EXPO STUDY

EXTENDED-RELEASE PHARMACOTHERAPY FOR OPIOID USE DISORDER STUDY

EXtended-release Pharmacotherapy for Opioid Use Disorder. The EXPO study

John Marsden, King's College London, United Kingdom

LISBON ADDICTIONS
Oral Presentation
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NHS South London and Maudsley NHS Foundation Trust
NHS Birmingham and Solihull Mental Health NHS Foundation Trust
NHS Greater Manchester Mental Health NHS Foundation Trust
NHS Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust
NHS Tayside

Affiliations, disclosures and acknowledgement

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Affiliations

- Professor of Addiction Psychology, Institute of Psychiatry, Psychology & Neuroscience (IoPPN)
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- Clinical Academic Consultant for Centre for Clinical Trials Network, NIDA

Disclosures

- Beckley PsyTech sponsored study of 5-MeO-DMT-assisted treatment for AUD (202-2023)
- Educational grant funding from Indivior for EXPO study of BUP-XR (2019-2022)
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Acknowledgement

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EXPO team

Co-Investigators

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Kind acknowledgement to Profs Richard Holland (Chair TSC)
And Tim Millar (Chair DMC)

Limitations of OAT standard-of-care…

- *Many service users do not stay for as long as they – or we – would hope*

  (English cohort study: 41,928 people admitted in England (2018-19), 16,477 (39.3%) left by 12 weeks **1**)

- *Early non-response predicts continued non-response*

  (US RCT: 95 [26.4%] of 360 service users were using non-medical opioids after 2 weeks of maintenance **2**)

- *Response is often sub-optimal during maintenance*

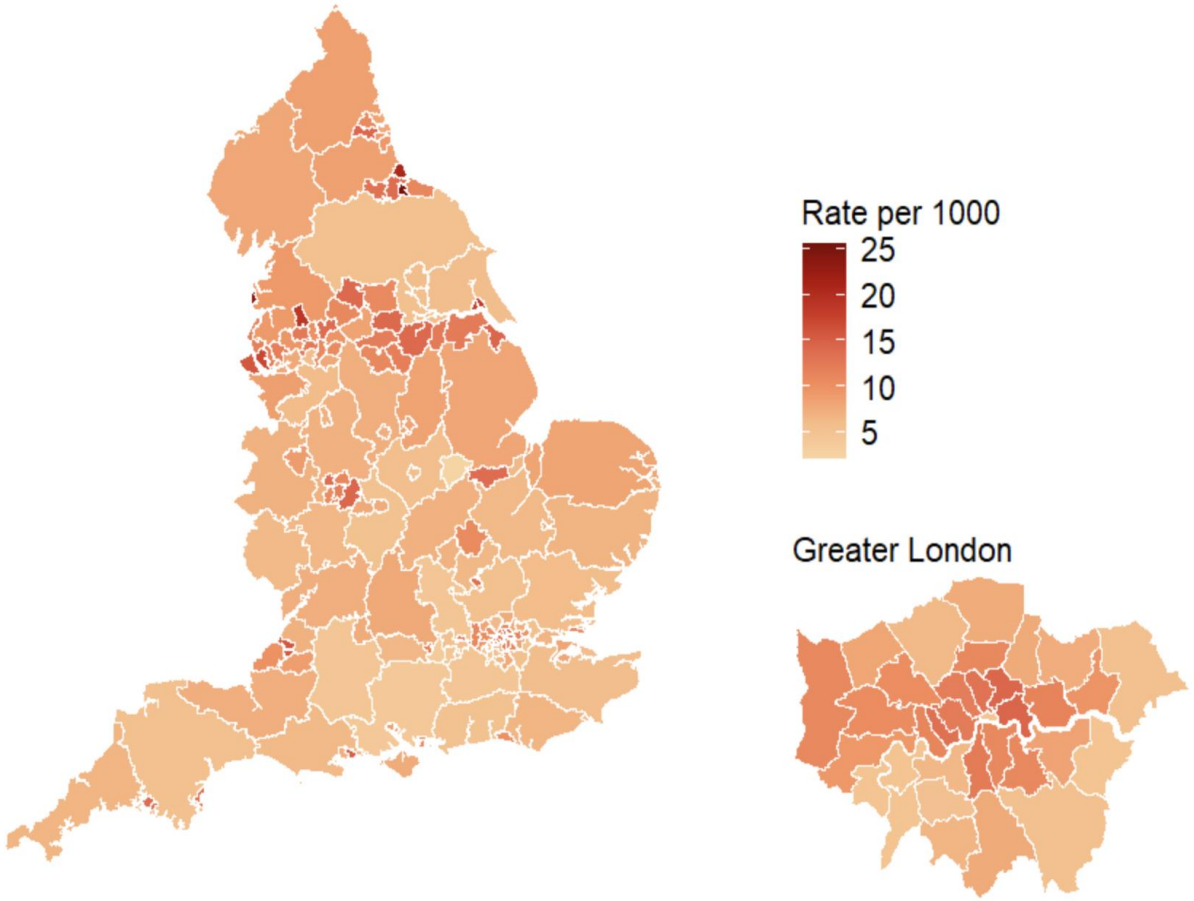
  (In an England study of 21,075 people, 37% abstinent after 6 months; 33% if using cocaine at admission **3**)

- *Even among the long-term retained, non-response is common*

  (English cohort study: 7,719 people retained for 5 years, 15% started well but then relapsed after 6 months, and a further 22% did well but then relapsed after 2.5 years **4**)

1 English National Drug Treatment Monitoring System; **2** McDermott et al. J Clin Psychiatry 2006; 76:189–94;
3 Marsden et al Lancet 2009; 374:1269–1270; **4** Adapted from Eastwood B, et al. *J. Drug Alcohol Depend* 2018;188:200–8.

