The Role of Long-Acting Depot Therapeutic Options in Opioid Addiction

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Disclosures

- Funding
  - NIDA, New York State

- Disclosures
  - Investigator for Braeburn/Camurus on CAM2038 injectable buprenorphine trials
  - Received medication for studies from Reckitt/Indivior, Alkermes
  - Received software for study from HealthSim
  - Unpaid consultant to Braeburn/Camurus, Alkermes, Pear Therapeutics

Long Acting Injectable or Implanted Buprenorphine

- Sublocade (Indivior)
  - Monthly formulation
  - Doses 300 mg for initial dosing, then 100mg
  - Prefilled syringe, refrigeration, subcutaneous
- CAM2038 (Buvidal; Braeburn-Camurus)
  - Weekly and Monthly formulations
  - Range of doses (4 doses each, weekly and monthly)
    - Prefilled syringe, < 1cc fluid load, no refrigeration, subcutaneous
- Probuphine (Braeburn, Titan)
  - 6 month implant (4 X 80 mg rods)
  - Indicated for maintenance treatment of patients stable on 8mg or less of sublingual buprenorphine

Long Acting Injectable or Implanted Naltrexone

- Vivitrol (Alkermes, Inc)
  - Monthly
  - 380 mg, intramuscular
  - Requires refrigeration
  - Mix powder with diluent fluid prior to injection

- Implants
  - Russian (2 to 3 months)
  - Australian (6 months)

Why Long Acting Buprenorphine?

- Adherence is secured for the duration of the injection/implant
  - Poor adherence is a significant barrier to effectiveness for sublingual buprenorphine, typically
  - >50% dropout by 6 months in clinical trials for sublingual buprenorphine
- Sustained blood level (no daily up and down)
- No diversion (clinician administered)
- No concern about accidental ingestions

Downsides of Long-Acting Buprenorphine?

- Patient does not have to see a clinician as often to get refills
  - Disincentive to participation in counseling?
  - Unstable patients need clinician contact and counseling
  - Versus: The hypothesis that unstable patients are most likely to have poor adherence to sublingual buprenorphine, thus are most likely to benefit from a long acting formulation
- If adverse reactions to subcutaneous injections
  - No way to lower the dose
  - Wait out the duration of the injection (week or month)
  - Or, depot could be surgically removed
  - Note that the 6-month implant can be removed any time
- Cost!
- Barriers to access (REMS program, Specialty Pharmacies)

Sublocade Buprenorphine XR Subcutaneous Injection (Indivior)

- Subcutaneous injection under skin of abdomen
- Polymer-based technology forms a solid depot in subcutaneous space after injection
- Monthly: 300 mg initially X 2 months, then 100mg monthly
  - Or, continue 300mg if needed
- Prescribing Information requires stabilization on sublingual buprenorphine for > 7 days @ 8mg to 24mg
  - Is this necessary? (vs more rapid initiation after sublingual test doses)
  - Blood level increases gradually over first 24 hours

Sublocade Blockade Study

(Nasser et al., J Clin Psychopharm 2016)

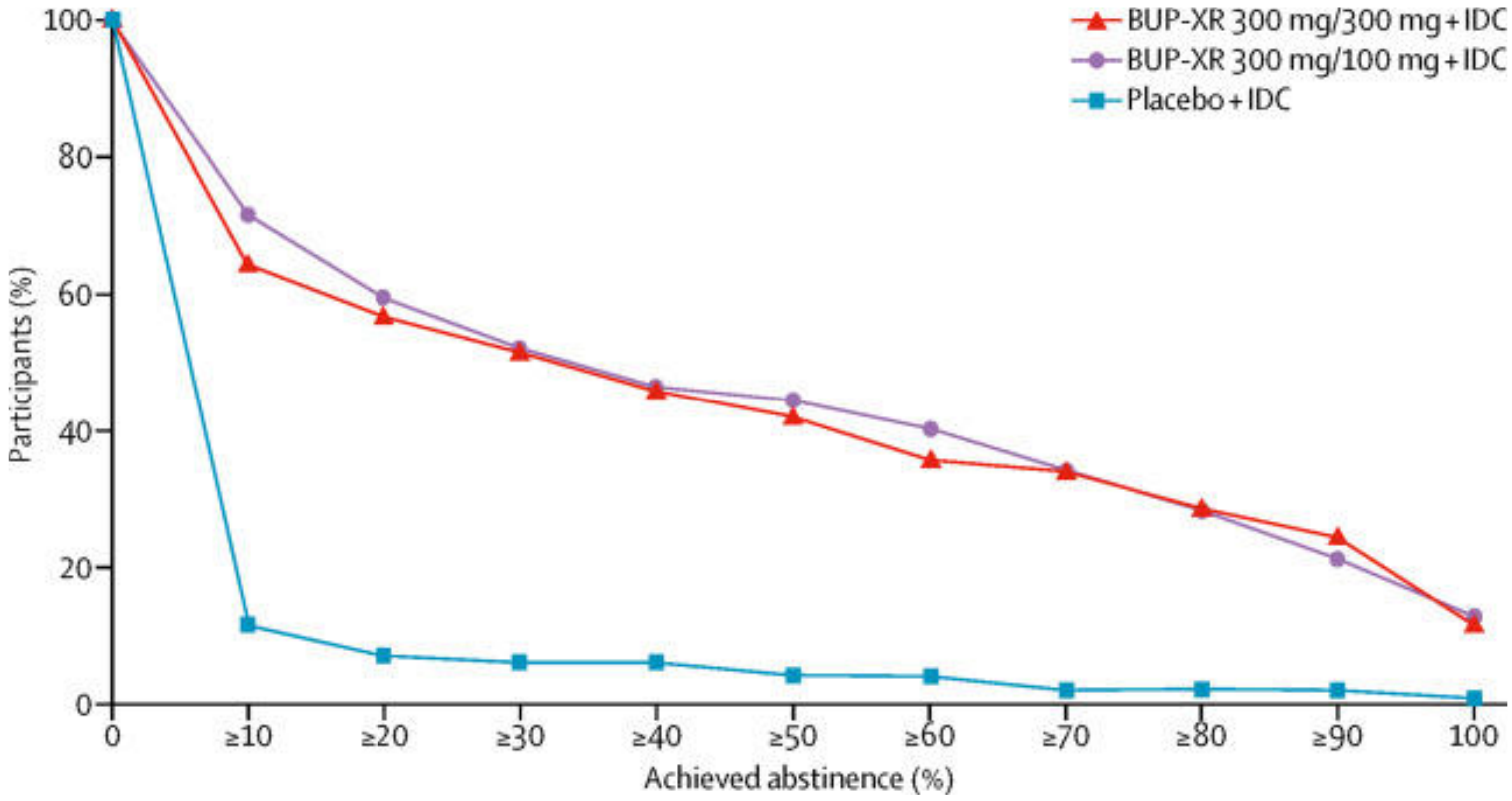
- N = 39 opioid dependent volunteers
- Stabilization on SL buprenorphine 8mg to 24mg
- Sublocade 300mg (Day 1, Day 29 – 2 monthly doses)
- Hydromorphone challenge (IM), 6 mg, 18 mg, placebo)
- Findings:
  - Sublocade blocked subjective hyrdomorphone liking effects (VAS)
  - Sublocade attenuated hydromorphone self-administration (choice of drug doses vs money), measured as reduced break point.

