Efficacy and safety comparison of weekly/monthly extended-release injectable buprenorphine (CAM2038) vs daily sublingual buprenorphine/naloxone (BPN/NX) for treatment of patients with OUD who inject opioids or use heroin.

Sonnie Kim, Pharm.D.
Vice President, Head of Medical Affairs
Braeburn Inc.

ISAM Annual Meeting 2018, 3-6 November 2018
Busan, South Korea

Disclosure

The study was funded and sponsored by Braeburn, Inc.

Dr. Kim is am employee of Braeburn Inc.

The information presented today relates to the clinical data associated with CAM2038, an investigational product for the potential treatment of Opioid Use Disorder. The New Drug Application for CAM2038 is currently under review with the US FDA and has been assigned a Prescription Drug User Fee Act (PDUFA) goal date of December 26, 2018. As an investigational product that has not been yet approved, the safety and efficacy of CAM2038 has not yet been established.

New Drug Application for CAM2038 is also currently under review with the Australian FDA and European Medicines Agency.

CAM2038: INVESTIGATIONAL BUPRENORPHINE EXTENDED-RELEASE INJECTION FOR SUBCUTANEOUS USE

Weekly or monthly formulations

- Multiple dose strengths

May allow for individualized dosing based on clinical response and tolerability

- Aligns with treatment guidelines
- Multiple injection sites (Evaluated buttock, abdomen, arm, thigh)

Low-volume, ready-to-use, pre-filled syringes with 23 gauge needles stored at room temperature

Administered by healthcare professional

Studied using SL BPN/NX as an active comparator

Evaluated use without need for SL BPN (direct initiation with CAM2038 in new to treat patients)



4 Weekly Doses



3 Monthly Doses

BACKGROUND

- Heroin and injection drug use are associated with treatment attrition and opioid misuse during treatment for OUD[1]
- Daily sublingual buprenorphine/ naloxone (SL BPN/NX) is known to be effective for the treatment of OUD, however treatment response is typically lower in people that use heroin or PWIO[1]
- 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]
- 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 overdose deaths, with an estimated 15,958 deaths from heroin-related overdoses in 2017 [4,5]

1) Potter JS, et al. J Stud Alcohol Drugs. 2013;74(4):605-13; 2) Binswanger IA, et al. Clin Infect Dis. 2000; 30:579-81; 3) Ciccarone D, et al. Drug Alcohol Depend. 2016;163:126-33; 4) Dismukes, LC. North Carolina Medical Journal. 2018 79:181-184; 5) https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates 6) Lofwall MR, et al. JAMA Intern Med. 2018;178(6):764–773.

Research

JAMA Internal Medicine | Original Investigation

Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder

A Randomized Clinical Trial

Michelle R. Lofwall, MD; Sharon L. Walsh, PhD; Edward V. Nunes, MD; Genie L. Bailey, MD; Stacey C. Sigmon, PhD; Kyle M. Kampman, MD; Michael Frost, MD; Fredrik Tiberg, PhD; Margareta Linden, PhD; Behshad Sheldon, BS; Sonia Oosman, BS; Stefan Peterson, PhD; Michael Chen, PhD; Sonnie Kim, PharmD

HS-11-421

JAMA Internal Medicine, 2018

STUDY 421: PARTICIPANT CHARACTERISTICS

	SL BPN/NX (n=215)	CAM2038 (n=213)
Age, years	38 (11)	39 (11)
Male	142 (66%)	121 (57%)
White	164 (76%)	159 (75%)
Employed full or part time	72 (34%)	76 (36%)
IV opioid use	110 (51%)	114 (54%)
Heroin as primary opioid of use	151 (70%)	152 (71%)
Urine toxicology positive for other substances of abuse*	149 (69%)	155 (73%)

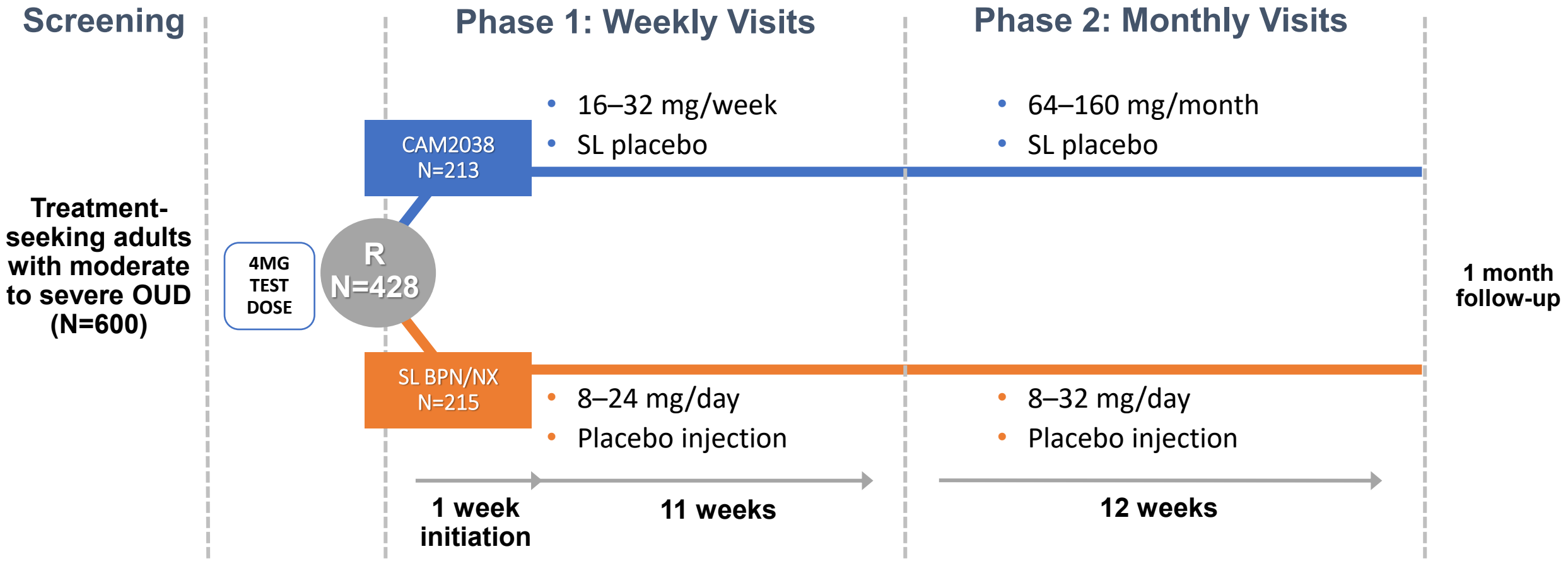
*Other substances of abuse = Cocaine, amphetamine, PCP, THC, benzodiazepine