Opioid and cocaine use disorder in England



2016–2017

- 261,000 people with opioid use disorder (OUD)[1]
- 180,000 people with cocaine use disorder (CUD)[1]
- Of 11,000 in treatment for CUD in EU, 65% from UK [2]

2019–2020

- 141,000 people in treatment [3]

Opioid agonist/partial agonist treatment:

- Specialist NHS clinics
- Primary care (GP practices)
- NGO services
- Retail pharmacies dispense medication

OAT, opioid agonist treatment for opioid use disorder

1. Hay et al. Available at: https://www.gov.uk/government/publications/opiate-and-crack-cocaine-use-prevalence-estimates-for-local-populations; 2. UK Focal Point. Available at: https://www.gov.uk/government/publications/united-kingdom-drug-situation-focal-point-annual-report/uk-drug-situation-2019-summary#main-drugs-used-in-the-uk; 3. Public Health England. November 2020. Available at: https://www.gov.uk/government/statistics/substance-misuse-treatment-for-adults-statistics-2019-to-2020/adult-substance-misuse-treatment-statistics-2019-to-2020-report

Buprenorphine medications for treatment of OUD

BUP-SL: Sublingual tablet [or film/wafer] buprenorphine *
Standard of care

BUP-SD: Subdermal implant depot buprenorphine
1 investigational medicinal product

BUP-XR: Subcutaneous injectable depot buprenorphine
2 investigational medicinal products:
a. CAM-2038 (Buvidal®)
b. RBP-6000 (Sublocade®; Subutex PRO®)

BUP, buprenorphine; SL, sublingual; SD, subdermal; XR, extended-release. * Mono BUP, or combination (4:1) with naloxone [Suboxone]

Long-acting depot buprenorphine – rationale and status before EXPO

- Break cycle of perceived stigmatizing attendance
- Simple dosing for patients
- Opioid blockade giving control of craving and subjective effects of opioid use
- Has received strong endorsement by patients
- Option for certain patients, but not for all [1]

- BUP-SD discontinued in the US [2]
- 2 long-acting products (CAM-2038 licensed in UK; RBP-6000 under MHRA review)
- CAM-2038 non-inferior to BUP-SL[3]
- **There has been no efficacy evaluation of BUP-SL and methadone and Sublocade**
- **EXPO is the first head-to-head efficacy evaluation**

BUP, buprenorphine; EXPO, extended-release pharmacotherapy for opioid use disorder; MHRA, Medicines and Healthcare products Regulatory Agency; SD, subdermal; SL, sublingual; US, United States; XR, extended release.

1. Speaker's views; 2. Titan Pharmaceuticals. Probuphine Notice. October 2020. Available at: https://www.titanpharm.com/Probuphine_Notice_October_2020 (Accessed October 2022);
3. Lowfall et al. 2018:178(6):764-773. doi:10.1001/jamainternmed.2018.1052.

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EXtended-release Pharmacotherapy for Opioid use disorder study

EXPO study: an open-label randomised controlled trial

Interventions [1]

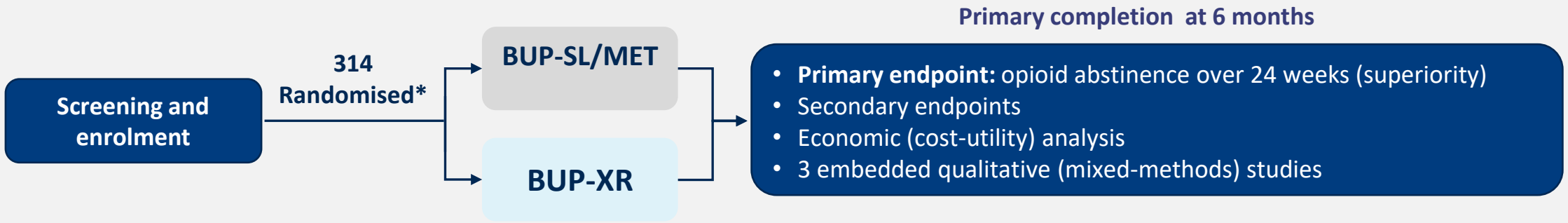
Standard of care (BUP-SL/MET)

- All forms of transmucosal buprenorphine
- Methadone
- Dose titrated to clinical effect

BUP-XR *(Sublocade®)*

- Loading dose: two 300 mg doses 1 month apart (≥ 21 days)
- Maintenance: 100 mg or 300 mg monthly
- Rescue sublingual buprenorphine at any time after first dose of BUP-XR

Study schema[2]



Schematic produced from EXPO Clinical Trial Protocol

*90% powered target sample was 304 participants

1 Marsden J et al. *Trials* 2022;23:697; 2. EXPO Clinical Trial Protocol, EudraCT number: 2018-004460-63.

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EXPO, extended-release pharmacotherapy for opioid use disorder.
Marsden J, et al. *Trials* 2022;23:697 https://doi.org/10.1186/s13063-022-06595-0mark

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EXPO Sublocade medication supply chain

USA manufacture and QP release

amri
Complex Science. Expert Solutions.

