FeDerSerD

FEDERAZIONE ITALIANA DEGLI OPERATORI DEI DIPARTIMENTI E DEI SERVIZI DELLE DIPENDENZE

BUPRENORFINA A RILASCIO PROLUNGATO MENSILE: SVILUPPO CLINICO ED EVIDENZE DAL REAL WORLD

Sarah Vecchio

Direttore S.C. Ser.D ASL NO

DISCLOSURES

Indivior Italia
CT Laboratori
Molteni farmaceutici

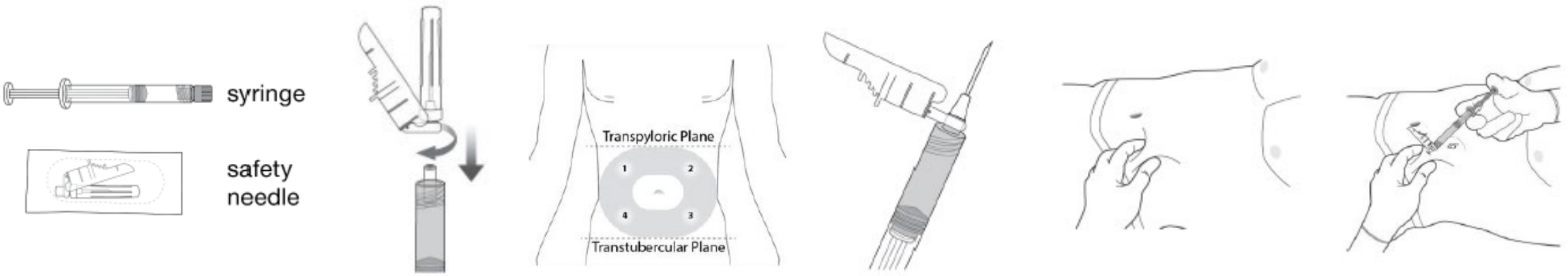
TOPICS

- Formulazione di buprenorfina a rilascio prolungato mensile (BUP-XR)
- Meccanismo d’azione di buprenorfina nella formulazione BUP-XR
- Risultati dei principali trial clinici nello sviluppo di BUP-XR
- Esperienze di real world con BUP-XR
- Utilizzo di BUP-XR in popolazioni a rischio

BUPRENORFINA A RILASCIO PROLUNGATO MENSILE

- Siringa preriempita da 1,5 mL di soluzione iniettabile a rilascio prolungato contenente **300 mg** di buprenorfina

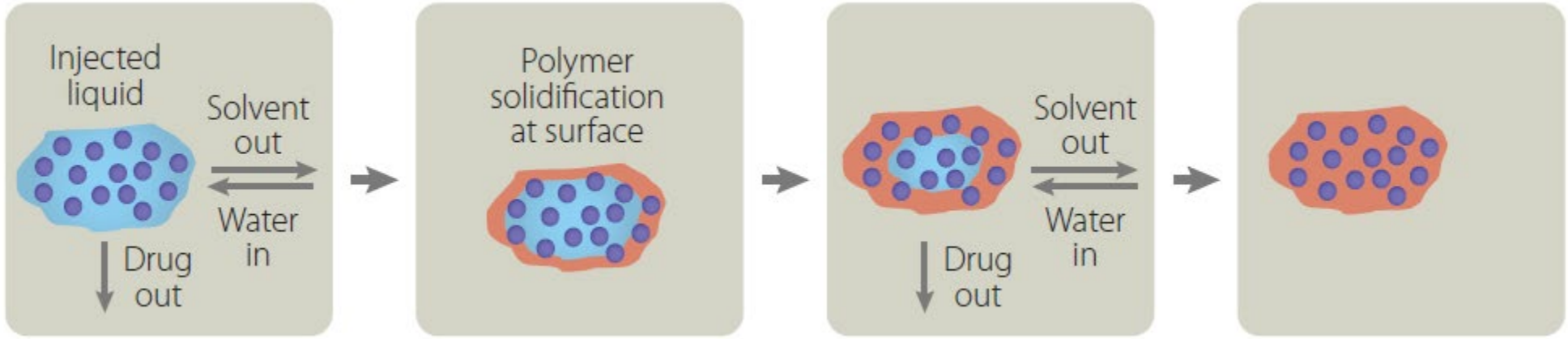
- Siringa preriempita da 0,5 mL di soluzione iniettabile a rilascio prolungato contenente **100 mg** di buprenorfina



https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2019-PI-01756-1&d=20240910172310101 (Accessed September 2024)

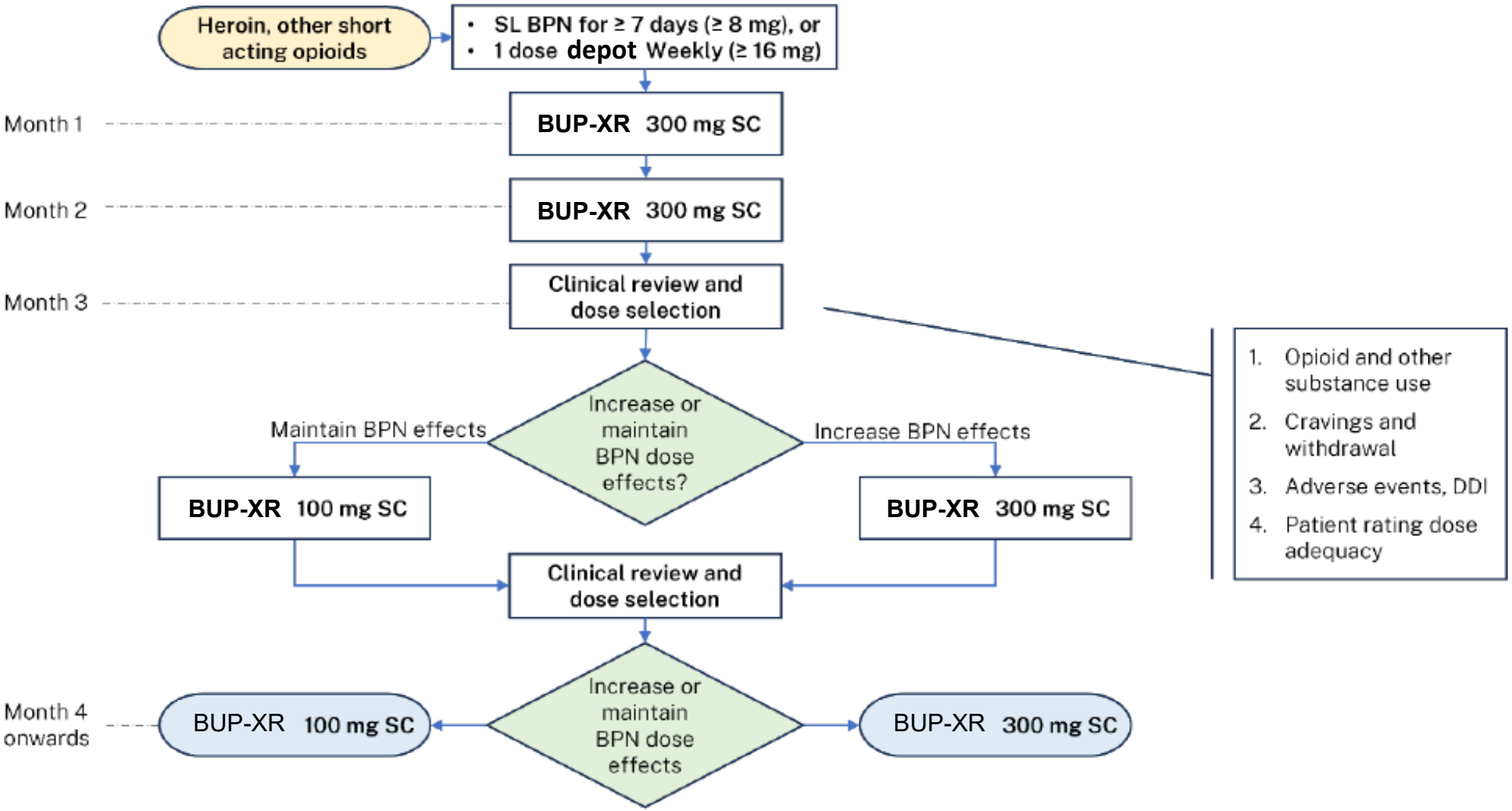
DELIVERY SYSTEM

Copolimero biodegradabile (PLGA) dissolto in N-metil-pirrolidone (NMP), solvente biocompatibile solubile in acqua. Dopo l'iniezione sottocutanea, l'NMP interagisce con i fluidi corporei che lo sostituiscono nella matrice innescando la polimerizzazione. La buprenorfina intrappolata nel polimero viene rilasciata gradualmente con la biodegradazione del polimero (non necessita rimozione).



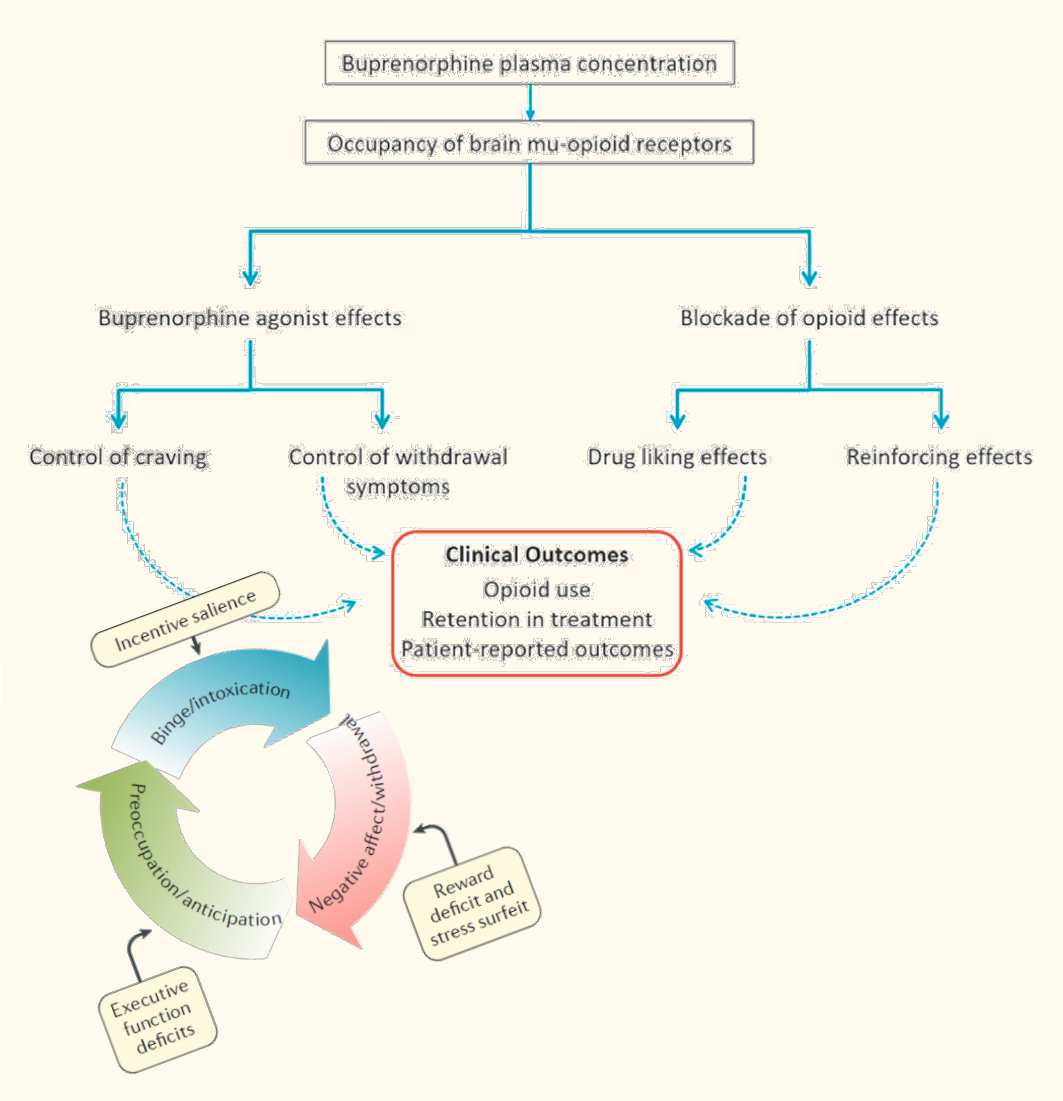
https://www.nature.com/articles/d43747-020-00404-w (Accessed September 2024)