HEROIN AND IV ROUTE OF USE SUBGROUP ANALYSES OBJECTIVES

- 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
- A post-hoc analysis was conducted (intent-to-treat [ITT] population) to assess efficacy of CAM2038 compared with SL BPN/NX in treating participants whom **heroin** was the primary opioid of abuse at baseline and participants whom used **injection as route** of illicit opioid use (PWIO)

Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine with Naloxone for Treatment of Opioid Use Disorder A Randomized Clinical Trial. *JAMA Intern Med*. Published online May 14, 2018. doi:10.1001/jamainternmed.2018.1052

STUDY 421 STUDY DESIGN: RANDOMIZED DOUBLE-BLIND, DOUBLE-DUMMY (all received SC injections and SL tablets)



SL BPN/NX = sublingual buprenorphine/naloxone; OUD = Opioid use disorder

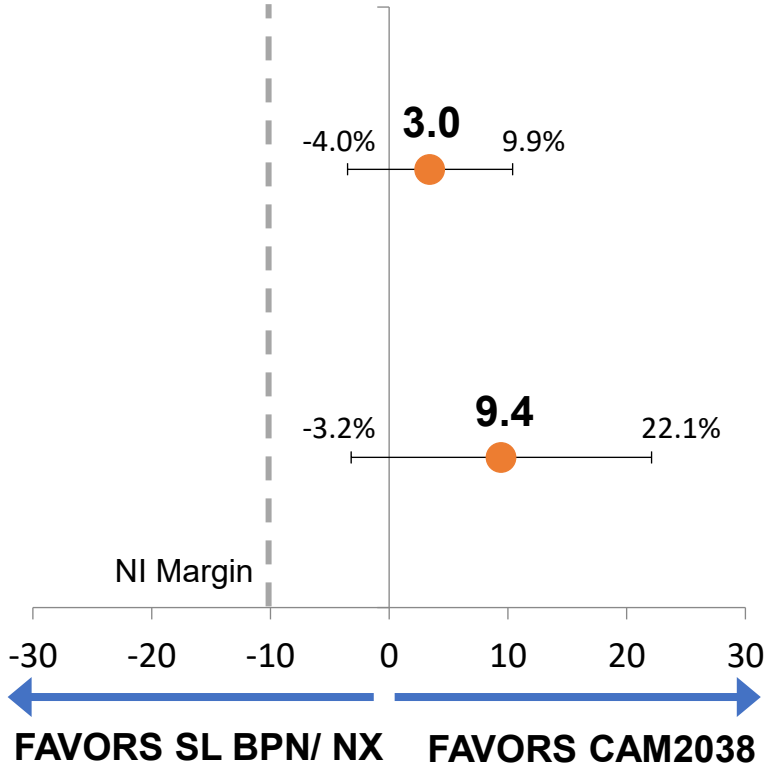
Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine with Naloxone for Treatment of Opioid Use Disorder A Randomized Clinical Trial. *JAMA Intern Med*. Published online May 14, 2018. doi:10.1001/jamainternmed.2018.1052

CATEGORY	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)
BMI, mean (SD), kg/m^2	25.2 (4.9)	25.5 (4.9)	25.3 (4.9)	25.01 (4.89)	25.41 (4.97)	25.21 (4.92)
Employed full or part time, No. (%)	42 (27.6)	41 (27.2)	83 (27.4)	34 (29.8)	28 (25.5)	62 (27.7)
Education status, No. (%)						
College or university degree/ Graduate	11 (7.2)	18 (12.0)	29 (9.6)	8 (7.0)	12 (10.9)	20 (8.9)
Did not complete high school	28 (18.4)	33 (21.9)	61 (20.1)	20 (17.5)	25 (22.7)	45 (20.1)
High school diploma or GED	62 (40.8)	56 (37.1)	118 (38.9)	43 (37.7)	40 (36.4)	83 (37.1)
Some college or certificate program	51 (33.6)	43 (28.5)	94 (31.0)	43 (37.7)	33 (30.0)	76 (33.9)
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)
COWS, 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)
SOWS, 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)
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)
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)

STUDY 421 PRIMARY ENDPOINT: RESPONDER RATE (NON-INFERIORITY)

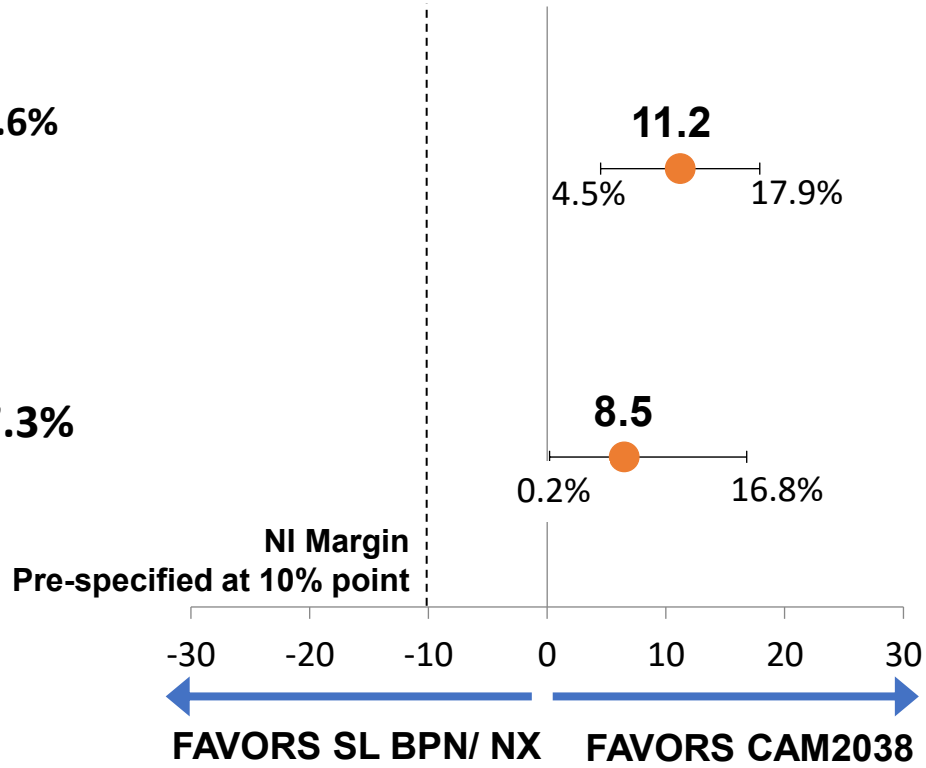
	RESPONDER RATE CAM2038 VS. SL BPN/NX	TREATMENT DIFFERENCE (95% CI)	NON-INFERIORITY p-value
Primary endpoint: Missing data imputed as positive urine sample for illicit opioids	**17.4% vs. 14.4%**	-4.0% **3.0** 9.9%	**< 0.001**
Sensitivity analysis: No missing data imputed	**35.6% vs. 26.2%**	-3.2% **9.4** 22.1%	**< 0.001**



Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine with Naloxone for Treatment of Opioid Use Disorder A Randomized Clinical Trial. *JAMA Intern Med*. Published online May 14, 2018. doi:10.1001/jamainternmed.2018.1052
Clinical Study Report (CSR) HS-11-421

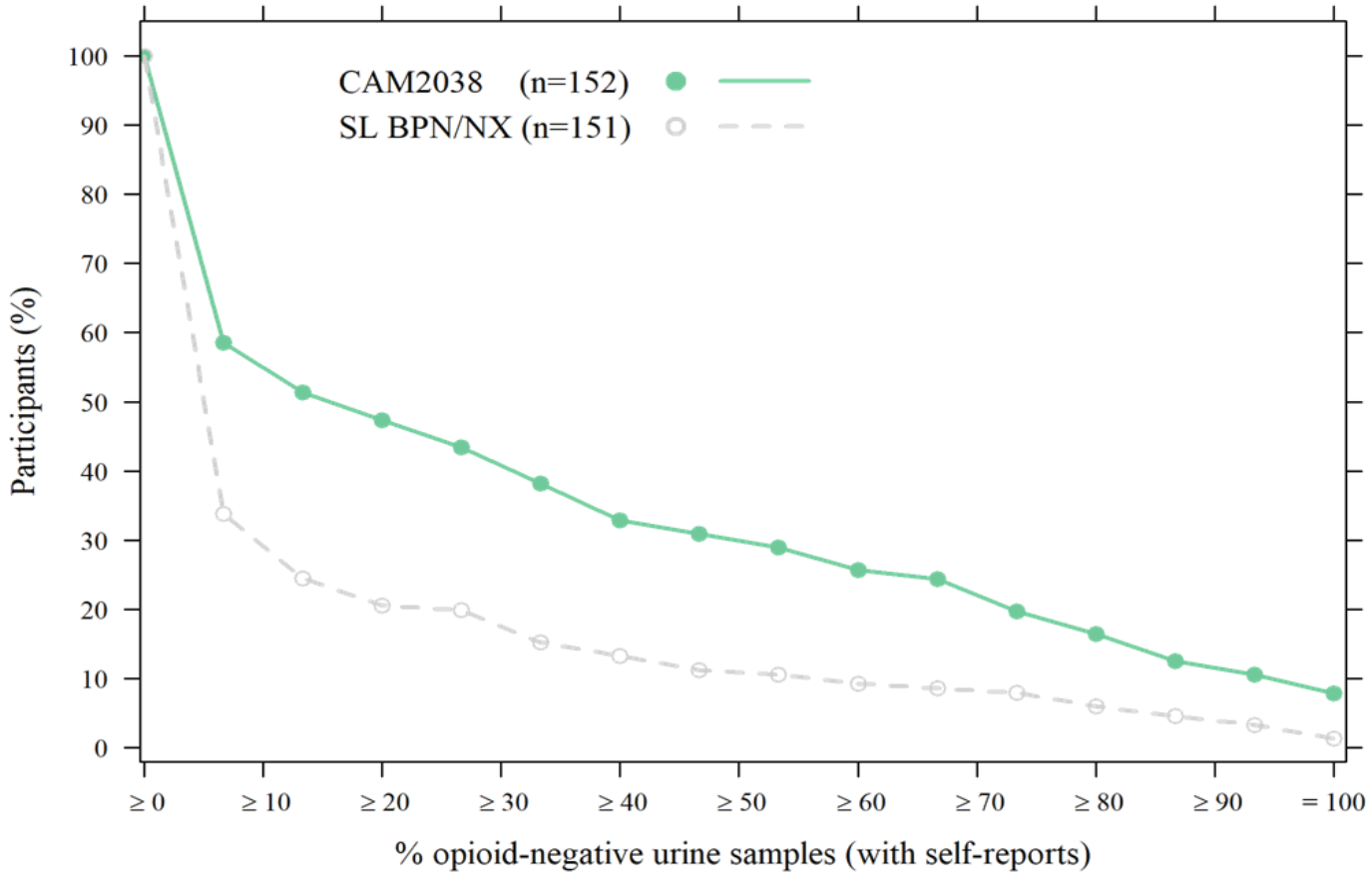
STUDY 421 Post-Hoc analyses in Heroin and Injection user Subgroup

	RESPONDER RATE CAM2038 VS. SL BPN/NX	TREATMENT DIFFERENCE (%) (95% CI)	P-VALUE (NON-INFERIORITY)	P-VALUE (SUPERIORITY)
Heroin Users	15.8% vs. 4.6%	11.2 (4.5% – 17.9%)	< 0.001	< 0.001
Injection Route Users (PWID)	15.8% vs. 7.3%	8.5 (0.2% – 16.8%)	< 0.001	= 0.047



P-value is based on the Chi Square Test for superiority
Clinical Study Report (CSR) HS-11-421
DATA ON FILE HS-11-421 BB Table 4.1 and BB Table 4.2

CDF OF PERCENTAGE OF ILLICIT OPIOID-NEGATIVE URINE SAMPLES CONFIRMED BY SELF-REPORT (Post-Hoc Analysis of Secondary Endpoint) HEROIN AS THE PRIMARY OPIOID OF ABUSE (N=303)

