Depot Medications for Unmet Treatment Needs in Opioid Use Disorder: Policy, Practice and Patient Care

Buprenorphine Implants and Injections: Clinical Trial Results and Implications for Patient Care

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Lisbon Addictions 2019

Disclosures

During the last 12 months:

- Consulting fees: Titan and Camurus
- Travel expenses: Camurus AB

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].

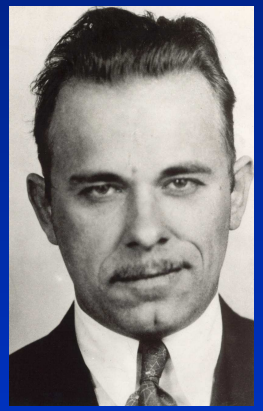
  - 2-fold increase in attending the first outpatient appointment if started sublingual BUP in the ER (78% vs. 37%). But many providers hesitant to prescribe because of concerns about diversion and misuse of sublingual BUP– what if they could just give a shot?

- 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.

Solid Matrix Subdermal Implant EMA-approved June 2019

EVA polymer + **Buprenorphine**

Inert component of several approved products

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

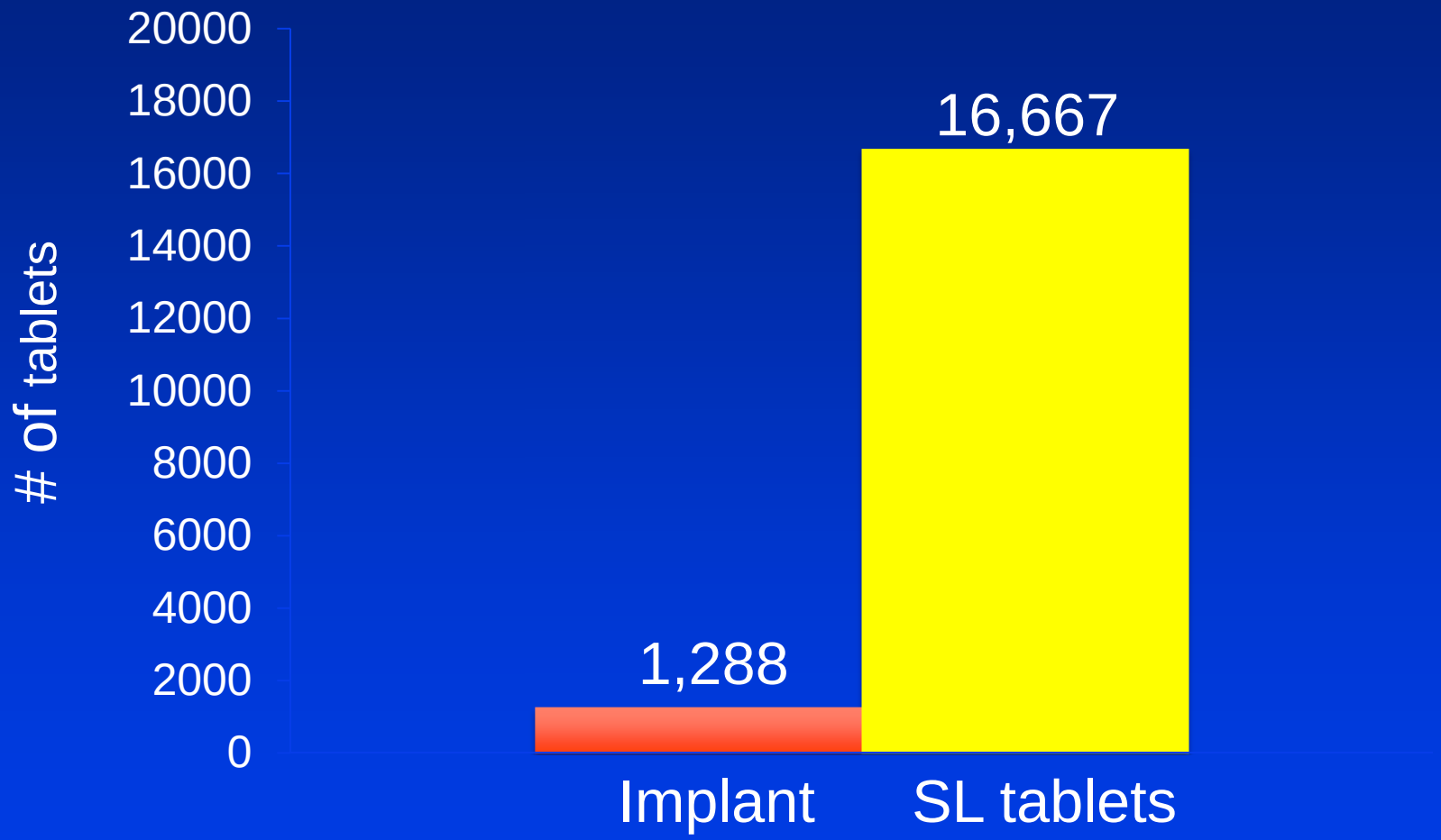
- 177 randomized; 166 completed (93.8% retention!!)

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

Relative use of SL buprenorphine/naloxone tablets



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

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 Indivior AdCom, 10/31/2018

- 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

Medications for OUD. Treatment Improvement Protocol TIP 63. https://store.samhsa.gov/system/files/sma18-5063fulldoc.pdf

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**

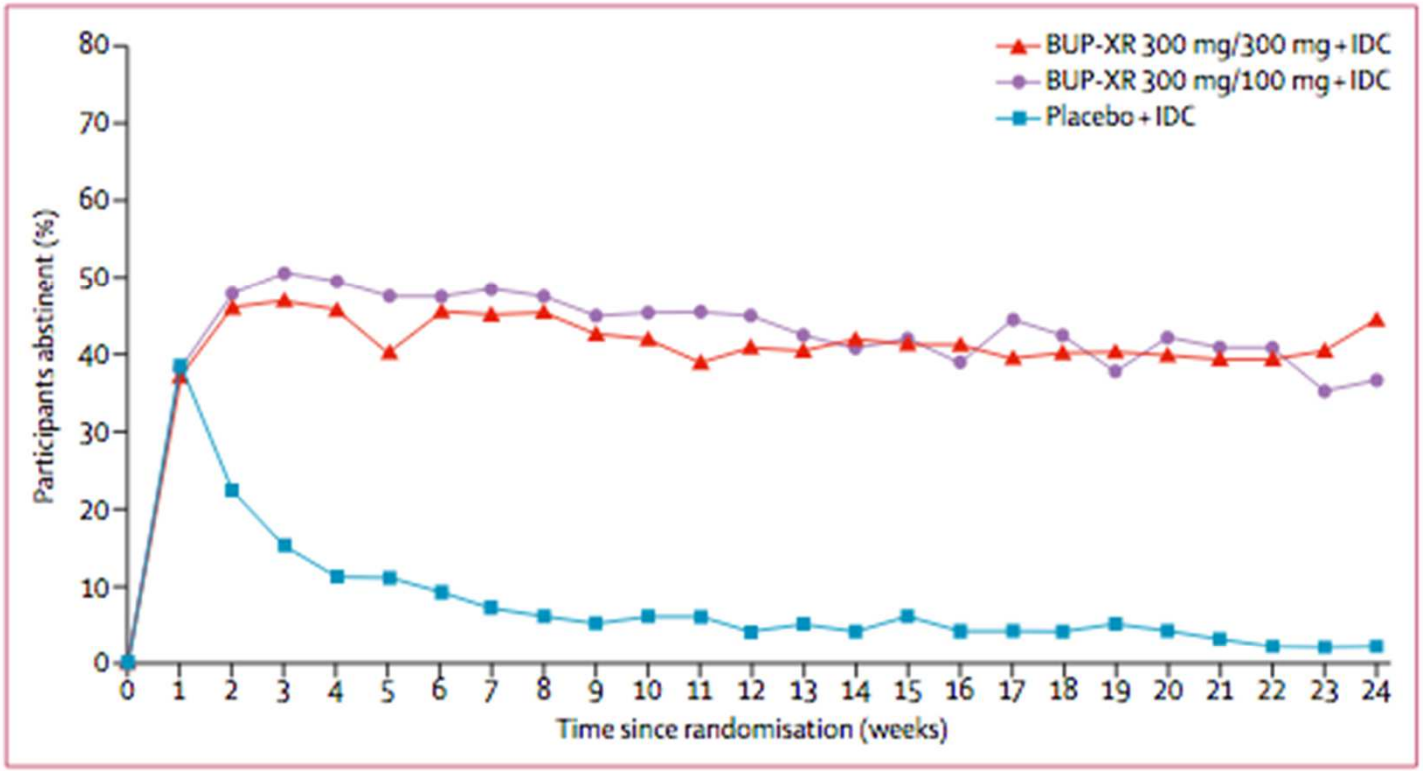


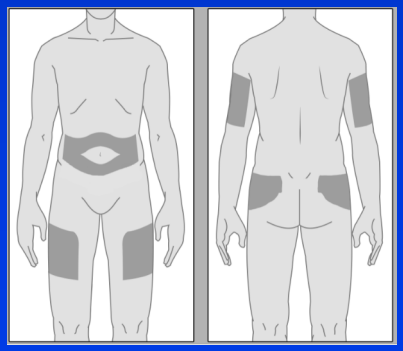
Figure 5: **Proportion of participants abstinent by week**
Missing measure of either urine drug screen or timeline followback interview at a week was imputed as positive opioid use. Week 0 represents the opioid usage assessment at screening, and week 1 represents the opioid usage assessment at week 1,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

Overview of Subcutaneous CAM2038

- Approved late 2018 in Europe & Australia, tentative approval in USA
- Weekly & monthly formulations with multiple doses
- Store 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

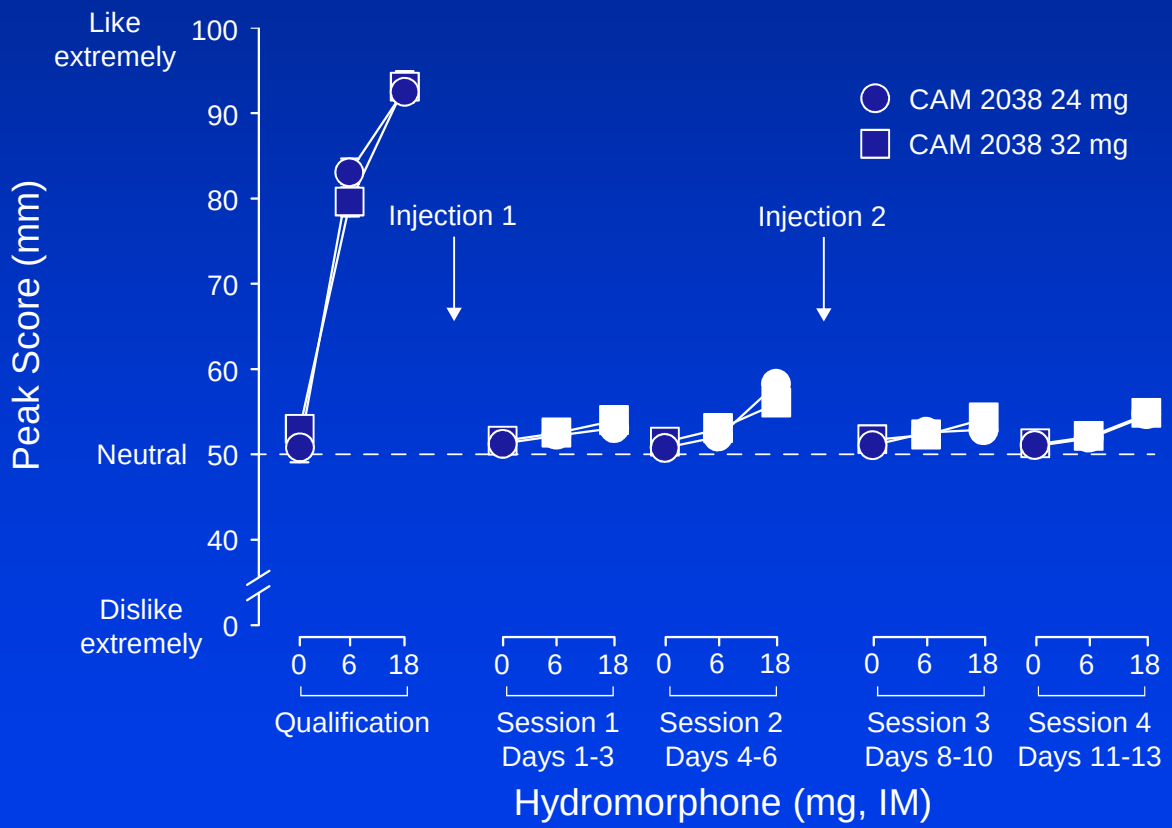
- Evaluate withdrawal suppression and blockade efficacy of weekly CAM2038
- 3-week inpatient, double-blind randomized within subject study
- Non-treatment seeking adults with moderate-severe opioid use disorder (OUD), otherwise healthy

