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Long-acting Buprenorphine Treatment for Opioid Use Disorder

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Center on Drug and Alcohol Research

Tuesday, February 11th, 2020
12:00 PM – 1:00 PM EST

Webinar Housekeeping

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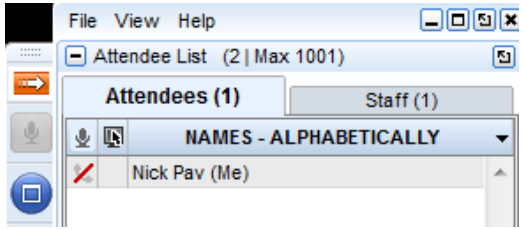
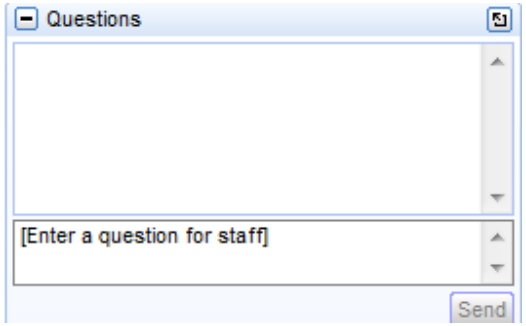


To be recognized, type your question in the “Question” box and select send.



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Disclosures

I have relevant financial relationships with two ACCME-defined commercial interests:

1. I have been a consultant for Titan Pharmaceuticals regarding OUD and their new indications/formulations and study designs.

2. I have received stipends and reimbursements from Camurus for developing talks on research conducted with their OUD buprenorphine injectables.

Outline for Today's Discussion

- Potential benefits of long-acting buprenorphine (bup) medications
  - How can they help us move forwards to improve opioid use disorder (OUD) treatment access, retention and remission?
- Three different products
- Conclusions

Moving forwards: Who may benefit?

- Patients with difficult transitions – e.g., leaving a hospital, emergency room, jail.

JAMA. 2015 Apr 28;313(16):1636-44. doi: 10.1001/jama.2015.3474.

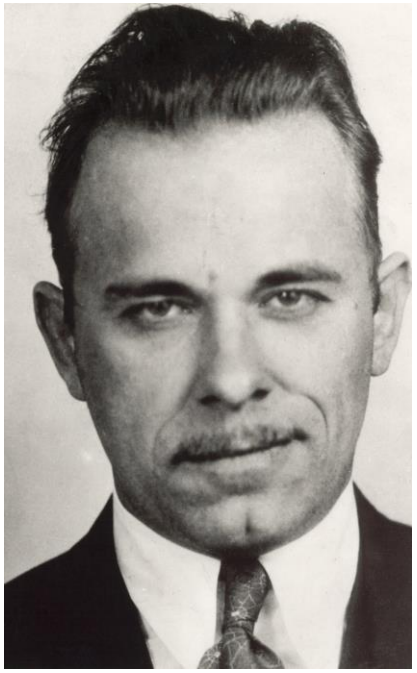
Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial.

D'Onofrio G[1], O'Connor PG[2], Pantalon MV[1], Chawarski MC[3], Busch SH[4], Owens PH[1], Bernstein SL[1], Fiellin DA[5].

  - 2-fold increase in attending the first outpatient appointment if started sublingual BUP in the ER (78% vs. 37%). But many providers hesitant to prescribe because of concerns about diversion and misuse of sublingual BUP– what if they could just give a shot?
- Pregnant women and newborns – might there be better outcomes from steady medication levels? Study underway.
- Patients at risk for non-adherence and misuse
  - Unstable living situations, transportation problems, addicted to injection
- Patient preference (e.g., no need for pharmacy visits, supervised dosing)

Moving forwards:
Where to deliver long-acting treatments?

- John Dillinger: infamous bank robber from the 1930s. “Why do you rob banks?”…“Because that’s *where* the money is.”
- Where are our potential patients?
  - Criminal justice
  - Emergency rooms, hospitals and primary care
  - Homeless
  - Must bring treatment to patients



Overview of long-acting buprenorphine products

	6-month implants (Sixmo®/Probuphine®)	Monthly injection (Sublocade®)	Weekly and monthly injection (Buvidal®/Brixadi®)
Approval	EMA & USA	Australia & USA	Australia, EMA, USA*
Indications	Clinically stable adults with OUD, already on SL bup 8mg/day or less and already receiving medical, psychological and social support	Adults with moderate-severe OUD, tolerating SL bup at 8-24 mg/day for at least 7 days. Counseling and psychological support should be part of treatment plan.	Treatment OUD (age 16yrs +) within framework of medical, psychological and social treatment
Mean bup concentration at steady state (ng/mL)	~0.82	100 mg injection: 3.21 300 mg injection: 6.54	Variable depending on dose but >1
Minor surgical procedure required	Yes	No	No
Medication administration site	Upper arm - subdermal	Abdomen –subcutaneous (SC)	Abdomen, arm, leg, buttock (SC)
Refrigeration required?	No	Yes	No

Coe MA, Lofwall MR, Walsh SL. Buprenorphine Pharmacology Review: Update on Transmucosal and Long-acting Formulations. J Addict Med Volume 13, Number 2, March/April 2019. *Not on US market due to Sublocade having exclusivity until 2020.

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Solid Matrix Subdermal Implant
FDA-approved May 2016

EVA polymer

Inert component of several approved products

+

Buprenorphine

Blended & Extruded

26 mm long, 2.5 mm diameter, 80 mg buprenorphine/rod

- 4 rods (320mg buprenorphine) provide sustained release of buprenorphine for up to 6 months.
- Remove and replace after 6 months.
- Peak concentration 12 hours after placement.
- Serious adverse events: uncommon but possible including migration and nerve damage, potential for extraction and misuse.

Slide pictures courtesy of Dr. Sonnie Kim, Braeburn Pharmaceuticals, an Apple Tree Company. https://www.ema.europa.eu/en/documents/product-information/sixmo-epar-product-information_en.pdf

Clinical stability criteria

- Period free from illicit opioid drug use
- Stability of living environment
- Participation in a structured activity/job
- Consistency in participation in recommended behavioral therapy/peer support program
- Consistency in compliance with clinic visit requirements
- Minimal to no desire or need to use illicit opioids
- Period without episodes of hospitalizations (addiction or mental health issues), emergency room visits, or crisis intervention

JAMA. 2016 July 19; 316(3): 282–290. doi:10.1001/jama.2016.9382.

Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine: A Randomized Clinical Trial.

Richard N. Rosenthal, MD.; Michelle R. Lofwall, MD; Sonnie Kim, PharmD; Michael Chen, PhD; Katherine L. Beebe, PhD.; Frank J. Vocci, PhD.; PRO-814 Study Group

177 randomized; 166 completed (93.8% retention!!)

Responder rate	Implant	SL Bup/naloxone	P value	NNT
Primary Analysis				
• At least 4 of 6 months without illicit opioid use	81/84 (96.4%)	78/89 (87.6%)	<0.001[a]	11.4
Secondary Analysis				
• All 6 months without illicit opioid use	72/84 (85.7%)	64/89 (71.9%)	0.03[b]	7.3

Consider SL supplementation if destabilize – 17.9% required SL, and it was low dose (2/0.5) and for a short period.

[a] Non-inferiority. [b] Superiority

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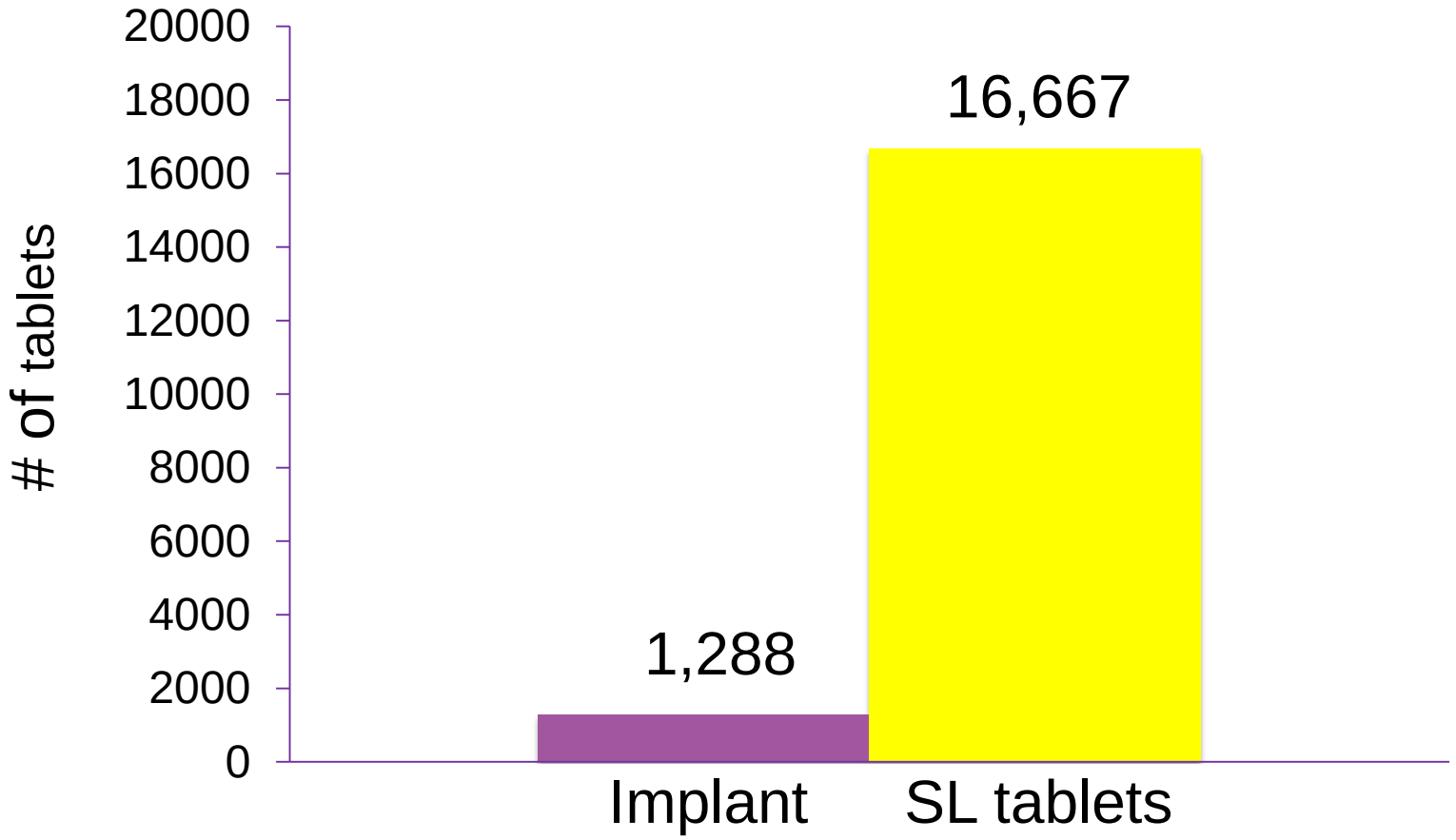
Relative use of SL buprenorphine/naloxone tablets



Data courtesy of Dr. Sonnie Kim, Braeburn Pharmaceuticals, an Apple Tree Company

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Conclusions about implant

- Implants targeting a subpopulation and suggesting potential benefit over standard treatment
- Patients report liking not to dose themselves daily, not having to worry when traveling or if need to reschedule
- Limited uptake in USA – many barriers
- Questions remain –Different locations besides the arm? How to make it easier for patients and providers to access?

