# Risk-Adjusted Abstinence Rates Are Higher With Greater Buprenorphine Plasma Exposure Among Patients Who Inject Opioids

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## Introduction

- RBP-6000 (BUP-XR, SUBLOCADE™) is the first once-monthly subcutaneous buprenorphine injection approved in the US for the treatment of moderate-to-severe opioid use disorder (OUD).[1]
- RBP-6000 is given as 2 initial doses of 300 mg followed by maintenance doses of 100 mg or 300 mg.
- The 300/100 mg dosing regimen achieves and maintains buprenorphine plasma concentrations of 2–3 ng/mL necessary to block the subjective effects of exogenous opioids in most subjects.
- The 300/300 mg dosing regimen provides higher concentrations that we hypothesise some patients may need as a function of their drug-use history and clinical condition.
- Post hoc analyses of data from a pivotal 24-week Phase III trial showed higher abstinence responses to RBP-6000 300/300 mg vs. 300/100 mg in injection drug users (IDU).[2]
  - No appreciable differences were observed in non-IDU or other subpopulations defined by demographic or other baseline characteristics.
  - A multivariate linear regression analysis showed that the interaction between IDU (yes/no) and RBP-6000 maintenance dose (300 mg vs. 100 mg) was the only statistically significant interaction term ($P$<0.05).[3]

## Objective

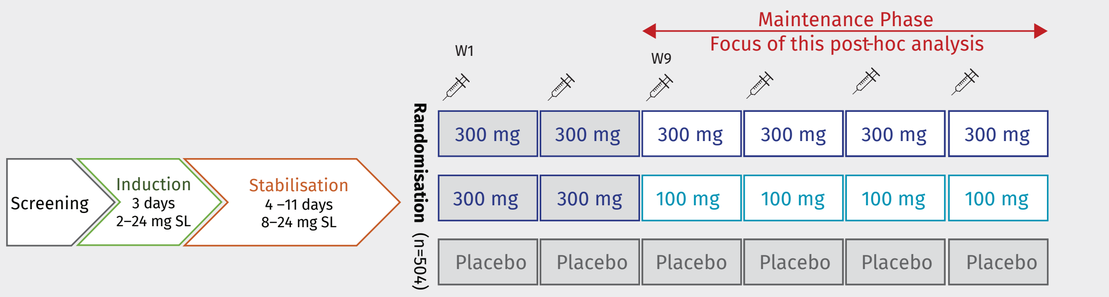
- To further evaluate differential abstinence responses to monthly maintenance doses of RBP-6000 300 mg vs. 100 mg in a population of opioid IDUs, with a focus on times when differences in plasma exposure were the greatest.

## Methods

### Study Design

- Participants were treatment-seeking adults who met the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) criteria for moderate or severe OUD at screening.
- Participants received up to 6 monthly doses of RBP-6000, as well as individual drug counselling (**Figure 1**).

**Figure 1.**




Placebo was volume-matched.
SL=sublingual; W=week.

### Analyses

- Abstinence was defined as opioid-negative urine samples (UDS) combined with negative self-reports (Timeline Followback interviews; TLFB).
  - UDS and self-reports were collected weekly.
  - Missing UDS or TLFB at a specific visit were treated as positive for opioid use for that week.
- Participants' percentage abstinence was calculated during Weeks 10–25 (pre-planned endpoint) and Weeks 21–25 (new endpoint) as the proportion (%) of negative opioid use results among the corresponding 16 and 5 weekly assessments, respectively.
- A Responder was defined as having at least 4 out of 5 (i.e., 80%) weeks of negative opioid use during Weeks 21–25.
- Participants' drug usage was classified based on the most frequent self-reported route of opioid use at screening.
  - Participants whose most frequent route was via injection were classified as IDU, and participants who did not use injection as the most frequent route were classified as non-IDU.
- As this analysis focused on the effect of the 2 maintenance doses, participants randomised to placebo and/or who discontinued prior to the start of maintenance treatment at Week 9 (Injection 3) were excluded.
- The risk-adjusted difference between RBP-6000 100 mg and 300 mg maintenance doses was estimated using inverse probability weighting with propensity score to balance risk factors that could potentially impact the treatment response post Week 9.
  - The risk factors included in the propensity score model ascertained at screening were age, gender, race (black vs. non-black), body mass index, years of opioid use, alcohol user (yes/no), tobacco user (yes/no) and cocaine user (yes/no). The variables ascertained prior to or at Week 9 were subject's percentage cocaine abstinence during Weeks 1–9 (combined UDS and self-reports), last Clinical Opiate Withdrawal Scale (COWS) score, last Opioid Craving Visual Analogue Scale score, employed (yes/no), opioid abstinence (yes/no) at Week 9.
- Buprenorphine pharmacokinetics and exposure-response relationships were evaluated by IDU vs. non-IDU populations.