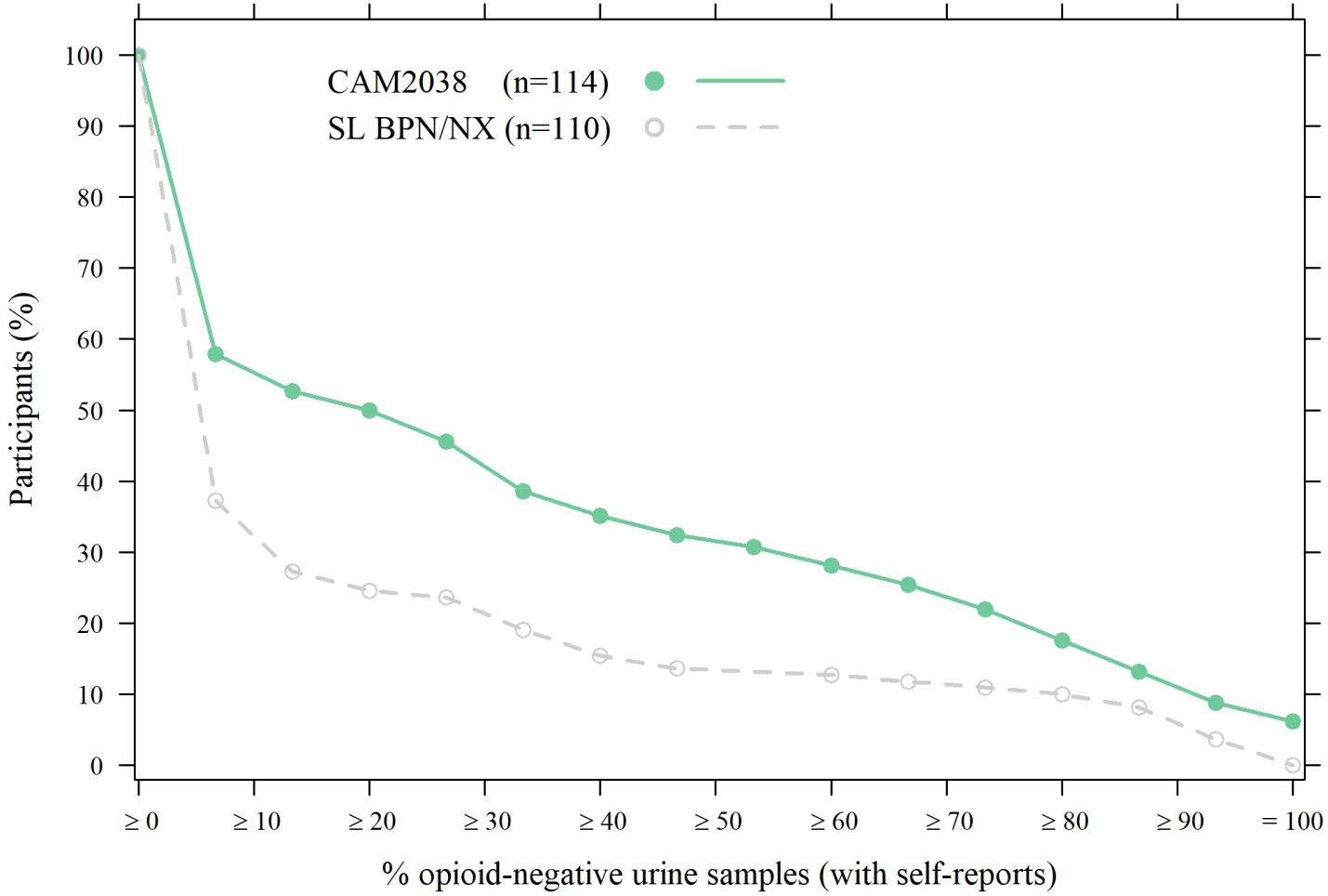


P<0.001
Wilcoxon, Superiority

Urine toxicology:
Highly sensitive
quantitative LC/MSMS

SL BPN/NX = sublingual buprenorphine/naloxone
Clinical Study Report (CSR) HS-11-421

CDF OF PERCENTAGE OF ILLICIT OPIOID-NEGATIVE URINE SAMPLES CONFIRMED BY SELF-REPORT (Post-Hoc Analysis of Secondary Endpoint) PARTICIPANTS WHO INJECT OPIOIDS (N=224)

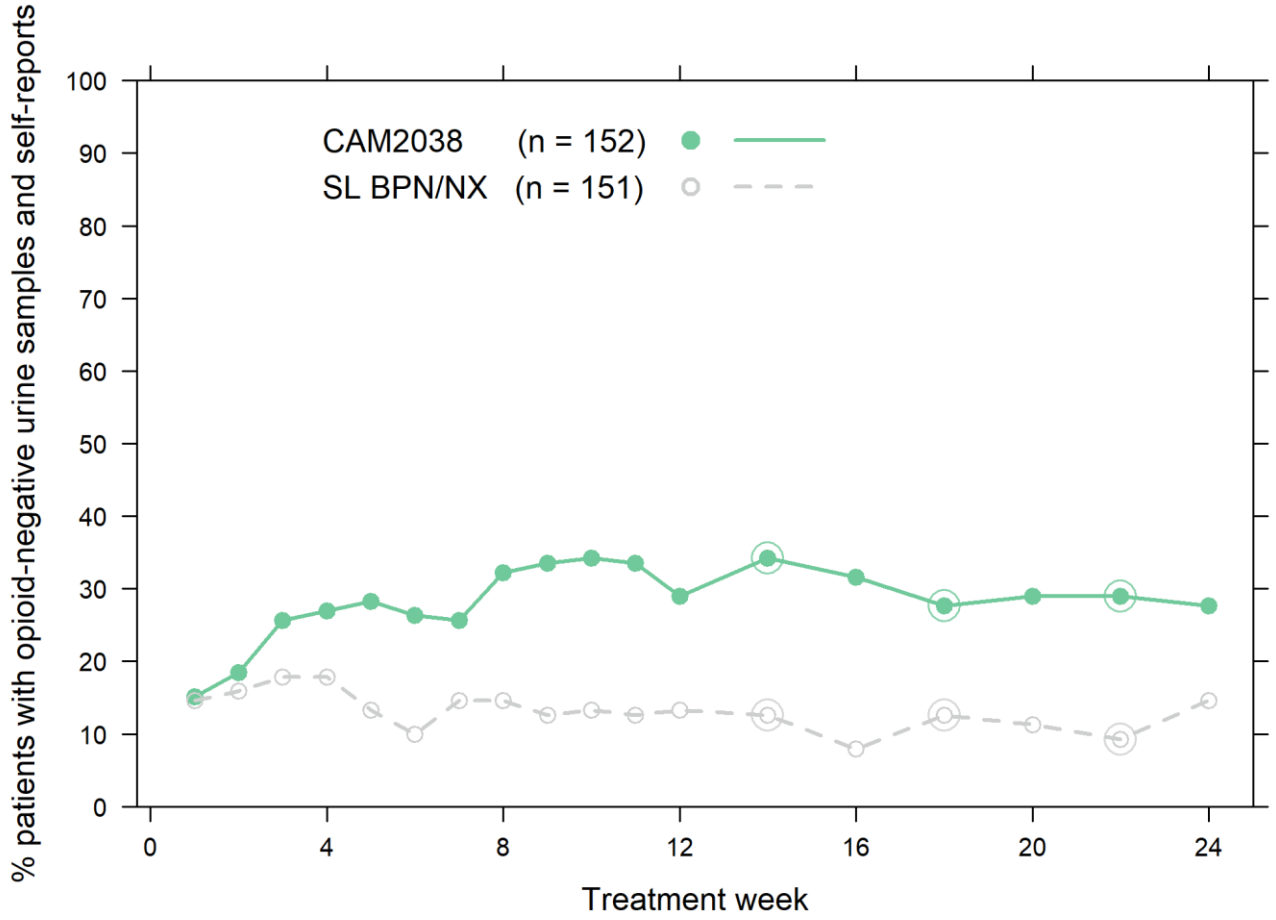


P<0.001
Wilcoxon, Superiority

Urine toxicology:
Highly sensitive
quantitative LC/MSMS

SL BPN/NX = sublingual buprenorphine/naloxone
Clinical Study Report (CSR) HS-11-421