Sublocade (300mg and 100mg SC monthly injections) (Haight et al., Lancet 2019)

- Placebo controlled, 24 week, pivotal trial
  - Sublocade 300mg (N = 196)
  - Sublocade 300mg x 2month, then 100mg (N = 194)
  - Placebo (N = 99)
- **Percent > 90% abstinent over week 5 to week 24**

Sublocade 300mg	Sublocade 300mg/100mg	Placebo
24.5	21.1	1.0

Sublocade Cumulative Distribution Function (Haight et al., Lancet 2019)



Risks (per Sublocade Prescribing Information)

- Do not administer IV
- Misuse-Abuse
- Respiratory depression esp. if benzodiazepines, alcohol, etc
- Neonatal opioid withdrawal
- Psychomotor impairment, operating machinery
- Hepatitis? (rare increase AST/ALT in Sublocade trials, ?muscle)
- Moderate to severe hepatic insufficiency increases bup blood levels
- Hypersensitivity (to buprenorphine, to vehicle)
- Precipitated opioid withdrawal
- Interference with pain management

Risks (per Prescribing Info—continued)

- Opioid withdrawal if abrupt discontinuation?
- Death in opioid naïve patients
- Long QT Syndrome
- Adrenal insufficiency?
- Orthostatic hypotension
- Elevated CSF pressure
- Elevated intracholedochal pressure
- Obscure diagnosis/course of acute abdomen syndromes
- Unintentional pediatric exposure
- Serotonin syndrome?
- Androgen insufficiency?

Sublocade Adverse Events – Drug Interactions

- Common Adverse Events
  - Injection site reactions
  - Common opioid related side effects
- Drug Interactions
  - Benzos, alcohol, other CNS depressants
  - CYP-3A4 inhibitors or inducers
  - Serotonin syndrome? (MAOIs, other serotonergic drugs)
  - Muscle relaxants
  - Diuretics
  - Anticholinerigics

Pregnancy

- Buprenorphine appears safe and effective in pregnancy
  - MOMS study
- Sublocade contains a solvent NMP which is teratogenic
- NIDA Clinical Trials Network multisite trial in pregnant women will use CAM2038 (Buvidal) weekly, which does not contain NMP

Sublocade Pharmacokinetics
(buprenorphine concentration ng/ml)

	SL – 12mg/day	SL – 24mg/day	Sublocade 300 1st dose	Sublocade 100 Steady State	Sublocade 300 Steady State
C-average	1.71	2.91	2.19	3.21	6.54
C-max	5.35	8.27	5.37	4.88	10.12
C-min	0.81	1.54	1.25	2.48	5.01

What is the relationship between buprenorphine dose, blood level, mu-opioid receptor occupancy, blockade of opioid effects, and clinical response?

CAM-2038 (Buvidal; Braeburn/Camurus) XR Injectable Buprenorphine

- Liquid crystal technology
- Forms a soft gel in subcutaneous space after injection
- Lower fluid load injected (< 1cc) (vs Sublocade)
- Does not require refridgeration
- Range of available doses-durations
  - Weekly or Monthly
  - Doses ranging from equivalent of < 8mg to 24mg SL buprenorphine

CAM2038 Injectable Buprenorphine

(Dose equivalencies, mg)

Sublingual Buprenorphine-Naloxone	Weekly CAM2038	Monthly CAM2038
< 8	8	n/a
8 - 10	16	64
12 - 16	24	96
18 - 24	32	128
26 - 32		160

CAM2038 Pivotal Trial

(Lofwall et al., JAMA Internal Medicine 2018)

- Randomized, double-blind, active controlled, 6 month multisite trial
  - Non-inferiority trial
  - N = 428, across 35 sites

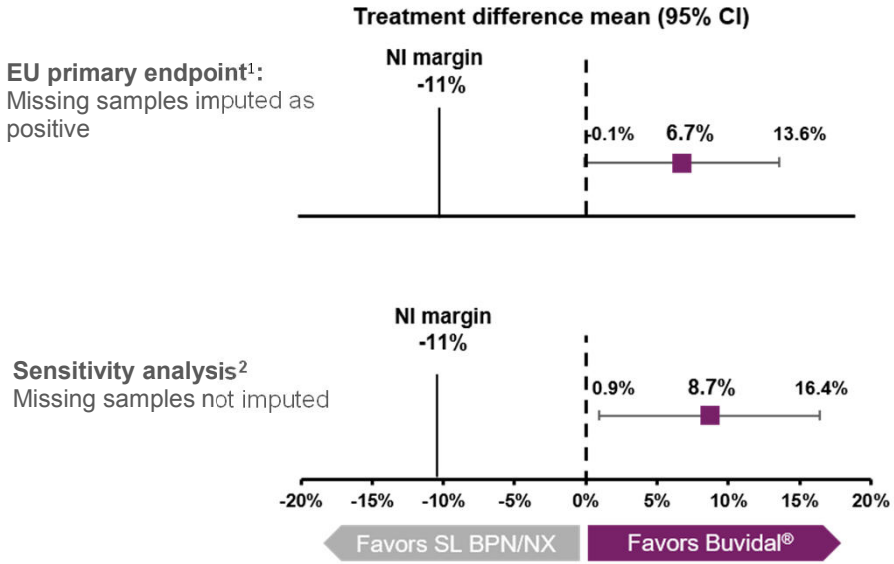
- Daily sublingual buprenorphine, flexible dose to effect
  - ***Versus***
- Weekly CAM2038 injection (weeks 1 to 12), then monthly CAM2038 injection (weeks 13 to 24), flexible dose to effect