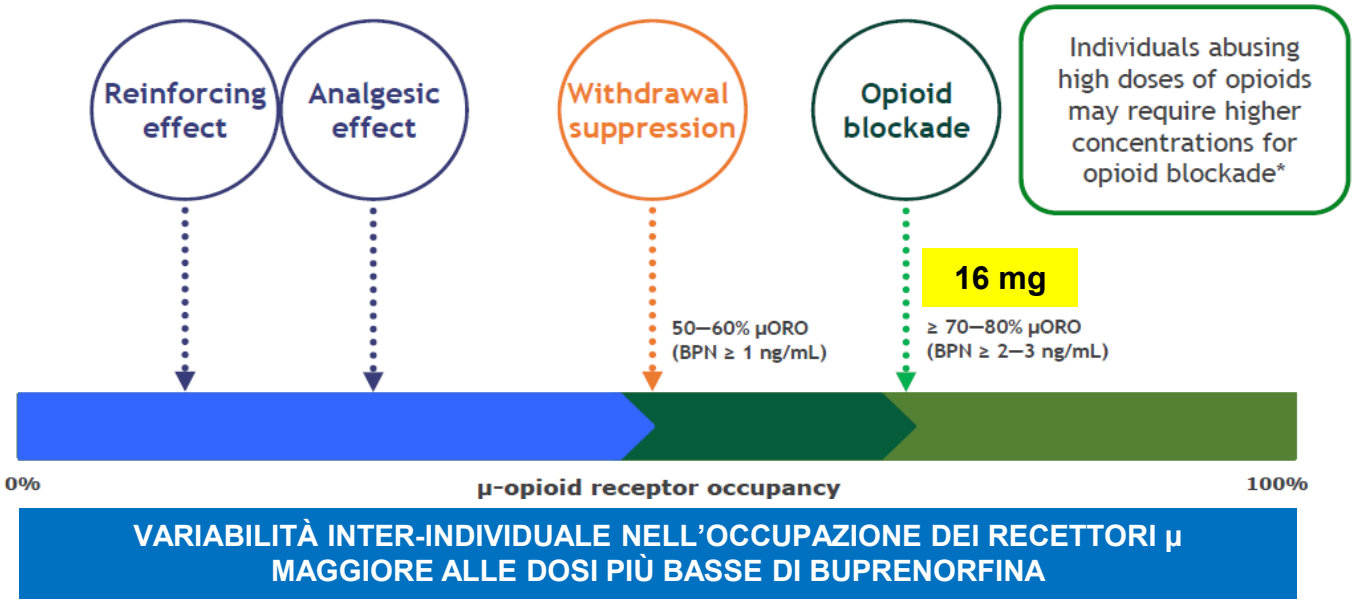
BUPRENORFINA A RILASCIO PROLUNGATO MENSILE



Lintzeris N, Dunlop A, Schulz M. Long-acting injectable buprenorphine (LAIB) for opioid dependence treatment: Practice Guide (2nd Ed). NSW Ministry of Health: Sydney (AU); 2024

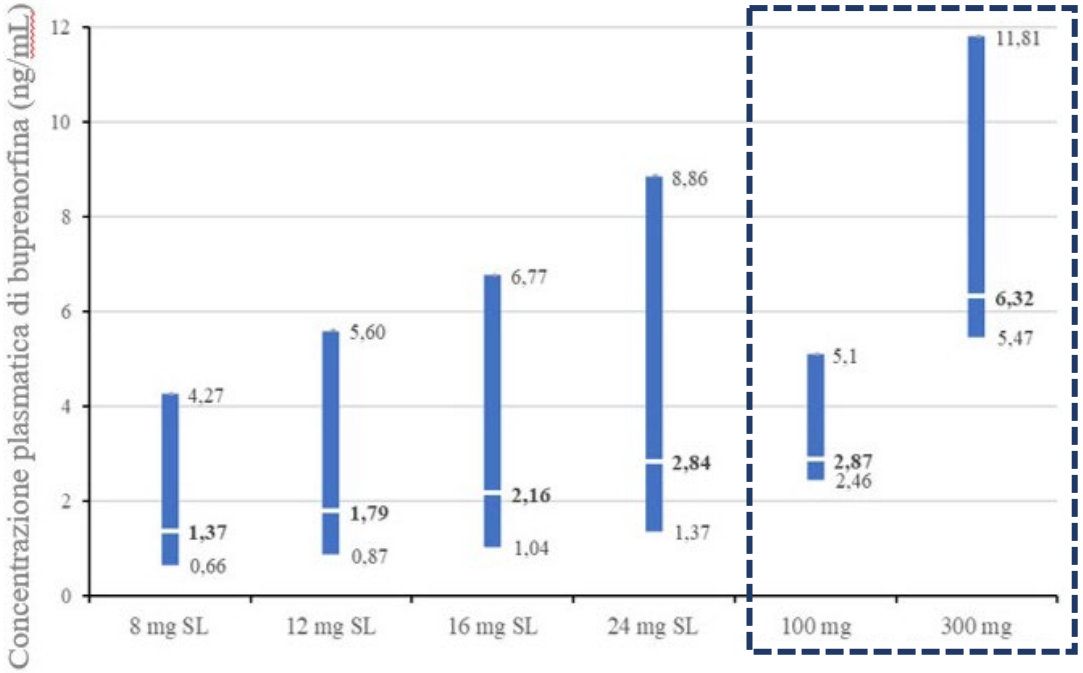
BUPRENORFINA: DOSAGGIO BLOCCANTE

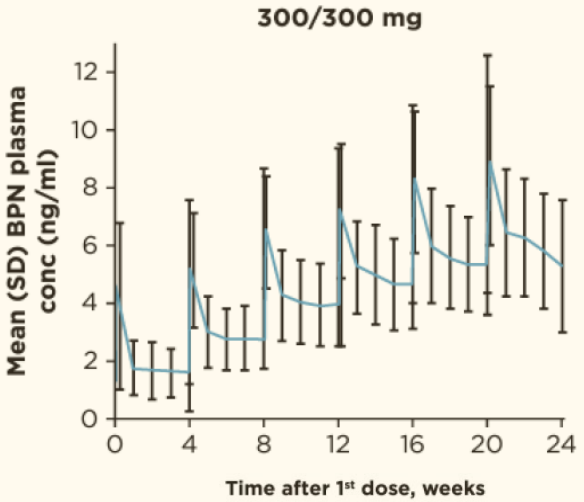




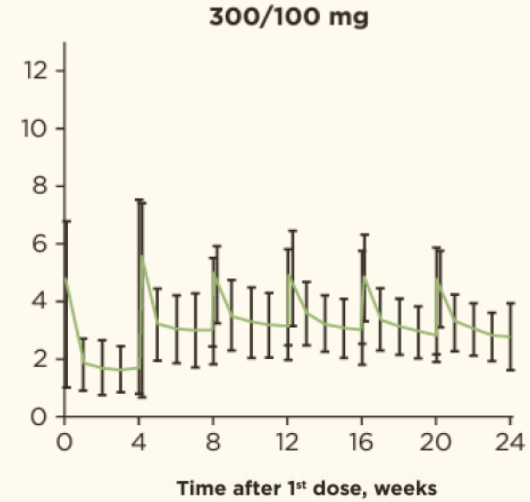
Greenwald M, Johanson CE, et al. Buprenorphine duration of action: mu-opioid receptor availability and pharmacokinetic and behavioral indices. Biol Psychiatry. 2007 Jan 1;61(1):101-10. Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug Alcohol Depend. 2014 Nov 1;144:1-11. Nasser AF, Heidbreder C, et al. A population pharmacokinetic and pharmacodynamic modelling approach to support the clinical development of RBP-6000, a new, subcutaneously injectable, long-acting, sustained-release formulation of buprenorphine, for the treatment of opioid dependence. Clin Pharmacokinet. 2014 Sep;53(9):813-24. Laffont CM, Ngaimisi E, et al. Buprenorphine exposure levels to optimize treatment outcomes in opioid use disorder. Front Pharmacol. 2022 Nov 18;13:1052113

BUPRENORFINA A RILASCIO PROLUNGATO MENSILE





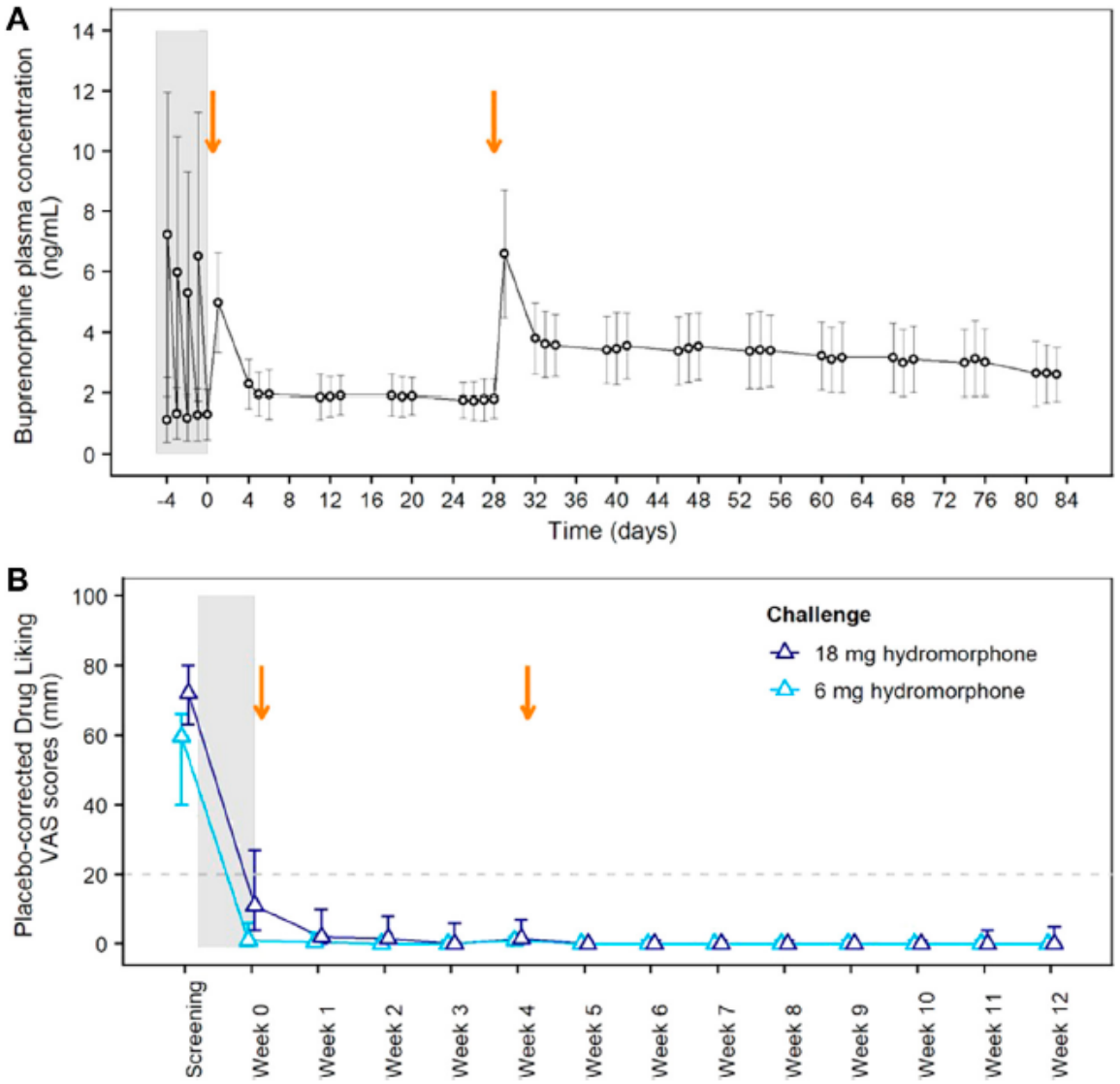
- Concentrazione target di 2 ng/ml raggiunta dopo la prima somministrazione
- Allo steady-state raggiunta una concentrazione media di 5 ng/ml