Sharp USA

Cold chain

Sharp UK

Sharp Clinical
Powys, Wales

Pharmacy

Local transit

Cold Chain Cooler Box
(internal temp. 2-8 C)

Clinic storage

CD, locked
temp display fridge in
secure locked room

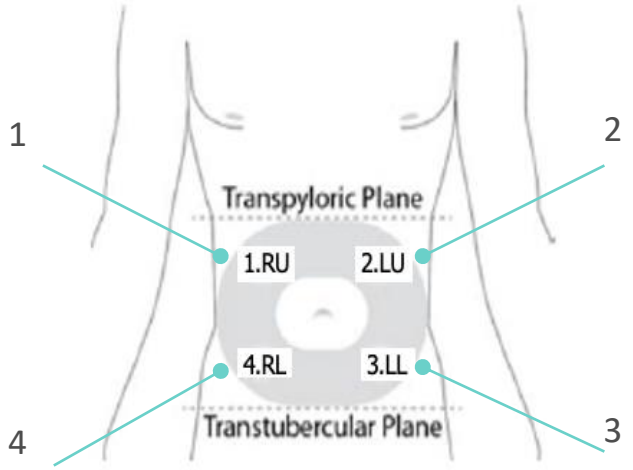
Logistics:

1. IMP is cold-chain protected
2. Cold chain transit to clinic fridge
3. IMP room temp (15 mins) before use
4. IMP used within 7 days or destroyed *

* modified for 2 x re-fridged if not used

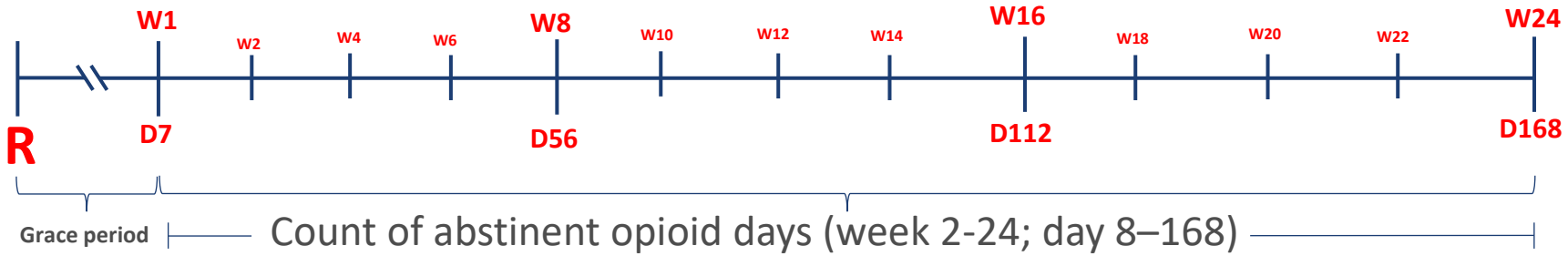
EXPO: BUP-XR dosing schedule

INJECTION	DAY	WEEK	WINDOW (days)	Dose (mg)
1	1	Baseline	-	300
2	28	4	21-42	300
3	56	8	54-70	100 or 300
4	84	12	82-98	100 or 300
5	112	16	110-126	100 or 300
6	140	20	138-168	100 or 300



Dose 3–6 could be adjusted according to symptom control, preference, and safety

Primary outcome



R Randomisation
W study week
D study day

Outcome measured by:

- Timeline Follow-back interview at visit every study week (recall period 14 days, but could be up to the maximum valid recall period for this interview method [i.e. 90 days]) [1]
- Point-of-care Urine Drug Screen (UDS) at visits from week 2 (12 tests)
- If UDS positive for opioids day of test and previous 2 days marked as using days
- UDS always trumped self-report
- Primary outcome ranged from 0–161 days

[1] Participants received local agreed payments for visits to complete research measures to offset travel costs and time

Secondary clinical outcomes, include:

Retention

- Days enrolled in OAT from weeks 2-24 (i.e. day 8–168; range 0–161 days; as primary outcome)
- Days from randomisation to first OAT discontinuation (if this occurred)

DSM-5 OUD and cocaine use disorder [CUD] remission

- By SCID-2-RV interview at week 12 and week 24 visit

Craving for opioids and craving for cocaine measured

- By frequency version of Craving Experiences Questionnaire (CEQ-F) at week 4,8,12,16,20,24

Abstinence from cocaine and benzodiazepines

- By TLFB and UDS as for the primary outcome (i.e. day 8-168; range 0–161 days)

Patient Reported Outcome (PRO) and Clinician Reported Outcome (ClinRO) for improvement

- PRO-I and Service Service User Recovery Evaluation (SURE) at week 24
- ClinRO Global Severity Index (GSI-I) at week 24

Who was eligible, took part, and what did they receive?

A Key inclusion/exclusion criteria

- Aged ≥ 18 years
- DSM-5 OUD (moderate–severe) at episode admission
- Enrolled on OAT and can convert to BUP-XR within 7 days
- No clinically significant medical/psychological condition
- No CJS involvement likely to preclude completion
- No recent clinical history of opioid antagonist therapy

B CONSORT trial profile

- 1,752 people identified, 1,366 excluded
- 386 people eligible, and 365 enrolled
- 346 people randomly allocated
- 156 to BUP-SL/MET
- 158 to BUP-XR
- 32 to BUP-SL/MET+PSI or BUP-XR+PSI
- 314 is full analysis set for the head-to-head

C Randomised sample (n=314)

- Mean aged 42 years
- 74% male (84% White-UK)
- 74% in maintenance OAT
- 44% using opioids in past 4 weeks
- 49% using cocaine in past 4 weeks
- 23% using benzodiazepines in past 4 weeks
- 9% non-medical injecting in past 4 weeks