Methods

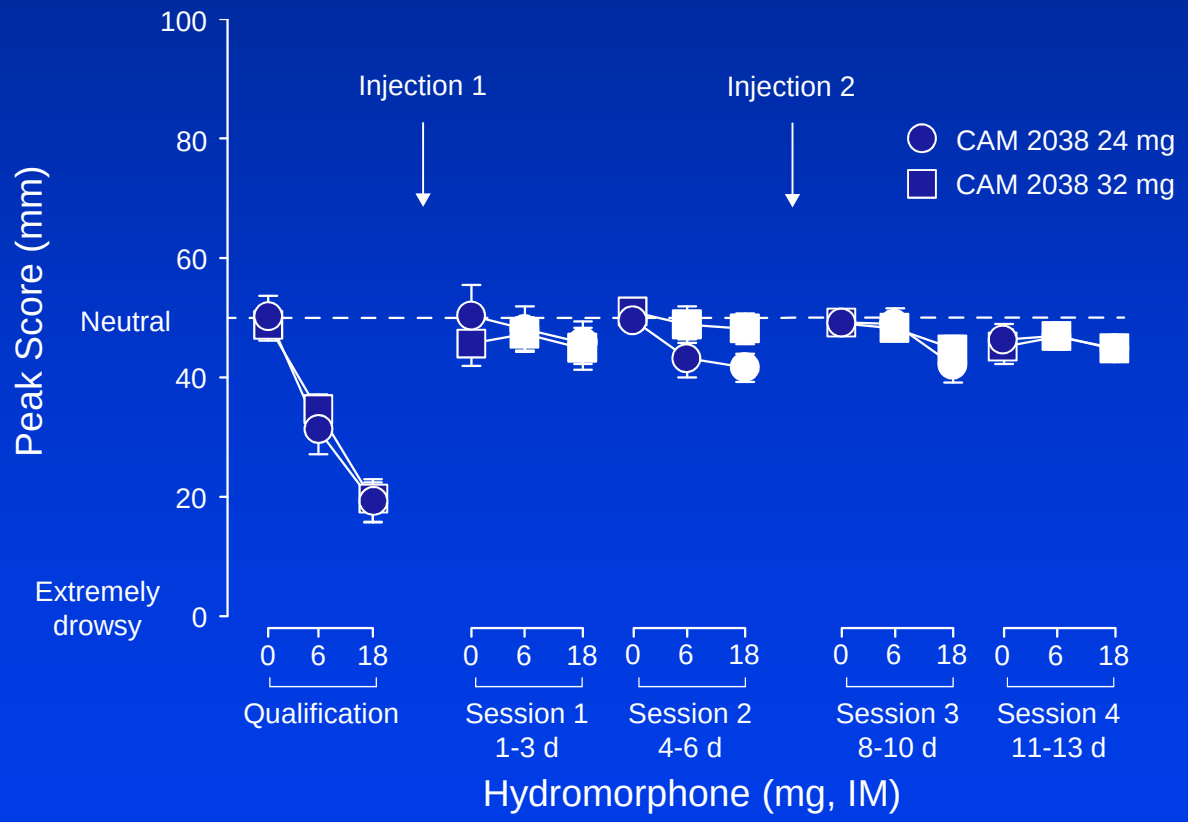
- Initial stabilization: Morphine 30 mg orally 4 times daily
- Qualification phase: Hydromorphone (HM 0, 6, 18 mg, IM; random order) – to ensure sensitive & like HM effects
- Randomized 1:1 to either:
  - CAM2038 24 mg weekly injections (~16 mg SL buprenorphine)
  - CAM2038 32 mg weekly injections (~24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

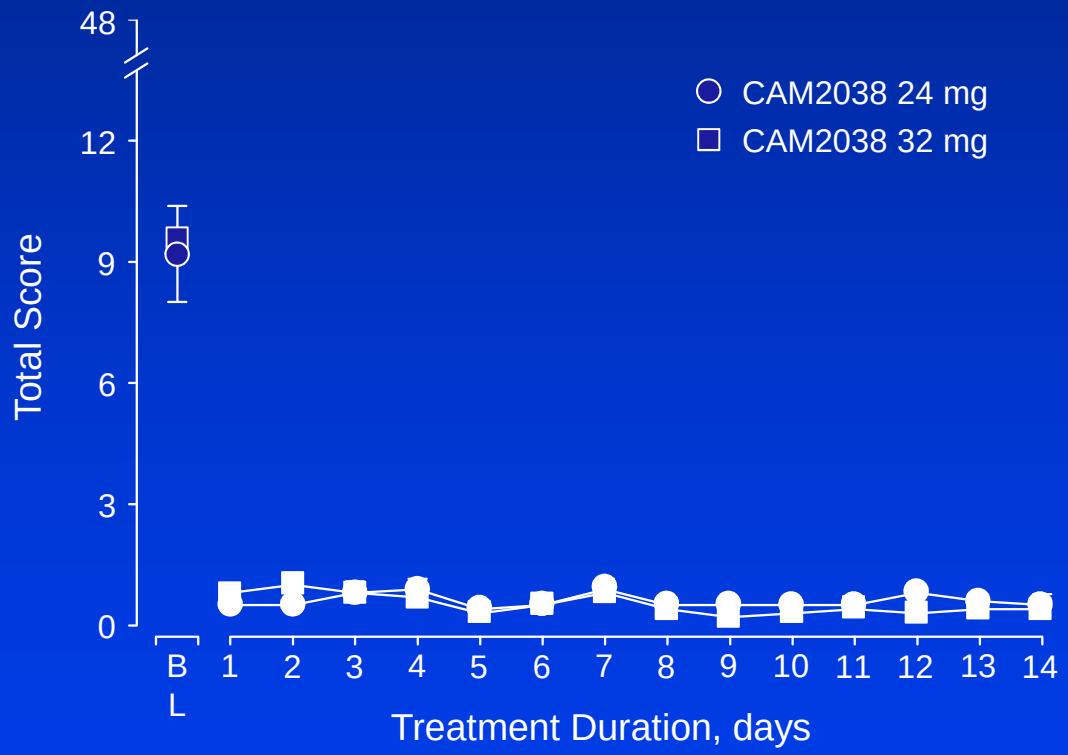
“At this moment, my liking for drug is”



Mental State (Drowsy to Alert)



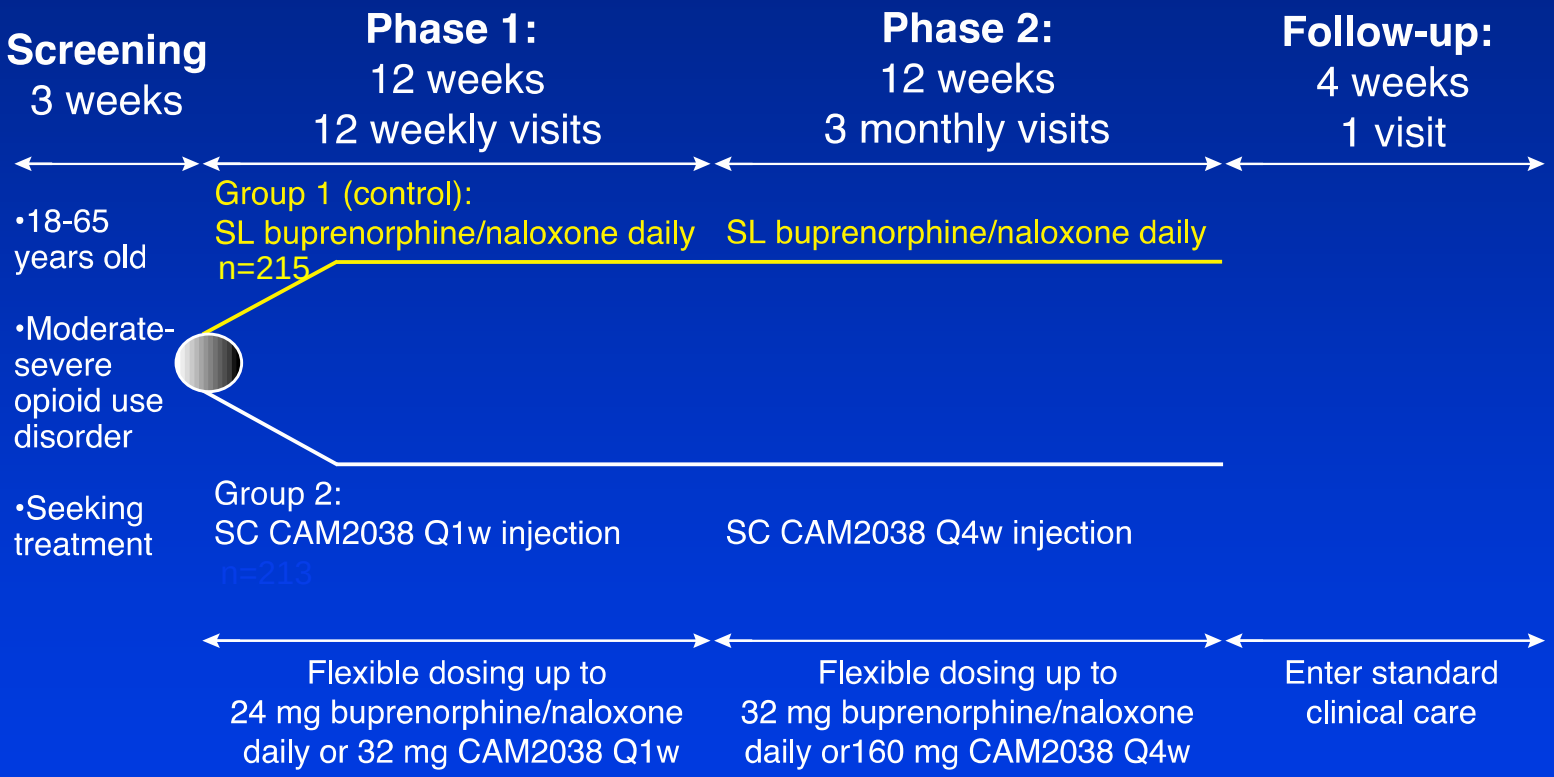
Clinical Opiate Withdrawal Scale



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



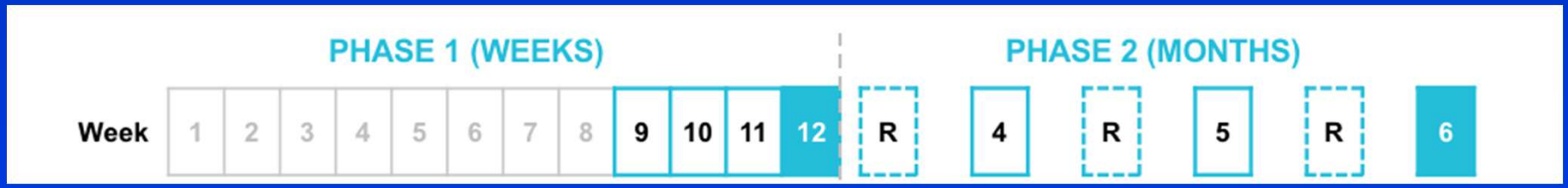
Counseling, UDT, self-report drug use, craving, and withdrawal assessed at each visit

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

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

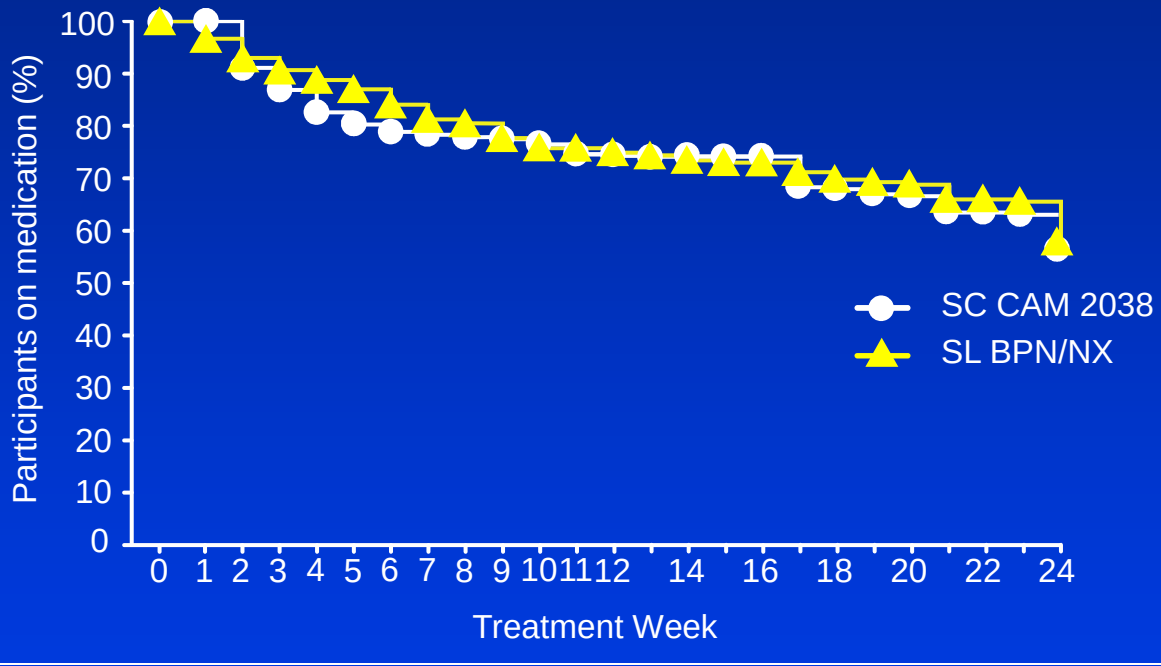
Baseline sample characteristics

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)

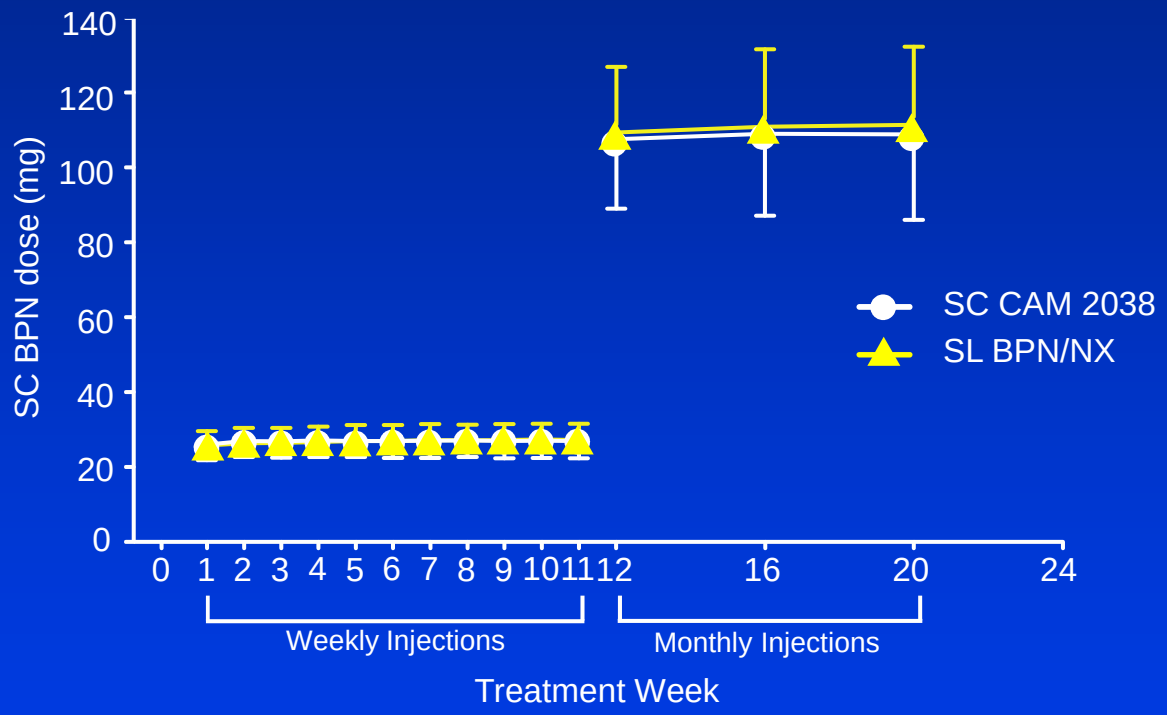
No significance difference between groups