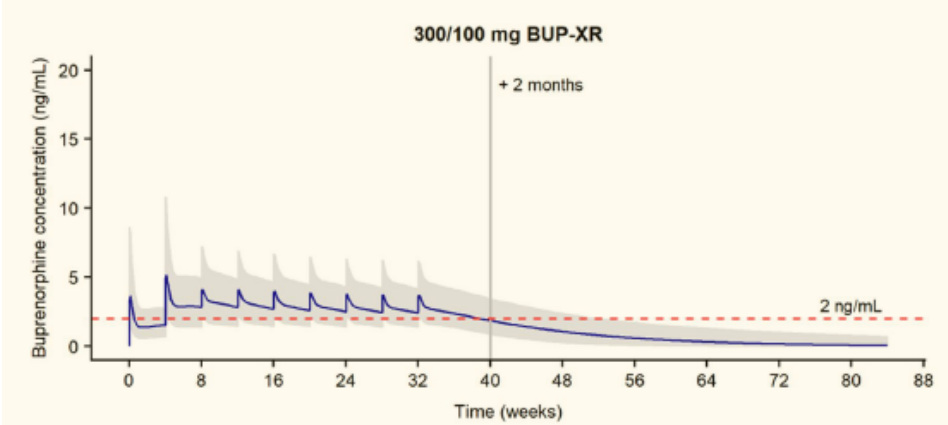


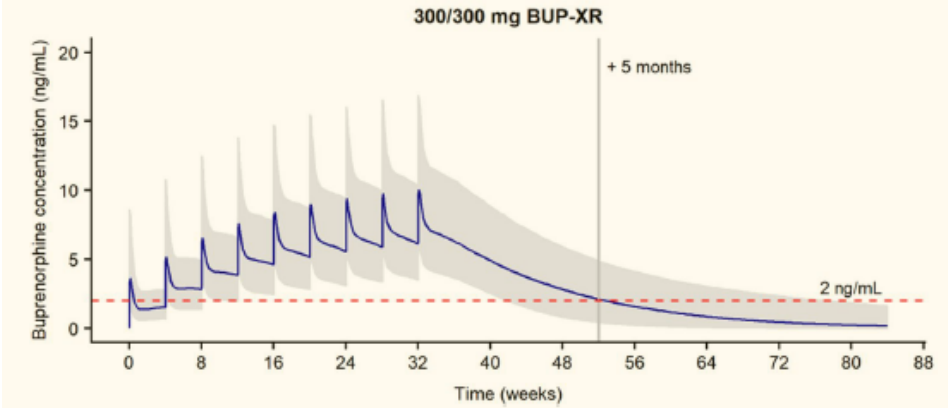
- Concentrazione target di 2-3 ng/ml raggiunta allo steady-state
- Due somministrazioni iniziali di 300 mg necessarie per raggiungere la concentrazione target

Adapted from Lintzeris N, Dunlop A, Schulz M. Long-acting injectable buprenorphine (LAIB) for opioid dependence treatment: Practice Guide (2nd Ed). NSW Ministry of Health: Sydney (AU); 2024

BUPRENORFINA A RILASCIO PROLUNGATO MENSILE







Half-life (at repeated doses)	Likely timeframe for onset and peak withdrawal symptoms after last maintenance depot dose
43–60 days	8–24 weeks after last dose

Jones AK, Ngaimisi E, Gopalakrishnan M, et al. Population Pharmacokinetics of a Monthly Buprenorphine Depot Injection for the Treatment of Opioid Use Disorder: A Combined Analysis of Phase II and Phase III Trials. Clin Pharmacokinet. 2021 Apr;60(4):527-540. Lintzeris N, Dunlop A, Schulz M. Long-acting injectable buprenorphine (LAIB) for opioid dependence treatment: Practice Guide (2nd Ed). NSW Ministry of Health: Sydney (AU); 2024

SVILUPPO DEL FARMACO (Clinical Trial Program)

Haight BR, Learned SM, Laffont CM, Fudala PJ, Zhao Y, Garofalo AS, Greenwald MK, Nadipelli VR, Ling W, Heidbreder C; RB-US-13-0001 Study Investigators.
Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.
Lancet. 2019 Feb 23;393(10173):778-790

Andorn AC, Haight BR, Shinde S, Fudala PJ, Zhao Y, Heidbreder C, Learned SM, Fox NL, Nadipelli VR, Hassman D, Rutrick D.
Treating Opioid Use Disorder With a Monthly Subcutaneous Buprenorphine Depot Injection: 12-Month Safety, Tolerability, and Efficacy Analysis.
J Clin Psychopharmacol. 2020 May / Jun;40(3):231-239

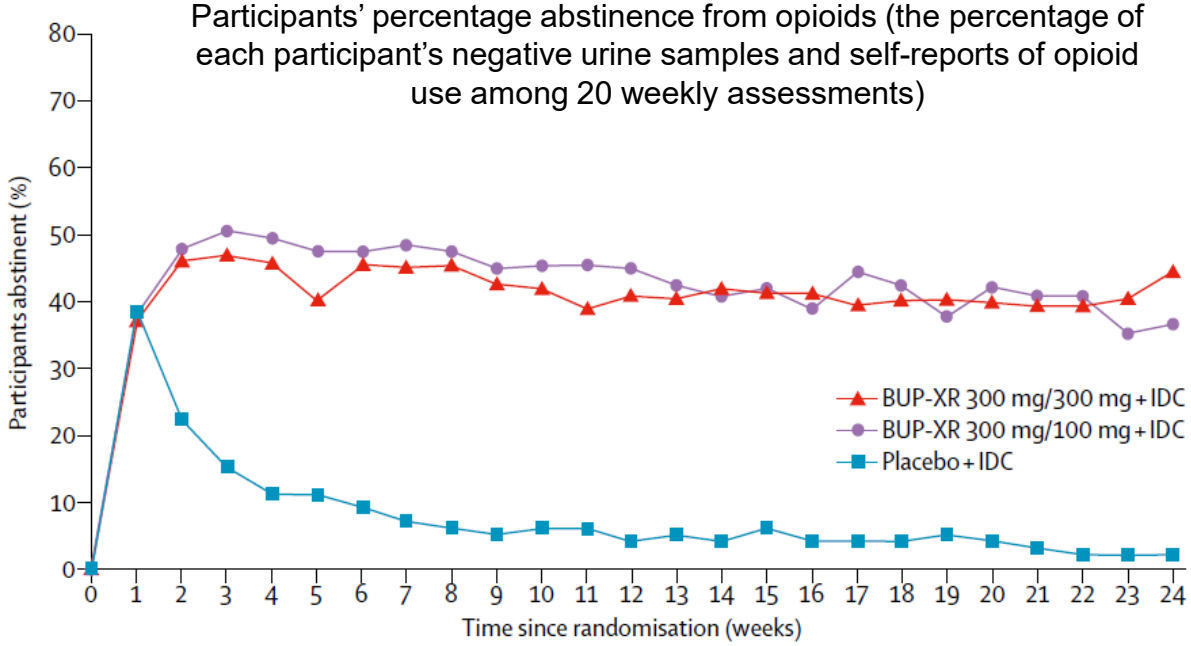
Wiest K., Andorn A., Fox N., Learned S., Zhao Y., Gray F.
Abstinence Response to 300 mg Vs 100 mg RBP-6000 among Opioid Injection Users.
Paper presented at the 50th Annual Conference of the ASAM, Orlando, FL, USA, April 4-7, 2019

Adapted from Ling W, Nadipelli VR, Ronquest NA, Albright VA, Aldridge AP, Learned SM, Mehra V, Heidbreder C. Remission from chronic opioid use-Studying environmental and socio-economic factors on recovery (RECOVER): Study design and participant characteristics. Contemp Clin Trials. 2019 Jan;76:93-103

EFFICACIA DI BUP-XR

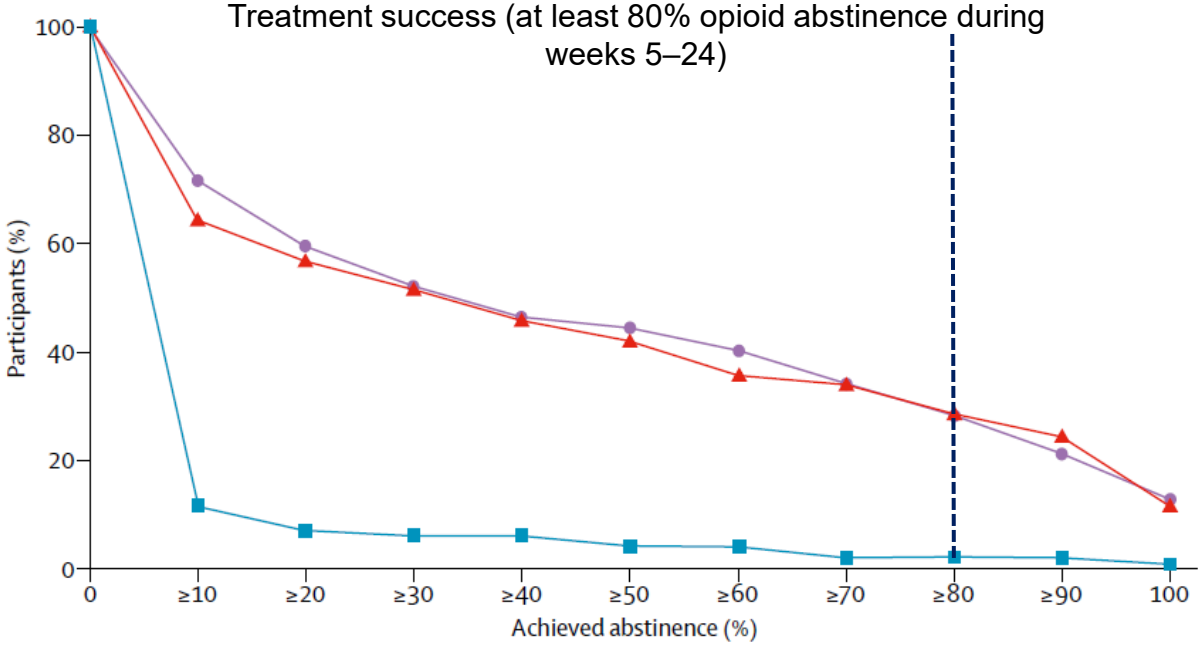
PRIMARY ENDPOINT

Participants' percentage abstinence from opioids (the percentage of each participant's negative urine samples and self-reports of opioid use among 20 weekly assessments)