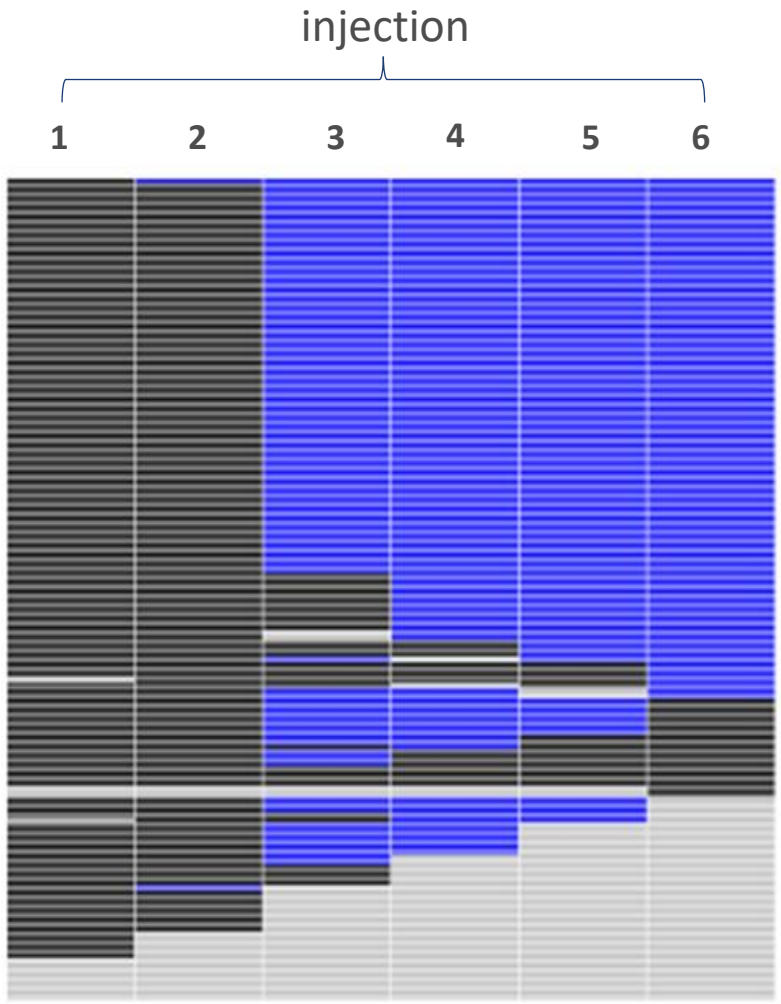
D BUP-SL/MET

- 155 [99.4%] of 156 received allocated treatment
- 71 (45.5%) did not complete follow-up
- 32 (20.5%) had at least 1 restart (56 overall)

BUP-XR

- 150 [94.9%] of 158 received allocated treatment
- 33 (28.9%) did not complete follow-up
- 18 (11.4%) had at least 1 restart (21 overall)

Results – Receipt of BUP-XR (n=158)



- Mean number of injections received was 4·98 (SD 1·84)
- 110 [69·6%] of 158 participants received all 6 injections.
- Most common dosing profile 2 x 300mg and 4 x 100mg (75%)
- 11 participants received 3 x 300mg then 3 x 100mg.
- 4 participants received 6 x 300mg.
- The remaining participants had a mixed pattern

Results – Primary outcome

Primary outcome – mean days abstinent

- BUP-SL/MET 104.9 days
- BUP-XR 123.4 days

  Adjusted IRR 1.18; 95% 1.05–1.33; p-value 0.004

Model is mixed-effects regression with stratification factors (fixed) and treatment centre (random intercept) and multiple imputation for management of missing data.

IRR, interval rate ratio.

Secondary outcomes – Retention in OAT

Days enrolled in OAT from day 8–168

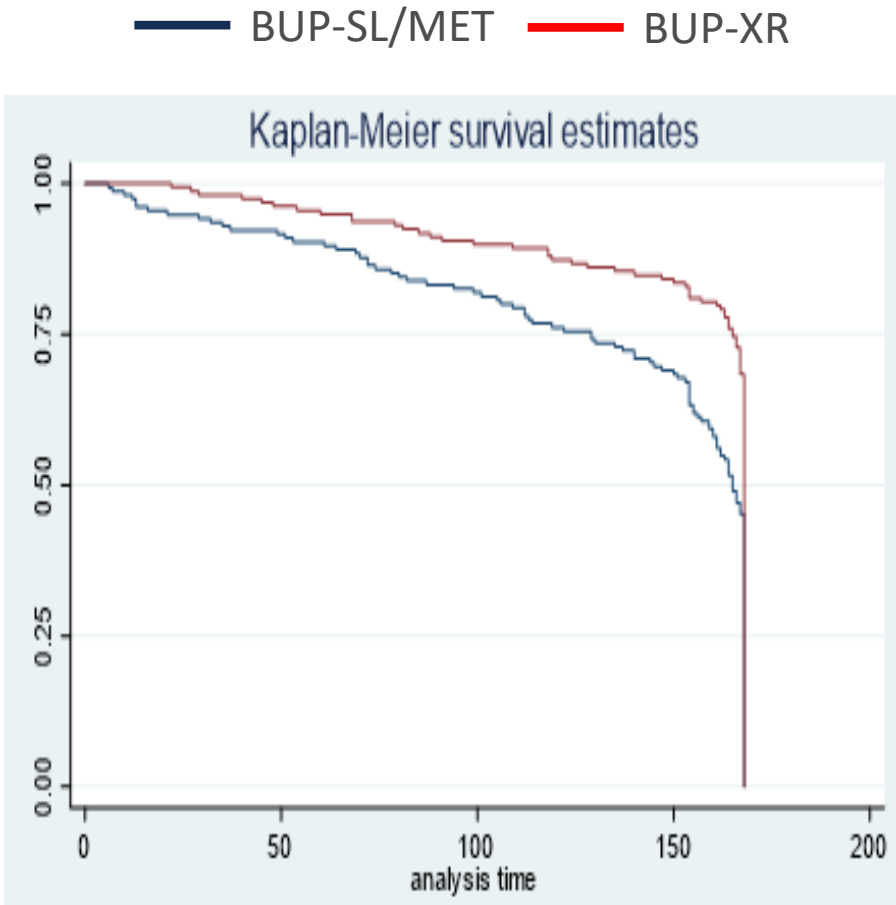
- 128·5 days (SE 4.82) in the BUP-SL/MET group
- 144·6 days (SE 2.54) in the BUP-XR group
- Adjusted IRR 1·12; 95% CI 1·01–1.25; p-value 0·029 *