RBP-6000: Monthly subcutaneous buprenorphine FDA-approved November 2017

- Comes in prefilled 19-gauge syringe.
- Refrigerate, keep at room temperature for at least 15 minutes prior to injection
- Dose: Months one and two = 300 mg, month 3 and thereafter = 100 mg (may increase if clinically indicated).
- Obtain baseline LFTS and monitor monthly, particularly with 300 mg dose.
- Most common side effects were: nausea, vomiting, headache, constipation, increased LFTs, tiredness, injection site itching and pain. Uncommon: need for surgical removal of injection.
- Also, limited uptake in USA although better than the implants

FDA Indivior AdCom, 10/31/2018
Medications for OUD. Treatment Improvement Protocol TIP 63.
https://store.samhsa.gov/system/files/sma18-5063fulldoc.pdf

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Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

*Barbara R Haight, Susan M Learned, Celine M Laffont, Paul J Fudala, Yue Zhao, Amanda S Garofalo, Mark K Greenwald, Vijay R Nadipelli, Walter Ling, Christian Heidbreder, for the RB-US-13-0001 Study Investigators**

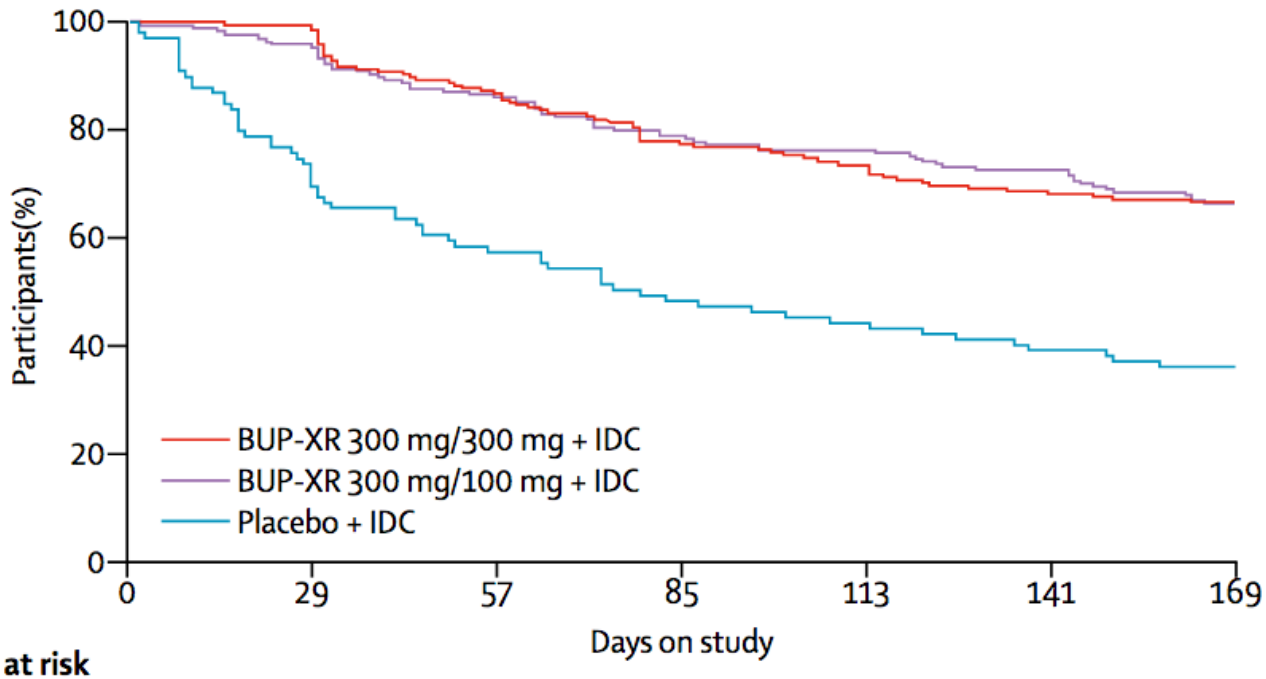
- Treatment seeking adults age 18-65 years with mod-severe OUD
- Two weeks open-label SL buprenorphine/naloxone film (n=665)
- If still eligible, randomized (n=504) 4:4:1 to:
  - BUP-XR 300 mg/300 mg (six injections of 300 mg every 28 days; n=201),
  - BUP-XR 300 mg/100 mg (two injections of 300 mg plus four injections of 100 mg; n=203),
  - Placebo injections every 28 days (n=100)
- Individual counseling throughout trial
- No prn SL buprenorphine/naloxone available
- Primary outcome: % abstinence from opioids by urine tests from weeks 5-24 confirmed by self-report

www.thelancet.com Vol 393 February 23, 2019

Randomized sample characteristics

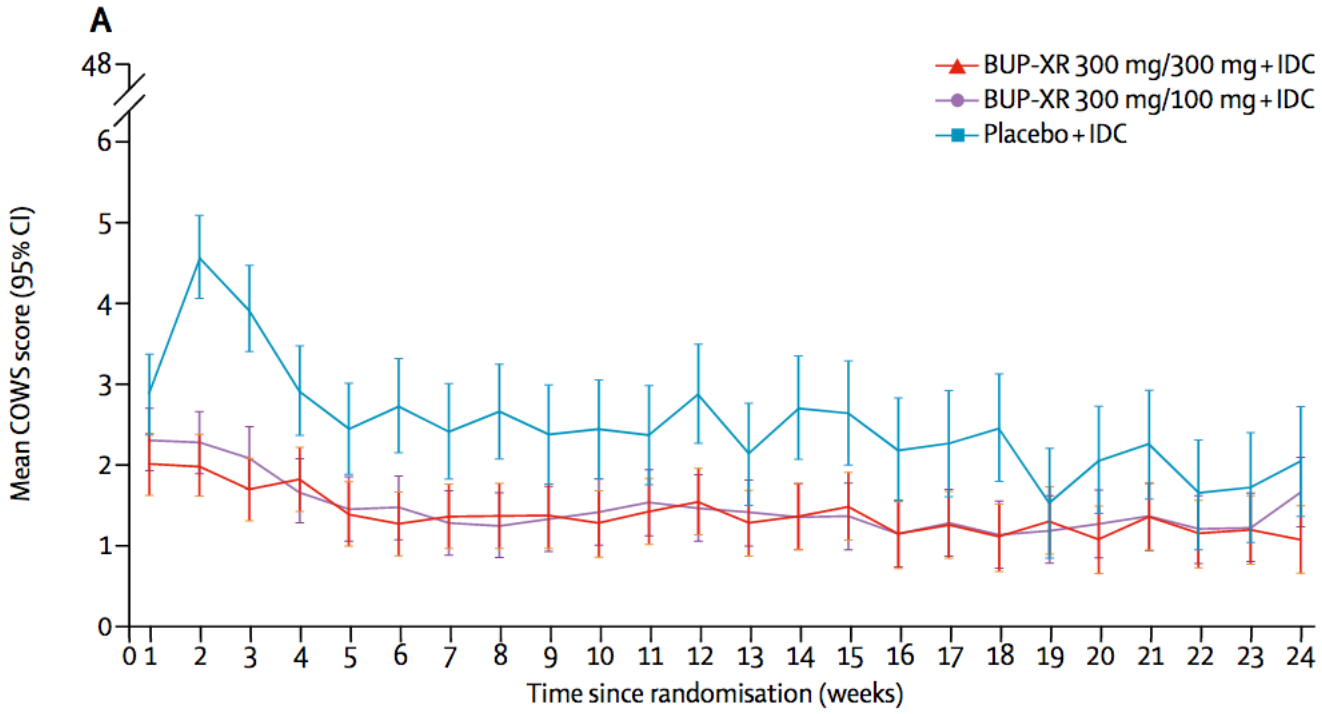
	300mg/300mg	300mg/100mg	Placebo
Mean age, yrs (SD)	39.3 (11.0)	40.4 (11.2)	39.2 (11.0)
Male, no. (%)	132 (67)	128 (66)	64 (65)
White, no. (%)	140 (71)	132 (68)	77 (78)
Mean BMI (SD)	26.4 (4.4)	25.3 (4.2)	25.3 (4.3)
Injection opioid use, no. (%)	79 (41)	84 (43)	50 (51)
Hep C +, no. (%)	24 (12)	31 (16)	10 (10)

Retention after randomization



Number at risk							
BUP-XR 300 mg/300 mg + IDC	196	193	170	152	144	134	95
BUP-XR 300 mg/100 mg + IDC	194	185	167	153	148	141	80
Placebo + IDC	99	69	57	48	44	39	23