Retention on medication



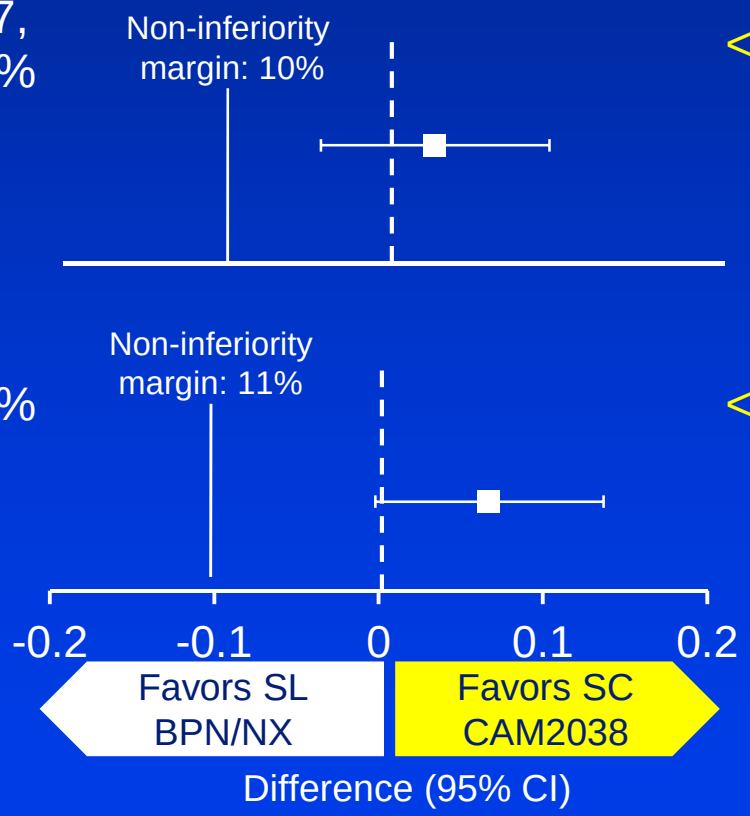
Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
SC BPN	213	213	194	185	176	171	168	167	166	165	163	159	159	158	158	158	158	146	145	143	142	136	136	135	121
SL BPN/NX	215	208	200	195	191	187	181	175	173	167	164	163	161	160	158	157	157	153	150	149	148	142	142	141	125

Medication dose

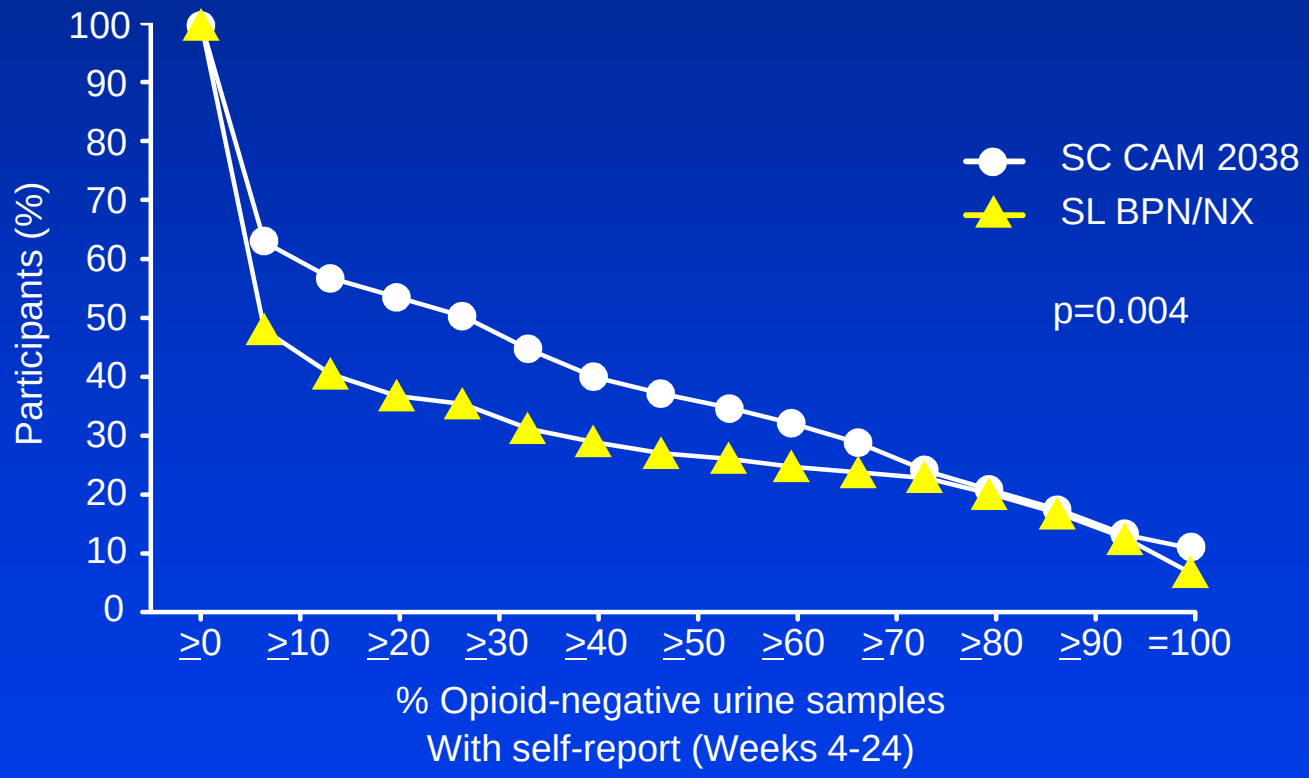


Primary Endpoints
(Intent to treat analyses for non-inferiority)

	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%)		



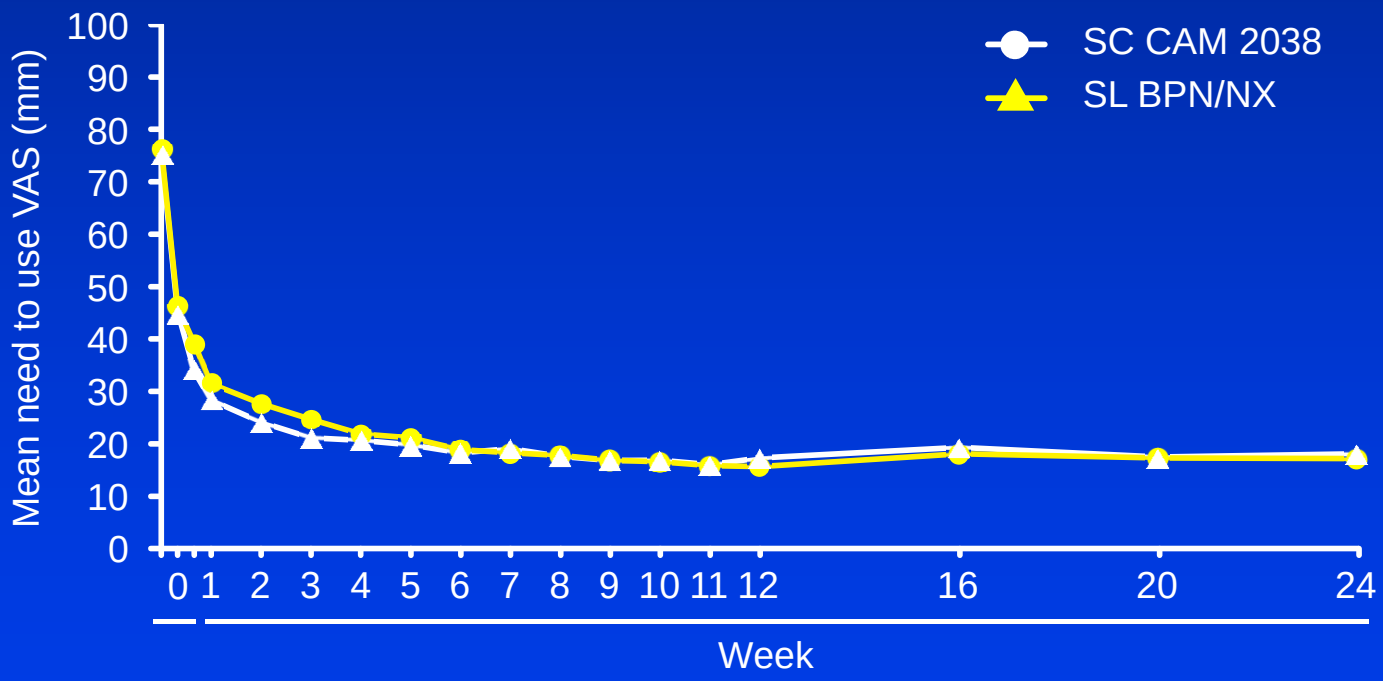
1st planned secondary outcome:
Cumulative Distribution Function of the % opioid negative urines (Weeks 4-24) tested for superiority



Negative urine supported by self-report of no use. Adjustment for multiplicity was made by a closed testing procedure to preserve family-wise type 1 error at .05.

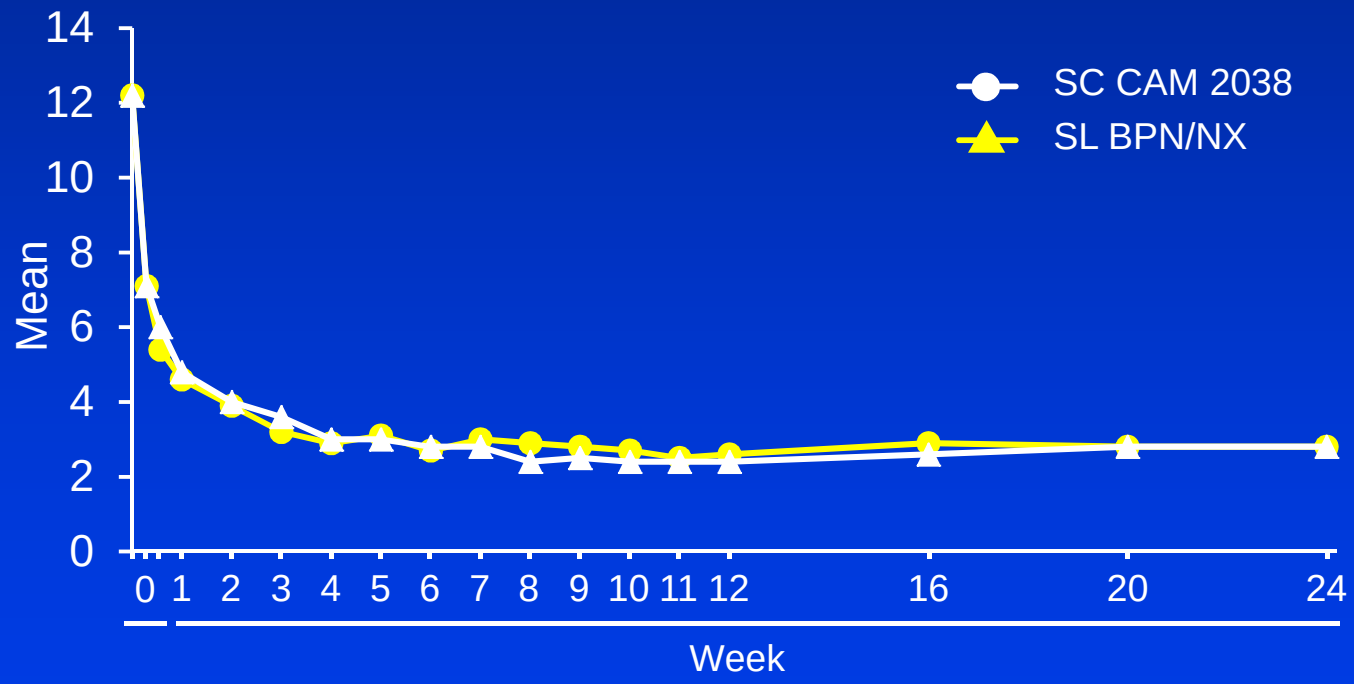
Opioid craving

"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."