BUP-XR group retained in more days of study treatment

Days from randomisation to first OAT discontinuation

- 138·2 days (SD 47.7) in the BUP-SL/MET group
- 154·0 days (SD 33.6), in the BUP-XR group
- Adjusted HR 0·46; 95% CI 0·33–0.66; p-value 0·001

BUP-SL/MET group likely to discontinue earlier



IRR, interval rate ratio; HR, hazard ratio;
* Model is mixed-effects regression with stratification factors (fixed) and treatment centre (random intercept)

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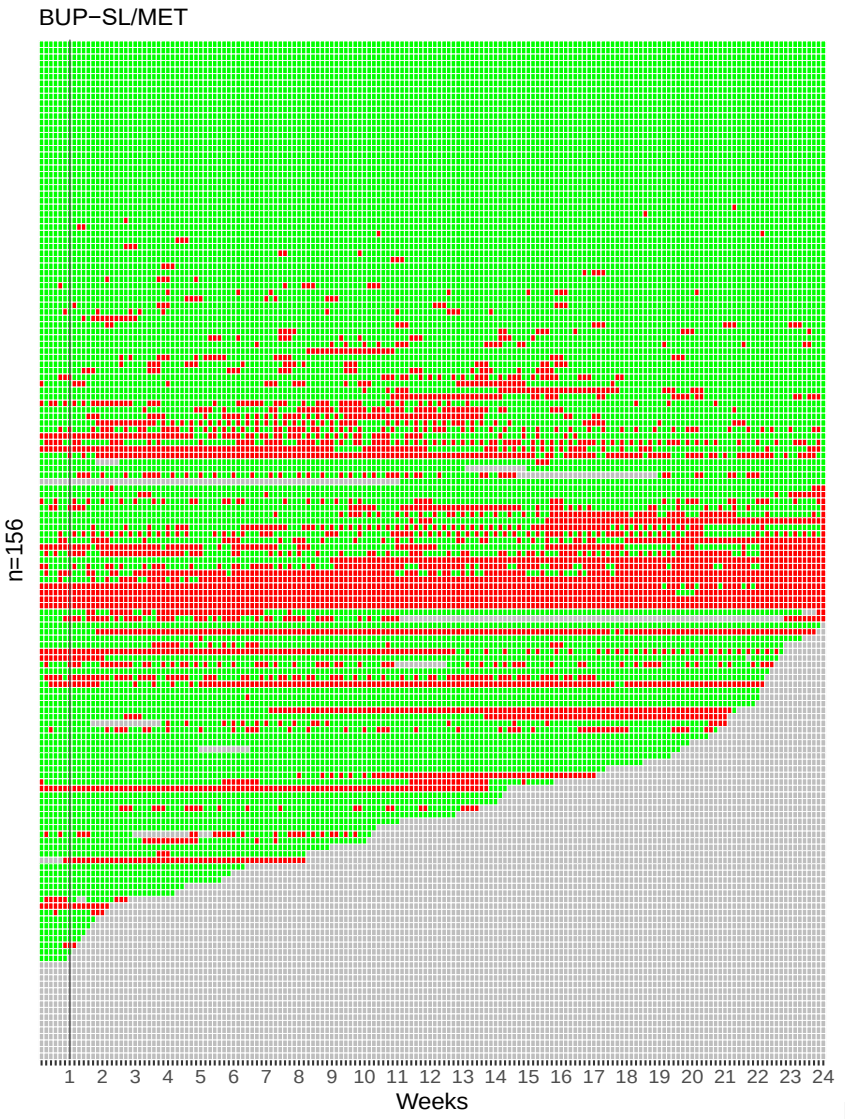
EXPO: Longitudinal course of opioid use for BUP-SL/MET