KEY SECONDARY ENDPOINT

Treatment success (at least 80% opioid abstinence during weeks 5–24)



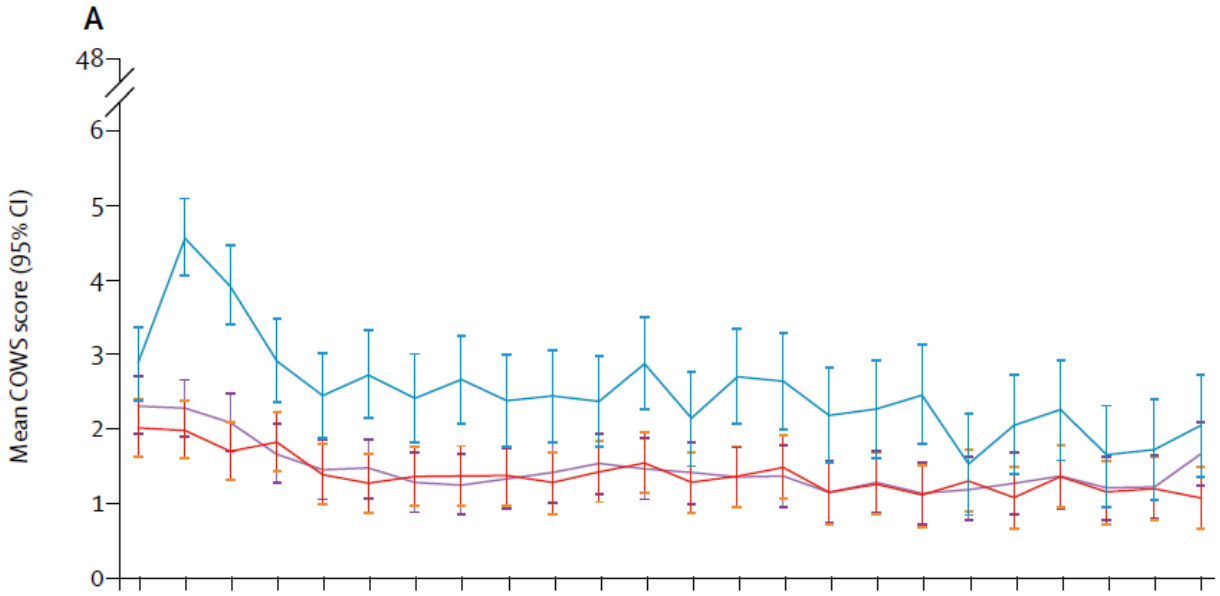
PERCENTUALE MEDIA ASTINENZA	
BUP-XR 300/100 mg + IDC (n=194)	42,7%
BUP-XR 300/300 mg + IDC (n=196)	41,3%
Placebo + IDC (n=99)	5%

SUCCESSO TERAPEUTICO (ASTINENZA ≥ 80%)	
BUP-XR 300/100 mg + IDC (n=194)	28%
BUP-XR 300/300 mg + IDC (n=196)	29%
Placebo + IDC (n=99)	2%

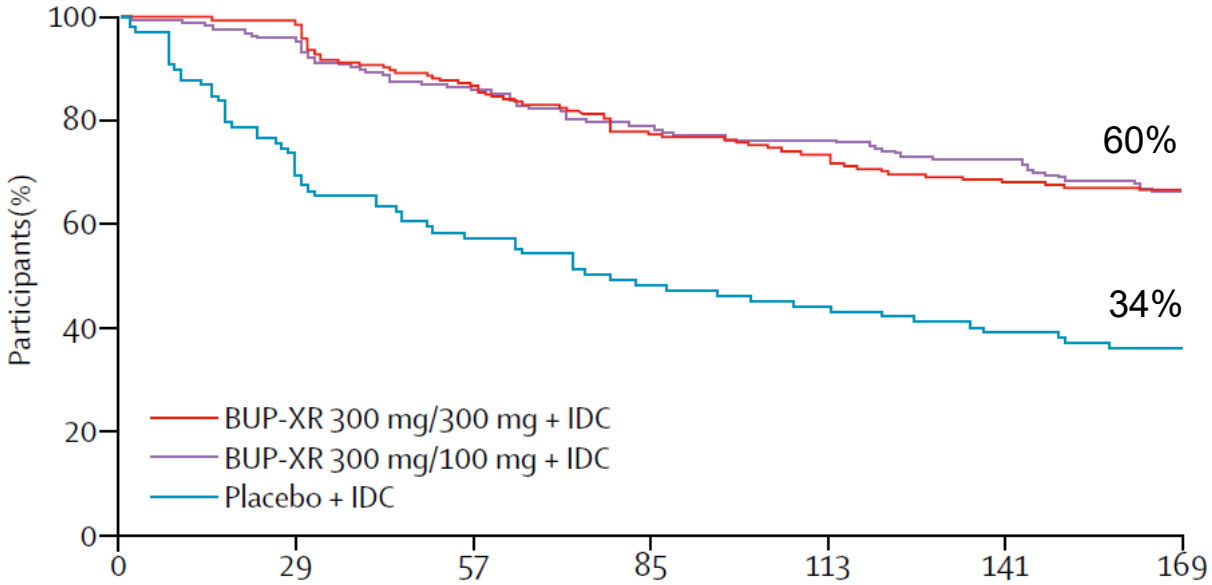
Haight BR, Learned SM, Laffont CM, Fudala PJ, Zhao Y, Garofalo AS, Greenwald MK, Nadipelli VR, Ling W, Heidbreder C; RB-US-13-0001 Study Investigators. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2019 Feb 23;393(10173):778-790

EFFICACIA DI BUP-XR

MEAN WITHDRAWAL SCORES



TIME FROM RANDOMISATION TO STUDY DISCONTINUATION



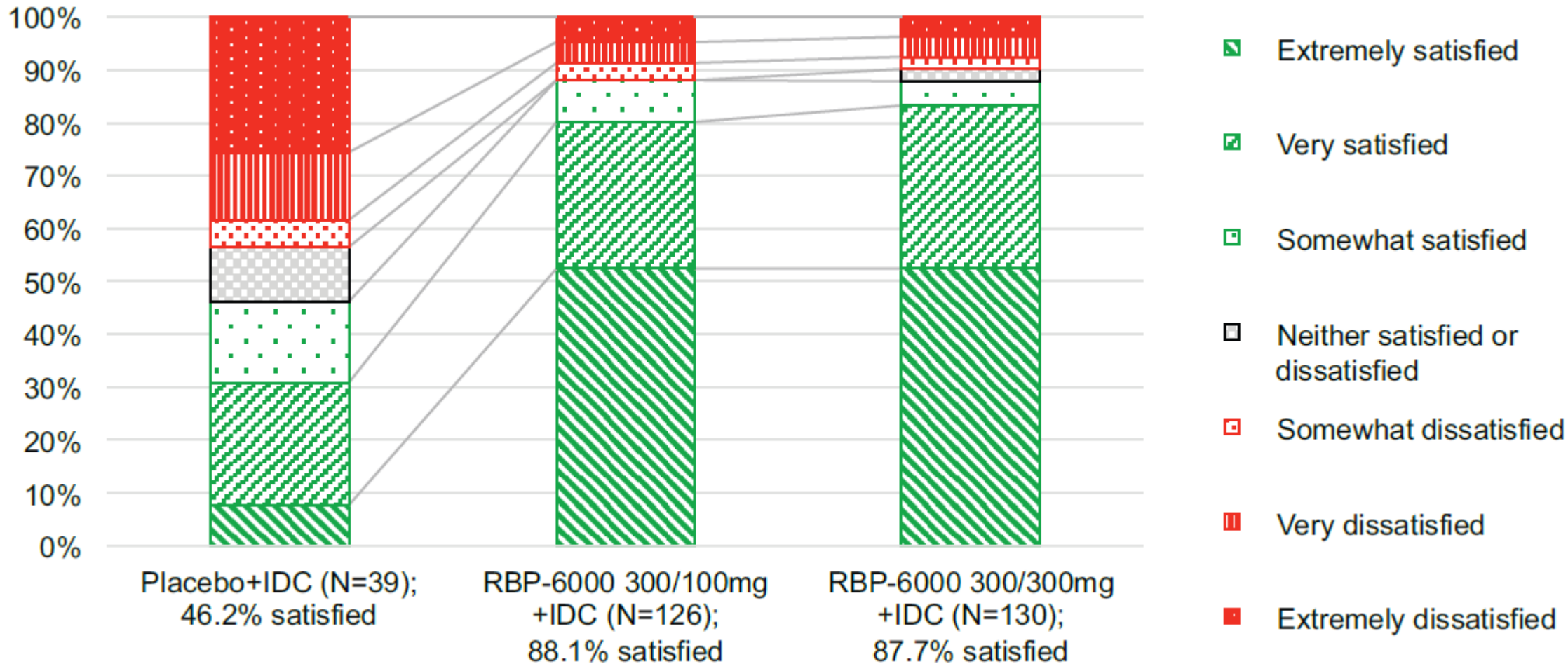
Haight BR, Learned SM, Laffont CM, Fudala PJ, Zhao Y, Garofalo AS, Greenwald MK, Nadipelli VR, Ling W, Heidbreder C; RB-US-13-0001 Study Investigators. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2019 Feb 23;393(10173):778-790

SICUREZZA DI BUP-XR

	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

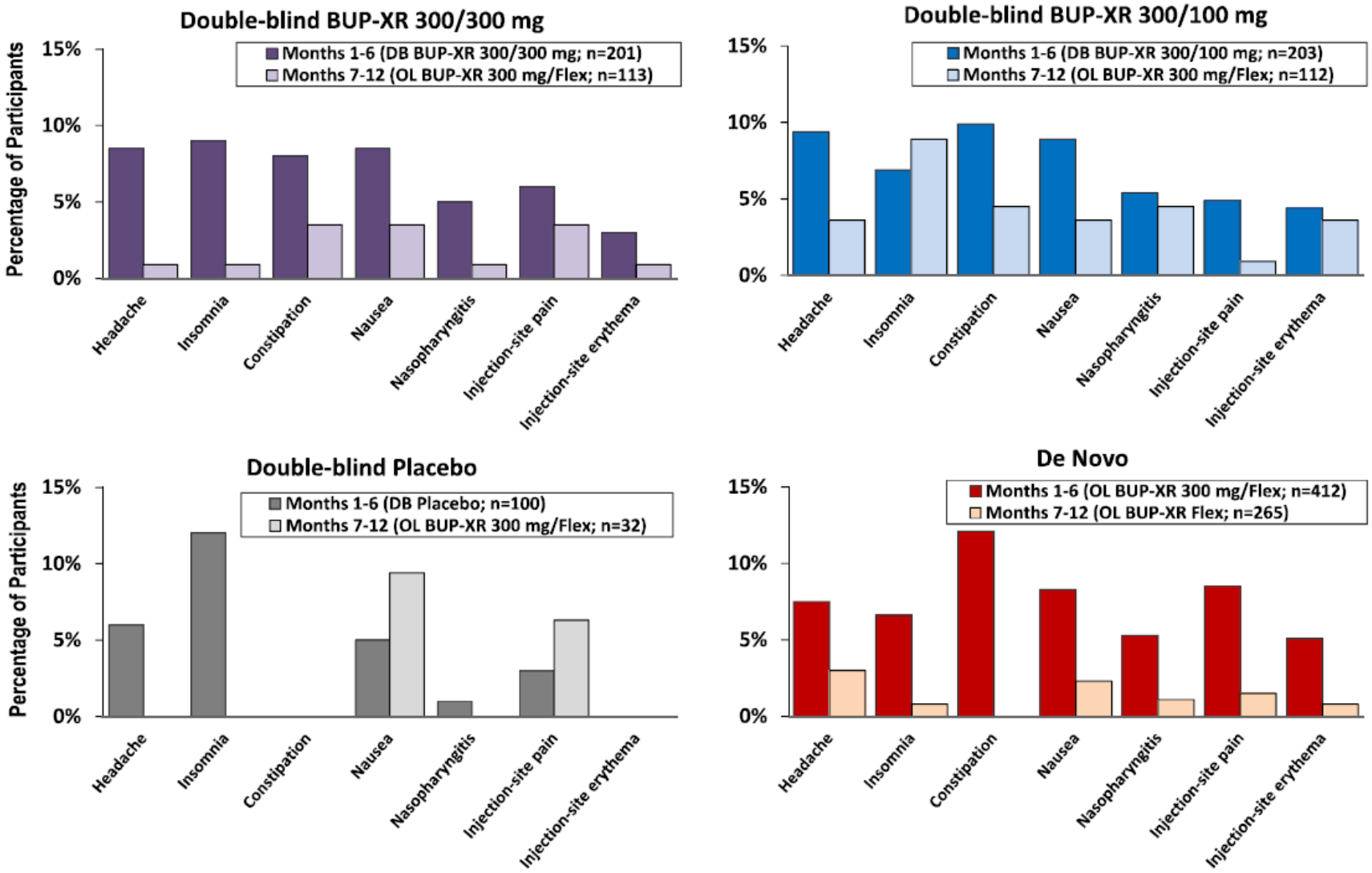
Haight BR, Learned SM, Laffont CM, Fudala PJ, Zhao Y, Garofalo AS, Greenwald MK, Nadipelli VR, Ling W, Heidbreder C; RB-US-13-0001 Study Investigators. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2019 Feb 23;393(10173):778-790