CAM2038 Main Outcomes

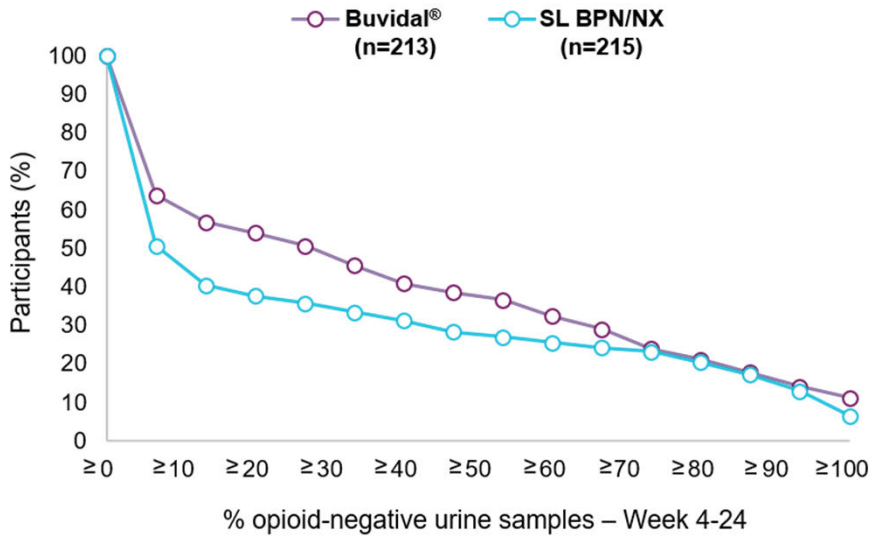
	Sublingual BUP-NX (18 to 20 mg/day)	CAM2038 (26mg/week) (108 mg/month)	Difference (95% CI)
Percentage Opioid Free Urine Samples	27.4	34.2	6.7 (0.0 – 13.6)
Responders (percent)	14.4	17.8	3.4 (-3.5 – 10.4)

Buvidal® met primary and secondary Phase 3 study endpoints (Study 421)

Non-inferiority for mean % urines negative for illicit opioids, p<0.001[1-3]



Superiority for CDF for negative urines weeks 4-24*; median 26.7% vs. 6.7%, p=0.008[1-3]

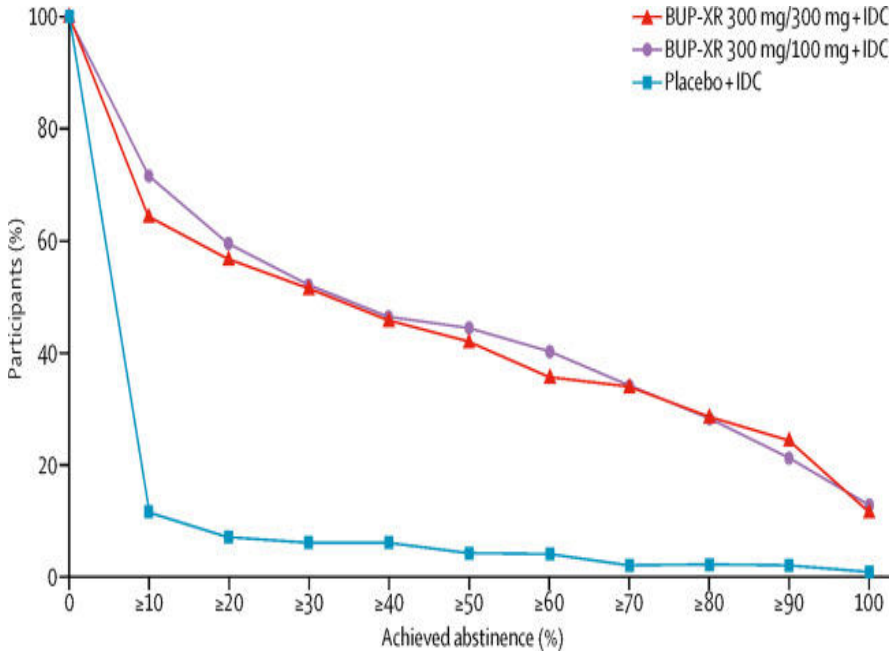


***Missing samples imputed as positive**
CDF = cumulative distribution function, EMA = European medicines agency, NI = non-inferiority, SL BPN/NX = sublingual buprenorphine/naloxone

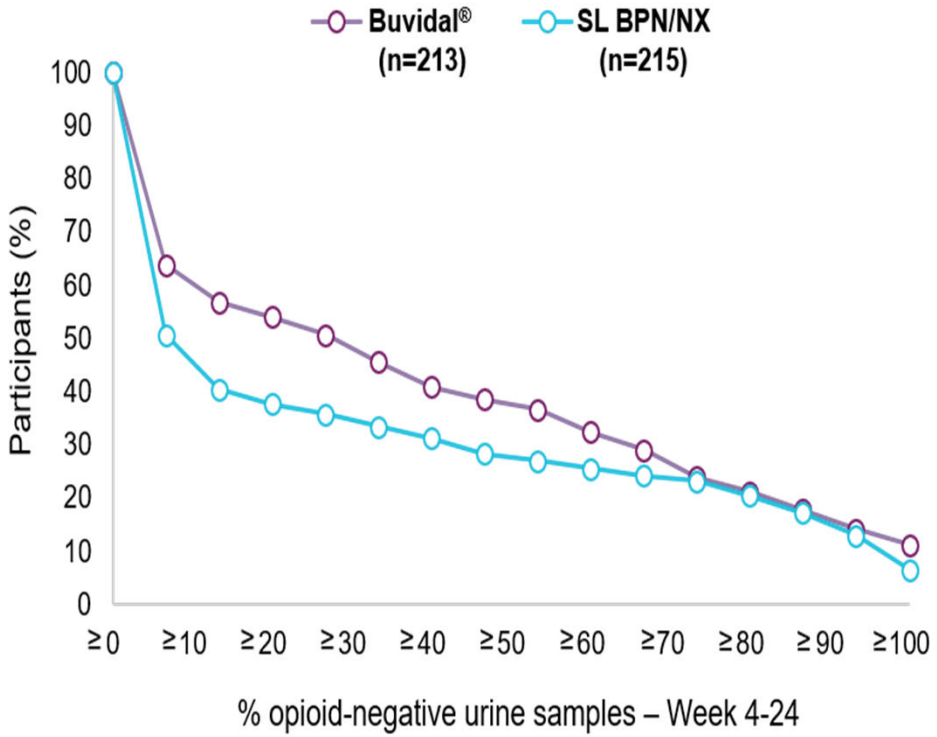
1. Lofwall M et al. JAMA Int. Med. 2018,178; 764-773. 2. EPAR December 2018 EMEA/H/C/004651/0000 https://www.ema.europa.eu/documents/assessment-report/buvidal-epar-public-assessment-report_en.pdf. 3. Camurus Buvidal® Summary of Product Characteristics (SmPC). Camurus AB, Sweden. November 2018.