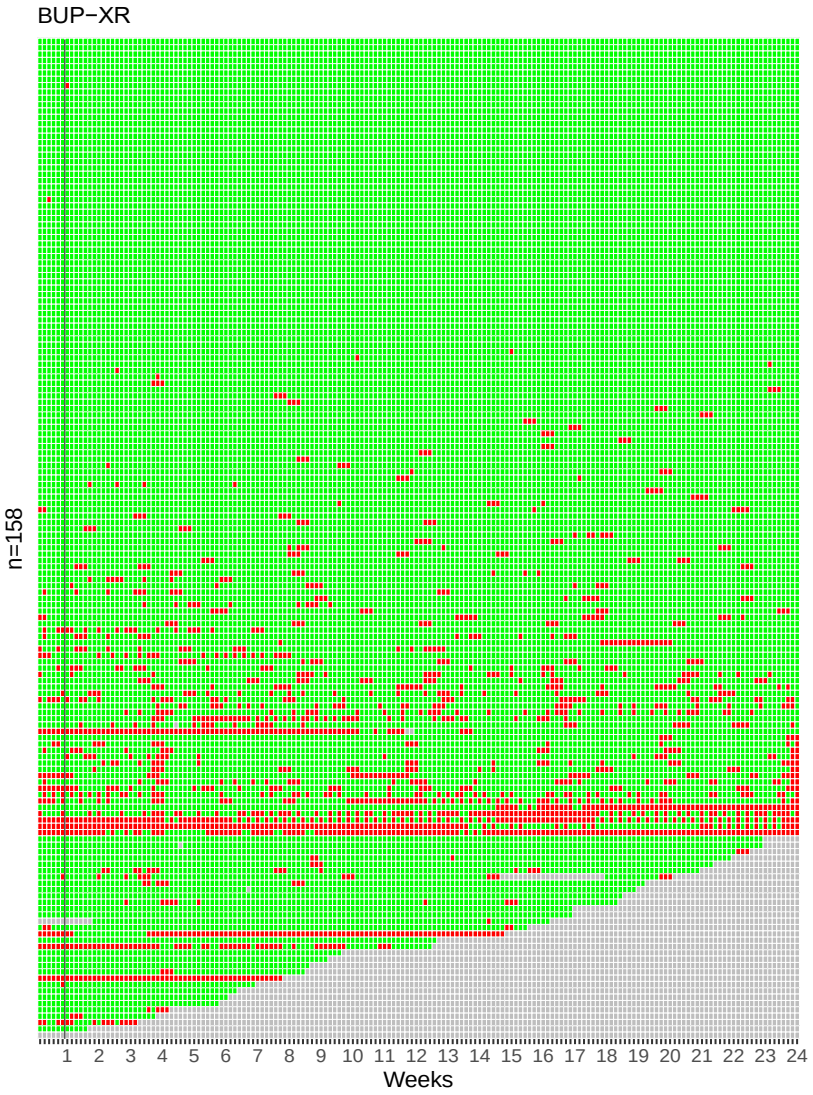


- Each row is data for for one participant from day 1–168.
- The participant rows are ordered by the number of days collected (decreasing), the number of days abstinent, and also whether day 168 was collected
- The vertical black line indicates the 1-week grace period after which primary effectiveness was assessed (days 8–168).
- **GREEN** is a day of opioid abstinence (negative report and available UDS negative).
- **RED** is a day of opioid use (positive report and available UDS positive).
- **GREY** denotes no data for that day (usually due to discontinuation).

Heat map shows:

- Sub-group retained and abstinent
- Larger sub-group retained but with sporadic/repeating opioid use
- Smaller sub-group retained but stably non-responding
- Mixed response among participants who discontinued