MEAN PERCENTAGE OF PARTICIPANTS WITH NO ILLICIT OPIOID USE BY URINE SAMPLE AND SELF-REPORTRED USE OVER TIME (Post-Hoc Analysis) HEROIN AS PRIMARY OPIOID OF ABUSE (N=303)

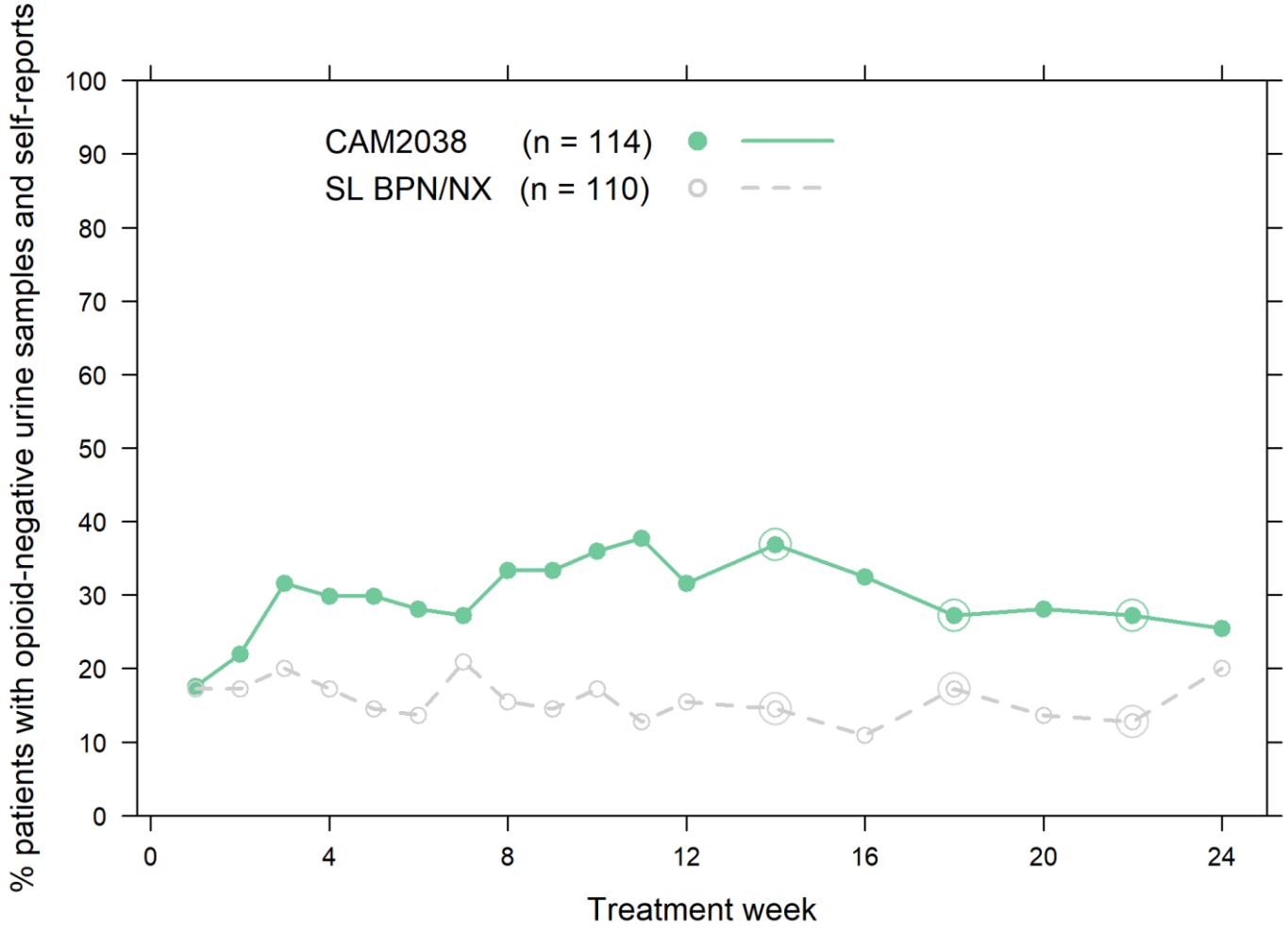


Mean percentage of no illicit opioid use:

- CAM2038 – 28.2% vs SL BPN – 13.2%
  - 15.0% difference (95% CI, 7.8%, 22.1%)
  - P<0.001 for superiority via 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.
Sublingual buprenorphine/naloxone (SL BPN/NX)

MEAN PERCENTAGE OF PARTICIPANTS WITH NO ILLICIT OPIOID USE BY URINE SAMPLE AND SELF-REPORTRED USE OVER TIME (Post-Hoc Analysis) PARTICIPANTS WHO INJECT OPIOIDS (N=224)



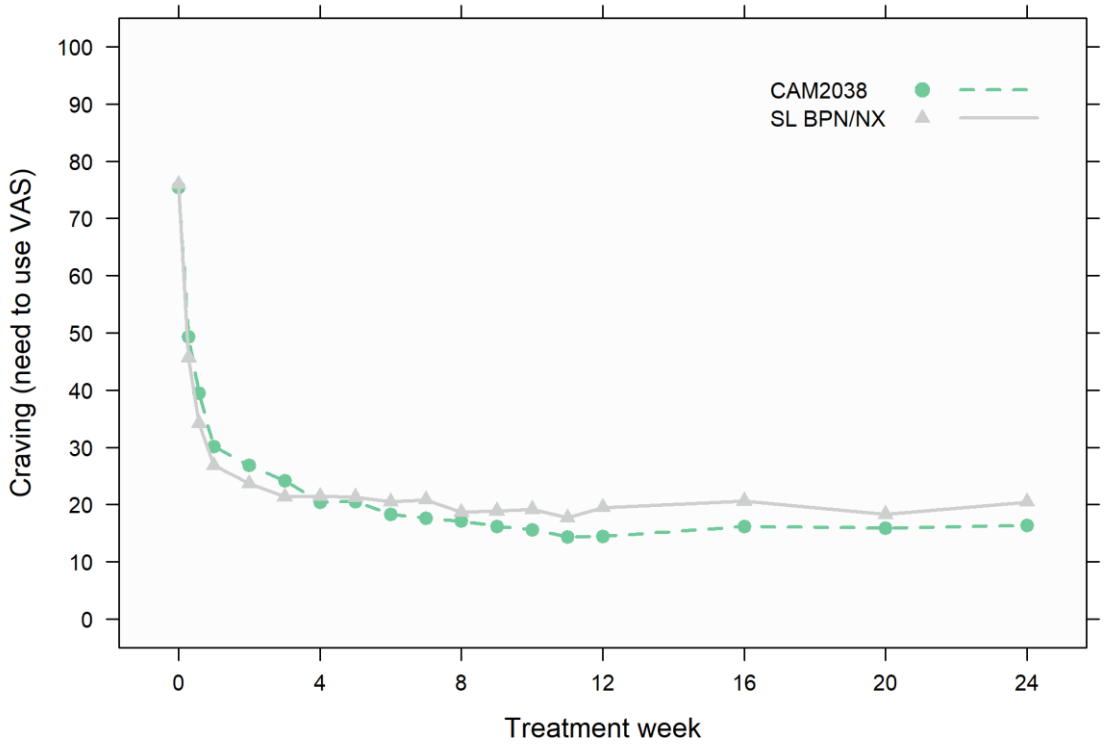
Mean percentage of no illicit opioid use