Opioid withdrawal



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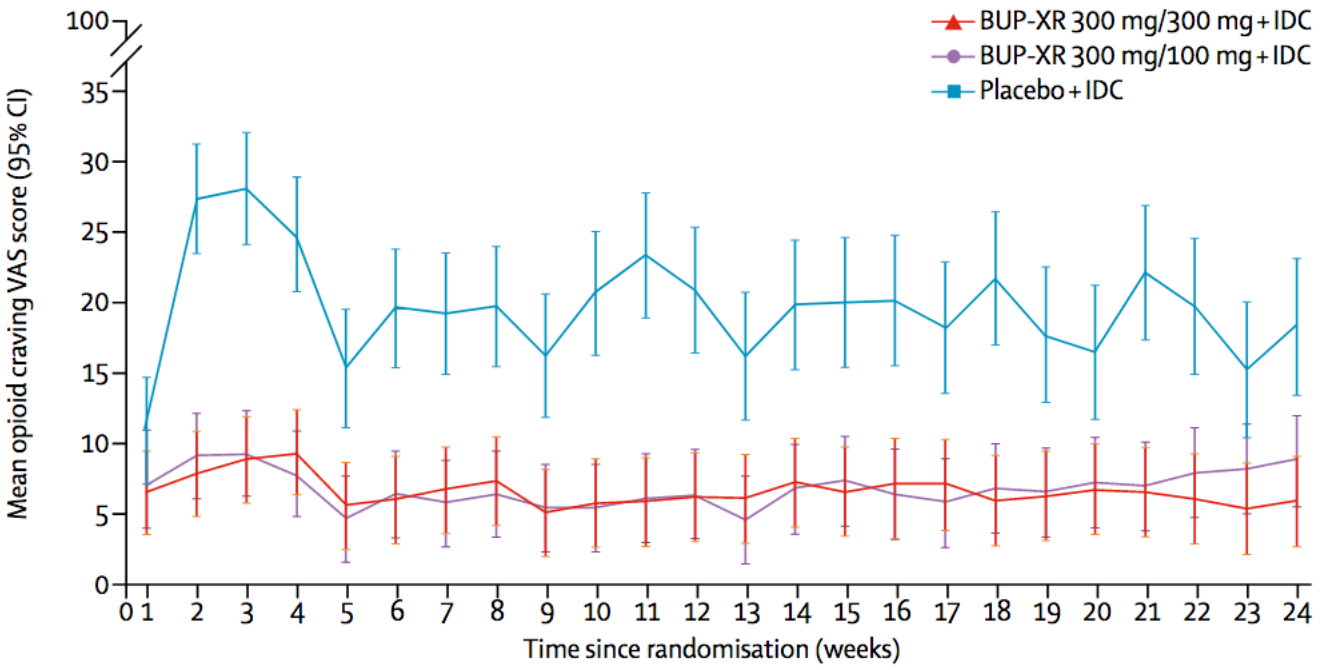
Opioid craving



Opioid use outcomes

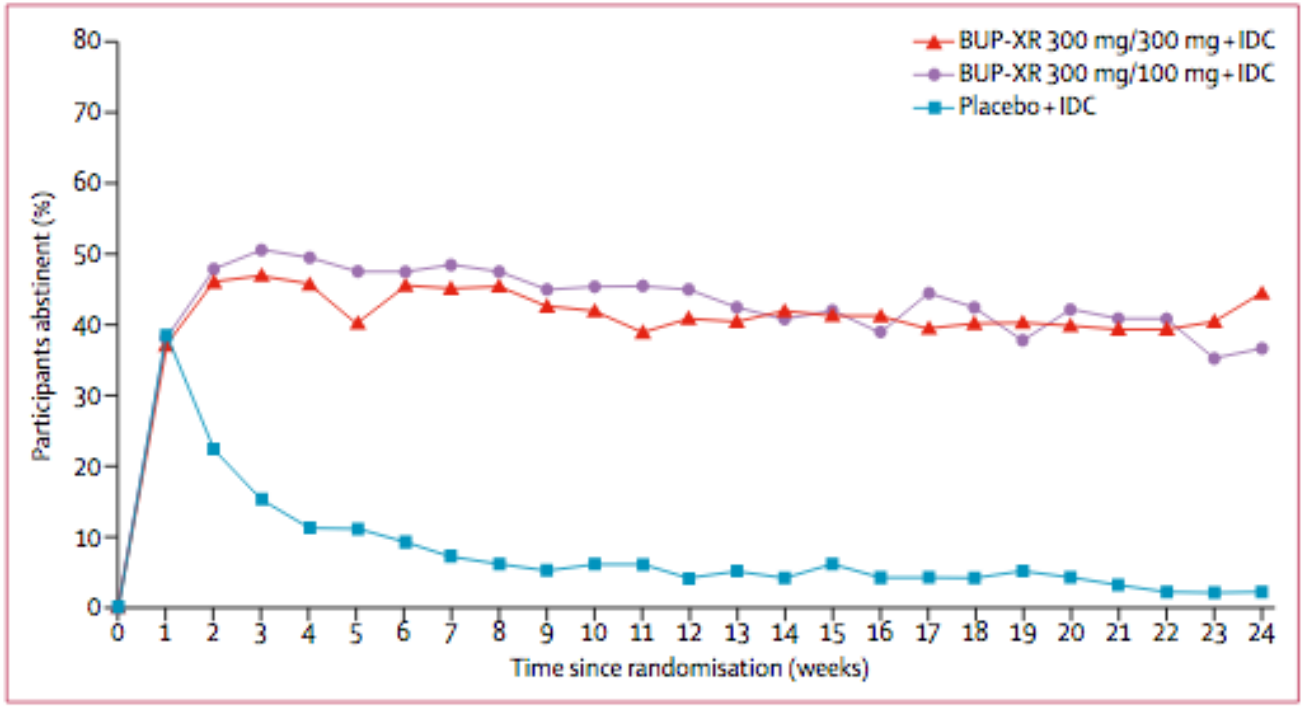


***Figure 5:* Proportion of participants abstinent by week**
Missing measure of either urine drug screen or timeline followback interview at a week was imputed as positive opioid use. Week 0 represents the opioid usage assessment at screening, and week 1 represents the opioid usage assessment at week 1, day 1 visit (baseline). IDC=individual drug counselling.

	300mg/ 300mg n=196	300mg/ 100mg n=194	Placebo n=99
Primary*:			
Mean % abstinence	41.3% (39.7%)	42.7% (38.5%)	5.0% (17.0%)
Key secondary:			
# ≥80% abstinent	57 (29%)	55 (28%)	2 (2%)

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Adverse Events

	BUP-XR 300/300 mg plus individual drug counselling (n=201) (n=201)	BUP-XR 300/100 mg plus individual drug counselling (n=203) (n=203)	Placebo plus individual drug counselling (n=100)
Any treatment-emergent adverse event	134 (67%)	155 (76%)	56 (56%)
Any serious treatment-emergent adverse event	7 (3%)	4 (2%)	5 (5%)
Any severe treatment-emergent adverse event	13 (6%)	15 (7%)	4 (4%)
Any treatment-emergent adverse event leading to discontinuation	10 (5%)	7 (3%)	2 (2%)
Any treatment-emergent adverse event leading to death	1 (<1%)	0	0

- One non-fatal opioid overdose in the placebo group
- Most participants (96%) reported local burning or stinging at the injection site, peaking about 1 minute after injection
- No injection required removal
- Some BUP XR LFT elevation but none met criteria for Hy's Law. FDA label recommends monitoring LFT, particularly with the 300 mg dose.

BUP-XR: MEDICATION SATISFACTION

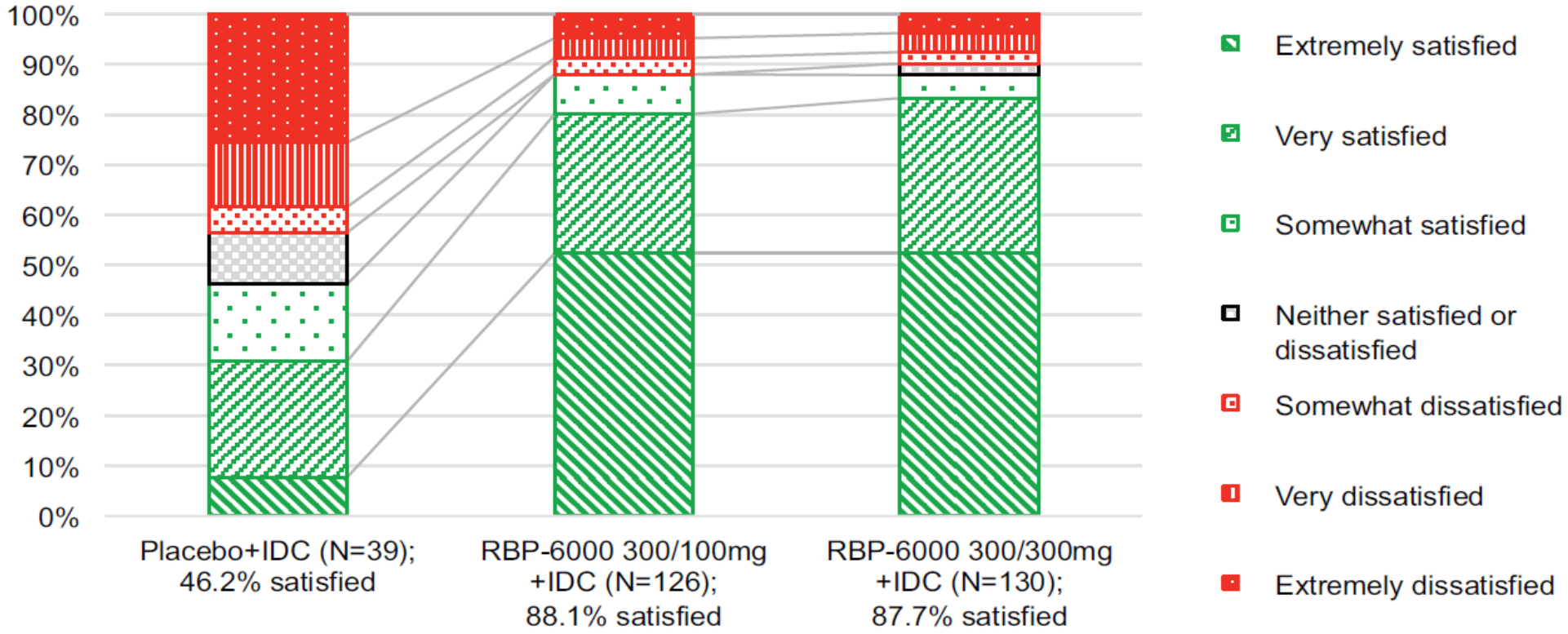


FIGURE 1. Percentage of subjects who were satisfied or dissatisfied with treatment at week 25[a]. BUP-XR, buprenorphine extended-release monthly injection, for subcutaneous use [CIII]; IDC, individual drug counselling; MSQ, Medication Satisfaction Questionnaire. [a]The MSQ is a 7-point scale with the following ratings: 1, extremely dissatisfied, 2, very dissatisfied, 3, somewhat dissatisfied, 4, neither satisfied nor dissatisfied, 5, somewhat satisfied, 6, very satisfied, and 7, extremely satisfied. MSQ scores were categorized as satisfied (5–7), neutral (4), or dissatisfied (1–3).

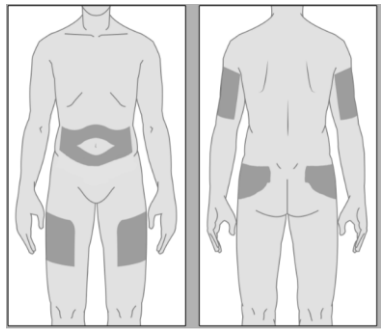
Ling, W., Nadipelli, V.R., Solem, C.T., Ronquest, N.A., Yeh, Y.-C., Learned, S.M., Mehra, V., Heidbreder, C., 9000. Patient-centered Outcomes in Participants of a Buprenorphine Monthly Depot (BUP-XR) Double-blind, Placebo-controlled, Multicenter, Phase 3 Study. Journal of Addiction Medicine Publish Ahead of Print.