For Comparison: Cumulative Distribution Functions

Sublocade

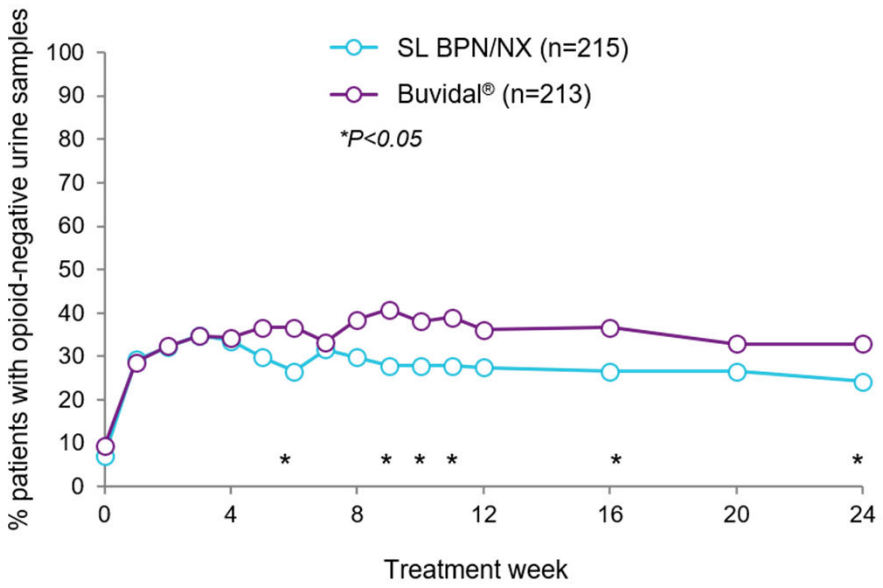


CAM2048 (Buvidal)

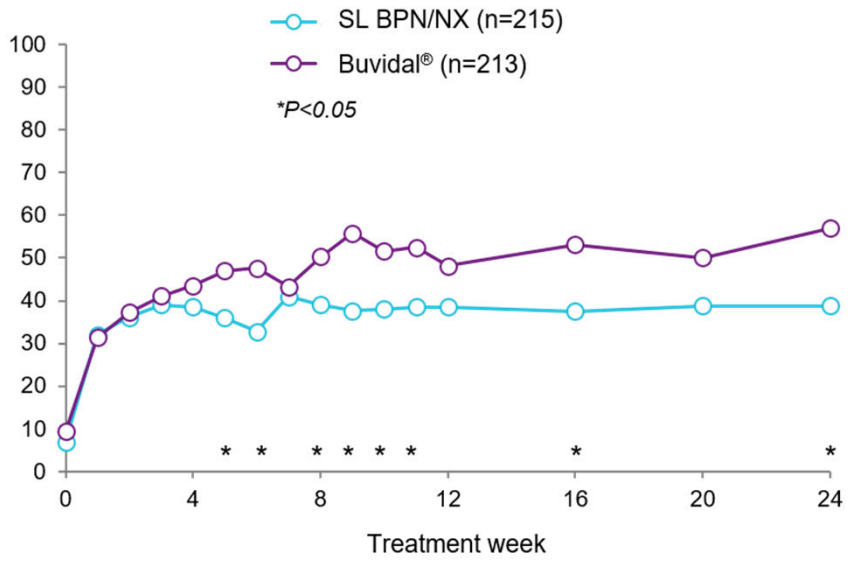


CAM2038: Percentage negative urine tests over time (Study 421)[1,2]

Missing urine samples assumed positive

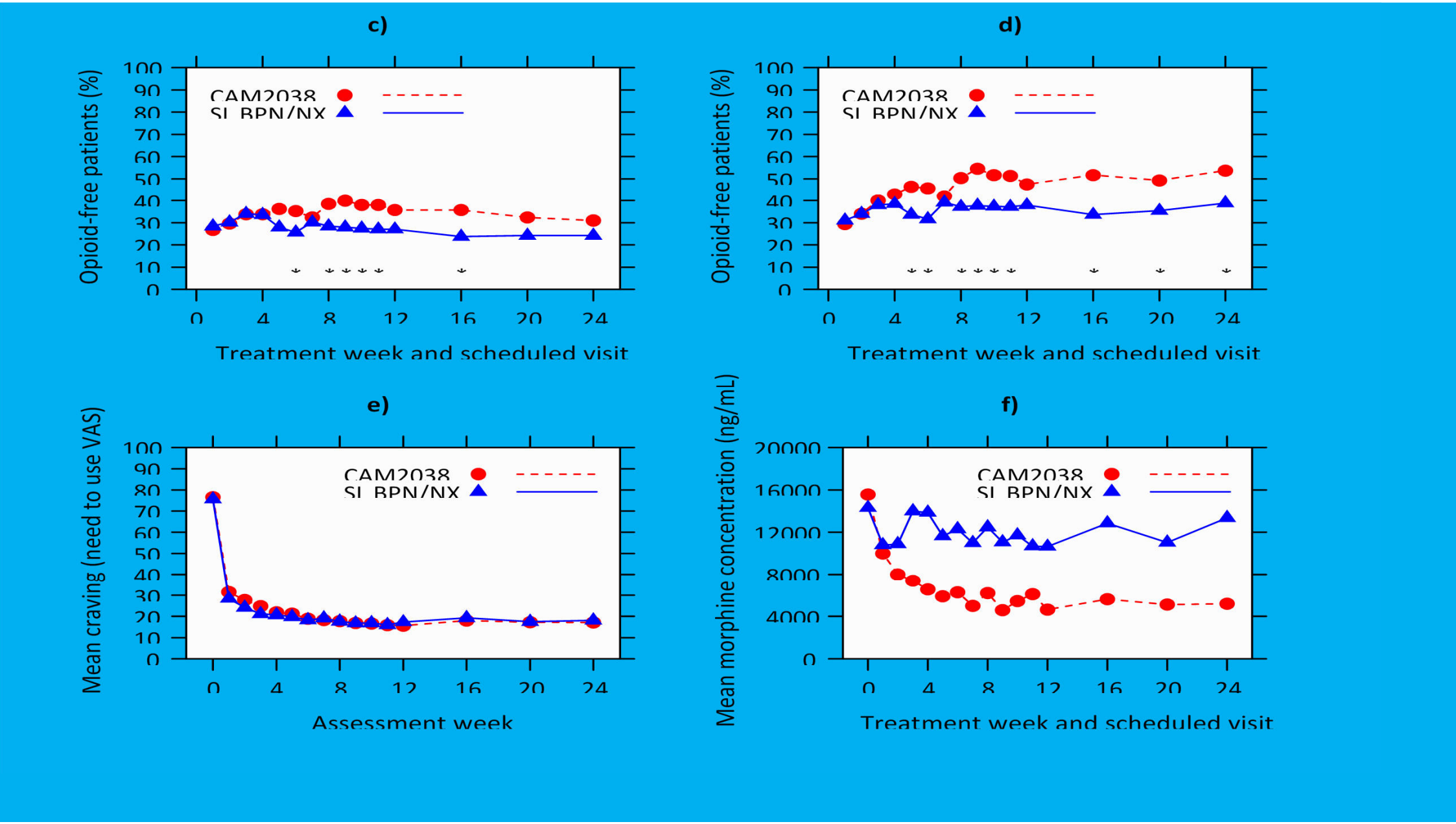


Missing urine samples not assumed positive (actual samples)