EXPO: Longitudinal course of opioid use for BUP-XR

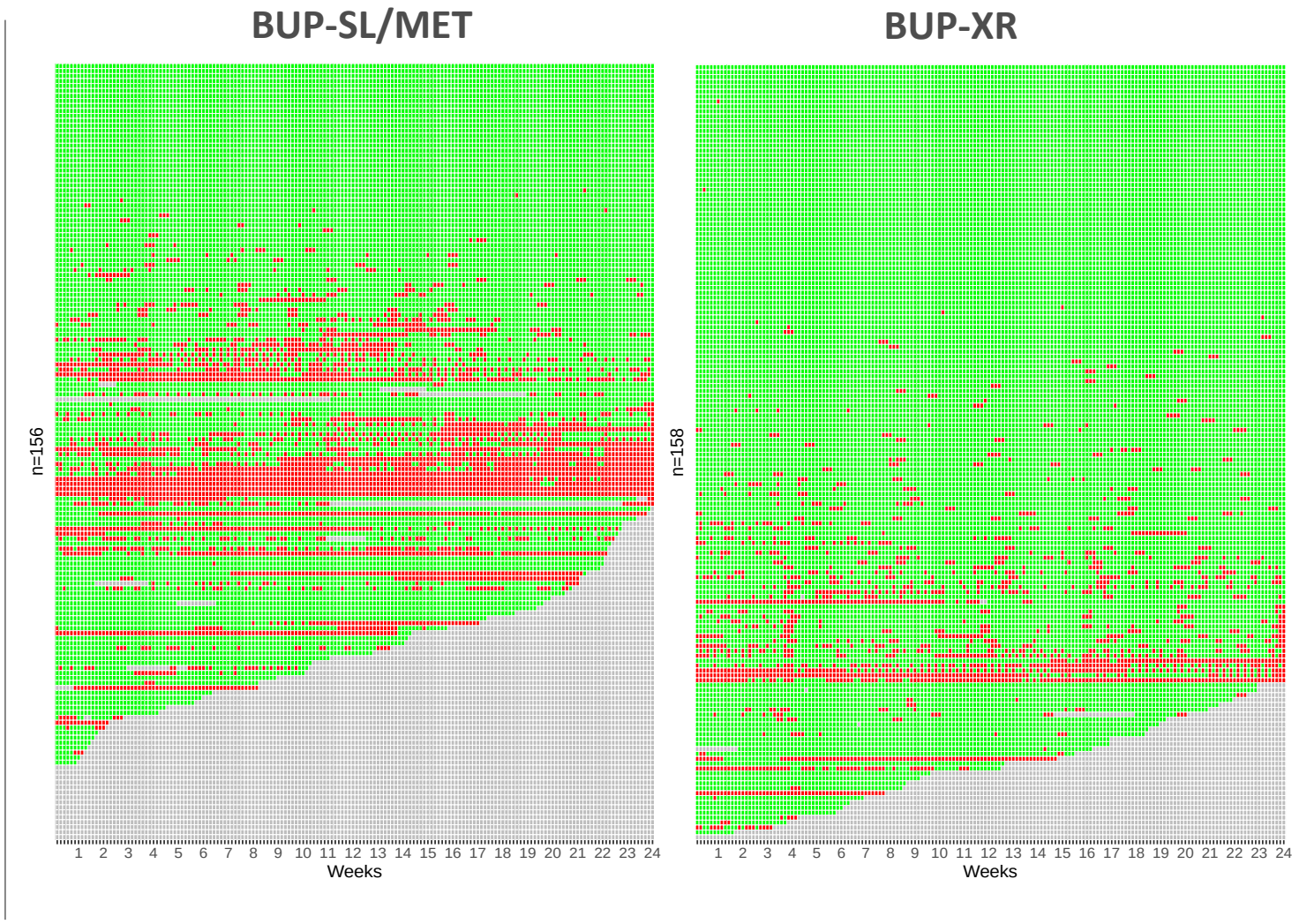


- Each row is data for for one participant from day 1–168.
- The participant rows are ordered by the number of days collected (decreasing), the number of days abstinent, and also whether day 168 was collected
- The vertical black line indicates the 1-week grace period after which primary effectiveness was assessed (days 8–168).
- **GREEN** is a day of opioid abstinence (negative report and available UDS negative).
- **RED** is a day of opioid use (positive report and available UDS positive).
- **GREY** denotes no data for that day (usually due to discontinuation).

Relative to BUP-SL/MET, heat map shows:

- Large sub-group retained and abstinent
- larger sub-group retained but with sporadic opioid use
- Very small sub-group retained but stably non-responding
- Generally abstinent pattern of response among those discontinued

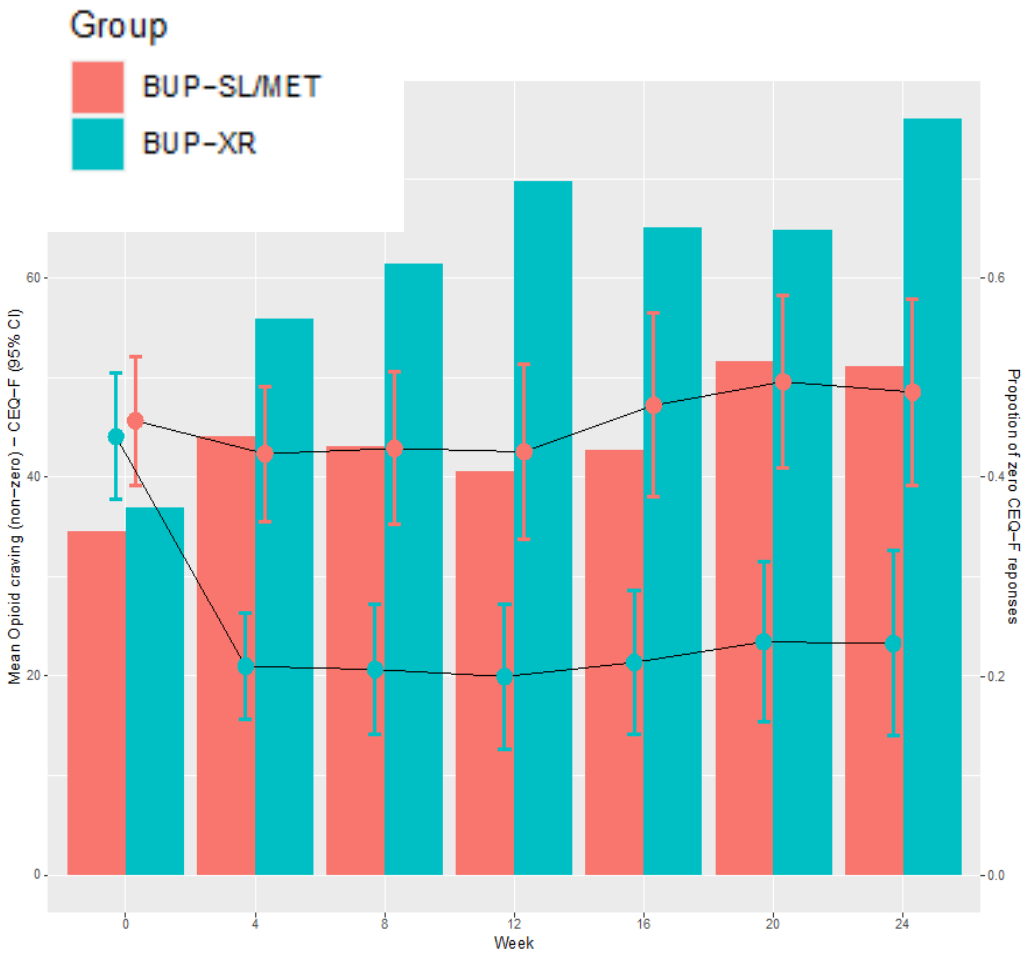
EXPO: Longitudinal course of opioid use by group



Relatively, BUP-XR associated with:

- More retention
- More continuous abstinence
- More retention and occasional opioid use
- Les retention and stable non-response

Secondary outcome – Craving for opioids



- Histogram is % with zero craving response in each group
- Lines are means (95% CI) for participants with non-zero response

BUP-XR

- Histogram shows progressive increase in zero craving *
- Line shows strong initial fall then stable craving frequency **

BUP-SL/MET

- Histogram shows slight increase in zero craving
- Line shows no change in craving frequency

* Adjusted endpoint analysis BUP-XR v BUP-SL/MET: OR 3.22; 95% CI 1.65–6.36; p-value 0.001