Subcutaneous weekly and monthly CAM2038

- Approved 2018 in Europe & Australia, tentative approval USA 2018 – exclusivity issue
- Weekly & monthly formulations with multiple doses
- Store at room temperature
- Pre-filled syringes with safety device
- Small volume (<1 mL), thin needle
- Several injection site locations

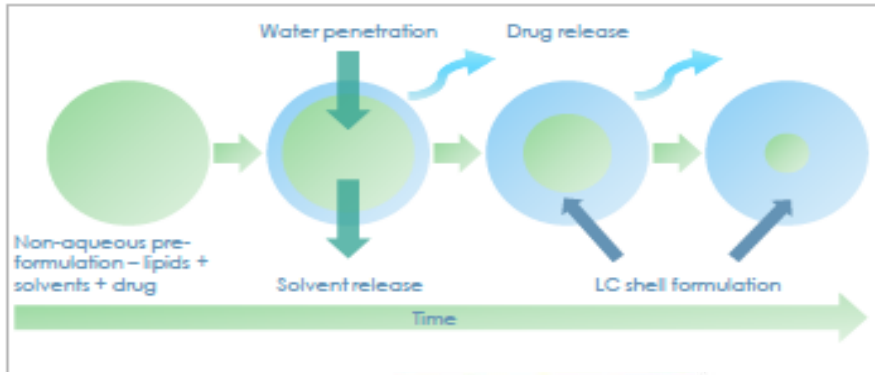
BUP-Sublingual	CAM2038 weekly	CAM2038 monthly
≤6 mg	8 mg (0.16 mL)	--
8-10 mg	16 mg (0.32 mL)	64 mg (0.18 mL)
12-16 mg	24 mg (0.48 mL)	96 mg (0.27 mL)
18-24 mg	32 mg (0.64 mL)	128 mg (0.36 mL)

BUP-SL dose and approximate equivalent weekly and monthly BUP-XR injections
NOTE: BUP-SL doses are in Subutex® equivalents



1. Albayaty et al. Advances in Therapy (2017)

FluidCrystal® nano-technology



Phase 2 Study: Purpose, Design & Eligibility

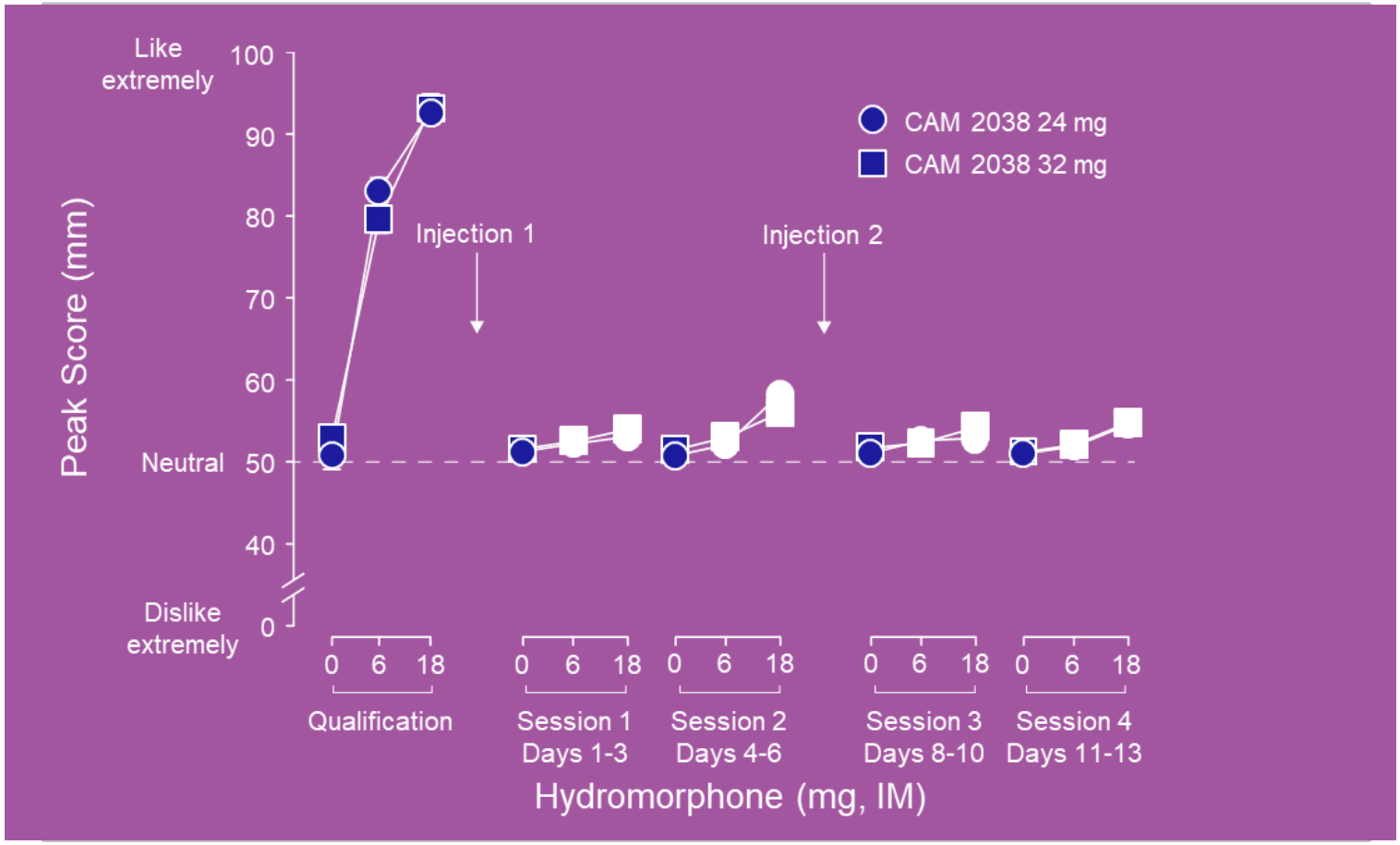
- Evaluate withdrawal suppression and blockade efficacy of weekly CAM2038
- 3-week inpatient, double-blind randomized within subject study
- Non-treatment seeking adults with moderate-severe opioid use disorder (OUD), otherwise healthy

Methods

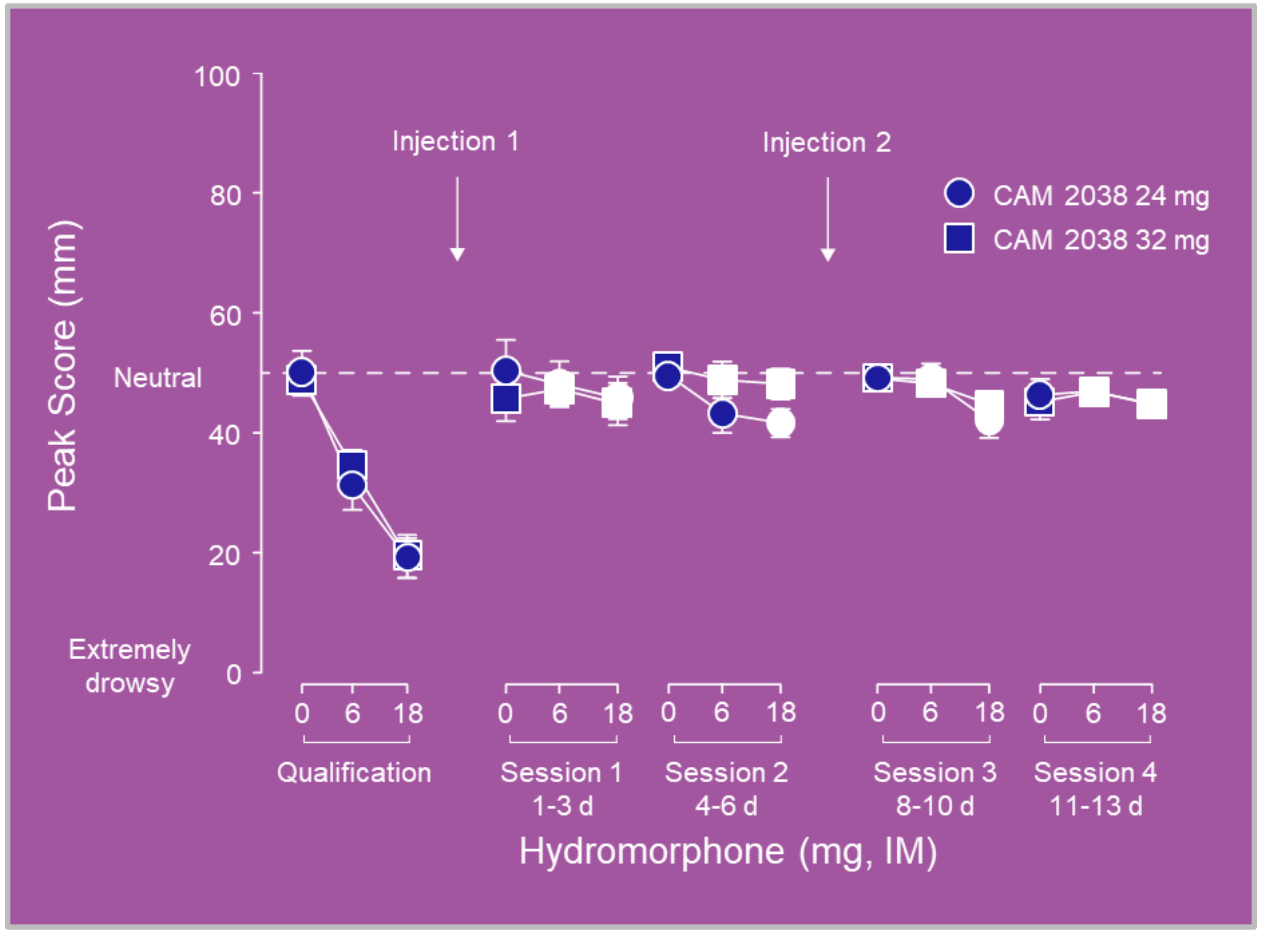
- Initial stabilization: Morphine 30 mg orally 4 times daily
- Qualification phase: Hydromorphone (HM 0, 6, 18 mg, IM; random order) – to ensure sensitive & like HM effects
- Randomized 1:1 to either:
  - CAM2038 24 mg weekly injections (~16 mg SL buprenorphine)
  - CAM2038 32 mg weekly injections (~24 mg SL buprenorphine)
- Four sets of HM challenge sessions

Walsh, Comer, Lofwall et al. Effect of Buprenorphine Weekly Depot (CAM2038) & Hydromorphone Blockade in Individuals with Opioid Use Disorder. *JAMA Psychiatry*.2017 Sep 1;74(9):894-902.