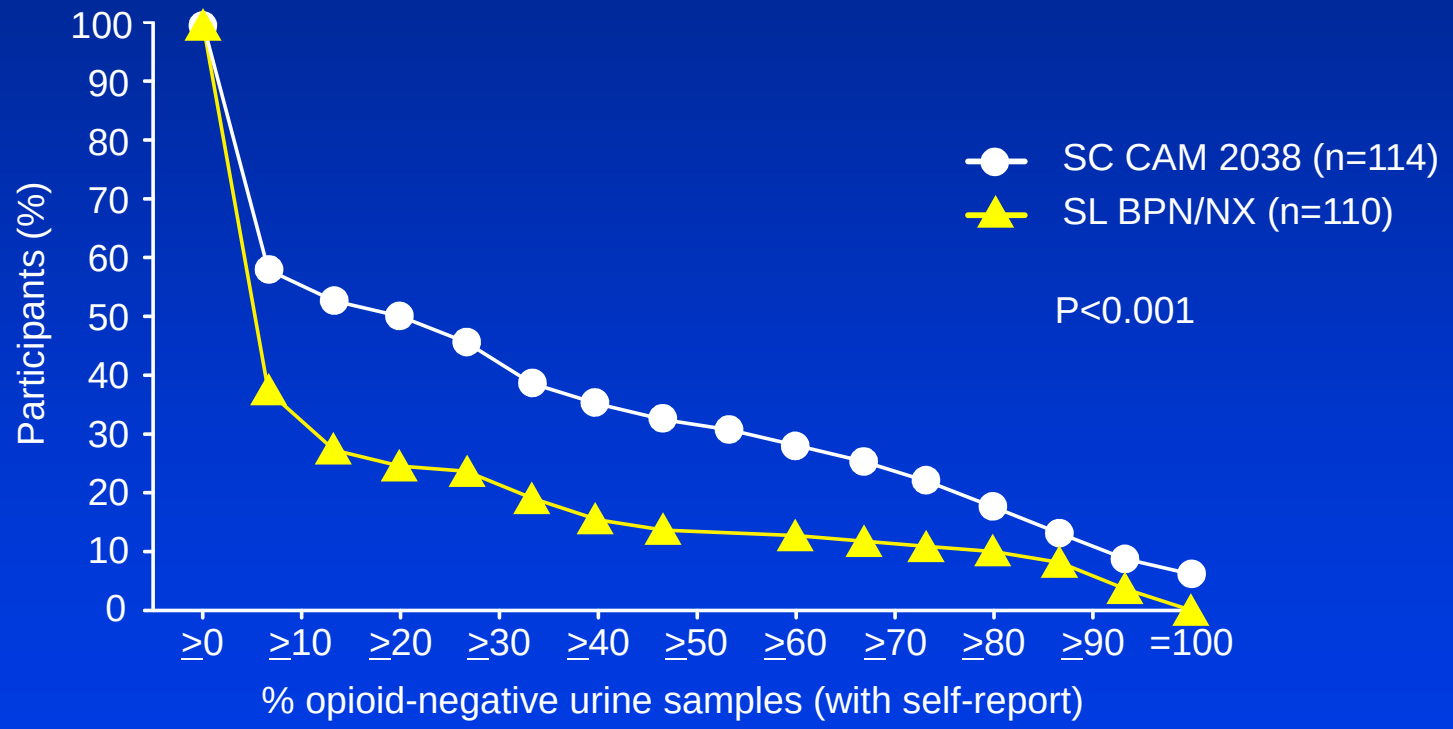
No significant difference between treatments

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.

Conclusions

- Long-acting medications for OUD hold much promise for improving treatment entry, retention and patient outcomes

- Must pro-actively look at each country’s situation in order to decrease barriers to accessing these new medications

Depot Medications for Unmet Treatment Needs in Opioid Use Disorder: Policy, Practice and Patient Care:

Patient Perspectives, Patient Satisfaction and Recent Evidence on Effectiveness of Long-acting Formulations

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Stanley Street Treatment and Resources

Lisbon Addictions 2019

Disclosures

During the last 12 months:

- Consulting fees: Alkermes, Braeburn Pharmaceuticals, Camurus AB, Otsuka, NIDA CTN
- Unpaid consulting: Titan Pharmaceuticals, NIDA CTN
- Speakers' bureau: Alkermes
- Travel expenses: Alkermes, Braeburn Pharmaceuticals, Camurus AB,

Opioid Use Disorder (OUD) is a chronic, relapsing disease:
Patients cycle through treatment episodes

Some of the factors that can lead to relapse include:

Triggers, cravings and non-compliance

Daily treatment means patients have a daily decision to continue treatment – increasing the risk of dropping out of treatment and facing the associated risks. [1,3,4,6]

Social and self-stigmatization

Stigma, as well as self-stigmatisation, associated with substance use is considered a significant barrier to treatment. [4,5]

Burden of daily supervised dosing

Supervision of every dose can be restrictive to patients, and limits the acceptability of treatment. [2,4-7]

Continued illicit use

On-top illicit drug use is frequent among patients, showing that current treatment options do not always meet patients' needs.[7]

1. Dale-Perera, A., Goulão, J., & Stöver, H. (2012). Quality of care provided to patients receiving opioid maintenance treatment in Europe: results from the EQUATOR analysis. *Heroin Addict Relat Clin Probl*, *14*(4):23-38. 2. Roman-Urrestarazu, A., Robertson, R., Yang, J., McCallum, A., Gray, C., McKee, M., & Middleton, J. (2018). European Monitoring Centre for Drugs and Drug Addiction: European Monitoring Centre for Drugs and Drug Addiction has a vital role in the UK's ability to respond to illicit drugs and organised crime. *Bmj*, *362*. 3. Compton WM, Volkow ND.(2016) Improving Outcomes for Persons With Opioid Use Disorders: Buprenorphine Implants to Improve Adherence and Access to Care. *JAMA.* 316(3):277–279. 4. Benyamina, A., & Stöver, H. (2012). Barriers to treatment access and informed patient choice in the treatment of opioid dependence in Europe. *Heroin Addict Relat Clin Probl* 2012; 14(4): 65-80. 5. Matthews, Steve et al. "Stigma and Self-Stigma in Addiction." *Journal of bioethical inquiry* vol. 14,2 (2017): 275-286. 6. Notley C, Holland R, Maskrey V, Nagar J, Kouimtsidis C.(2014) Regaining control: The patient experience of supervised compared with unsupervised consumption in opiate substitution treatment. *Drug Alcohol Rev.* 33:64–70. 7. Fischer G, Nava F, Stöver H. Outcomes of opioid-dependence treatment across Europe: identifying opportunities for improvement. *Heroin Addict Relat Clin Probl.* 2012;14(4):39–50.

Limitations of Daily Buprenorphine

- **DIVERSION**: Patients share, sell, and trade medication
  - In 2013, 33% entering opioid treatment reported use of diverted buprenorphine in last month[1]
- **MISUSE**: "Bridge" between periods of illicit opioid use
- **NONADHERERENCE**: 10 times greater likelihood of relapse when daily buprenorphine adherence drops below 80%[2]
- **ACCIDENTIAL POISONING** in children is public health concern, [3] > 8100 ER visits for children < 6 years old for ingesting buprenorphine from 2008-2016

1. Cicero et al. *Drug Alcohol Depend* 2014;142:98-104. 2. Tkacz et al. *Am J Addict* 2011;21:55-62. 3. MMWR 2016;65:1148-1149.
FDA Indivior AdCom, 10/31/2018

Extended-release formulations can advance the continuum of care for OUD

- Flexible dosing to meet patient individual needs across treatment phases[1]
- Simple transfer from daily sublingual buprenorphine with dose matching[1]
- Easy initiation/induction for new patients [1]
- Reduces burden and stigma of daily medication[2,3]
- HCP administration safeguards against diversion, misuse and pediatric exposure[2,3]

1. Camurus. CAM2038 Summary of Product Characteristics (SmPC). Camurus AB, Sweden. November 2018. 2. EPAR December 2018 EMEA/H/C/004651/0000 https://www.ema.europa.eu/documents/assessment-report/CAM2038-epar-public-assessment-report_en.pdf *3.* . Compton WM, Volkow ND.(2016) Improving Outcomes for Persons With Opioid Use Disorders: Buprenorphine Implants to Improve Adherence and Access to Care. *JAMA.* 316(3):277–279.

Patient Satisfaction

- Patient satisfaction is an important healthcare outcome used as a measure of quality of care in OUD[1,2]
- Evidence suggests that patient satisfaction is a signal for positive outcomes in OUD treatment[3]
- Evidence also suggests user perspectives do not correlate with staff perspectives[4]

1. Barry DT, Moore BA, Pantalon MV, et al. Patient satisfaction with primary care office-based buprenorphine/naloxone treatment. *J Gen Intern Med*. 2007;22(2):242–245. 2. Trujols J, Iraurgi I, Oviedo-Joekes E, Guàrdia-Olmos J. A critical analysis of user satisfaction surveys in addiction services: opioid maintenance treatment as a representative case study. *Patient Prefer Adherence*. 2014;8:107–117. Published 2014 Jan 21. 3. Carlson, MJ, Gabriel, RM. Patient Satisfaction, Use of Services, and One-Year Outcomes in Publicly Funded Substance Abuse Treatment. Psychiatric Serv. 2001;52(9):1230-6. 4. Pulford J, Adams P, Sheridan J. Client/clinician discrepancies in perceived problem improvement and the potential influence on dropout response. Int J Ment Health Addict. 2009;7(4):497–505.

Patient Preference and Adherence

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ORIGINAL RESEARCH

Current and future options for opioid use disorder: a survey assessing real-world opinion of service users on novel therapies including depot formulations of buprenorphine

This article was published in the following Dove Press journal:
Patient Preference and Adherence

Mark Gilman[1]
Li Li[2]
Kerrie Hudson[3]
Tara Lumley[2]
Georgia Myers[2]
Camilla Corte[2]
Richard Littlewood[2]

[1]Discovering Health, Manchester, UK; [2]Applied Strategic, London, UK; [3]The Well Communities CIC, Lancaster, UK

Purpose: Integrated treatment for opioid use disorder (OUD) includes opioid agonist therapy (OAT) such as methadone and buprenorphine with well-evidenced benefits. Treatment with typical existing oral medications is associated with burdens and limits to successful outcomes (frequent dosing, attendance for collection/consumption, difficulty in achieving optimal dosing, misuse, diversion, accidental exposure, and stigma from the treatment process). Novel medications include injected depot formulations with less frequent administration, providing consistent drug levels after dosing. This survey assesses the opinion of those with OUD treatment services lived experience to inform future medication choices.

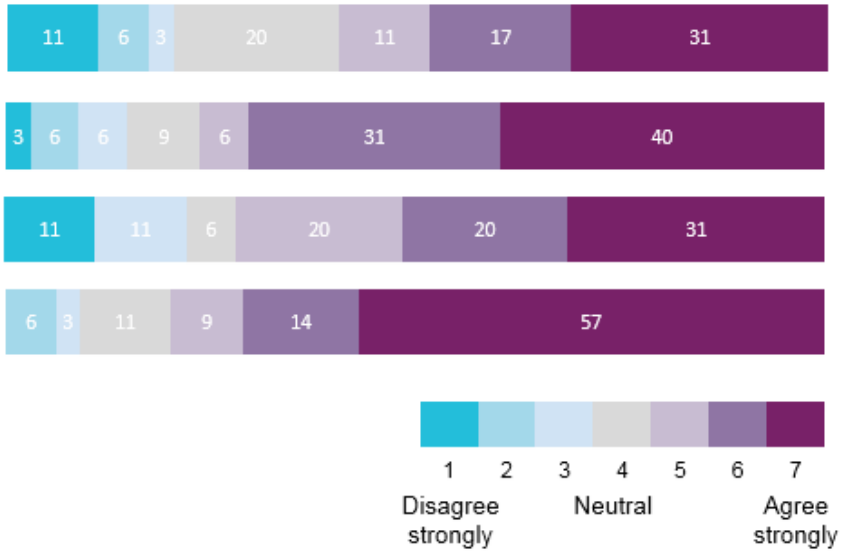
Patients and methods: A survey of people with experience of OUD pharmacotherapy – the treatment system – was completed. Participants reviewed statements describing elements of OUD care using 7-point Likert scales to indicate their level of agreement or disagreement. Data were assessed using descriptive analysis.

Results: In total, 35 people (16 in treatment; 19 with previous history of treatment) completed the survey. Average drug-use duration, 20 years, commonly included injected opioids. The majority agreed treatment was effective, but not tailored to their individual needs and limited normal day-to-day activities. Opinions on novel depot medications included the following: agreement on its potential to make life easier, reduce stigma, free-up time for preferred activities. Participants did not report concerns over the effectiveness and safety of depot medications, nor about reduced contact with treatment services that could be associated with less frequent dosing.

- N=35
- Attendees of national service user involvement conference all with OUD pharmacology experience in UK
- Average drug use = 20 years
- Representing **400 years** of combined experience in the treatment system

Potential benefits of a depot medication for people with OUD: a patient survey

- ✓ Makes life easier
- ✓ No need for daily medication pick up
- ✓ Reduce problem of stigma or privacy related to taking medication
- ✓ Right dose consistently



Gilman M, Li L, Hudson K, et al. Current and future options for opioid use disorder: a survey assessing real-world opinion of service users on novel therapies including depot formulations of buprenorphine. *Patient Prefer Adherence*. 2018;12:2123–2129. Published 2018 Oct 11.

RBP-6000: Sublocade

Long-Acting Subcutaneous Monthly Injection

FDA Indivior AdCom, 10/31/2018

- ATRIGEL® Delivery System
  - Biodegradable polymer and solvent create solid depot of buprenorphine
  - Two targeted release phases: rapid achievement of therapeutic levels that are sustained over monthly dosing interval
  - Used in 7 FDA-approved products
- 100 mg and 300 mg dosage strengths
  - Prefilled **19G syringe**, administered subcutaneously monthly by HCP in health care setting
- Recommended dosing regimen
  - Two initial monthly 300 mg doses
  - Monthly maintenance doses of 100 mg or 300 mg based on clinical condition of patient

Patient-centered Outcomes in Participants of a Buprenorphine Monthly Depot (BUP-XR) Double-blind, Placebo-controlled, Multicenter, Phase 3 Study

Walter Ling, MD, Vijay R. Nadipelli, MS, Caitlyn T. Solem, PhD, Naoko A. Ronquest, PhD
Yu-Chen Yeh, MS, Susan M. Learned, MD, Vishaal Mehra, MD, and Christian Heidbreder, PhD

- N=489
- Mean age=40 , largely white, non-= Hispanic males
- Patient centered outcomes:
  - EQ-5, 5D-5L (general health status from mobility to anxiety/depression)
  - SF36v2 (Physical and mental domains: mobility, physical function, vitality, social functioning, emotional role achievement and mental health)
  - Medication satisfaction (single question, 7-point Likert scale)
  - Customized questions about employment, health insurance

participants with moderate-to-severe OUD. Measures included the EQ-5D-5L, SF-36v2, Medication Satisfaction Questionnaire, employment/insurance status, and healthcare resource utilization (HCRU). Changes from baseline to end of study were compared across treatment arms, using mixed models for repeated measures.

and 4.7% with 300/100 mg but decreased by 12.6% and 8.4% with placebo. Participants receiving BUP-XR compared with placebo had significantly fewer hospital days per person-year observed.

Conclusions: These results show the feasibility of measuring

Patient-Centered Findings

- BUP-XR showed positive effects and statistically significantly improvements in health status
- Several patient reports measure declined in placebo group suggesting BUP –XR plus psychotherapy was superior of psychotherapy alone
- Improvements occurred with out concurrent increase in health care resource utilization

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.