- CAM2038 – 29.7% vs SL BPN – 15.9%
  - 13.9% difference (95% CI, 4.7%, 23.0%)
  - P<0.003 for superiority via ANOVA

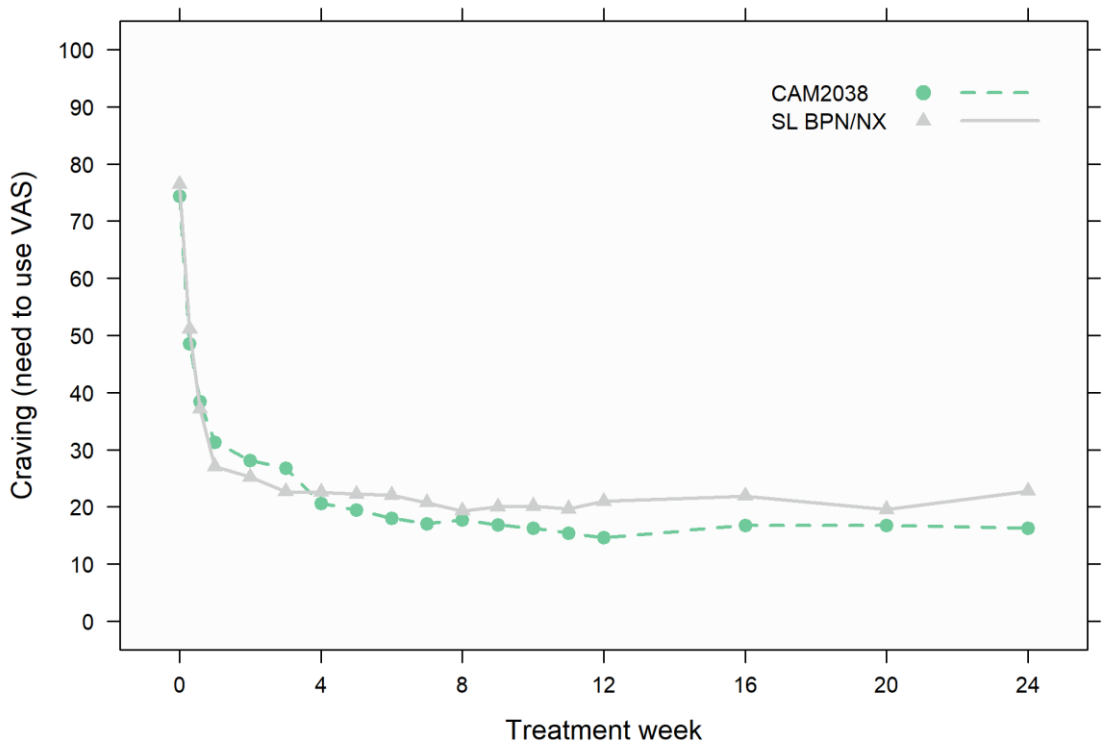
Open circles denote random samples. Random samples are the first, second, and third random sample, respectively, and these could occur in another period than shown.
Sublingual buprenorphine/naloxone (SL BPN/NX)

MEAN CRAVING ASSESSED BY NEED TO USE VAS BY TREATMENT WEEK AND TREATMENT GROUP IN PARTICIPANTS IDENTIFYING HEROIN AS THE PRIMARY OPIOID OF ABUSE (N=303) AND PARTICIPANTS WHO INJECT OPIOIDS(N=224) (Post-Hoc analyses)

HEROIN



PWIO

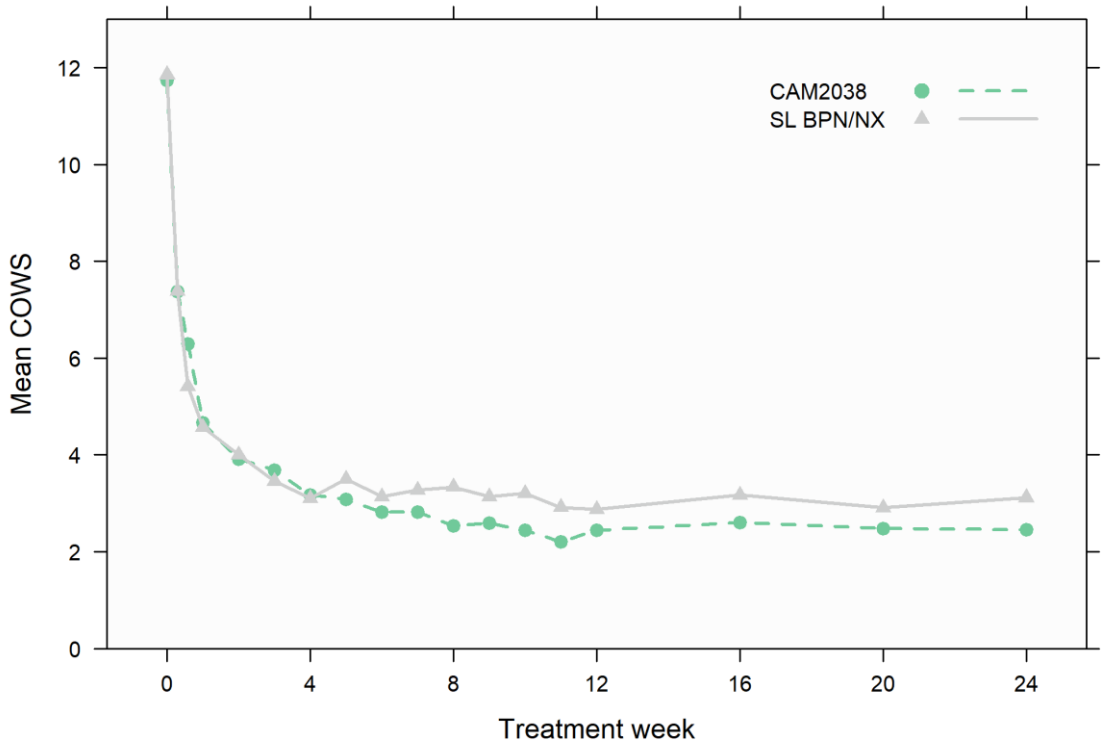


Analysis of covariance (ANCOVA) showed no significant treatment effect. SL BPN/NX sublingual buprenorphine/naloxone. Clinical Study Report (CSR) HS-11-421