PATIENT-CENTERED OUTCOMES



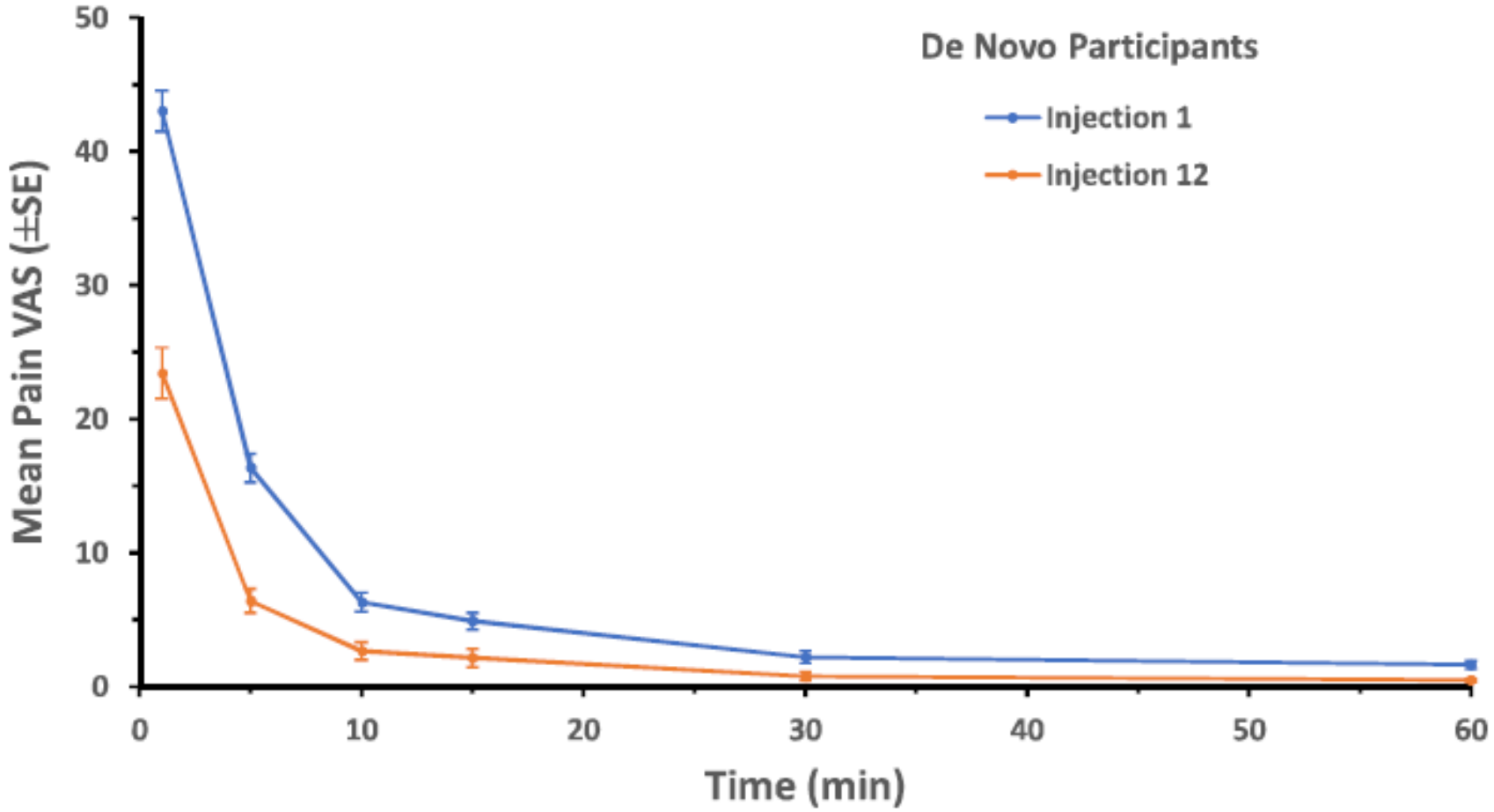
Ling W, Nadipelli VR, Solem CT, Ronquest NA, Yeh YC, Learned SM, Mehra V, Heidbreder C.
Patient-centered Outcomes in Participants of a Buprenorphine Monthly Depot (BUP-XR) Double-blind, Placebo-controlled, Multicenter, Phase 3 Study. J Addict Med. 2019 Nov/Dec;13(6):442-449

BUP-XR: SICUREZZA E TOLLERABILITA’



Andorn AC, Haight BR, Shinde S, Fudala PJ, Zhao Y, Heidbreder C, Learned SM, Fox NL, Nadipelli VR, Hassman D, Rutrick D. Treating Opioid Use Disorder With a Monthly Subcutaneous Buprenorphine Depot Injection: 12-Month Safety, Tolerability, and Efficacy Analysis. J Clin Psychopharmacol. 2020 May/Jun;40(3):231-239

BUP-XR: SICUREZZA E TOLLERABILITA’



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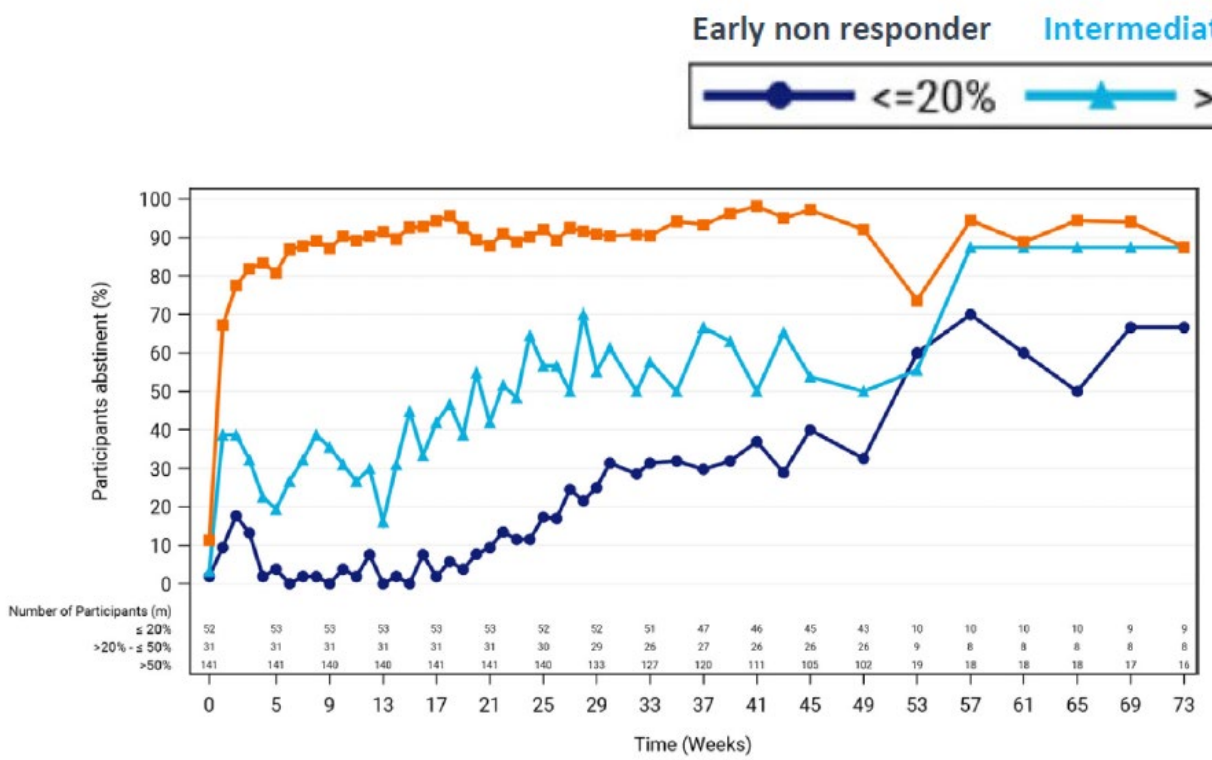
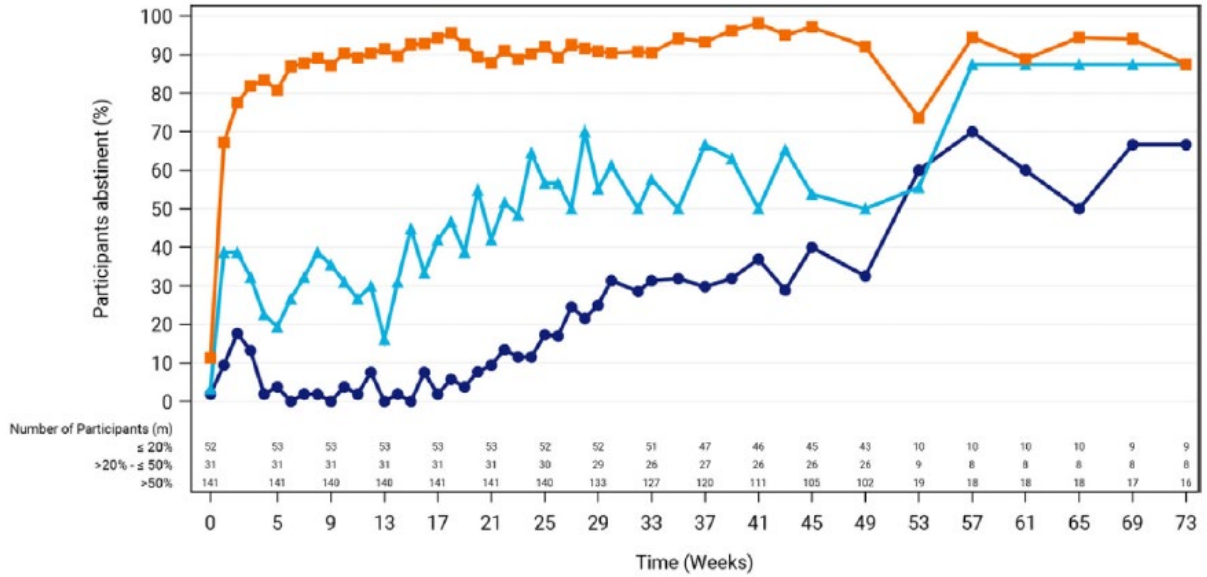
EFFICACIA A 18 MESI