BUP-XR: MEDICATION SATISFACTION

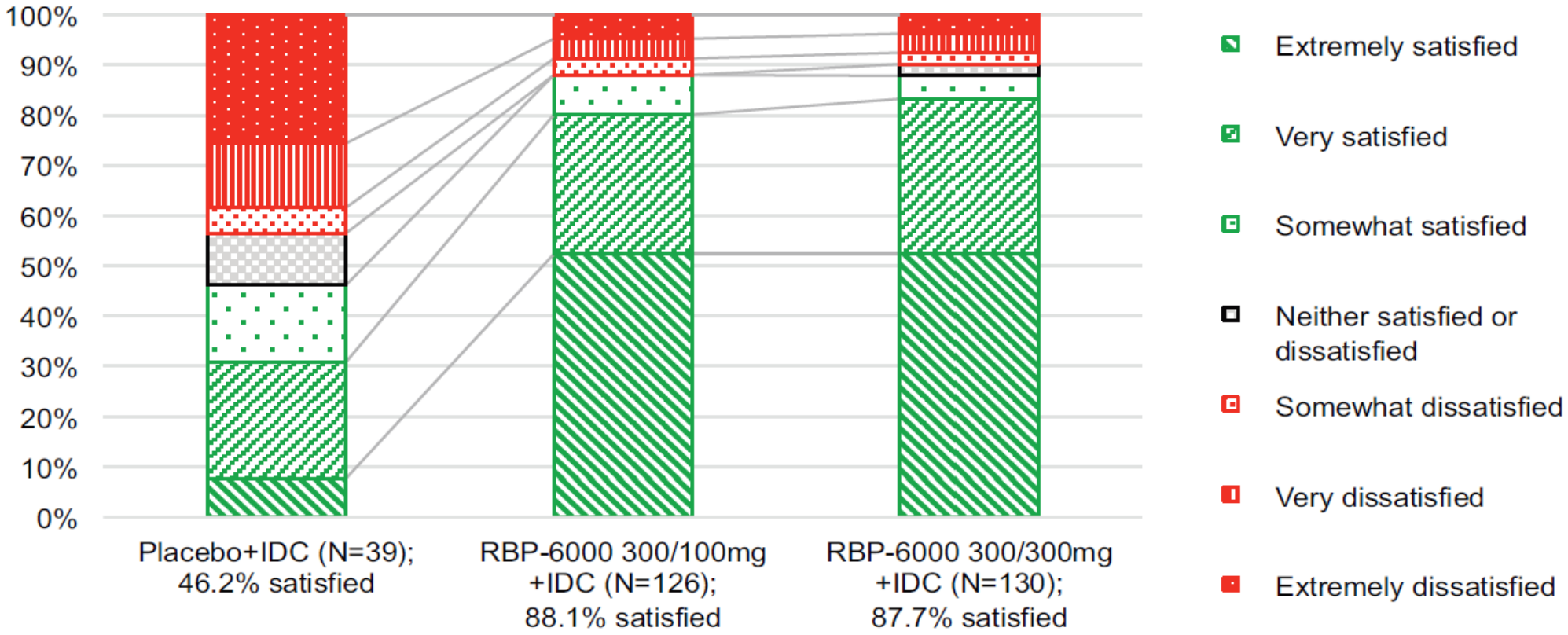


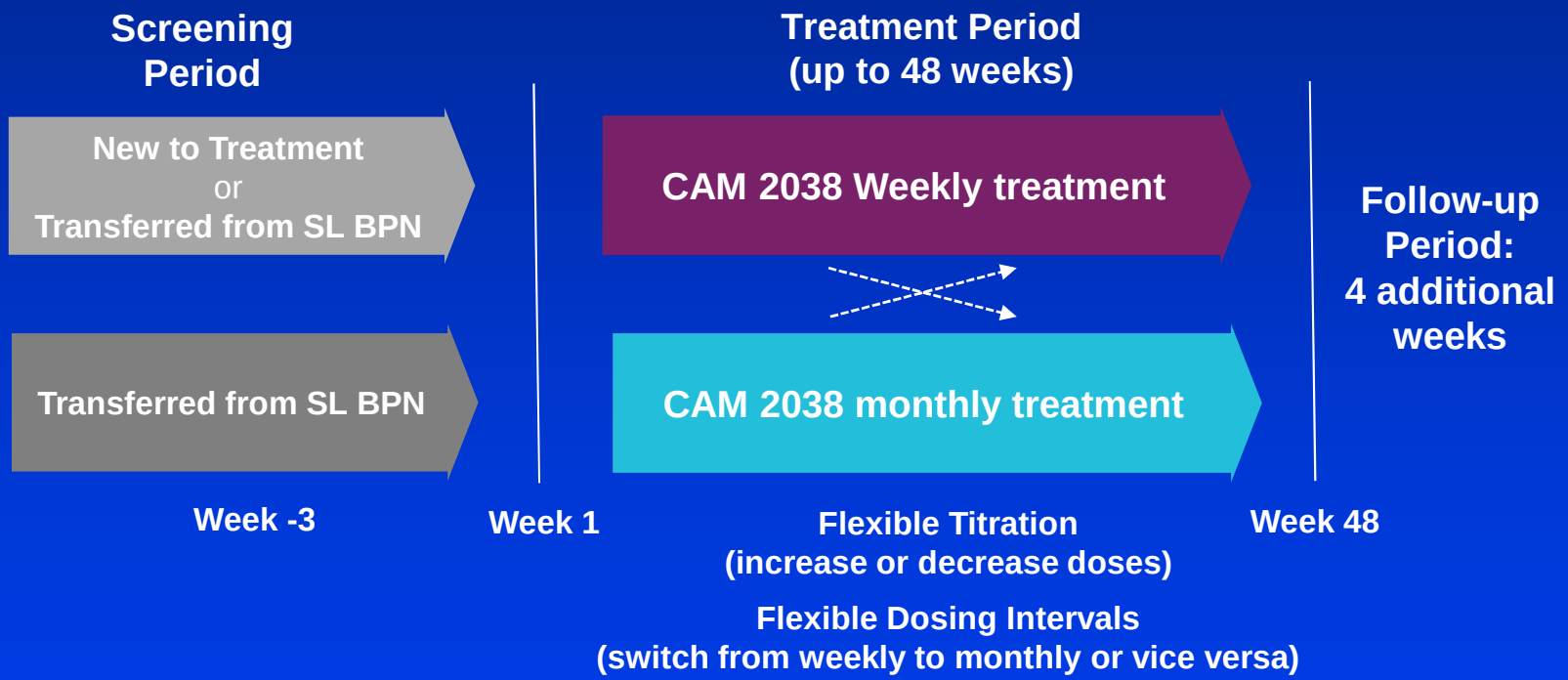
FIGURE 1. Percentage of subjects who were satisfied or dissatisfied with treatment at week 25[a]. BUP-XR, buprenorphine extended-release monthly injection, for subcutaneous use [CIII]; IDC, individual drug counselling; MSQ, Medication Satisfaction Questionnaire. [a]The MSQ is a 7-point scale with the 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.

CAM2038: Buvidal
Subcutaneous Buprenorphine Depot with Sustained Release Formulation

- Weekly or monthly injection
  - Multiple dose strengths
- Administered by healthcare provider (HCP)
  - Ensures medication adherence and exposure
  - Minimizes risk of misuse, abuse, diversion and accidental pediatric exposure
- Allows for individualized dosing
  - Aligns with treatment guidelines

Study 499: Phase 3, long-term (48-week), open-label, safety design of CAM 2038 with flexible dosing



Frost M, Bailey GL, Linrzeris N, Strang J, Dunlop A, Nunes EV, Jansen JB, Frey LC, Weber B, Haber P, Oosman S, Kim S, Tiberg F, Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM 2038) in the treatment of adults out-patients with opioid use disorder. *Addiction*. 2019 Aug;114(8):1416-1426. [Epub 2019 Jun 3].

Study 499: Phase 3, long-term (48-week), open-label, safety design of CAM 2038

- 26 out-patient sites (US, UK, Hungary, Denmark, Sweden, Germany, Australia)
- N=227
    - 37 initiated onto CAM2038
    - 190 converted from sublingual buprenorphine
- 56.4% AEs were rated mild or moderate
- Injection-site reactions were reported by 46 of 227 (20.3%) participants, with most [45 of 46 (97.8%)] reported as mild to moderate

Frost M, Bailey GL, Linrzeris N, Strang J, Dunlop A, Nunes EV, Jansen JB, Frey LC, Weber B, Haber P, Oosman S, Kim S, Tiberg F, Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM 2038) in the treatment of adults out-patients with opioid use disorder. *Addiction*. 2019 Aug;114(8):1416-1426. [Epub 2019 Jun 3].

CAM2038: High treatment retention at 24 and 48 weeks for transfer and new to treatment patients

74% of patients completed the 48-week treatment period

Frost M, Bailey GL, Linrzeris N, Strang J, Dunlop A, Nunes EV, Jansen JB, Frey LC, Weber B, Haber P, Oosman S, Kim S, Tiberg F, Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM 2038) in the treatment of adults out-patients with opioid use disorder. *Addiction*. 2019 Aug;114(8):1416-1426. [Epub 2019 Jun 3].

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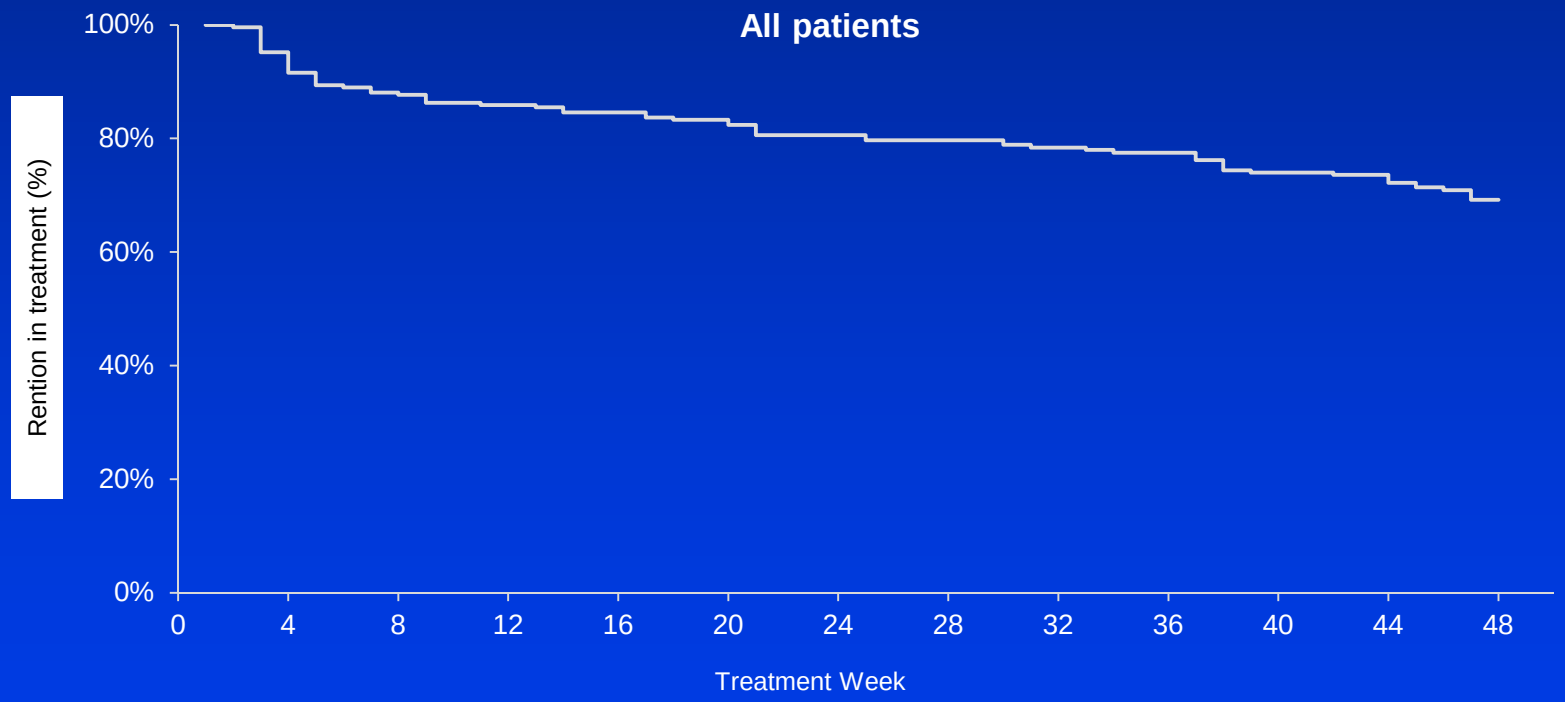