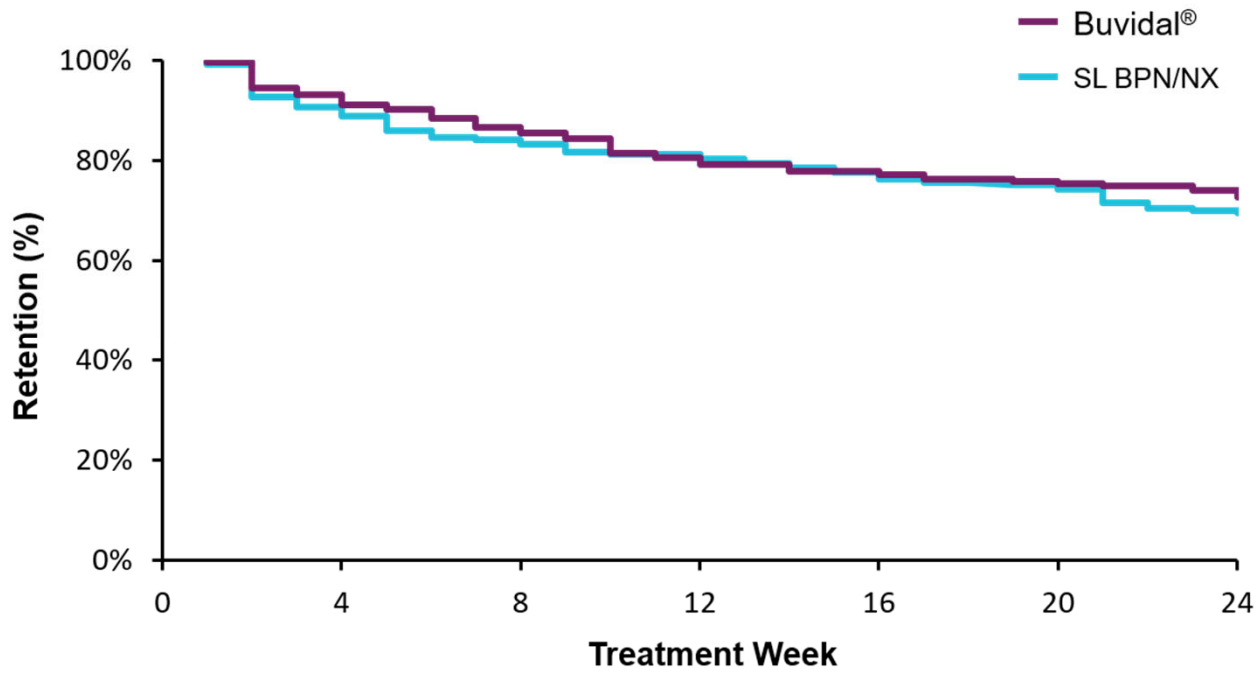


SL BPN/NX = sublingual buprenorphine/naloxone

1. Lofwall M et al. JAMA Int. Med. 2018,178(6); 764-773. 2.EPAR December 2018 EMEA/H/C/004651/0000 https://www.ema.europa.eu/documents/assessment-report/buvidal-epar-public-assessment-report_en.pdf.


c)
Opioid-free patients (%)
CAM2038
SL BPN/NX
Treatment week and scheduled visit
d)
Opioid-free patients (%)
CAM2038
SL BPN/NX
Treatment week and scheduled visit
e)
Mean craving (need to use VAS)
CAM2038
SL BPN/NX
Assessment week
f)
Mean morphine concentration (ng/mL)
CAM2038
SL BPN/NX
Treatment week and scheduled visit

Retention during 24 weeks study with Buvidal® (Study 421)



69.0% of participants randomized to Buvidal® and 72.6% randomized to SL-BPN/NX completed the 24-week study

SL BPN/NX = sublingual buprenorphine/naloxone

Lofwall M et al. JAMA Int. Med. 2018,178; 764-773 & Data on file Camurus AB

Serious Adverse Events

	Sublingual Bup-NX	CAM2038 Subcutaneous Bup
Non-Fatal SAEs	13	5
Deaths	0	1
Hospitalizations	12	3
Drug Overdoses	5	0

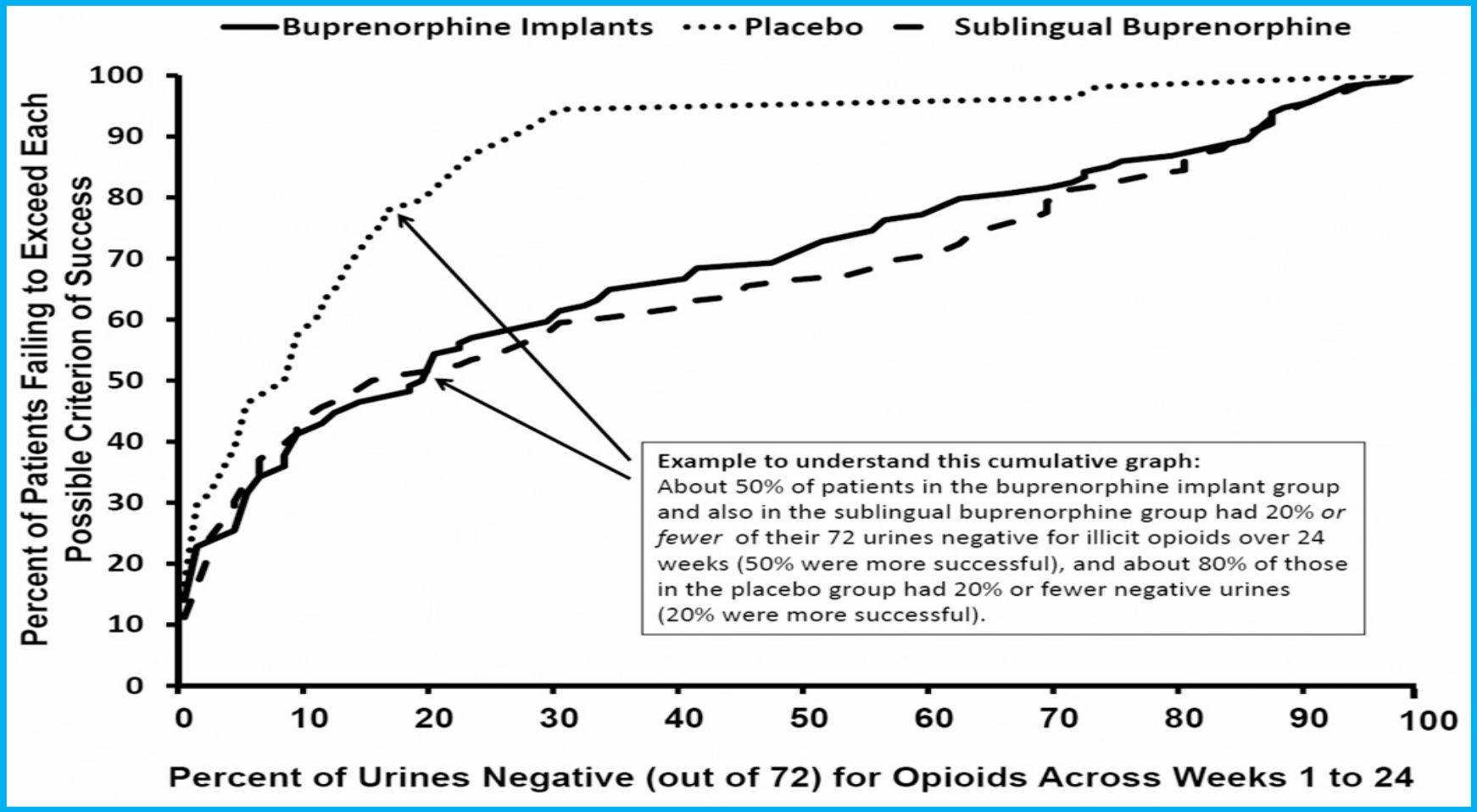
Summary: CAM2038 Weekly and Monthly Buprenorphine Injection