“At this moment, my liking for drug is”



Mental State (Drowsy to Alert)



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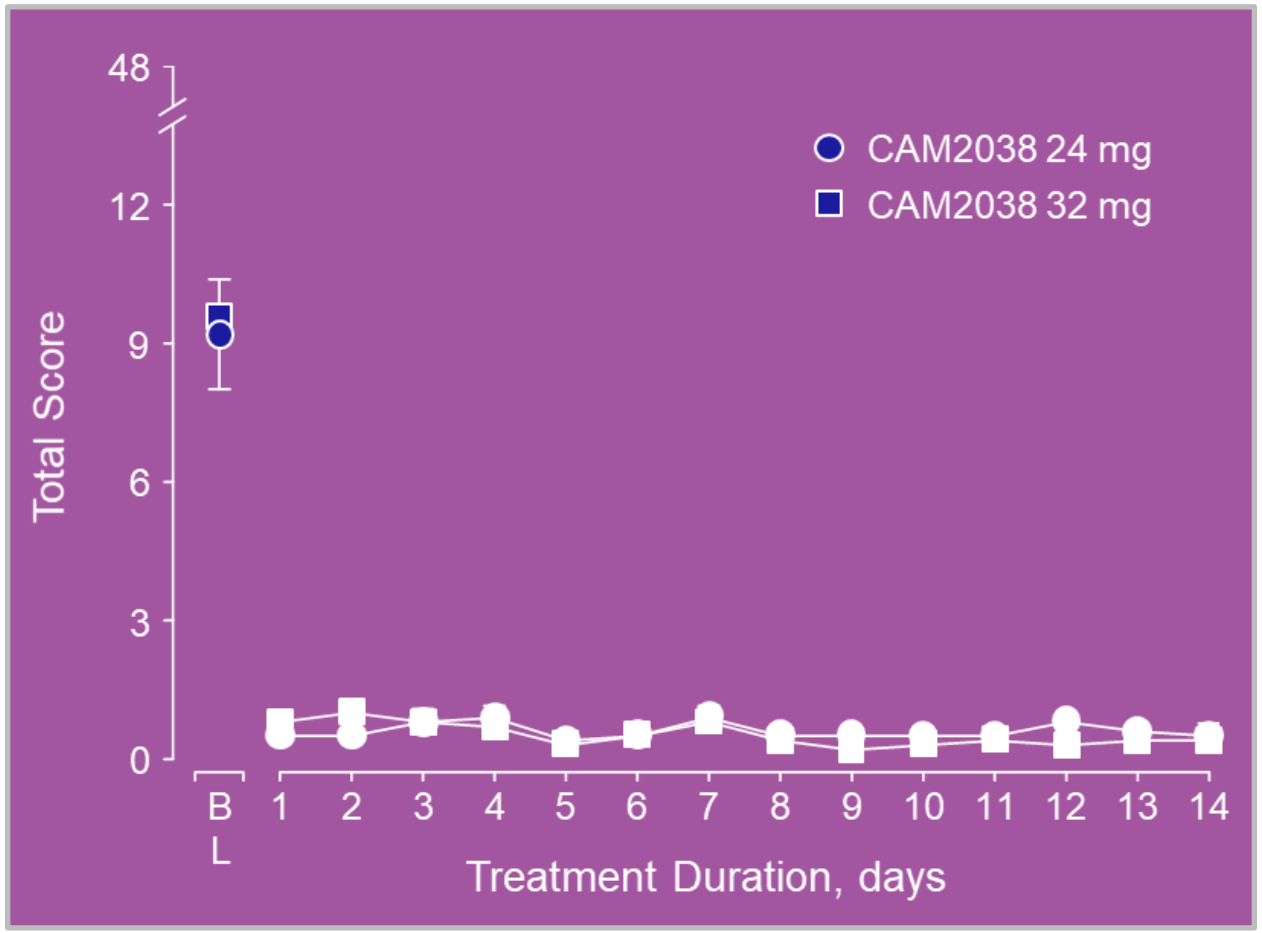
Clinical Opiate Withdrawal Scale



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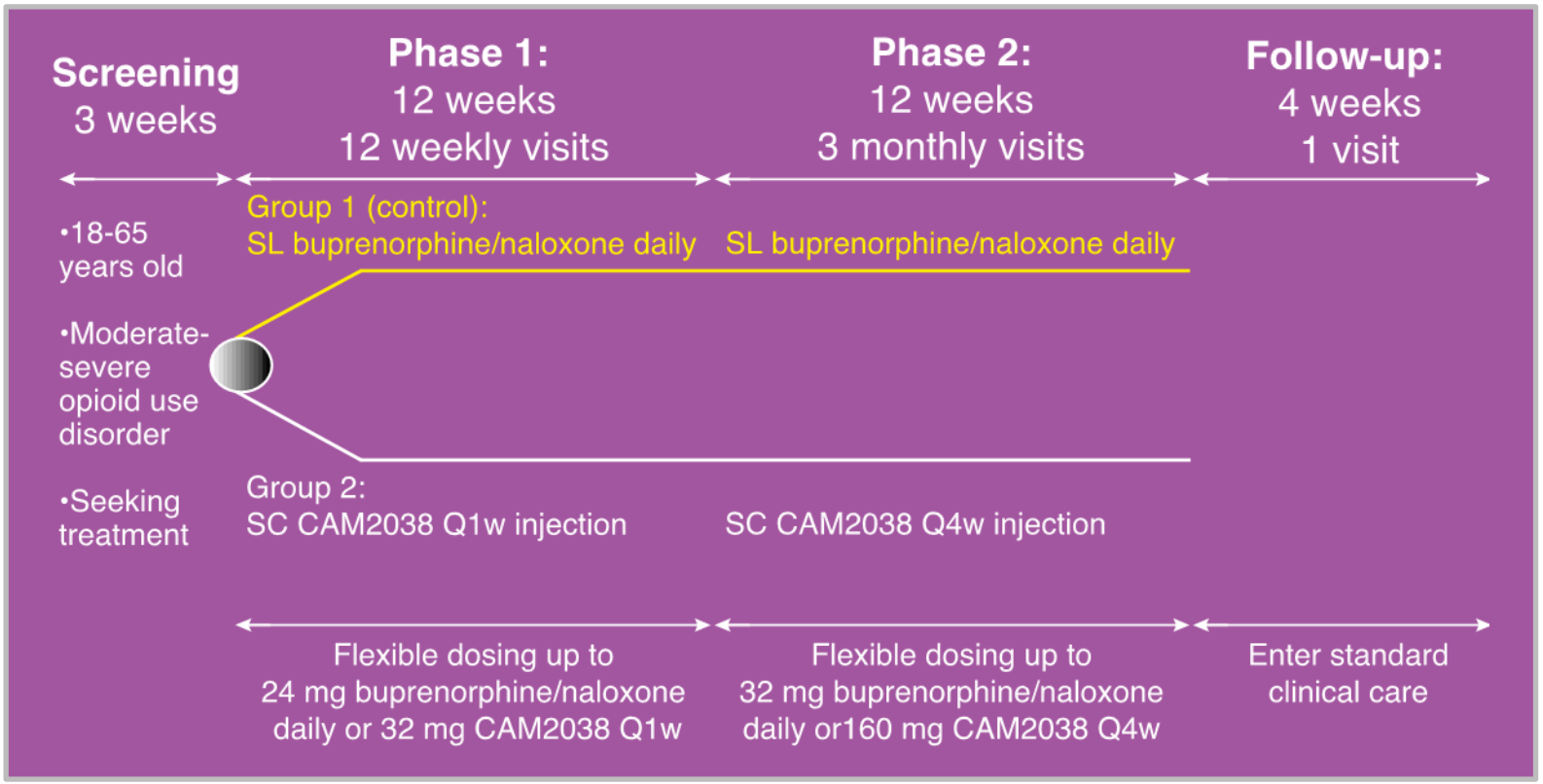
Results

- Blockade of liking, high, good effects
- Diminished craving and rapid withdrawal suppression (without need for a sublingual buprenorphine lead-in)
- No SAEs – constipation most common side effect

Phase 3 randomized, double-blind, double-dummy, active control study



Counseling, UDT, self-report drug use, craving, and withdrawal assessed at each visit

Lofwall, Walsh, Nunes 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 Internal Medicine* 2018

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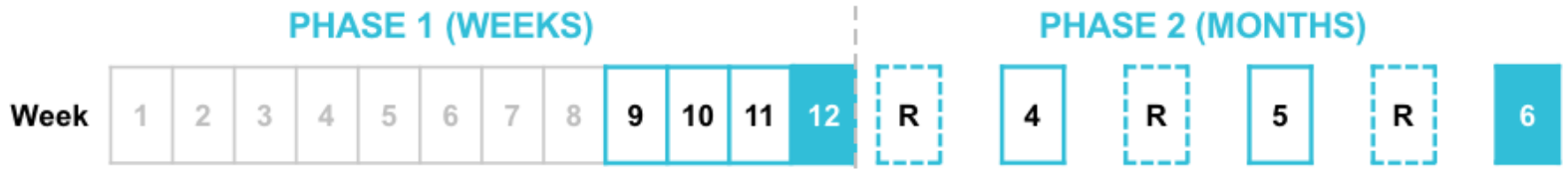
Primary Outcomes

- European Medicines Agency: Proportion of urine toxicology results negative for illicit opioids

- US Food and Drug Administration: Responder rate whereby a responder required to have no illicit opioid-positive urines (supported by self-report) in:
  - Phase 1: at Week 12 and for at least 2 of the 3 weeks between Weeks 9–11, and in
  - Phase 2: during Month 6 (Weeks 21-24) and for at least 5 of the 6 assessments during Weeks 13-24.