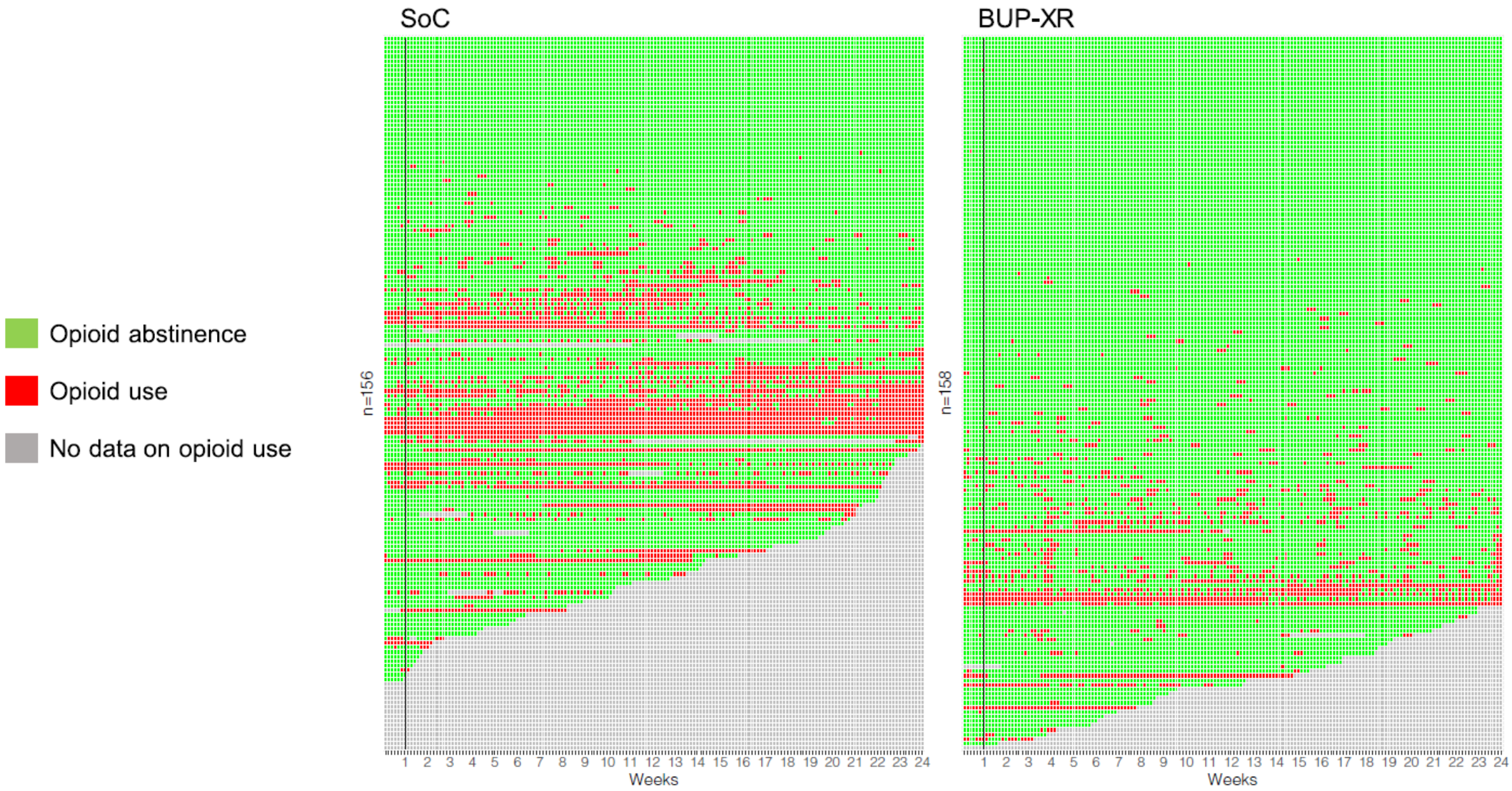
Proportion of participants achieving negative urine drug screening for opioids by visit week by early treatment response subgroups with treatment duration longer than 6 months (de novo cohort)



Proportion of participants achieving negative urine drug screening for opioids by early treatment response subgroups with treatment duration longer than 6 months (combined cohorts of BUP-XR 300/100 and BUP-XR 300/300 to 300/flex)

Rutrick D, Learned SM, Boyett B, Hassman D, Shinde S, Zhao Y. 18-Month efficacy and safety analysis of monthly subcutaneous buprenorphine injection for opioid use disorder: Integrated analysis of phase 3 studies. J Subst Use Addict Treat. 2023 Nov;154:209155

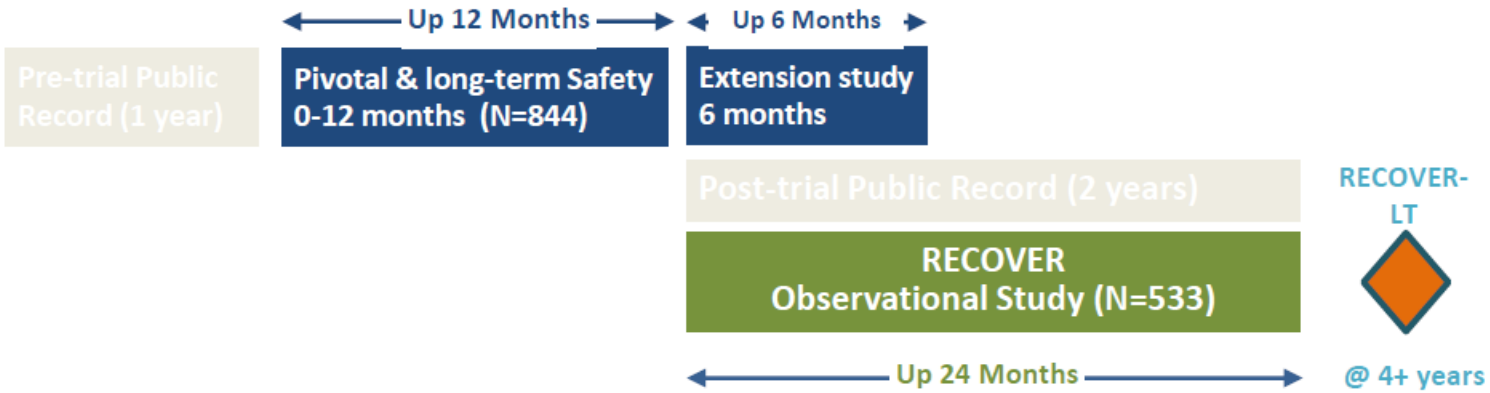
BUP-XR: SUPERIORITA' VS STANDARD OF CARE (SoC)



Marsden J, Kelleher M, et al. Superiority and cost-effectiveness of monthly extended-release buprenorphine versus daily standard of care medication: a pragmatic, parallel-group, open-label, multicentre, randomised, controlled, phase 3 trial. EClinicalMedicine. 2023 Nov 17;66:102311

DAI TRIAL AL REAL WORLD

STUDIO **RECOVER** (REMISSION FROM CHRONIC OPIOID USE – STUDYING ENVIRONMENTAL AND SOCIO-ECONOMIC FACTORS ON RECOVERY)



Measures collected over a 2-year period and at 4 years

Substance Use	Lifestyle	Health	Community
• Self-reported opioid use • Opioid craving • Opioid withdrawal • SUD/OUD treatment utilization • Overdose history • Treatment Effectiveness Assessment: Substance Use	• Marital status/Education • Delay discounting • Household chaos • Stressful life events • Treatment Effectiveness Assessment: Responsibilities • WHO Quality of Life: Environment	• Depression (BDI-II) • Psychological distress • Sheehan Disability Scale • WHO Quality of Life: Physical and Psychological • Treatment Effectiveness Assessment: Health • Healthcare utilization	• Family/social relationships • WHO Quality of Life: Social Relationships • Employment • Self-reported crime • Know someone who is symptomatic

"When taken together, these results highlight that participants reported high levels of psychosocial functioning, improvements in lifestyle, health, and community measures, and high rates of abstinence from opioid drugs".

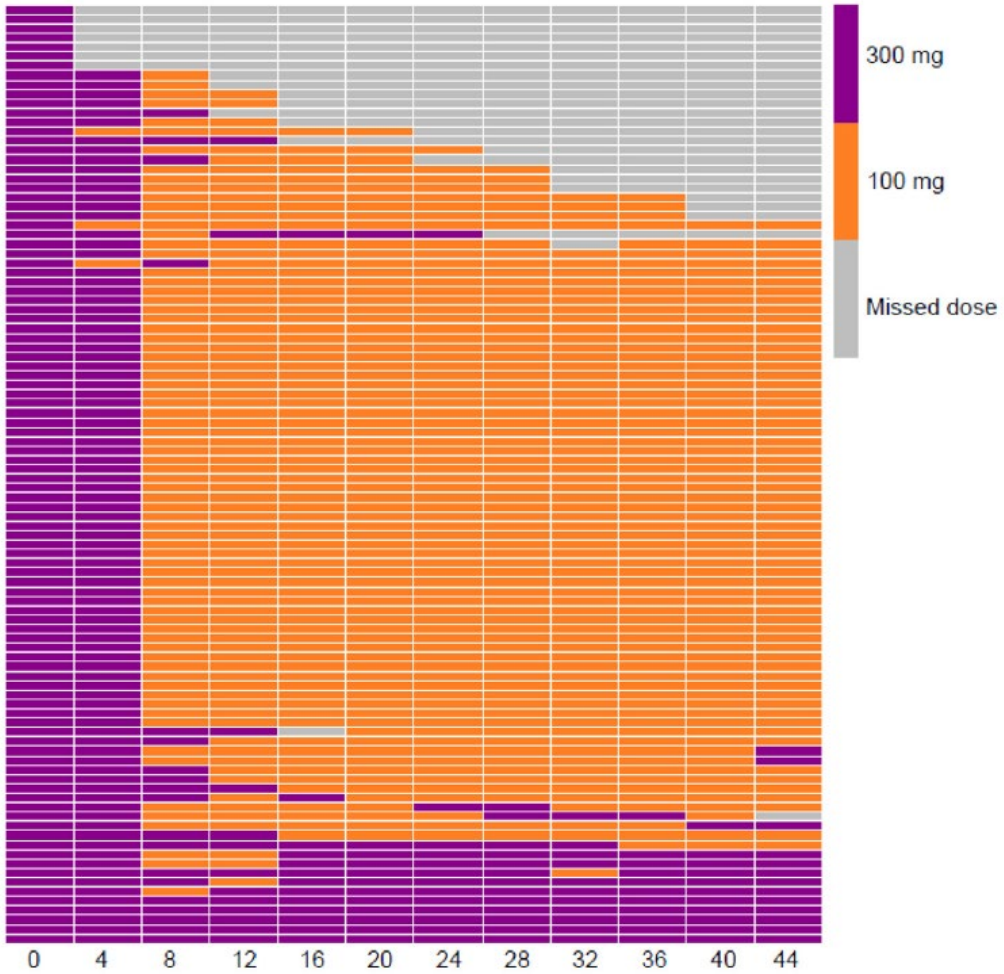
Frank Gray. Sublocade®, from the clinic into the real world. ATHS October 19-22, 2021. Craft WH, Tegge AN, Keith DR, Shin H, Williams J, Athamneh LN, Stein JS, Chilcoat HD, Le Moigne A, DeVeaugh-Geiss A, Bickel WK. Recovery from opioid use disorder: A 4-year post-clinical trial outcomes study. Drug Alcohol Depend. 2022 May 1;234:109389