- Abstinence outcomes: CAM2038 was non-inferior on FDA primary outcome, superior on secondary outcomes, compared to sublingual Buprenorphine-naloxone
- No difference in retention in treatment
- Well tolerated
- CAM2038 appears to be a viable alternative for treatment of opioid use disorder, with the advantages of a long acting injection

Probuphine 6 Month Buprenorphine Implant

- Plastic rods (80mg buprenorphine per rod)
- 4 rods implanted subcutaneously in upper arm (320mg total)
- Minor surgical procedure to implant
- Requires removal after 6 months (rods do not dissolve) – may require some surgical skill
- Indicated for continuation of long term treatment for patients stable on 8mg or less of sublingual buprenorphine
  - Not indicated for acute treatment where higher doses would typically be needed
  - ?? Useful as a foundation for patients with likely variable/poor adherence?

Probuphine vs SL Bup in Patients with OUD *(Rosenthal et al., Addiction 2013)*



Summary: Long Acting Formulations of Buprenorphine

- Injectable 1-week (CAM2038) or 1-month (CAM2038; Sublocade) formulations
  - At least as effective as Sublingual Bup (maybe better), with potential advantages for adherence, diversion
  - Cost More
- 6-month implant (Probuphine), lower blood levels, effective for maintaining patients stable on low doses of sublingual Buprenorphine
  - Also some evidence for efficacy in newly admitted OUD patients
- Future Research
  - Effectiveness and Implementation
  - Which patients/populations/settings will most benefit from the long-acting formulations?

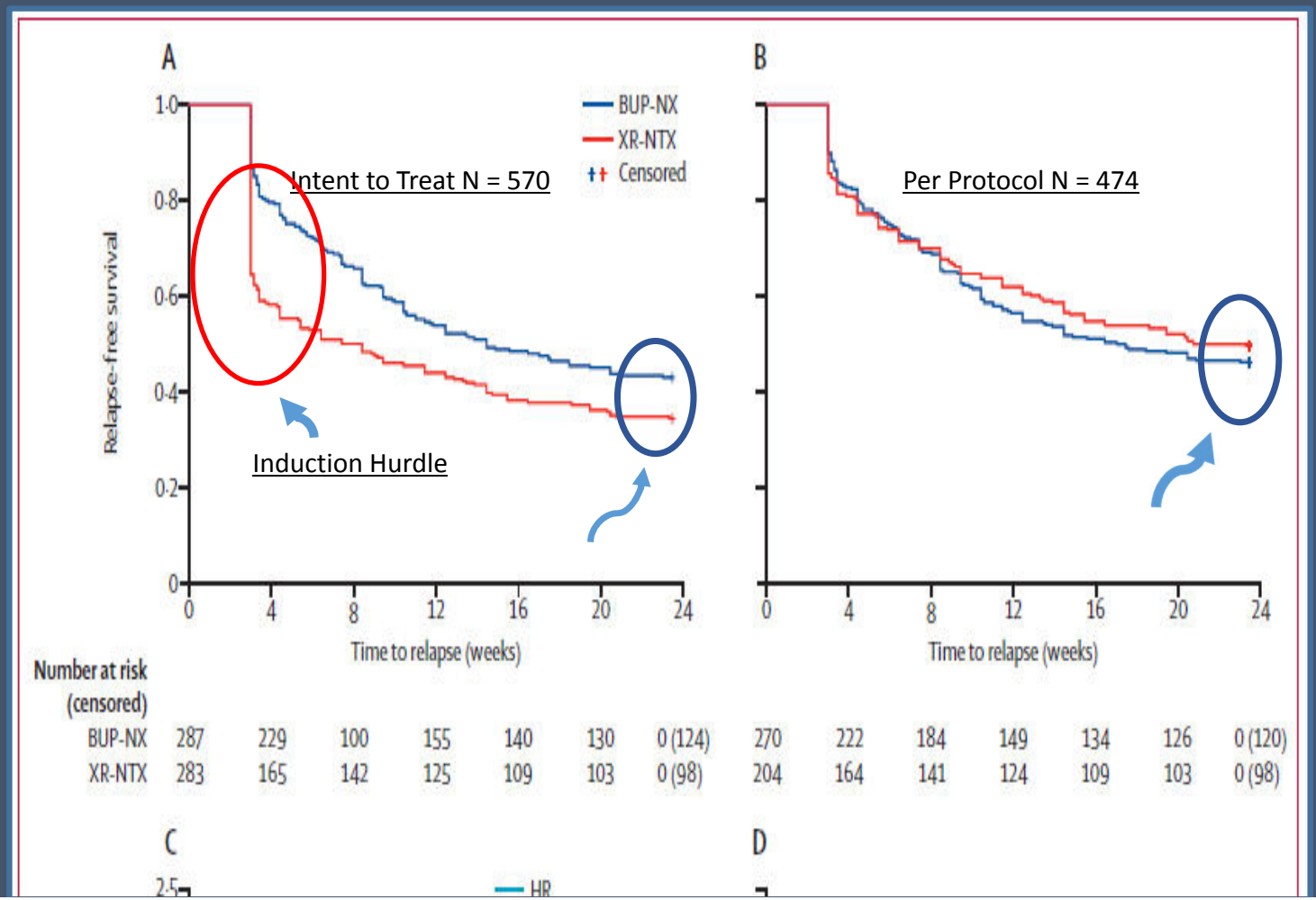
Why use a long-acting buprenorphine formulation?

