatment groups for participants identifying heroin as the primary opioid of abuse and PWIO at baseline

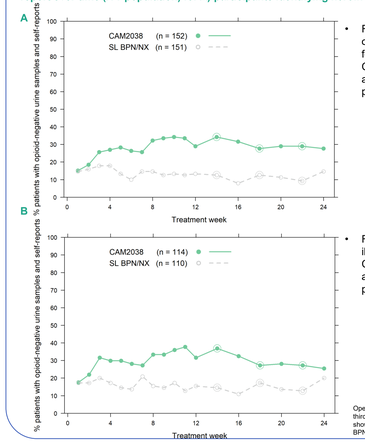
Figure 1: Cumulative distribution function of percentage of illicit opioid-negative urine samples confirmed by self-report for treatment weeks 5 to 25 for A) participants identifying heroin as the primary opioid of abuse and B) PWIO



- Analysis of the CDF from weeks 5 to 25 demonstrated that for participants identifying heroin as the primary opioid of abuse, the CAM2038 group achieved a higher percentage of urine samples negative for illicit opioids (mean, 29.9%) compared with the SL BPN/NX group (LS mean, 12.7%; p <0.001 [Wilcoxon], superiority)
- Analysis of the CDF from weeks 5 to 25 demonstrated that for PWIO, the CAM2038 group achieved a higher percentage of urine samples negative for illicit opioids (mean [SD], 30.9% [3.3%]) compared with the SL BPN/NX group (LS mean [SD], 15.4% [2.7%]; p <0.001 [Wilcoxon], superiority)

People who inject opioids (PWIO); Sublingual buprenorphine/naloxone (SL BPN/NX)

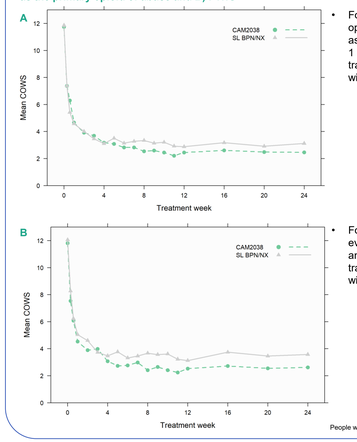
Figure 2. Mean percentage of participants with urine toxicology results negative for illicit opioids supported by self-report over time (ITT population) for A) participants identifying heroin as the primary opioid of abuse and B) PWIO



- For participants identifying heroin as the primary opioid of abuse, the mean urine samples negative for illicit opioids (with self-reports) was higher for CAM2038 (28.2%) relative to SL BPN/NX (13.2%), a 15.0% difference (95% CI, 7.8%, 22.1%; p<0.001; superiority [ANOVA])
- For PWIO, the mean urine samples negative for illicit opioids (with self-reports) was higher for CAM2038 (29.7%) relative to SL BPN/NX (15.9%), a 13.9% difference (95% CI, 4.7%, 23.0%; p=0.003; superiority [ANOVA])

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

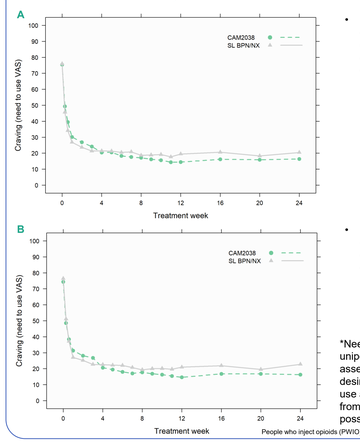
Figure 4. Mean Clinical Opioid Withdrawal Scale (COWS) total score over time in A) participants identifying heroin as the primary opioid of abuse and B) PWIO



- For participants identifying heroin as the primary opioid of abuse, 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
- For PWIO, 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

People who inject opioids (PWIO); Sublingual buprenorphine/naloxone (SL BPN/NX)

Figure 3. Mean craving assessed by need to use VAS* by treatment week and treatment group in A) participants identifying heroin as the primary opioid of abuse and B) PWIO



- For participants identifying heroin as the primary opioid of abuse, in both groups, 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 PWIO, in both groups, 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

*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")

People who inject opioids (PWIO); Sublingual buprenorphine/naloxone (SL BPN/NX); Visual analog scale (VAS)

Table 2. Summary of Non-Fatal Serious Adverse Events in Participants Identifying Heroin as the Primary Opioid of Abuse and PWIO (Safety Population)