STUDIO COLAB (COMMUNITY LONG-ACTING BUPRENORPHINE)

High retention rates were observed (primary endpoint)

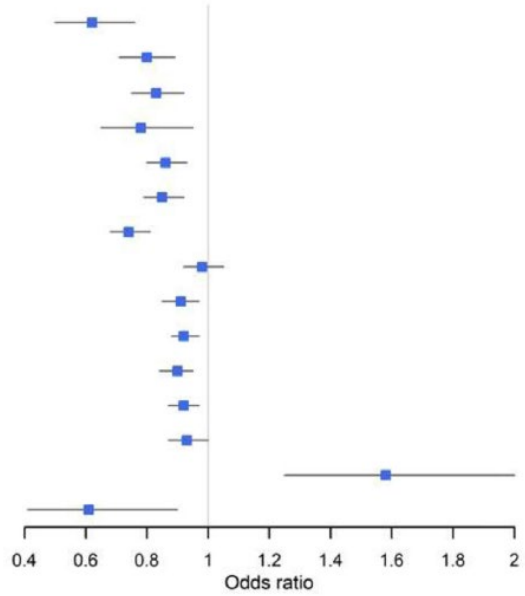
12 months	75%
6 months	86%

The odds of use of all surveyed illicit substances in a given month decreased significantly with time retained in BUP-XR, except for cannabis



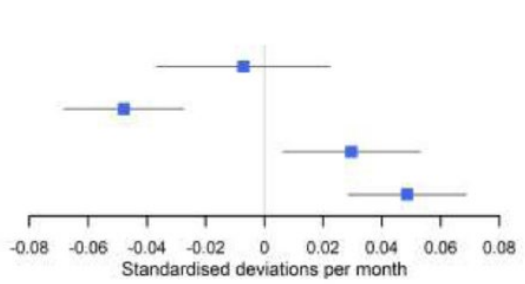
a

	OR	Conf Int 95%
Opioid craving	0.62	0.5-0.76
Heroin	0.80	0.71-0.89
Other opioids	0.83	0.75-0.92
Cocaine	0.78	0.65-0.95
Amphetamine	0.86	0.80-0.93
Stimulants	0.85	0.79-0.92
Injecting drug use	0.74	0.68-0.81
Cannabis	0.98	0.92-1.05
Benzodiazepines	0.91	0.85-0.97
Any illicit drug	0.92	0.88-0.97
Daily tobacco	0.90	0.84-0.95
Alcohol	0.92	0.87-0.97
Moderate-severe depression	0.93	0.87-1.00
Employed last month	1.58	1.25-2.00
Satisfied with medication (5+)	0.61	0.41-0.90



b

	β_{std}	Conf Int 95%
Medication satisfaction	-0.01	-0.04-0.02
Pain score	-0.05	-0.07--0.03
Quality of life	0.03	0.01-0.05
Global treatment satisfaction	0.05	0.03-0.07



Farrell M, Shahbazi J, Byrne M, Grebely J, Lintzeris N, Chambers M, Larance B, Ali R, Nielsen S, Dunlop A, Dore GJ, McDonough M, Montebello M, Nicholas T, Weiss R, Rodgers C, Cook J, Degenhardt L; CoLAB study team. Outcomes of a single-arm implementation trial of extended-release subcutaneous buprenorphine depot injections in people with opioid dependence. Int J Drug Policy. 2022 Feb;100:103492

REAL WORLD: INMATES TREATMENT WITH BUP-XR

Table 2. Acceptability, Feasibility, and Postrelease Comparative Outcomes

Characteristics	Participants, No. (%)			
	XRB (n = 26)	95% CI	SLB (n = 26)	95% CI
Received assigned study medication	24 (92)	NA	26 (100)	NA
Received assigned study medication prior to release as scheduled	21 (81)	NA	26 (100)	NA
Jail medical clinic visits following study medication induction, mean (SD), visits/d	0.11 (0.03)	0.05-0.16	1.06 (0.08)	0.88-1.23
Retained on any form of community buprenorphine treatment at week 8	18 (69)	50-84	9 (35)	19-54
Retained on assigned treatment at week 8	15 (58)	39-74	9 (35)	19-54
Weeks on buprenorphine treatment, mean (SD)	6.1 (3.5)	4.7-7.5	2.6 (3.2)	1.3-3.9
XRB participants who switched back to SLB postrelease	7 (27)	14-46	NA	NA
Urine samples opioid-negative[a]	72 (55.4)	47-64	50 (38.5)	30-47
Reincarcerated	2 (8)	2-24	4 (15)	6-34

Lee JD, Malone M, McDonald R, Cheng A, Vasudevan K, Tofighi B, Garment A, Porter B, Goldfeld KS, Matteo M, Mangat J, Katyal M, Giftos J, MacDonald R. Comparison of Treatment Retention of Adults With Opioid Addiction Managed With Extended-Release Buprenorphine vs Daily Sublingual Buprenorphine-Naloxone at Time of Release From Jail. JAMA Netw Open. 2021 Sep 1;4(9):e2123032

REAL WORLD: NON FATAL OVERDOSE

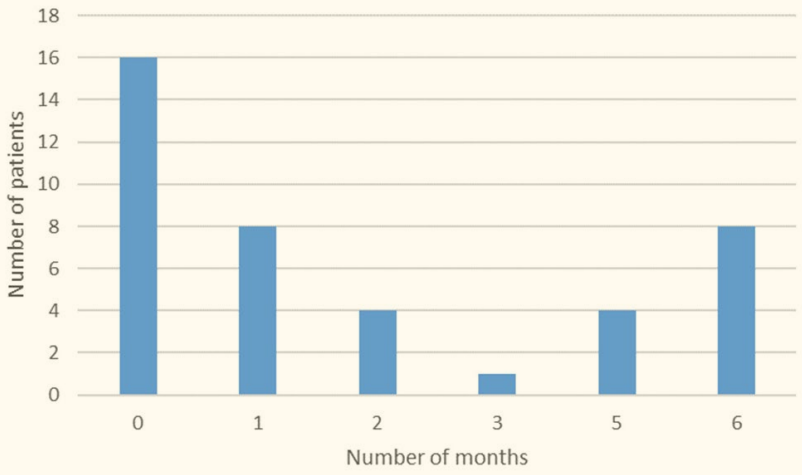
TABLE 3. Nonfatal Overdose during Follow-Up by Intended Treatment Cohort

	BUP-XR (n = 128)	BUP-SL (n = 139)	MET (n = 112)	Total (N = 379)
Patient-reported NF-OD events	1	10	18	29
Incidence rate (N events per 100 person-years)	1.7	19.3	46.8	19.6
Patients with ≥1 NF-OD event	1 (0.8%)	8 (5.8%)	12 (10.7%)	21 (5.5%)
Subgroup analysis, n/m (%)				
History of injectable opioid/illicit drug use	1/61 (1.6%)	7/62 (11.3%)	12/89 (13.5%)	20/212 (9.4%)
History of patient-reported NF-OD events	1/57 (1.8%)	8/36 (22.2%)	9/26 (34.6%)	18/119 (15.1%)
Comparison to BUP-XR cohort: proportion of patients who experienced NF-OD event				
Unadjusted difference, % (95% CI)		5.05 (0.84, 9.27) $P = 0.0189$	10.02 (4.05, 16.00) $P = 0.0010$	
Risk-adjusted* difference, % (95% CI)		6.51 (1.46, 11.56) $P = 0.0115$	8.59 (3.10, 14.08) $P = 0.0022$	

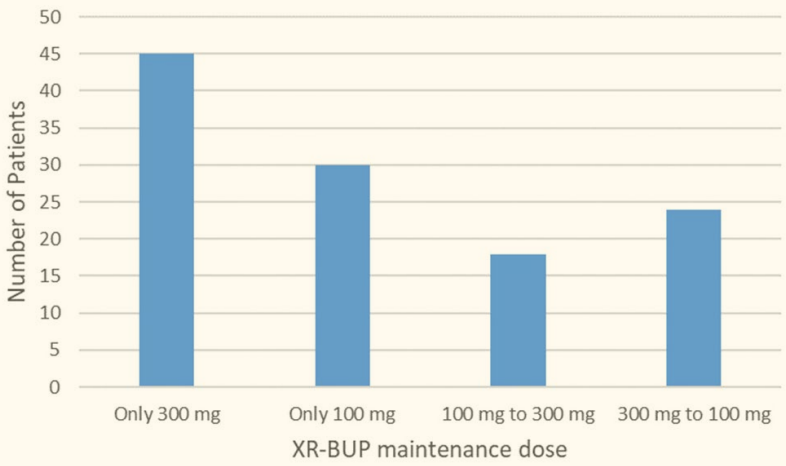
Lee K, Zhao Y, Merali T, Fraser C, Kozicky JM, Mormont MC, Conway B. Real-world Evidence for Impact of Opioid Agonist Therapy on Nonfatal Overdose in Patients with Opioid Use Disorder during the COVID-19 Pandemic. J Addict Med. 2023 Nov-Dec 01;17(6):e374-e381

REAL WORLD: HARM REDUCTION SETTING

Months on supplemental SL-bup in patients who received 6 BUP-XR injections (*n* = 41)



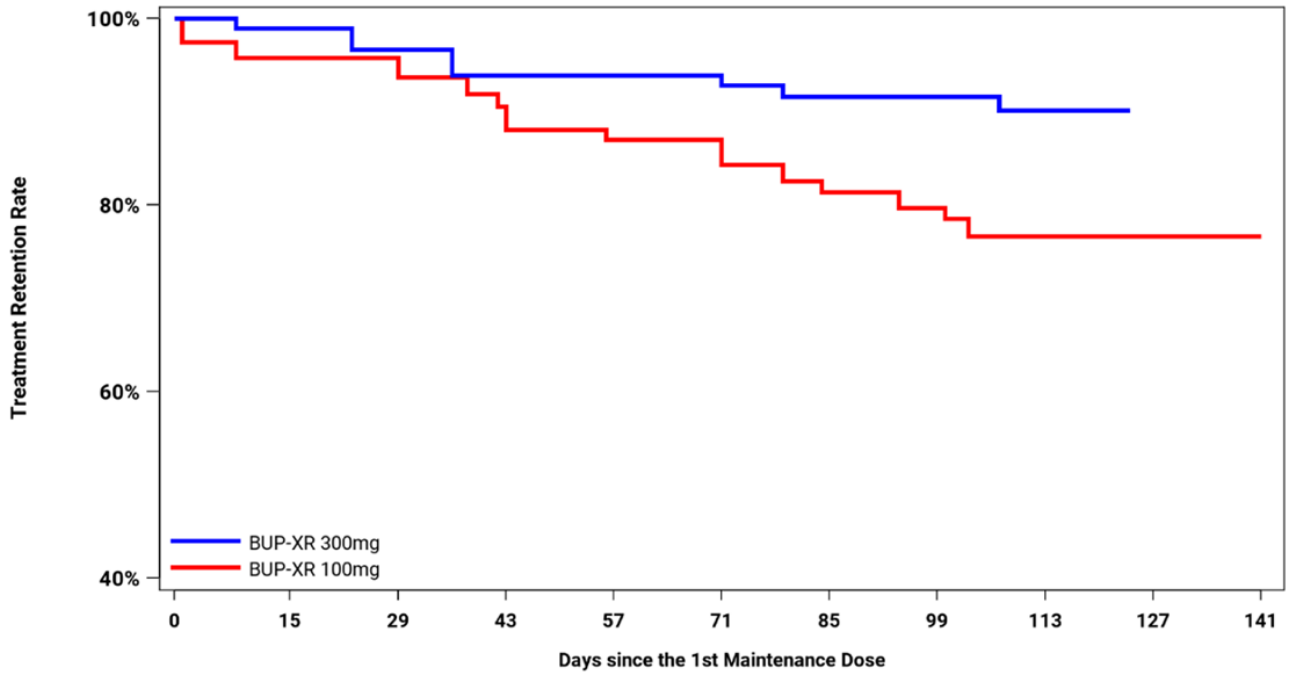
BUP-XR maintenance doses in patients who received >2 doses (n = 72)