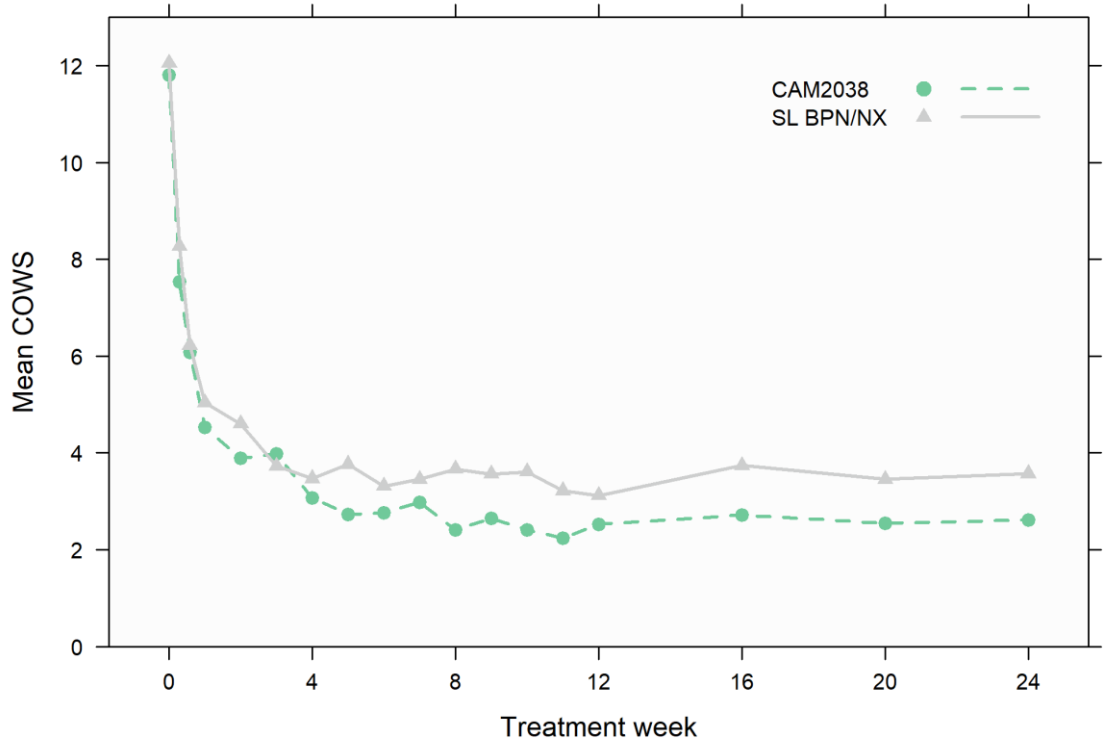
Need to Use (opioid cravings) were assessed using unipolar 100 mm VAS ("Since your last scheduled assessment visit, indicate your worst or strongest desire/need to use opioids, where 0 = No desire to use and 100 mm = Strongest possible desire, and from 0 = No need to use and 100 mm = Strongest possible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

MEAN CLINICAL OPIOID WITHDRAWAL SCALE (COWS) TOTAL SCORE OVER TIME IN PARTICIPANTS IDENTIFYING HEROIN AS THE PRIMARY OPIOID OF ABUSE (N=303) AND PARTICIPANTS WHO INJECT OPIOIDS (N=224) (Post-Hoc Analyses)

HEROIN



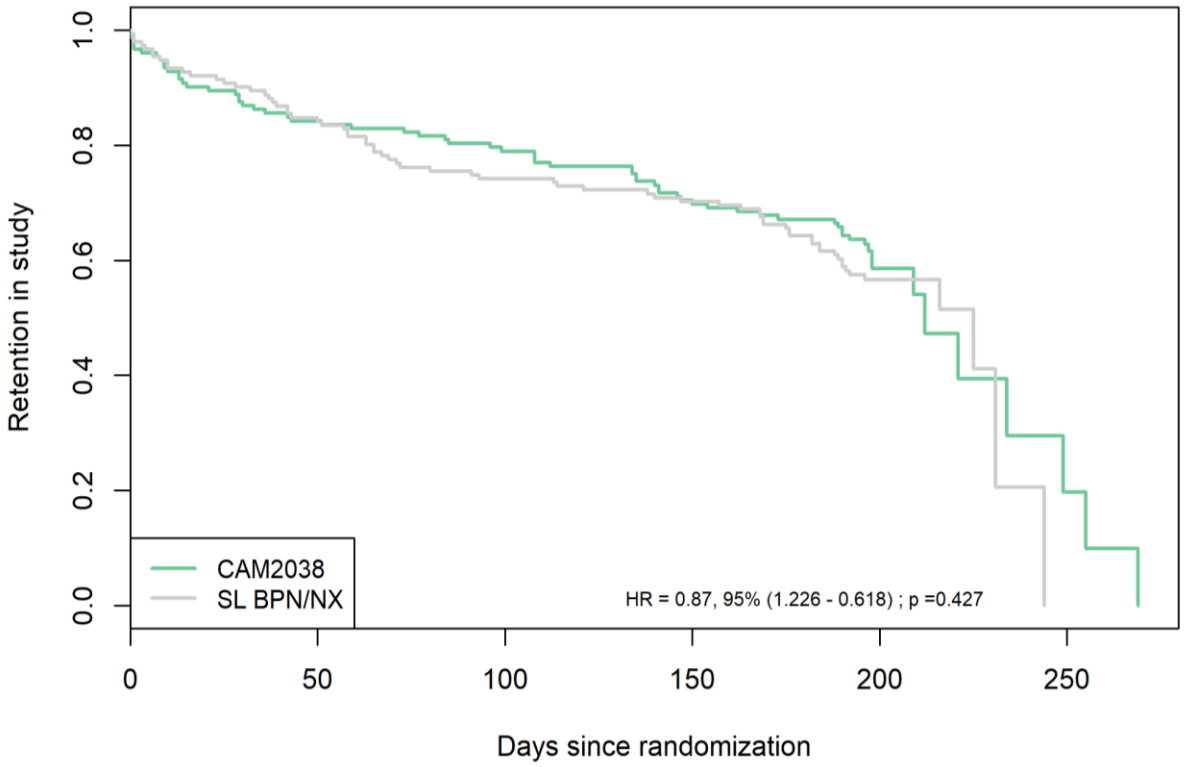
PWIO



Analysis of covariance (ANCOVA) showed no significant treatment effect. SL BPN/NX sublingual buprenorphine/naloxone. Clinical Study Report (CSR) HS-11-421
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