- Sublingual buprenorphine is relatively inexpensive, feasible, well tolerated
- Implants, injections are expensive
- Advantages:
  - Evidence to date suggests a small advantage for injection bup overall (from CAM2038 non-inferiority study)
  - Safety, no diversion
- What types of patients will most benefit from a long-acting formulation?

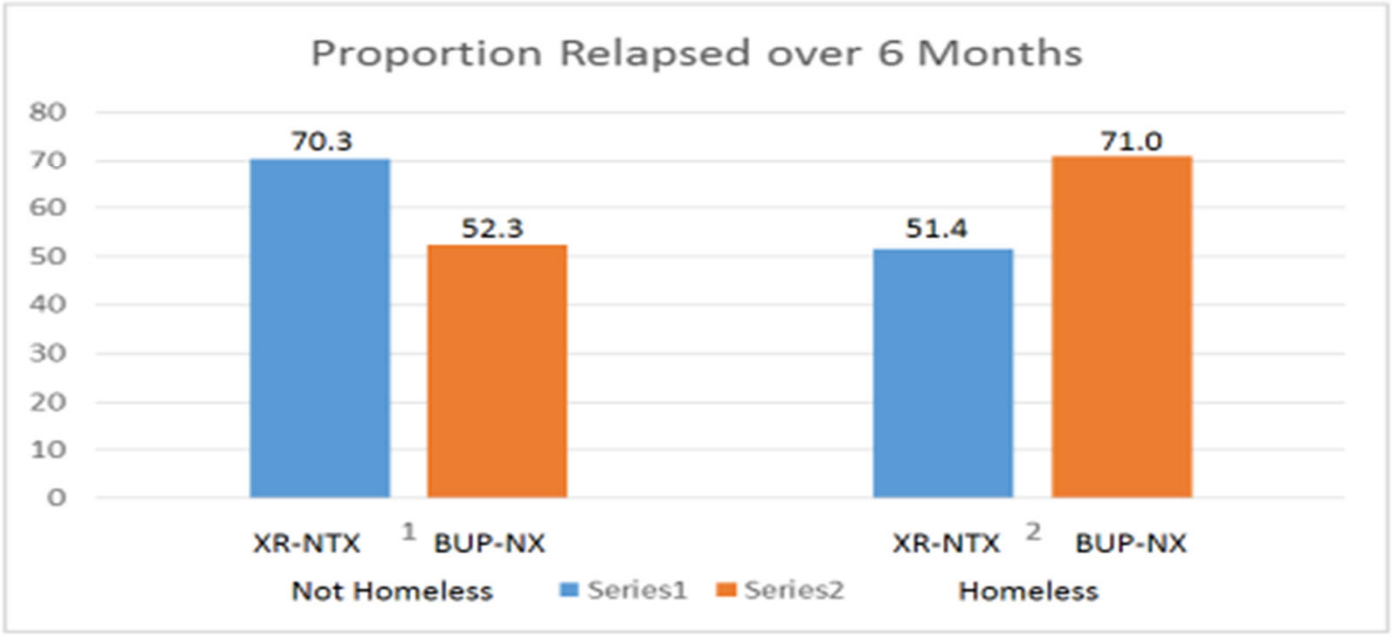
Extended Release Injection Naltrexone (Vivitrol)

- Monthly intramuscular injection given in buttocks
- **"Induction hurdle"**: Patient must be fully detoxified from opioids before starting naltrexone
- Prescribing Information recommends 7 to 10 days to elapse between last dose of opioids and first dose of Vivtrol
  - Rapid 5 to 7 day procedures have been tested (*Sullivan, Bisaga et al., American Journal of Psychiatry 2017*)
- Blocks effects of IV heroin for 4 to 5 weeks
- Subacute withdrawal symptoms may occur 1 - 2 weeks after first injection
  - After that patients usually feel well

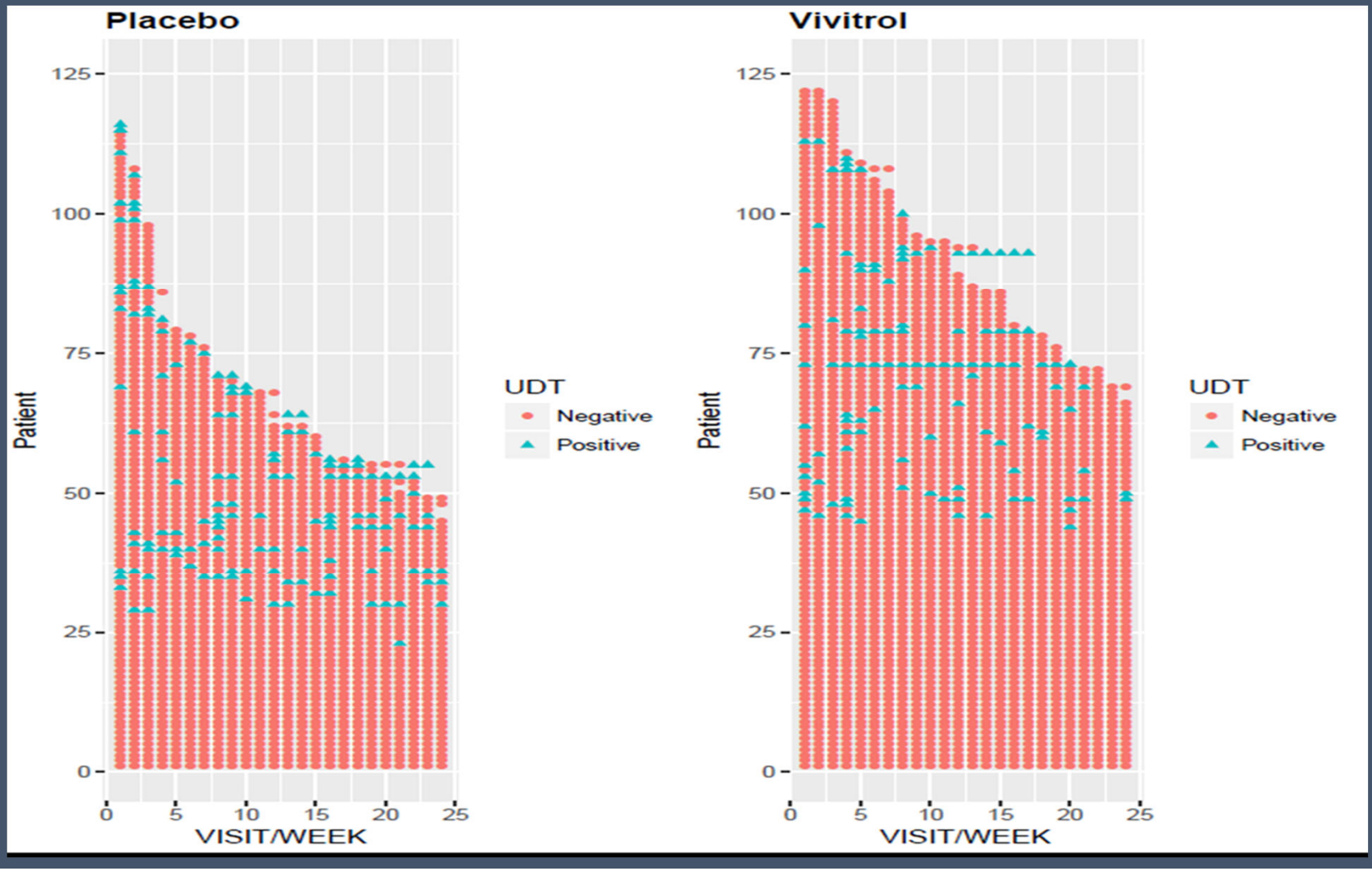
XBOT Study: XR-Naltrexone (Vivitrol) vs SL Buprenorphine-Nalox
(Lee, Nunes et al., Lancet 2018)