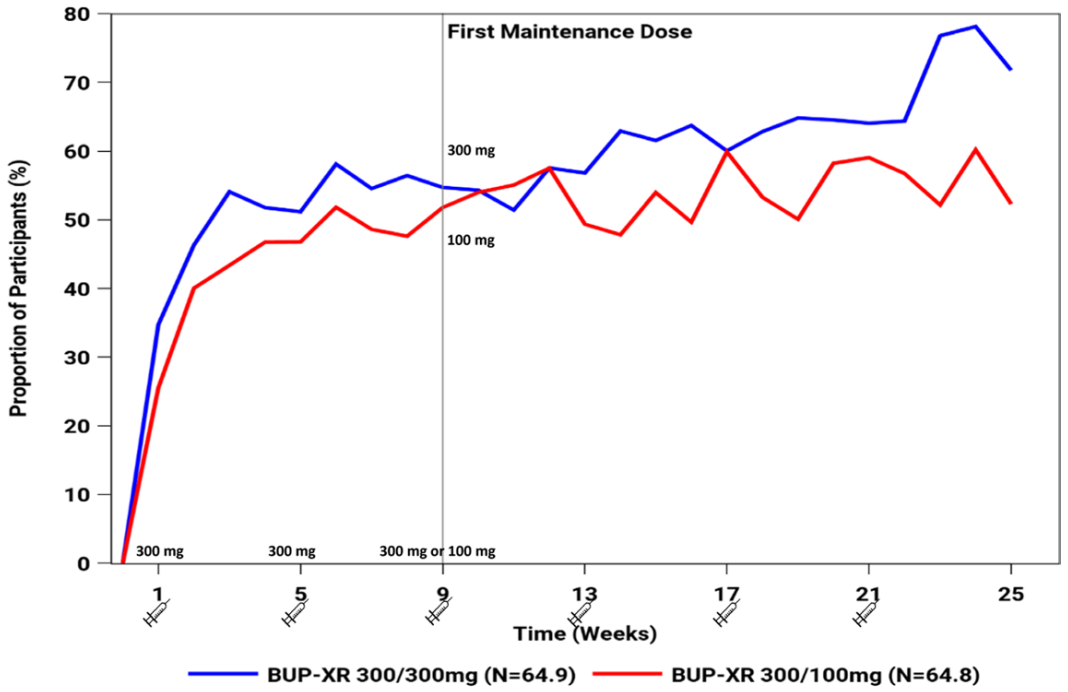


"*XR-BUP improved 6-month treatment retention and resulted in a greater proportion of opioid-negative urine toxicology tests compared to a comparison group of patients who were prescribed but did not initiate XR-BUP. Patients with unstable OUD had lower odds of XR-BUP initiation, suggesting the need for targeted interventions to increase XR-BUP uptake in this high-risk population*".

Heil J, Salzman M, Hunter K, Baston KE, Milburn C, Schmidt R, Haroz R, Ganetsky VS. Evaluation of an injectable monthly extended-release buprenorphine program in a low-barrier specialty addiction medicine clinic. J Subst Use Addict Treat. 2024 Jan;156:209183

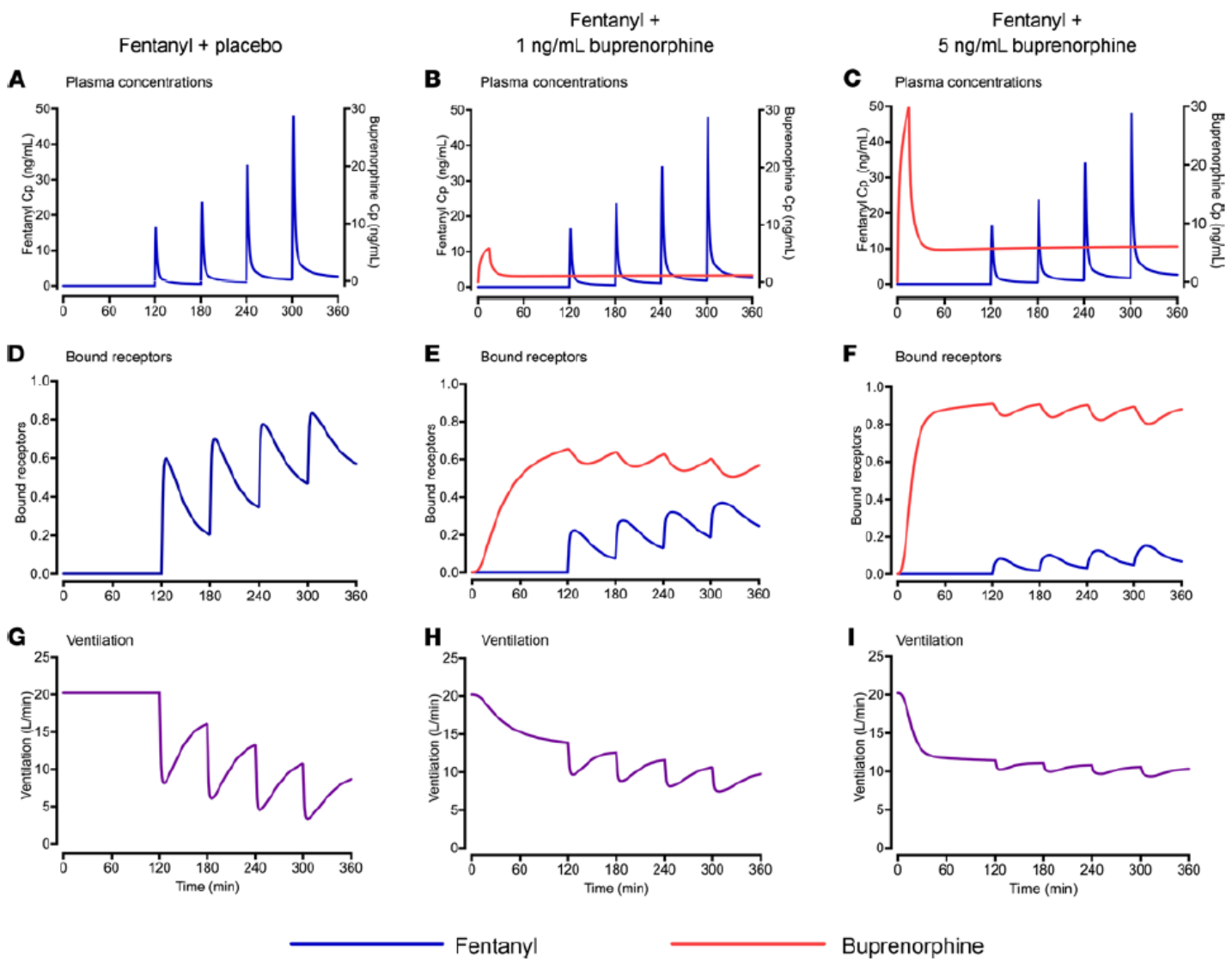
POPOLAZIONI A RISCHIO: INJECTING DRUG USERS

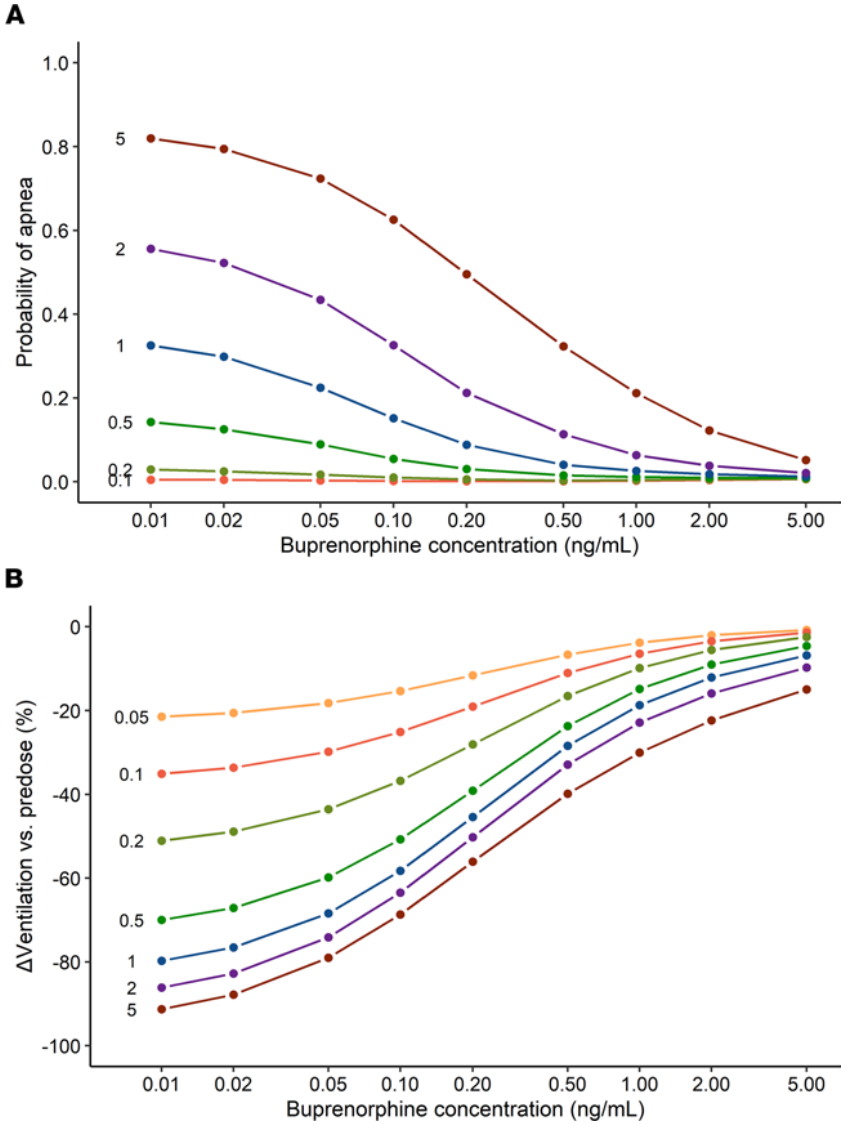




Greenwald MK, Wiest KL, Haight BR, Laffont CM, Zhao Y.
Examining the benefit of a higher maintenance dose of extended-release buprenorphine in opioid-injecting participants treated for opioid use disorder. Harm Reduct J. 2023 Dec 2;20(1):173

POPOLAZIONI A RISCHIO: FENTANYL





Olofsen E, Algera MH, et al. Modeling buprenorphine reduction of fentanyl-induced respiratory depression. JCI Insight. 2022 May 9;7(9):e156973

CONCLUSIONI

- Certezza dell'assunzione
- Dosaggio bloccante dalla prima somministrazione
- Controllo dei sintomi astinenziali e del craving
- Dosaggio 300/300 mg efficace in popolazioni a rischio
- Azzeramento misuso, diversione, overdose accidentale
- Effetti avversi sovrapponibili alle formulazioni orali
- Le reazioni locali non limitano il trattamento
- Sicurezza all'uscita da contesti protetti
- Riduzione dello stigma e del carico per i pazienti

Speaker's personal opinion

GRAZIE!

BUPRENORFINA A RILASCIO PROLUNGATO MENSILE: SVILUPPO CLINICO ED EVIDENZE DAL REAL WORLD

sarah.vecchio@asl.novara.it