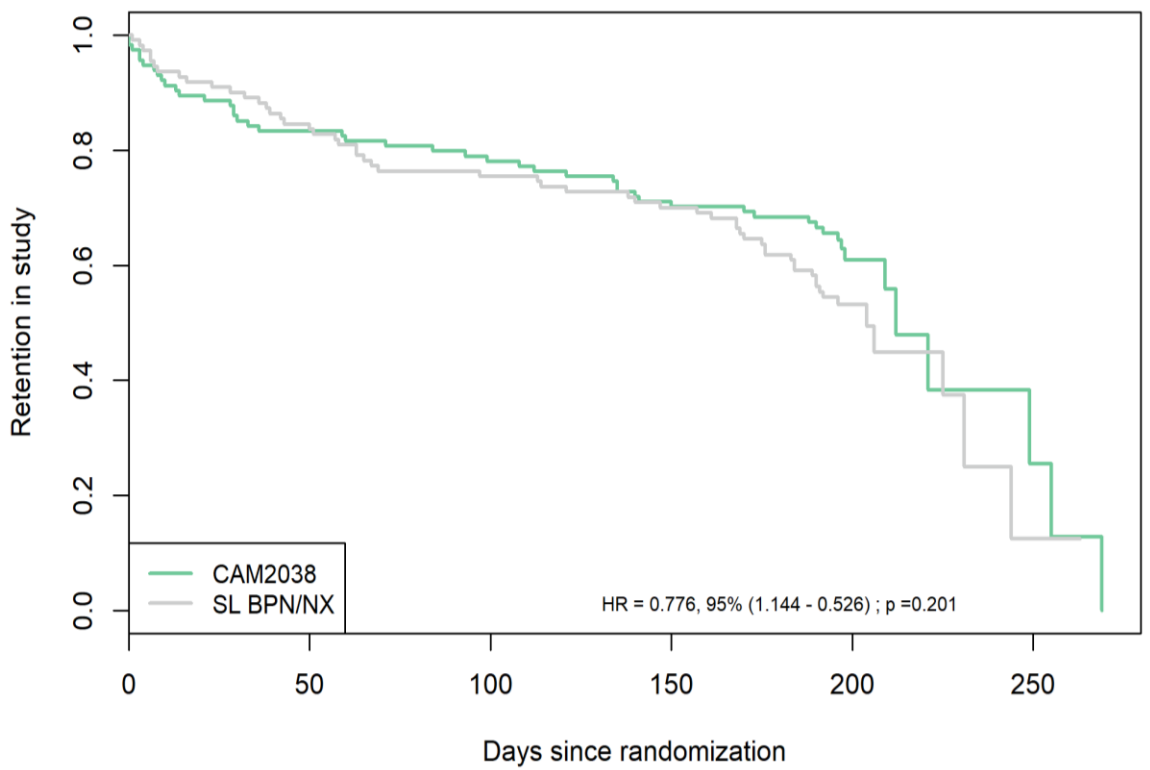
RETENTION IN STUDY FOR PARTICIPANTS IDENTIFYING HEROIN AS THE PRIMARY OPIOID OF ABUSE (N=303) AND PARTICIPANTS WHO INJECT OPIOIDS (N=224) (Post-Hoc Analyses)

HEROIN



Retention for participants identifying heroin as the primary opioid of abuse was 56% for CAM2038 and 54% for BPN/NX.

PWIO



Retention for PWIO was 55% for CAM2038 group compared to 49% for the SL BPN/NX

Summary of Non-Fatal Serious Adverse Events in Participants Identifying Heroin as the Primary Opioid of Abuse and Participants who Inject Opioids (Subgroup Post-Hoc Analyses)

System Organ Class/Preferred Term	HEROIN			PWIO		
	CAM2038 N = 152 n (%)	SL BPN/NX N = 151 n (%)	Total N=303 n (%)	CAM2038 N=114 n (%)	SL BPN/NX N=110 n (%)	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)
Localized 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

STUDY 421 SUBGROUP ANALYSIS: CONCLUSIONS

- Among patients who were heroin users or those who injected opioids at treatment initiation, CAM2038 Weekly and Monthly injections reduced illicit opioid use compared to SL BPN/NX
  - Significant reduction in responder rate
  - Significant reduction in the CDF of percent illicit opioid negative urines and self-reported use; and
  - Significant reduction in the mean percent of illicit opioid negative urines and self-reported use
- CAM2038 demonstrated sustained opioid withdrawal and craving suppression from treatment initiation through maintenance for both heroin and injection users
- 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

SL BPN/NX, sublingual buprenorphine/naloxone

Acknowledgements

Study volunteers

Braeburn and Camurus Teams

<u>35 Sites principal investigators</u>:

Dr. Jason Andersen, UT

Dr. Genie Bailey, MA

Dr. John Bernard, NJ

Dr. Aaron Blackledge, CA

Dr. Brent Boyett, AL

Dr. Robert P. Chang, CA

Dr. Eduardo Cifuentes, SC

Dr. Otto Dueno, OH

Dr. Michael Frost, PA

Dr. Daniel Gruener, MO

Dr. Boyde J. Harrison, AL

Dr. David Hassman, NJ

Dr. Kent Hoffman,FL

Dr. Valentin Isacescu, CA

Dr. Rishi Kakar, FL

Dr. Kyle M. Kampman, PA

Dr. Joseph A. Kwentus, MS

Dr. Gregory Lakin, KS

Dr. Dagmar Liepa, CA

Dr. Michelle Lofwall, KY

Dr. Shishuka Malhotra, OH

Dr. Mohd A. Malik, MO

Dr. Vishaal Mehra, CA

Dr. Mohammad Munir, MA

Dr. Edward V. Nunes, NY

Dr. Marvin Lane Peyton, OK

Dr. Scott Segal, FL

Dr. Charmaine I. Semeniuk, CA

Dr. Raj Shiwach, TX

Dr. Stacey Sigmon, VT

Dr. James Sullivan, AL

Dr. Amit Vijapura, FL

Dr. James Walsh, WA

Dr. James J. Whalen, RI

Dr. Mark J. Woyshville, OH