- Note: Highly sensitive urine testing: 5 ng/mL was the lower limit of detection for for codeine, morphine, hydrocodone, oxycodone; also tested for methadone and its metabolite, oxymorphone, fentanyl and norfentanyl

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Baseline sample characteristics

Characteristic	SL BPN/NX (n=215)	CAM2038 (n=213)
Age, mean (SD)	38.0 (10.9)	38.7 (11.2)
Male, No. (%)	142 (66.0)	121 (56.8)
White, No. (%)	164 (76.3)	159 (74.6)
BMI, mean (SD)	26.2 (5.6)	25.6 (5.0)
Employed, No. (%)	72 (33.5)	76 (35.7)
History of any arrest, No. (%)	144 (67.0)	130 (61.0)
Primary opioid of use, No. (%)		
Heroin	151 (70.2)	152 (71.4)
Prescription opioids	64 (29.8)	61 (28.6)
Injection use history, No. (%)	110 (51.2)	114 (53.5)
Hepatitis C antibody pos., No (%)	81 (37.7)	81 (38.0)

Characteristic	SL BPN/NX (n=215)	CAM2038 (n=213)
Fentanyl + screening, No. (%)	42 (22.8)	62 (29.1)
Non-opioid drug use screening, No. (%)	149 (69.3)	155 (72.8)
Amphetamine	32 (14.9)	38 (18.0)
Benzodiazepine	35 (16.3)	30 (14.2)
Cocaine	53 (24.7)	53 (25.1)
Marijuana	64 (29.8)	57 (27.0)
Baseline opioid craving and withdrawal scores, mean (SD)		
Craving: need to use VAS (0–100)	76 (24.9)	77 (25.4)
Craving: desire to use VAS (0–100)	77 (25.4)	77 (26.2)
COWS score (0-48)	12 (6.0)	12 (5.4)
SOWS score (0-64)	31 (16.1)	32 (15.4)

No significance difference between groups

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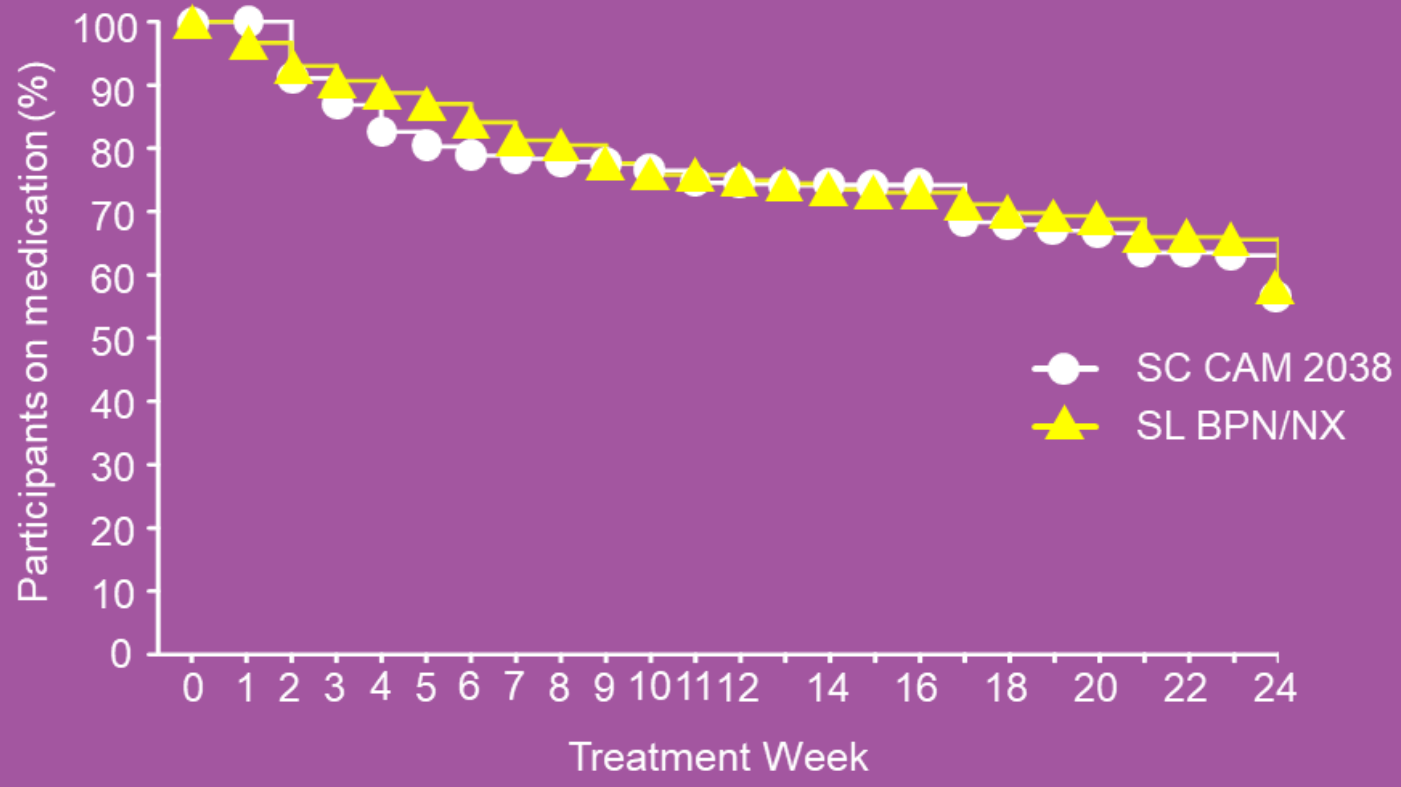
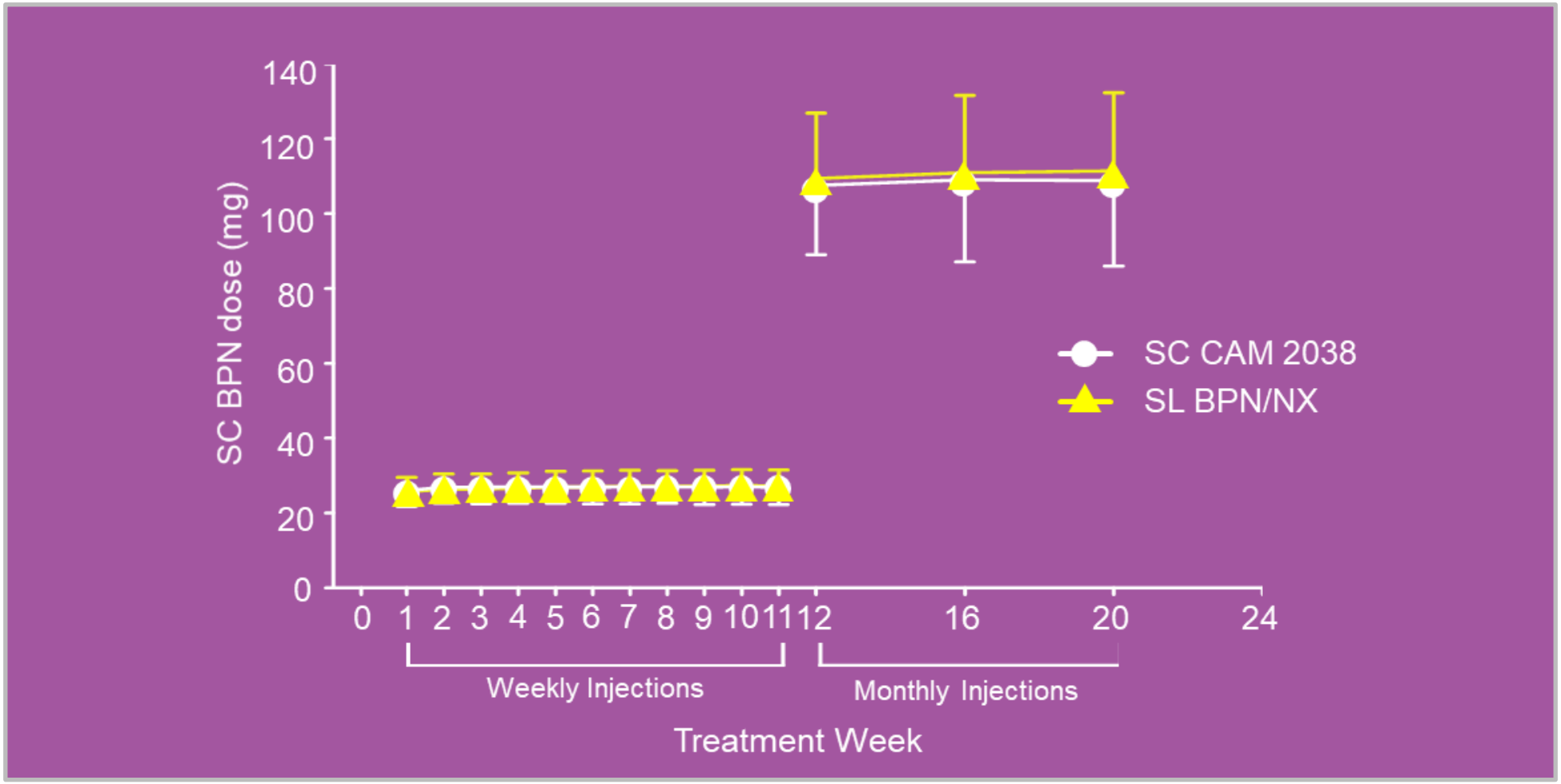
Retention on medication



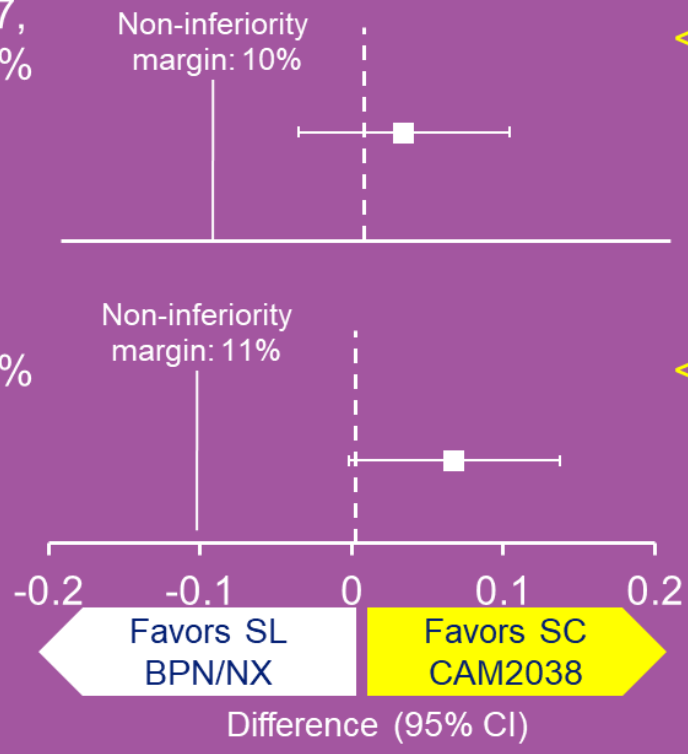
Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
SC BPN	213	213	194	185	176	171	168	167	166	165	163	159	159	158	158	158	158	146	145	143	142	136	136	135	121
SL BPN/NX	215	208	200	195	191	187	181	175	173	167	164	163	161	160	158	157	157	153	150	149	148	142	142	141	125