System Organ Class/Preferred Term	Heroin CAM2038 N = 152 n (%)	Heroin SL BPN/NX N = 151 n (%)	Heroin Total N=303 n (%)	PWIO CAM2038 N=114 n (%)	PWIO SL BPN/NX N=110 n (%)	PWIO Total N=224 n (%)
Infections and infestations	0	8 (5.3)	8 (2.6)	0	8 (7.3)	8 (3.6)
Abscess limb	0	1 (0.7)	1 (0.3)	0	1 (0.9)	1 (0.4)
Acute hepatitis C	0	1 (0.7)	1 (0.3)	0	1 (0.9)	1 (0.4)
Cellulitis	0	1 (0.7)	1 (0.3)	0	1 (0.9)	1 (0.4)
Localised infection	0	1 (0.7)	1 (0.3)	0	1 (0.9)	1 (0.4)
Osteomyelitis	0	1 (0.7)	1 (0.3)	0	1 (0.9)	1 (0.4)
Pneumonia	0	1 (0.7)	1 (0.3)	0	1 (0.9)	1 (0.4)
Sepsis	0	1 (0.7)	1 (0.3)	0	1 (0.9)	1 (0.4)
Subcutaneous abscess	0	1 (0.7)	1 (0.3)	0	1 (0.9)	1 (0.4)
Injury, poisoning and procedural complications	1 (0.6)	4 (2.6)	5 (1.6)	0	4 (3.6)	5 (2.2)
Accidental overdose	0	3 (2)	3 (1)	0	3 (2.7)	3 (1.3)
Intentional overdose	0	1 (0.7)	1 (0.3)	0	1 (0.9)	1 (0.4)
Road traffic accident	1 (0.6)	0	1 (0.3)	0	0	0
Psychiatric disorders	0	3 (2)	2 (0.7)	0	3 (2.7)	2 (0.9)
Bipolar disorder	0	1 (0.7)	1 (0.3)	0	1 (0.9)	1 (0.4)
Substance-induced mood disorder	0	1 (0.7)	1 (0.3)	0	1 (0.9)	1 (0.4)
Suicidal ideation	0	1 (0.7)	2 (0.7)	0	1 (0.9)	2 (0.9)
Congenital, familial and genetic	0	1 (0.7)	1 (0.3)	0	1 (0.9)	1 (0.4)
Haemophilia	0	1 (0.7)	1 (0.3)	0	1 (0.9)	1 (0.4)
Gastrointestinal disorders	0	0	0	1 (0.9)	0	1 (0.4)
Vomiting	0	0	0	1 (0.9)	0	1 (0.4)
Pregnancy, puerperium and perinatal conditions	1 (0.6)	0	1 (0.3)	1 (0.9)	0	1 (0.4)
Abortion spontaneous	1 (0.6)	0	1 (0.3)	1 (0.9)	0	1 (0.4)
General disorders and administration site conditions	1 (0.6)	0	1 (0.3)	0	0	0
Non-cardiac chest pain	1 (0.6)	0	1 (0.3)	0	0	0

People who inject opioids (PWIO); Sublingual buprenorphine/naloxone (SL BPN/NX); Serious adverse event (SAE); System organ class (SOC)

- Of participants identifying heroin as the primary opioid of abuse and PWIO, all four accidental overdoses 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
- There were no clinically meaningful differences between the treatments for SAEs; however, all SAEs in the Infections and Infestations System Organ Class, including abscess (n = 1, limb; n = 1 subcutaneous), acute hepatitis C (n = 1), cellulitis (n = 1), localized infection (n = 1), osteomyelitis (n = 1), pneumonia (n = 1), and sepsis (n = 1), occurred in the SL BPN/NX group, suggesting ongoing IV drug use
- 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

- Treatment with CAM2038 weekly and monthly showed less illicit opioid use in in participants whose primary opioid of abuse at baseline was heroin and PWIO compared with current standard of care treatment with daily SL BPN/NX
- CAM2038 weekly and monthly was effective in treating heroin dependent individuals and PWIO, showing sustained opioid withdrawal and craving suppression from treatment initiation through maintenance, including during transition from weekly to monthly injections
- The results of these subgroup analyses suggest reductions in the occurrence of skin, soft tissue, and blood bacterial infections and risk of overdose with CAM2038 compared with current standard of treatment with daily SL BPN/NX
- 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

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ACKNOWLEDGEMENTS

This study was sponsored by Braeburn. The authors would like to thank study participants and investigators for their contribution to research and Camurus AB for their support. Writing and editorial support was funded by Braeburn.

DISCLOSURES

GB has received grant support from the National Institutes of Drug Abuse, Reckitt-Benckiser/Indivior and Braeburn; consulting fees and travel support from Alkermes, Braeburn and Indivior; and speaker bureaus for Alkermes, Indivior and BioDelivey Sciences International. MF has received fees from BioDelivery Sciences, Braeburn, Indivior, and Knight Therapeutics; and served as an advisor for Kaleo. ML has received research funding from Braeburn, and consulting fees from Braeburn, and Indivior. SW received contract research funding and consulting fees from Braeburn, consulting fees from Camurus AB, and travel support from Indivior. NB-K and SK are employees of and may hold stock in Braeburn. FT is an employee and shareholder of Camurus AB.

Presented at the State of the Art Conference of the California Society of Addiction Medicine, August 29 – September 1, 2018, San Francisco, CA.