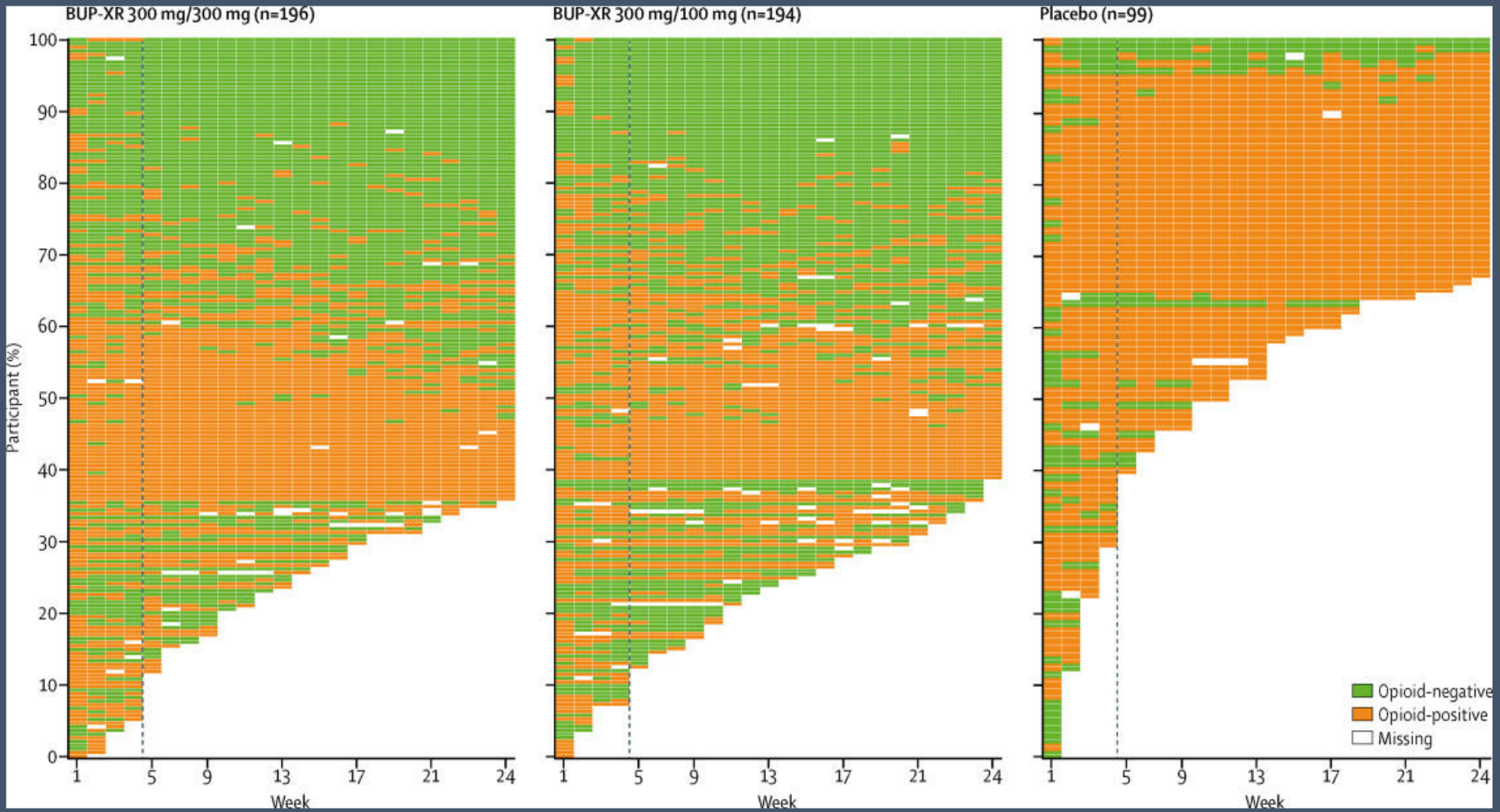
XBOT--Injection Naltrexone (XR-NTX) vs SL Bup: Homeless patients fare better on XR-NTX



Abstinence by Week in Russian Vivitrol Trial (*Krupitsky, Nunes et al., Lancet 2011; Nunes et al., Addiction in press*)



For Comparison:
Sublocade Trial: Abstinence by Week (Haight et al., Lancet 2019)



Conclusions

- Several promising buprenorphine and naltrexone injections and implants
  - Effective
  - Well tolerated
- Differ in dose, pharmacokinetics, tolerability issues
- Adherence does not depend on daily dosing
- Provide options for patients and their clinicians to consider when choosing a treatment for opioid use disorder

Future Research

- Which patients/populations/settings will most benefit from the long-acting formulations?
  - Patients living in more chaotic environments?
    - Homelessness, family or friends using drugs, criminal justice, emergency departments
  - Patients with history of poor adherence, impulsivity?

- Improved formulations
  - Implant with higher blood levels? Not requiring explantation?

- Effectiveness and implementation
  - Integration into various treatment settings?
  - How to increase abstinence?
  - Strategic combination with behavioral therapies? (e.g contingency management)
  - Supplementation with SL Buprenorphine?