** Adjusted endpoint analysis BUP-XR v BUP-SL/MET: IRR 0.52; 95% CI 0.345–0.81; p-value 0.004

Craving measured by Craving Experiences Questionnaire (CEQ-F), score range 0-110

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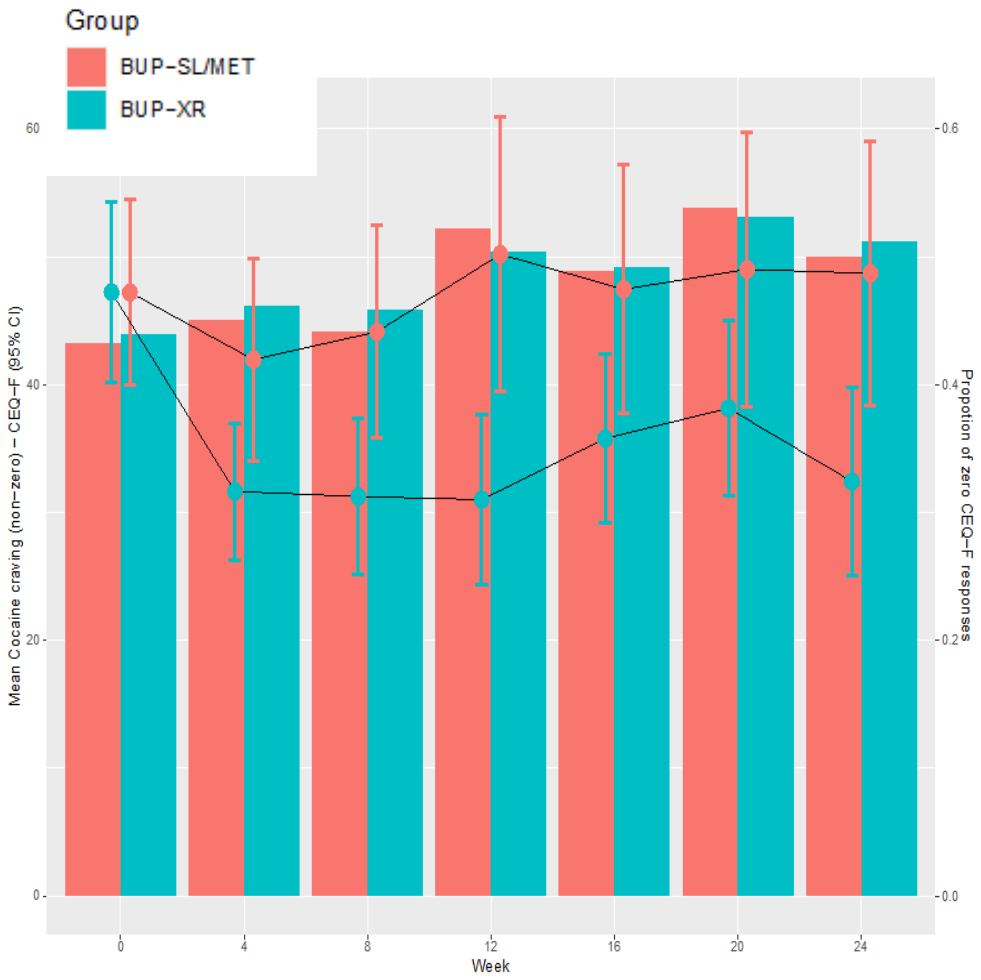
Secondary outcome – Craving for cocaine



- Histogram is % with zero craving response in each group
- Lines are means (95% CI) for participants with non-zero response

BUP-XR

- Histogram shows progressive slight increase in zero craving *
- Line shows initial fall then variable craving frequency **

BUP-SL/MET

- Histogram shows progressive slight increase in zero craving
- Line shows no identifiable change in craving frequency

* Adjusted endpoint analysis BUP-XR v BUP-SL/MET: OR 0.94; 95% CI 0.41–2.166; p-value 0.885

** Adjusted endpoint analysis BUP-XR v BUP-SL/MET: IRR 0.71; 95% CI 0.46–1.10; p-value 0.124

Craving measured by Craving Experiences Questionnaire (CEQ-F), score range 0-110

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Results – Secondary endpoints

Early remission from OUD

- 97 [62.2%] of 156 in BUP-SL/MET
- 119 [75.3%] of 158 in BUP-XR

  Adjusted OR 1.9; 95% CI 1.02–3.52; p-value 0.042

PRO and ClinRO outcomes – BUP-XR effect

- PRO-I Odds Ratio 5.5; 95% CI 2.6–11.5; p-value 0.001
- SURE mean diff. 6.3; 95% CI 3.6–9.0; p-value 0.001
- GSI-I Odds ratio 6.9; 95% CI 3.2–4.9; p-value 0.001

Secondary outcome – mean days abstinent

Cocaine

- BUP-SL/MET 102.9 days
- BUP-XR 112.2 days
- Adjusted IRR 1.09; 95% 0.95–1.25; p-value 0.230

Benzodiazepines

- BUP-SL/MET 115.1 days
- BUP-XR 121.2 days
- Adjusted IRR 1.05; 95% 0.95–1.16; p-value 0.312

EXPO – summary and interpretation

EXPO indicates that BUP-XR (Sublocade®) is superior to the standard of care – achieving:

- More opioid abstinence
- Greater retention and total time in treatment
- Greater likelihood of early remission from OUD
- More craving control for opioids
- More improvement and recovery

EXPO suggests that BUP-XR (Sublocade®):

- Does not significantly impact on craving for cocaine or cocaine use
- Does not significantly impact on benzodiazepine use

The implications from this evidence are:

- BUP-XR (Sublocade®) is a simple and acceptable treatment
- BUP-XR (Sublocade®) is an effective option for OUD symptom control
- OAT adjunctive medications and/or psychosocial interventions are – or novel pharmacotherapies – needed to attenuate cocaine and non-medical benzodiazepine use
- To highlight future study of BUP-XR (Sublocade) as a maintenance-to-taper intervention

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Thank you!

More information:

John Marsden (john.marsden@kcl.ac.uk)

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