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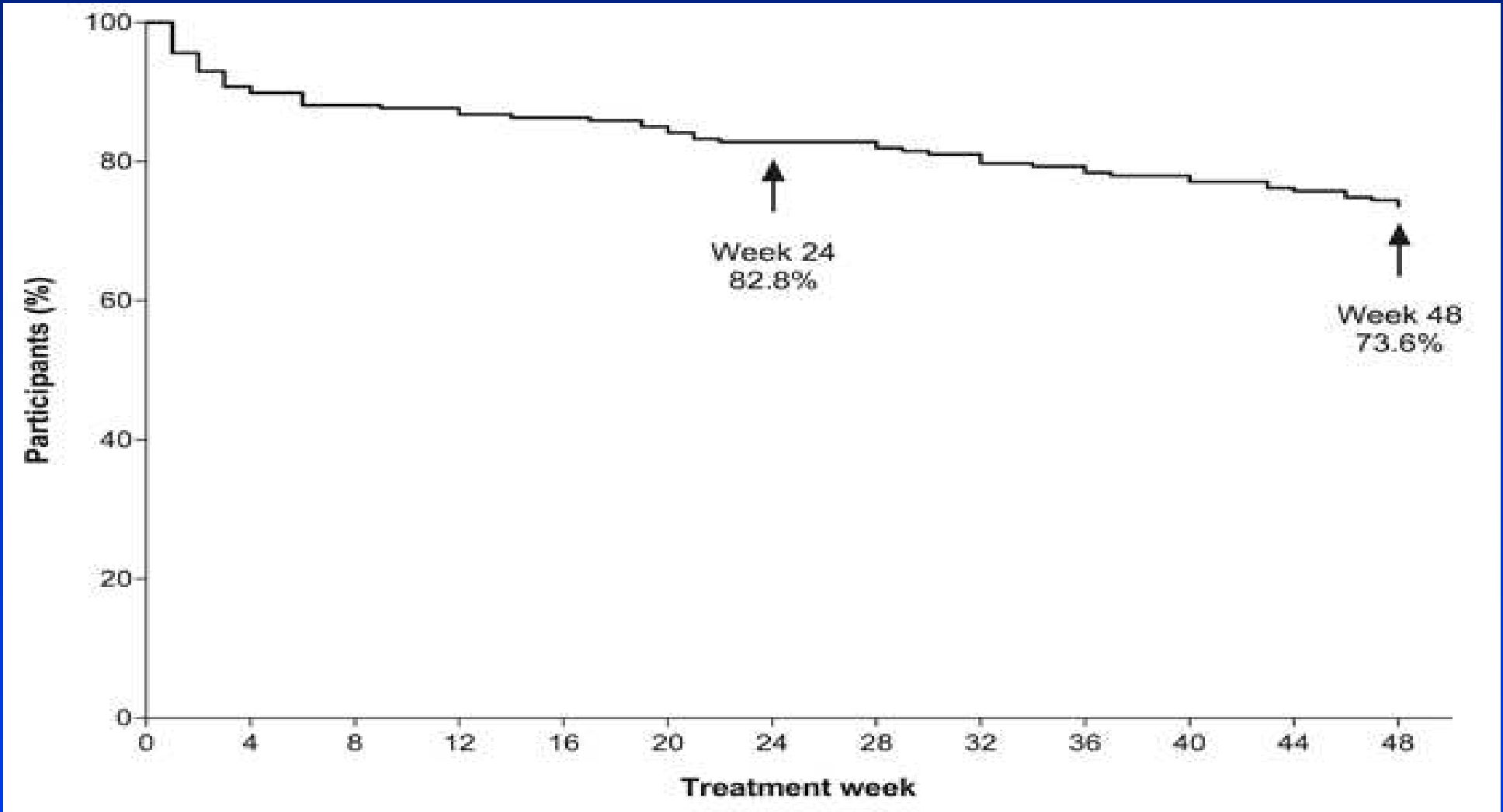

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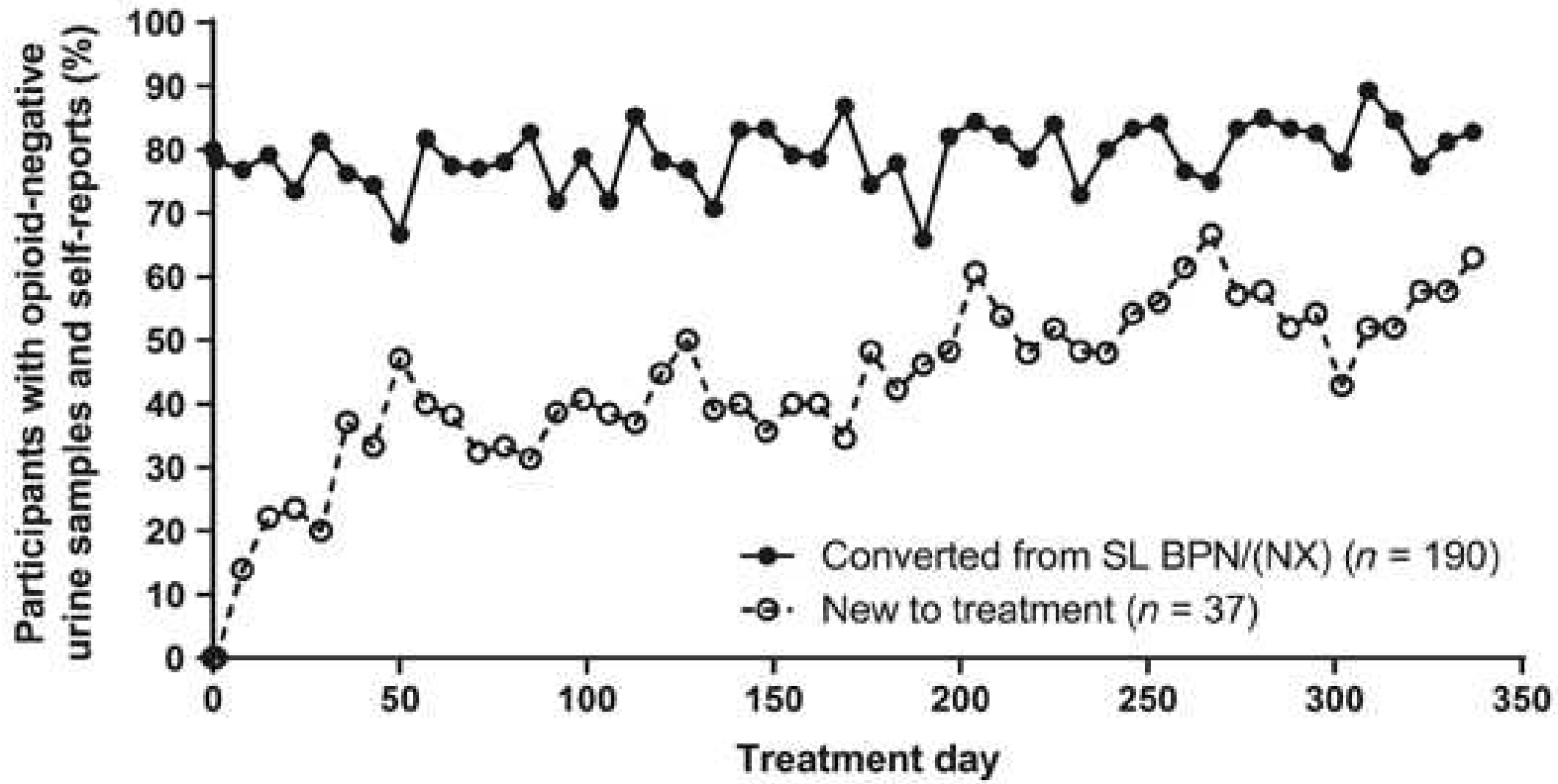
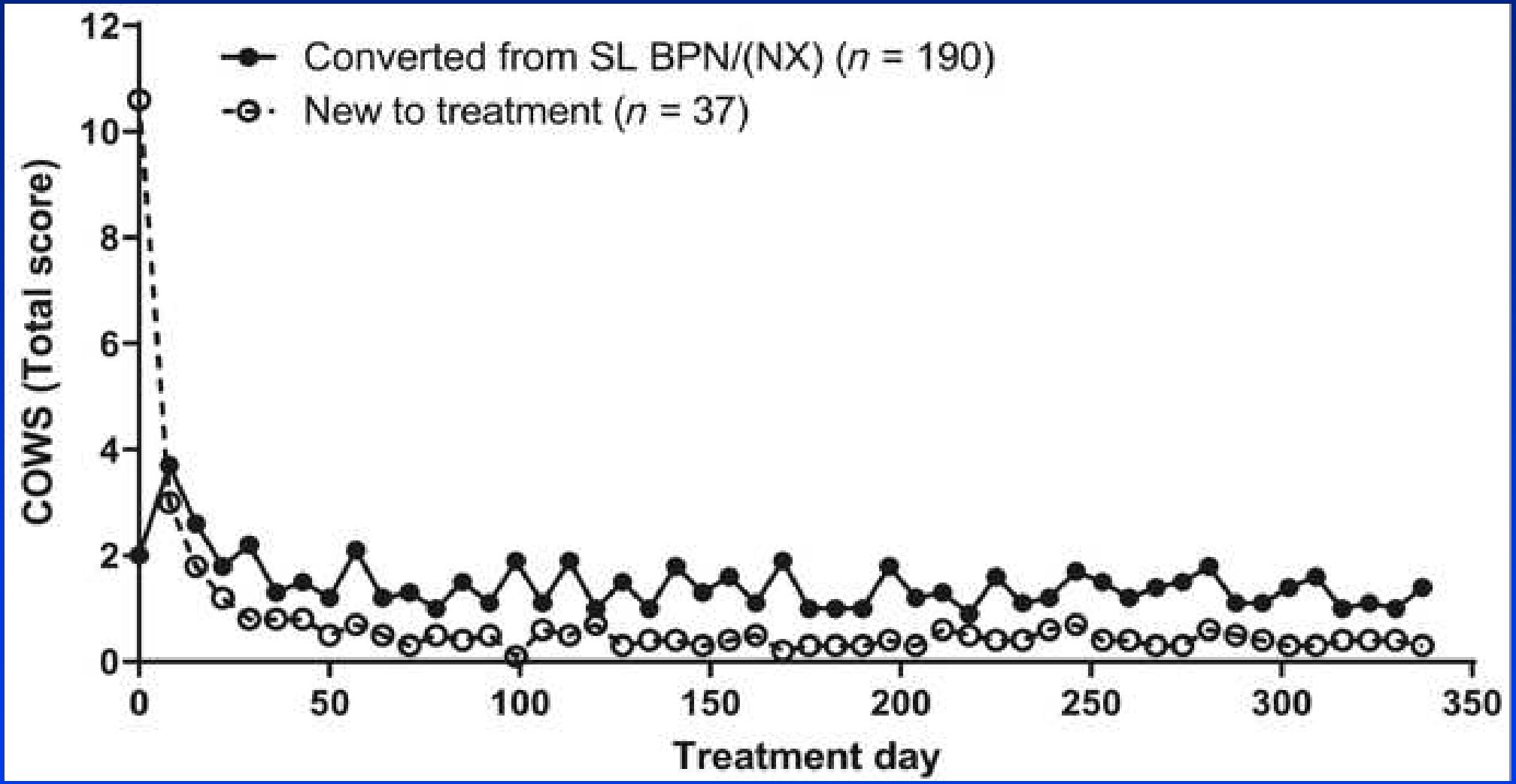
Study 499: %Opioid negative urines AND no use per self report



Treatment day	1	29	57	85	113	141	169	197	225	253	281	309	337
Converted from SL BPN/(NX), n	190	166	142	133	129	118	114	117	112	107	107	103	134
New to treatment, n	37	35	35	35	27	25	26	29	27	25	26	25	27

Frost M, Bailey GL, Linrzeris N, Strang J, Dunlop A, Nunes EV, Jansen JB, Frey LC, Weber B, Haber P, Oosman S, Kim S, Tiberg F, Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM 2038) in the treatment of adults out-patients with opioid use disorder. *Addiction*. 2019 Aug;114(8):1416-1426. [Epub 2019 Jun 3].

Study 499: COWS scores over 48 weeks



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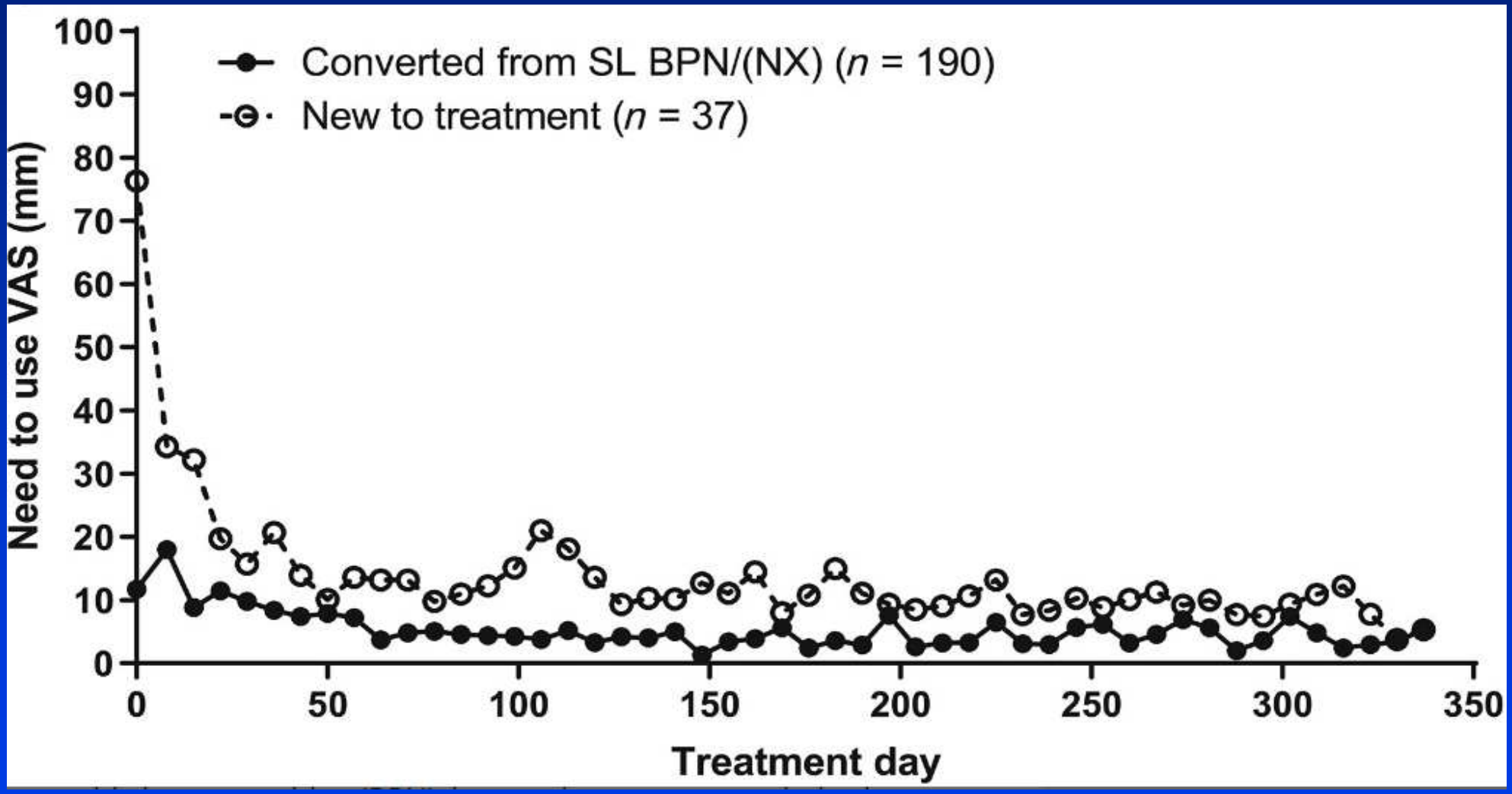
Study 499: Need to use visual analogue over 48 weeks