Medication dose

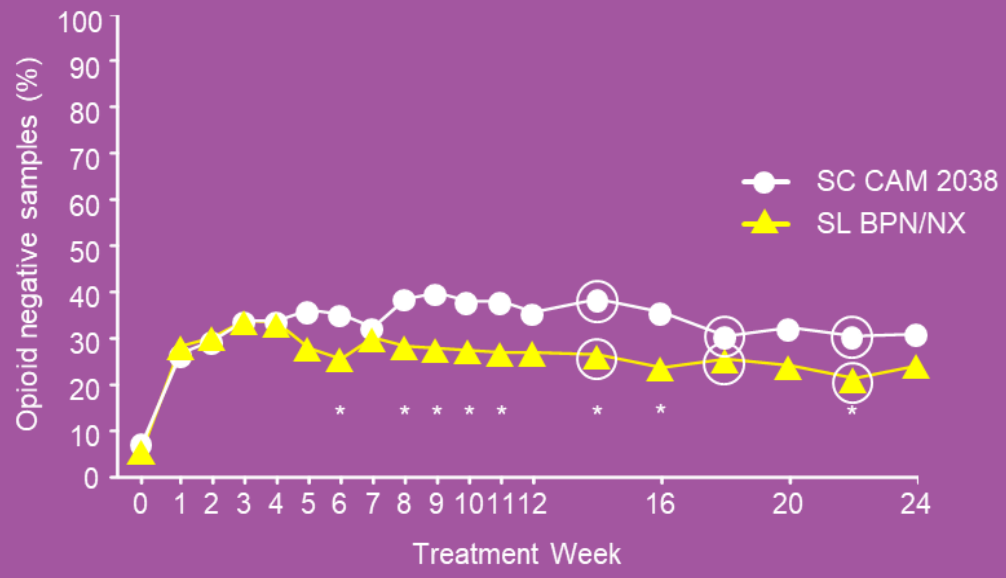


Primary Endpoints
(Intent to treat analyses for non-inferiority)

	SL BPN/NX	SC CAM2038	P-value non-inferiority
FDA: Responder rate	n=31, 14.4%	n=37, 17.4%	<0.001
Difference %, (95% CI)	3.0% (-4.0%, 9.9%)		
EMA: Mean % opioid negative urine	28.4%	35.1%	<0.001
Difference %, (95% CI)	6.7% (-0.1%, 13.6%)		



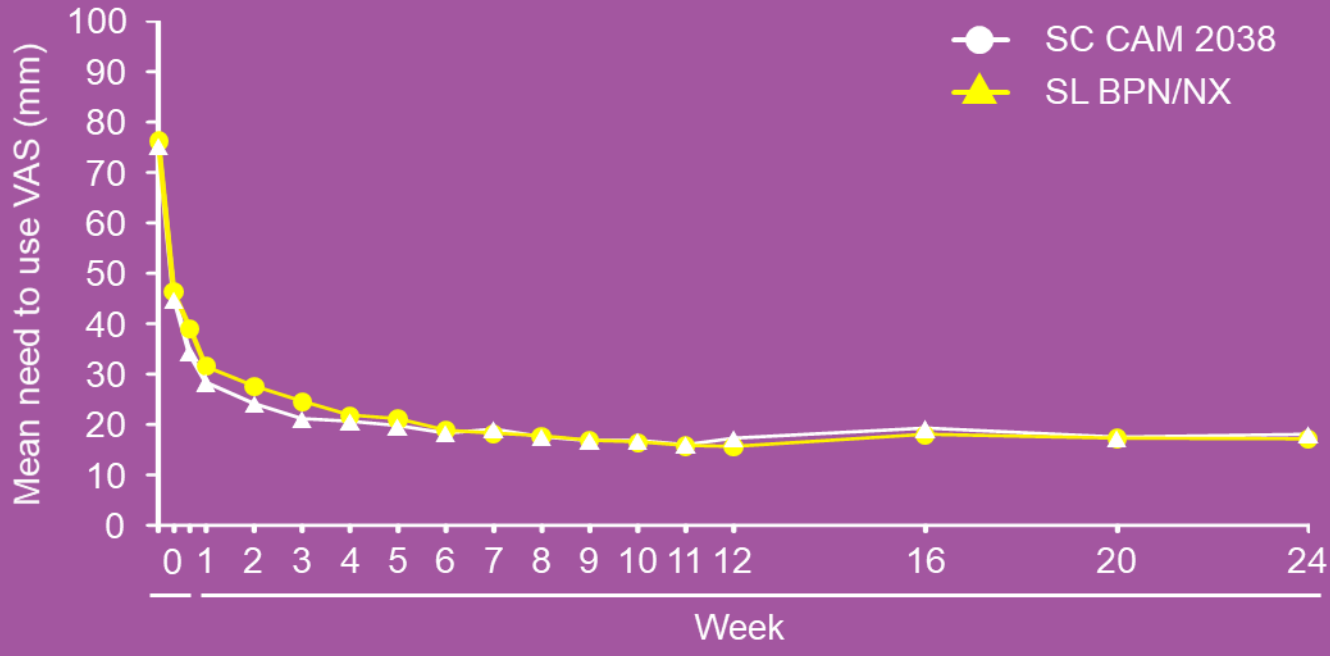
Urine tests with self-report



Missing samples imputed as positive. All negative urines supported by self-report. BL, baseline. * indicates significant difference at that time point.

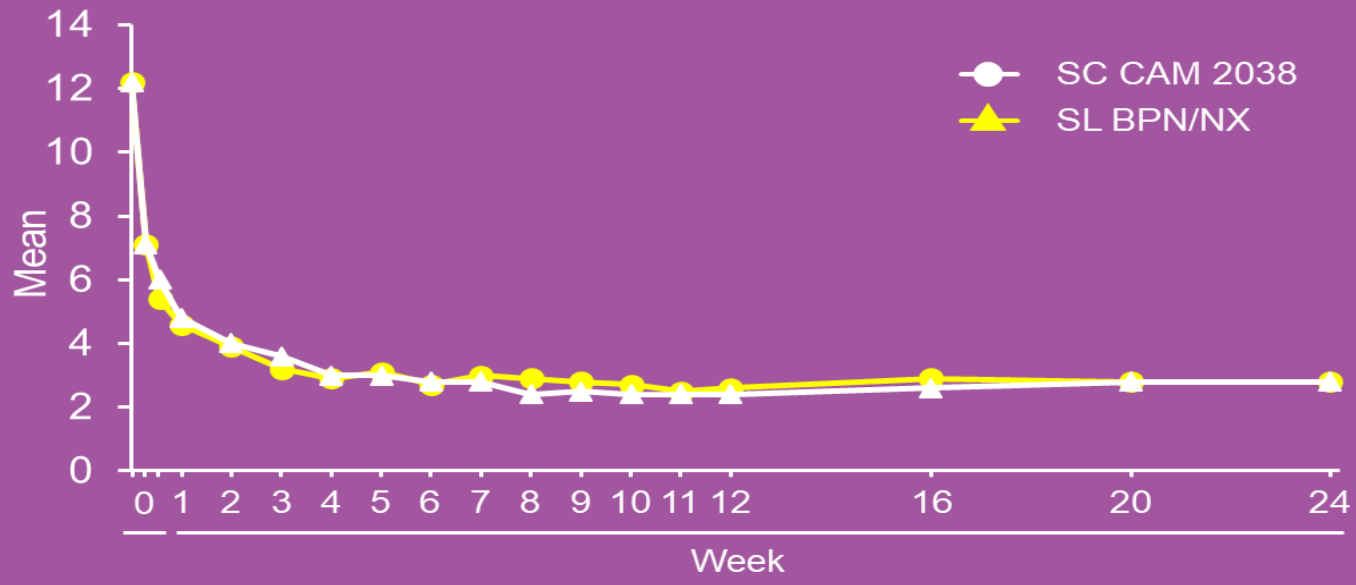
Opioid craving

"Since your last scheduled visit, indicate your worst or strongest *need to use opioids* between 0 (No Need to Use) and 100 (Maximum Need to Use) on this scale."



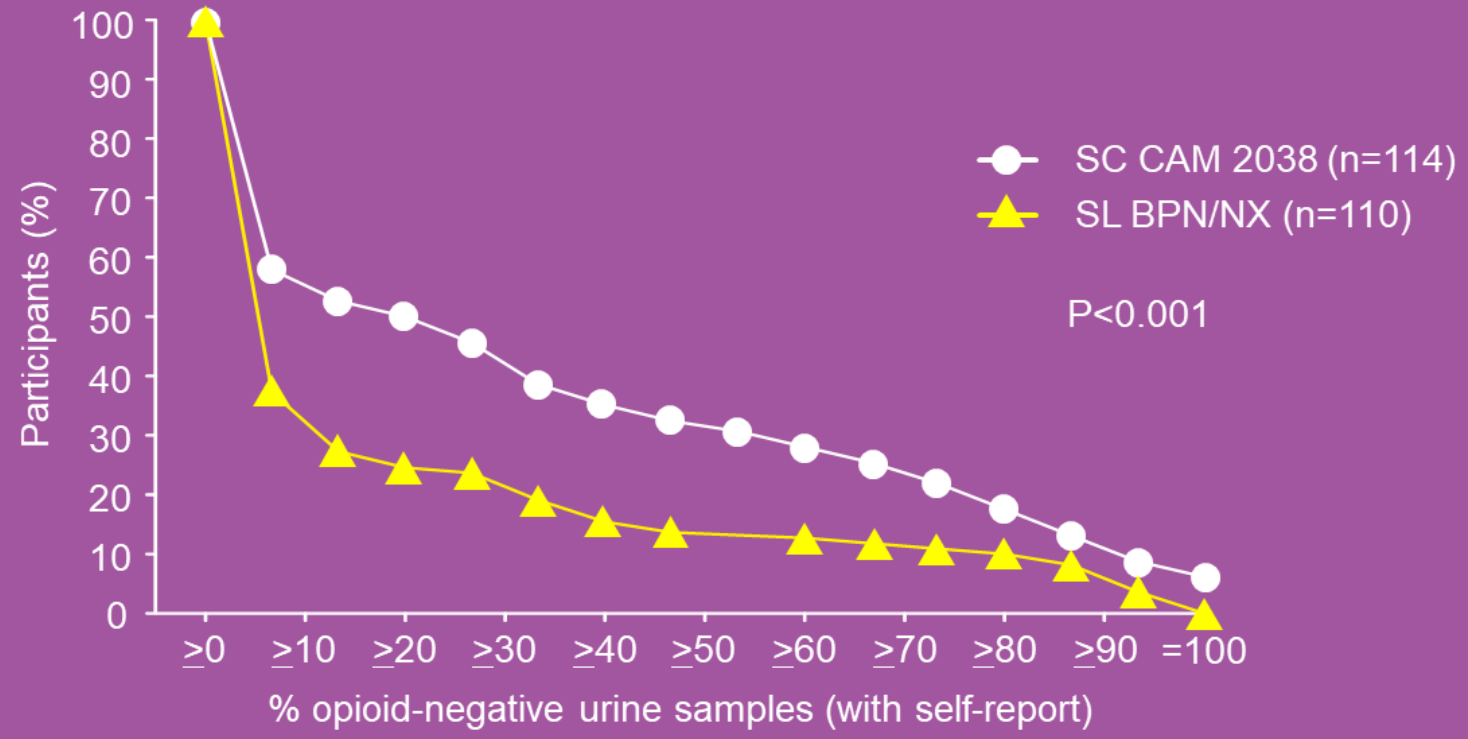
No significant difference between treatments