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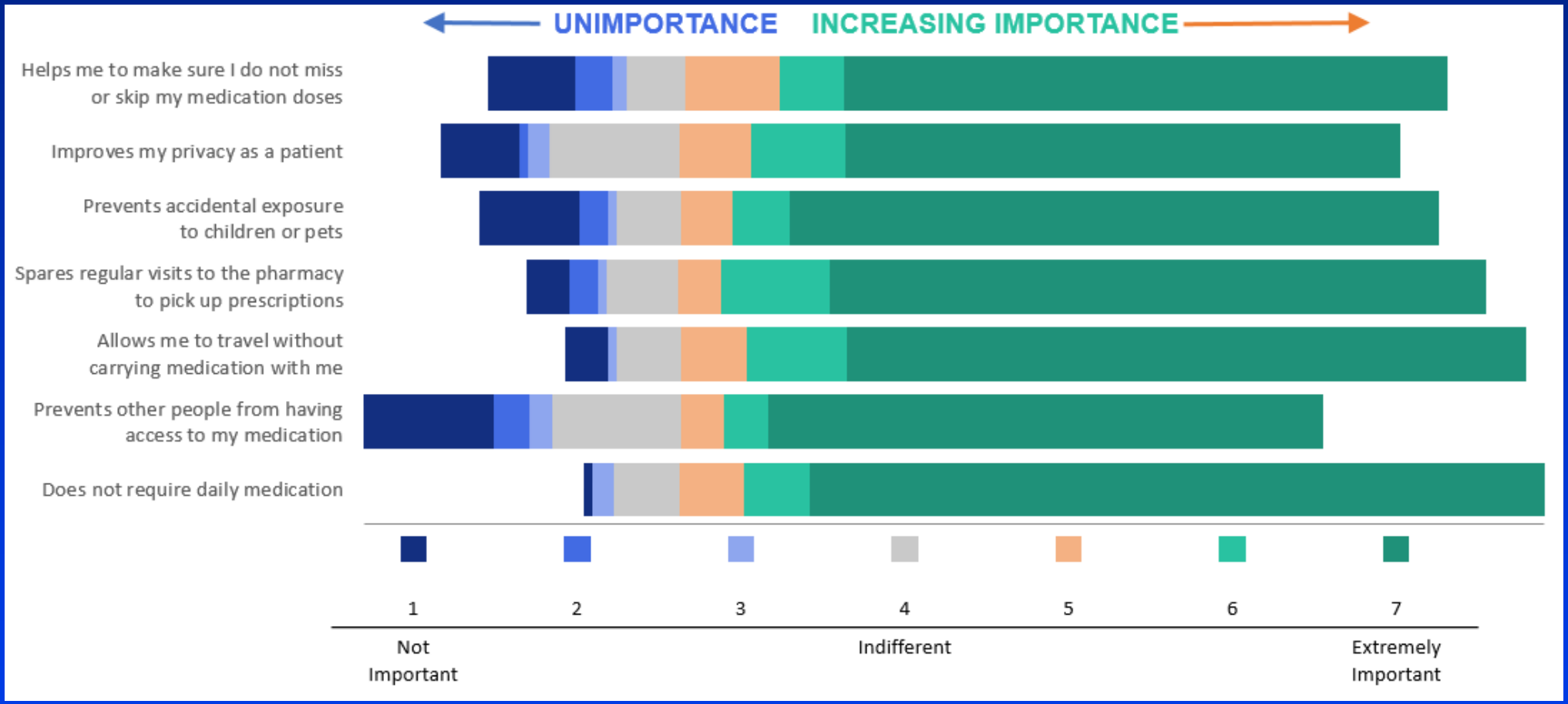
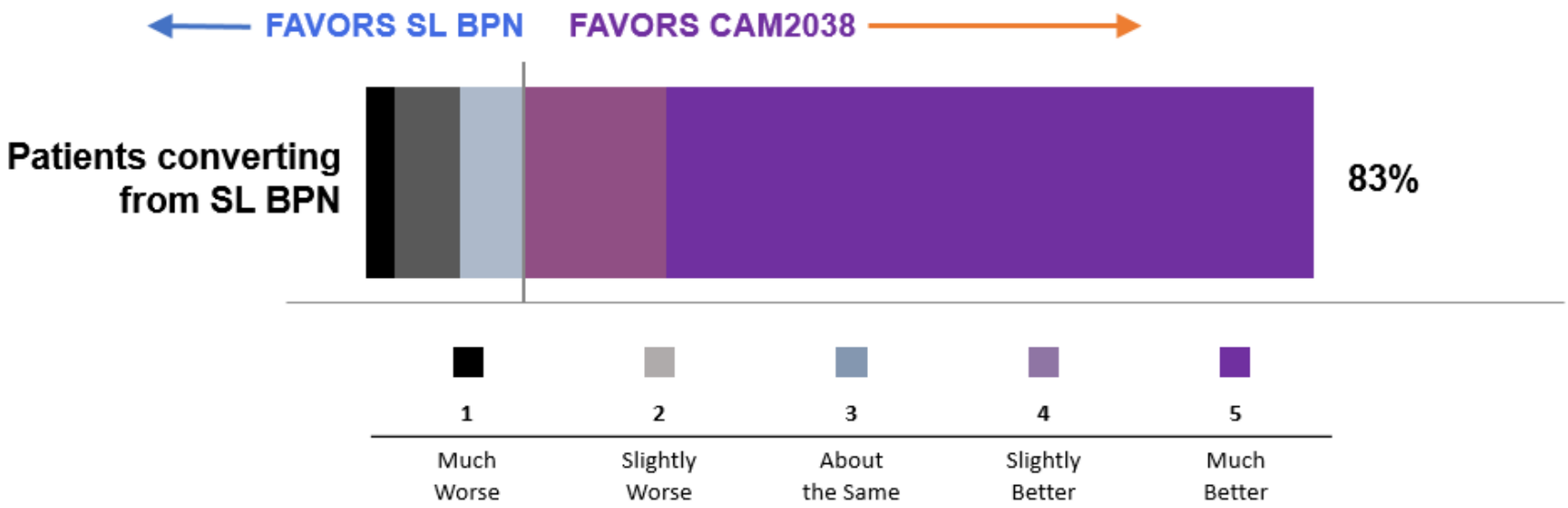
STUDY 499: Characteristics that are important to patients in their buprenorphine treatment (N=162)



Bailey GL, Frost MP, Kim S, Tiberg F, Budilovsky-Kelley N. Patient satisfaction and experience with weekly/monthly sustained-release injectable buprenorphine. Presented at the American Academy of Addiction Psychiatry, December 6-9, 2018b; Bonita Springs, Florida. Frost M, Bailey GL, Linrzeris N, Strang J, Dunlop A, Nunes EV, Jansen JB, Frey LC, Weber B, Haber P, Oosman S, Kim S, Tiberg F, Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM 2038) in the treatment of adults out-patients with opioid use disorder. *Addiction*. 2019 Aug;114(8):1416-1426. [Epub 2019 Jun 3].

STUDY 499: Patient satisfaction with CAM2038 compared to previously prescribed SL BPN (N=133)

"The study medication compared to my previously prescribed SL BPN treatment is_____"



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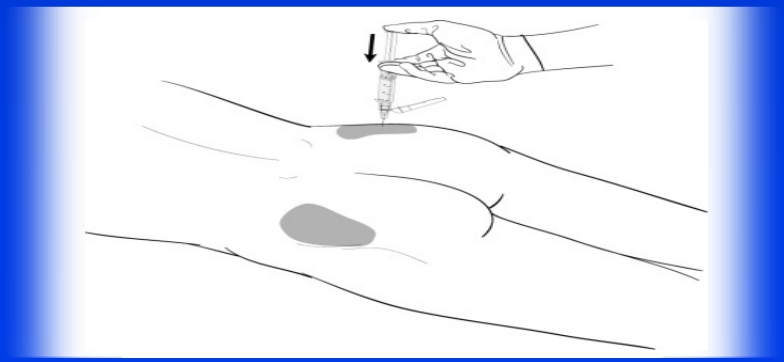
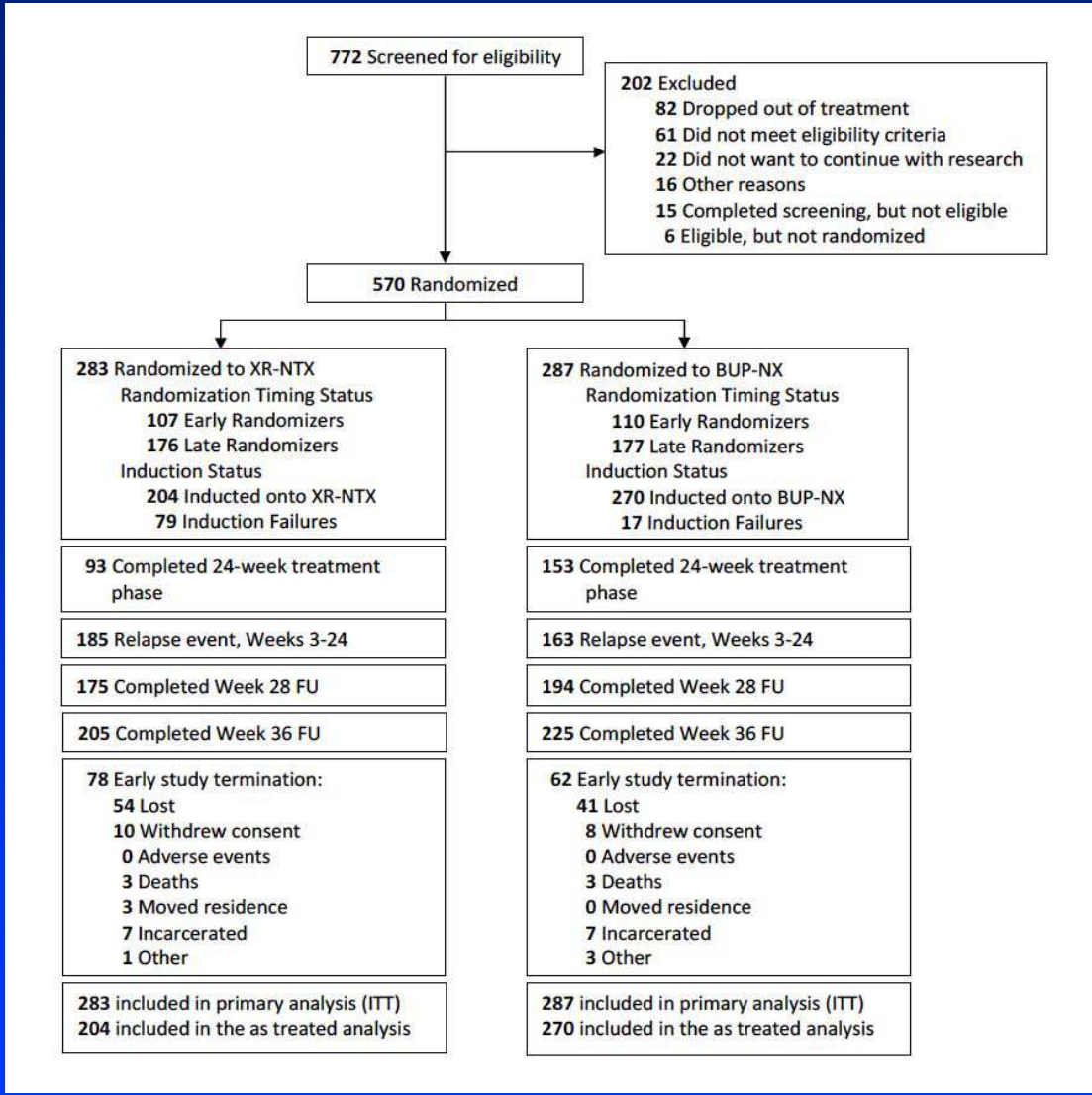
Naltrexone for Extended-Release Injectable Suspension: Vivitrol

- Approved for opioid addiction in 2010
- Monthly, gluteal **IM injection** of 380 mg naltrexone microspheres
- Prepackaged with microspheres, diluent, and **2-20G** needles
- Needs refrigeration and to be reconstituted
- Patient must be **completely opioid-free**



CTN-0051: Extended-Release Naltrexone vs SL Buprenorphine for Opioid Treatment (XBOT)



Lee JD, Nunes EV Jr, Novo P, Bachrach K, Bailey GL, Bhatt S, Farkas S, Fishman M, Gauthier P, Hodgkins CC, King J, Lindblad R, Liu D, Matthews AG, May J, Peavy KM, Ross S, Salazar D, Schkolnik P, Shmueli-Blumberg D, Stablein D, Subramaniam G, Rotrosen J. Comparative effectiveness of extended-release naltrexone versus buprenorphine for opioid relapse prevention(XBOT): a multicenter, open-label, randomized control trial.*Lancet*. 2018 Jan 27;391(10118):309-318. [Epub 2017 Nov 14].

XBOT: Buprenorphine-Naloxone Superior by ITT

	XR-NTX group (n=283)	BUP-NX group (n=287)	Treatment effect
Inducted to study medication			
Intention-to-treat group	204 (72%)	270 (94%)	OR 0·16, 95% CI 0·09–0·28; *P*<0·0001
Opioid relapse, weeks 3–24			
Intention-to-treat group	185 (65%)	163 (57%)	OR 1·44, 95% CI 1·02–2·01; *P*=0·036
Per-protocol group	106/204 (52%)	150/270 (56%)	OR 0·87, 95% CI 0·60–1·25; *P*=0·44
Relapse-free-survival (weeks), range 3–24			
Intention-to-treat group	8·4 (3·0–23·4)	14·4 (5·1–234)	HR 1·36, 95% CI 1·10–1·68; *P*=0·0040
Per-protocol group	20·4 (5·4–23·4)	15·2 (5·7–23·4)	HR 0·92, 95% CI 0·71–1·18; *P*=0·49
Total number of weekly opioid-negative urine samples, range 0–24			
Intention-to-treat group	4 (0–19)	10 (3–20)	*P*<0·0001
Per-protocol group	13 (3–21)	11 (3–20)	*P*=0·81

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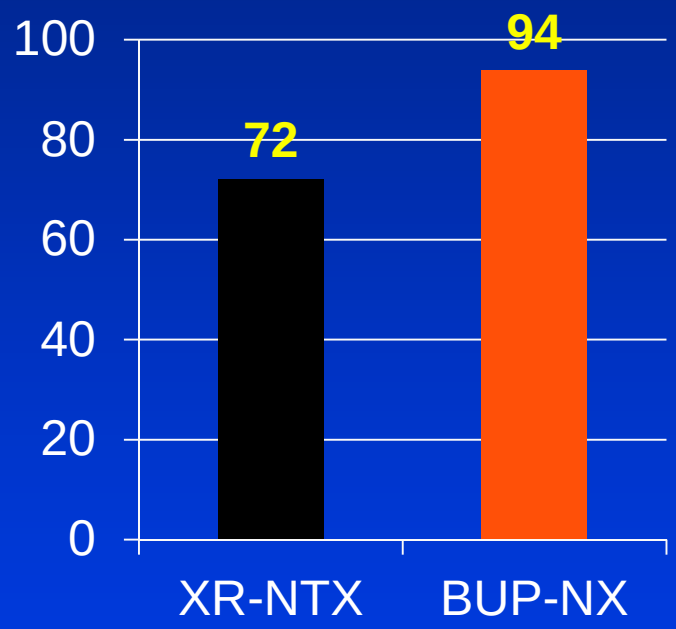
OXBOT: Induction Success (%)



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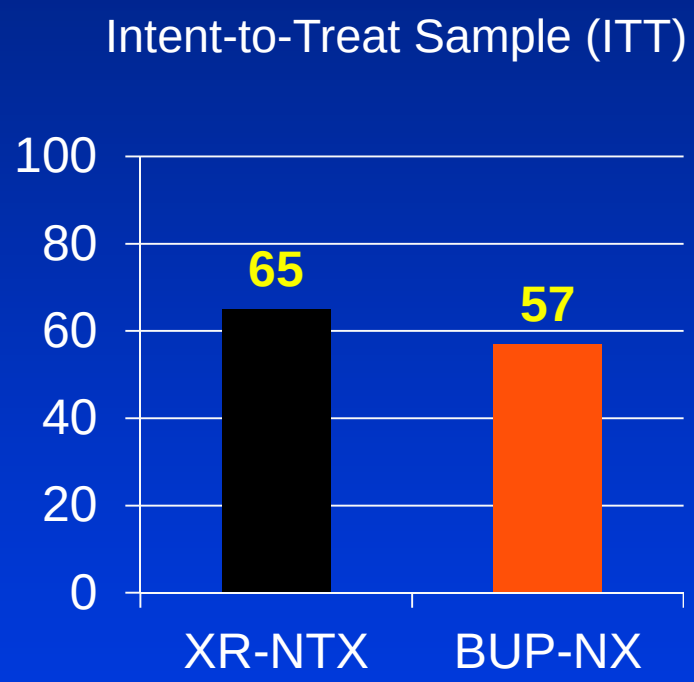
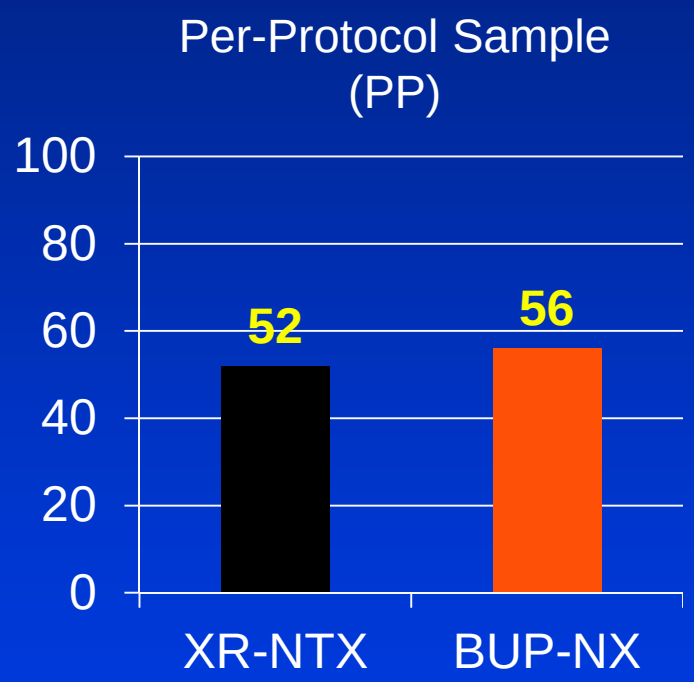
XBOT: 24-Week Relapse Rates (%)



OR=1.44 (95% CI: 1.02-2.01)
p = 0.04



OR=0.87 (95% CI: 0.60-1.25)
p = 0.44

Lee JD, Nunes EV Jr, Novo P, Bachrach K, Bailey GL, Bhatt S, Farkas S, Fishman M, Gauthier P, Hodgkins CC, King J, Lindblad R, Liu D, Matthews AG, May J, Peavy KM, Ross S, Salazar D, Schkolnik P, Shmueli-Blumberg D, Stablein D, Subramaniam G, Rotrosen J. Comparative effectiveness of extended-release naltrexone versus buprenorphine for opioid relapse prevention(XBOT): a multicenter, open-label, randomized control trial.*Lancet*. 2018 Jan 27;391(10118):309-318. [Epub 2017 Nov 14].

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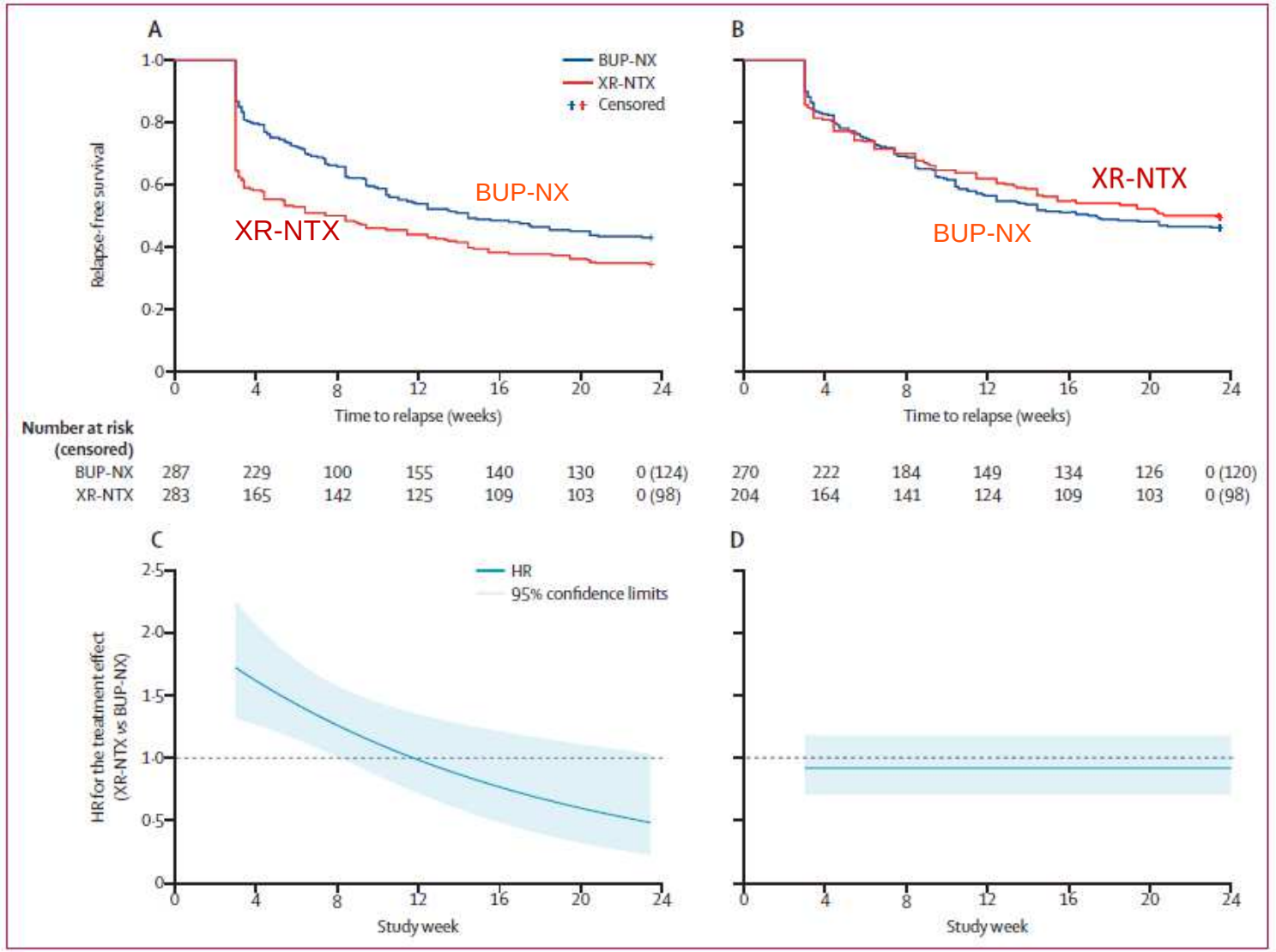
XBOT: Relapse-Free Survival

Intent-to-Treat Sample (n=570)

Per-Protocol Sample (n=474)



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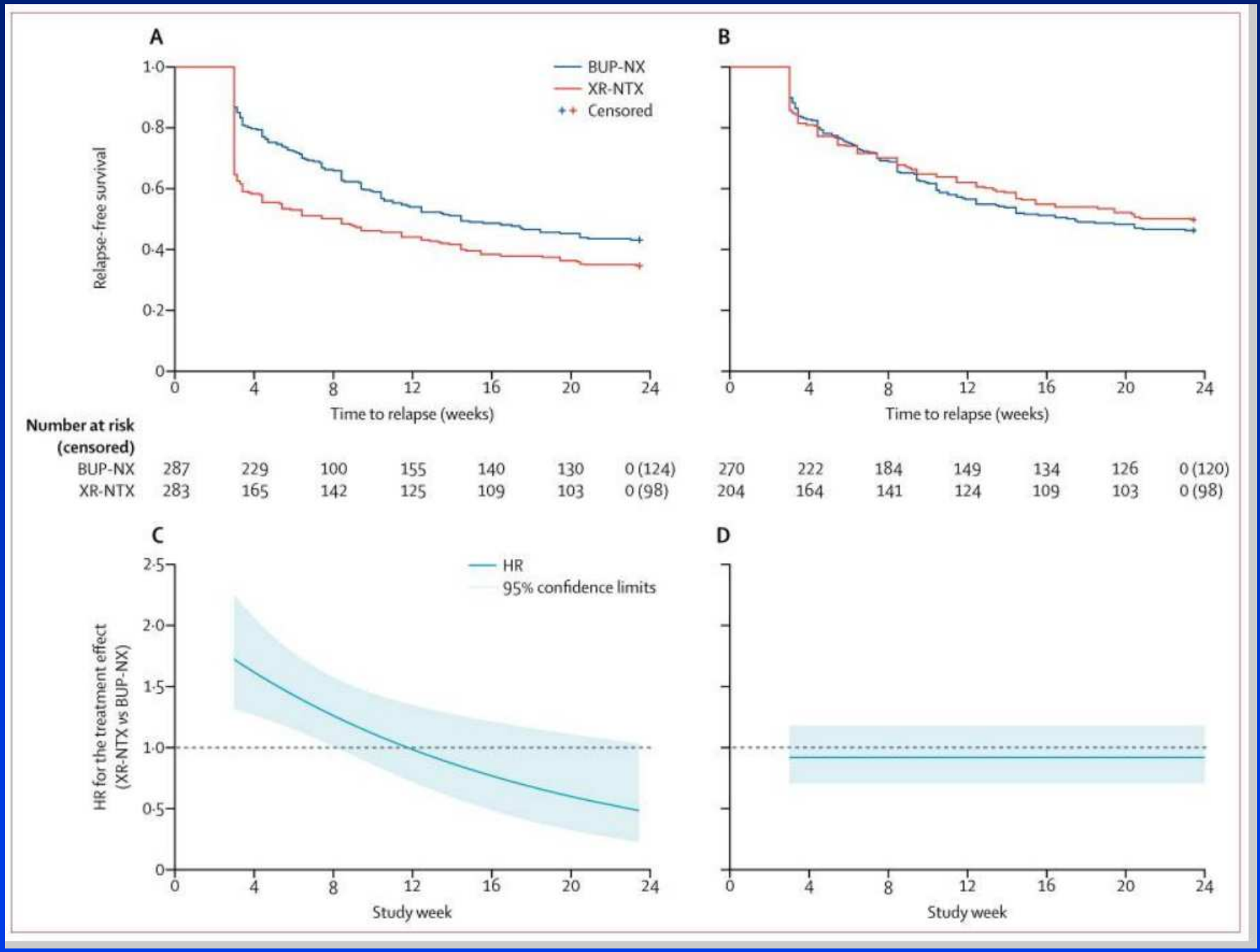
A
B
BUP-NX
XR-NTX
Censored
Relapse-free survival
1·0
0·8
0·6
0·4
0·2
0
0
4
8
12
16
20
24
Time to relapse (weeks)
Number at risk (censored)
BUP-NX 287 229 100 155 140 130 0 (124) 270 222 184 149 134 126 0 (120)
XR-NTX 283 165 142 125 109 103 0 (98) 204 164 141 124 109 103 0 (98)
C
D
HR
95% confidence limits
HR for the treatment effect (XR-NTX vs BUP-NX)
2·5
2·0
1·5
1·0
0·5
0
Study week

XBOT: Overdose data

	XR-NTX group (n=283)	BUP-NX group (n=287)
Overdose events		
Participants with one or more overdose event (all)†	15	8
Participants with one or more overdose event (per protocol)‡	9	7
Number of overdose events (all)§	18	10
Number of overdose events (per protocol)	10	9
Fatal overdose events		
Number of fatal overdose events (all)	2	3
Number of fatal overdose events (per protocol)	2	3

XBOT: Conclusions

1. Better overall opioid outcomes for BUP-NX group in Intention-to-Treat Sample, however difference is directly related to differential induction failure
2. Essentially equivalent safety and effectiveness for XR-NTX and BUP-NX in Per-Protocol Sample
3. Medication appears to reduce OD risk

Discussion

- Drs. Gabriele Fischer and Sharon Walsh