Clinical opiate withdrawal scale



No significant difference between treatments

Distribution of percent opioid-negative weeks (with self-reports) in group with injection use at baseline (Weeks 4-24)

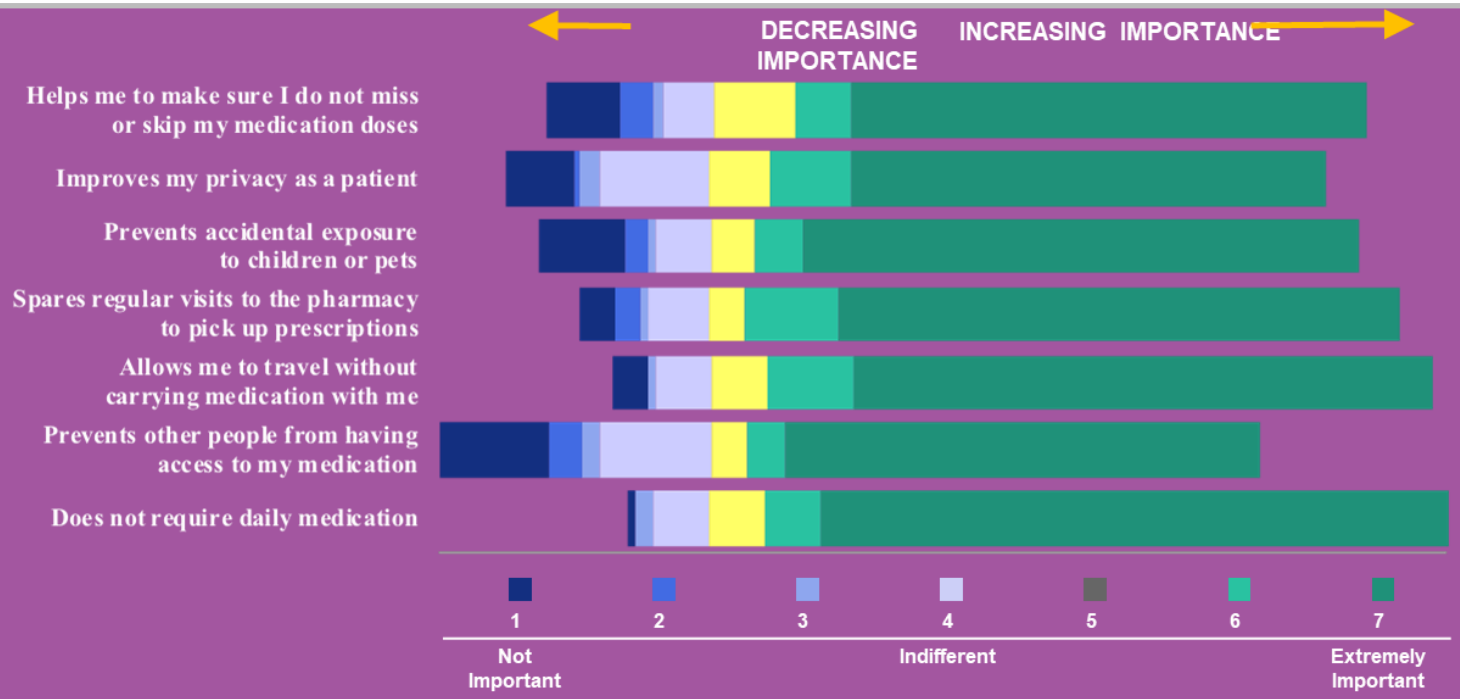


Adverse events

Adverse event (AE) characteristic	SL-BPN/NX (n = 215)	CAM2038 (n = 213)
Non-fatal serious	13 (6.0%)	5 (2.3%)
Death	0	1 (0.5%)
Hospitalisations	12 (5.6%)	3 (1.4%)
Drug overdoses	5 (2.3%)	0
Led to discontinuation of treatment	3 (1.4%)	7 (3.3%)
Treatment emergent AE in >5% of participants		
Injection site pain	17 (7.9%)	19 (8.9%)
Headache	17 (7.9%)	16 (7.5%)
Constipation	16 (7.4%)	16 (7.5%)
Nausea	17 (7.9%)	15 (7.0%)
Injection-site pruritus	13 (6.0%)	13 (6.1%)
Injection-site erythema	12 (5.6%)	12 (5.6%)
Urinary tract infection	10 (4.7%)	11 (5.2%)
Insomnia	6 (2.8%)	12 (5.6%)

Overall, CAM2038 safety profile comparable to daily SL with addition of injection site reactions, which all were mild (74%) or moderate (26%) severity.

Open-label study: Patient ratings of important features of CAM2038 (N=133)



Among patients switching from SL BUP to SC BUP in an open-label study, majority (83%) rate SC BUP as "somewhat better" or "much better" compared to SL.

Clinical Study Report (CSR) HS-14-499. Figure courtesy of Sonnie Kim, Pharm D Braeburn Pharmaceuticals. Frost, Bailey et al. Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult outpaitients with opioid use disorder. *Addiction* 2019.

Conclusions

- Long-acting medications for OUD hold much promise for improving treatment entry, retention and patient outcomes
- Look forward to many ongoing studies and learning about real world clinical implementation and effectiveness

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- TIP 63 Medications for Opioid Use Disorder [available for free download @ https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder]

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PCSS Mentoring Program

- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid use disorder.
- PCSS Mentors are a national network of providers with expertise in **addictions, pain, evidence-based treatment including medications for addiction treatment**.
- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.
- No cost.

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https://pcssNOW.org/mentoring/

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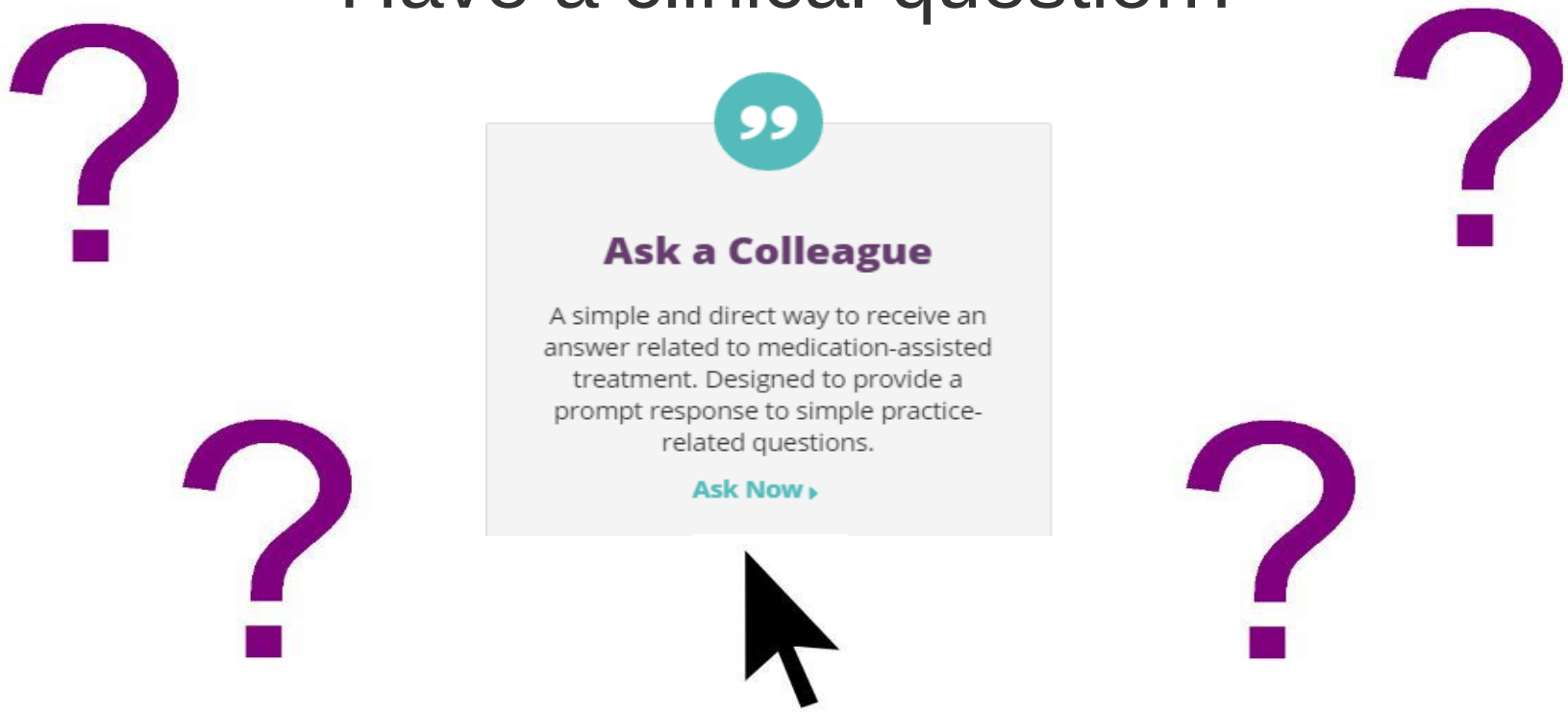
Have a clinical question?



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PCSS Providers Clinical Support System

PCSS Providers Clinical Support System

PCSS is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

Addiction Technology Transfer Center	American Society of Addiction Medicine
American Academy of Family Physicians	American Society for Pain Management Nursing
American Academy of Pain Medicine	Association for Multidisciplinary Education and Research in Substance use and Addiction
American Academy of Pediatrics	Council on Social Work Education
American Pharmacists Association	International Nurses Society on Addictions
American College of Emergency Physicians	National Association for Community Health Centers
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