## Results

### Population

- Of the 164 IDU and 225 non-IDU participants, 130 and 183, respectively, entered the maintenance dose phase and were included in the risk-adjusted analyses.
- **Tables 1** and **2** display the observed summary statistics of the IDU and non-IDU participants who entered the maintenance dose phase.
  - The IDU population included a higher percentage of white subjects (75% IDU, 65% non-IDU) and cocaine users at screening (64% IDU, 41% non-IDU). The mean percentage of cocaine abstinence before the first injection of the maintenance dose (Weeks 1–9) was also lower in the IDU population (56.4%) than in the non-IDU population (79.1%). All other characteristics were similar between the IDU and non-IDU populations.
  - Risk factors were also similar between the RBP-6000 300 mg and 100 mg treatment groups when looking at the IDU and non-IDU populations separately.
    - The distribution of patient risk factors (included in the propensity model) across the 2 maintenance doses was similar.
  - After inverse probability weighting, the difference in covariates was reduced and within 5% of the standardised difference (**Tables 1** and **2**), indicating a good balance of baseline risk factors.

**Table 1. Population Characteristics (Risk Factors Included in the Propensity Model) Before and After Inverse Probability Weighting for Opioid Injectors**

| | Before Inverse Probability Weighting | | After Inverse Probability Weighting[a] | |
|---|---|---|---|---|
| | 100 mg (n=67) | 300 mg (n=63) | 100 mg (n=67) | 300 mg (n=63) |
| Mean age (SD), years | 40.04 (11.81) | 39.57 (11.28) | 39.68 (11.26) | 39.84 (11.32) |
| Male gender, n (%) | 40 (59.7) | 46 (73.0) | 65.9 | 64.7 |
| Race, n (%) | | | | |
| Black | 20 (29.9) | 13 (20.6) | 25.5 | 23.3 |
| White/other | 47 (70.1) | 50 (79.4) | 74.5 | 76.7 |
| BMI, mean (SD), kg/m$^2$ | 24.63 (3.98) | 25.16 (3.75) | 24.93 (4.01) | 24.83 (3.64) |
| Lifetime opioid use (SD), years | 13.25 (12.12) | 12.14 (9.27) | 12.66 (11.76) | 12.20 (9.57) |
| Alcohol user, n (%) | 52 (77.6) | 54 (85.7) | 82.6 | 84.7 |
| Tobacco user, n (%) | 62 (92.5) | 62 (98.4) | 95.3 | 93.3 |
| Cocaine user, n (%) | 46.0 (68.7) | 37 (58.7) | 66.0 | 66.8 |
| Cocaine use during weeks 1–9, % (SD) | 57.38 (44.60) | 55.33 (43.71) | 55.88 (44.04) | 57.67 (43.20) |
| Last COWS, mean (SD)[b] | 1.60 (2.69) | 1.67 (2.26) | 1.63 (2.68) | 1.54 (2.15) |
| Last Opioid Craving VAS, mean (SD)[b] | 4.76 (12.92) | 6.17 (14.41) | 5.56 (14.77) | 5.69 (13.00) |
| Currently employed, n (%)[b] | 32 (47.8) | 34 (54.0) | 50.6 | 52.5 |
| Positive opioid assessment, n (%)[b] | 34 (50.7) | 28 (44.4) | 48.9 | 46.3 |
| Negative opioid assessment, n (%)[b] | 33 (49.3) | 35 (55.6) | 51.1 | 53.7 |

[a]With propensity score to balance risk factors that could potentially impact the treatment response post-Week 9. Only re-weighted percentages are provided.
[b]Last measurement at or before Week 9.
BMI=body mass index; COWS=Clinical Opiate Withdrawal Scale; SD=standard deviation; VAS=visual analogue scale.

**Table 2. Population Characteristics (Risk Factors Included in the Propensity Model) Before and After Inverse Probability Weighting for Opioid Non-injectors**

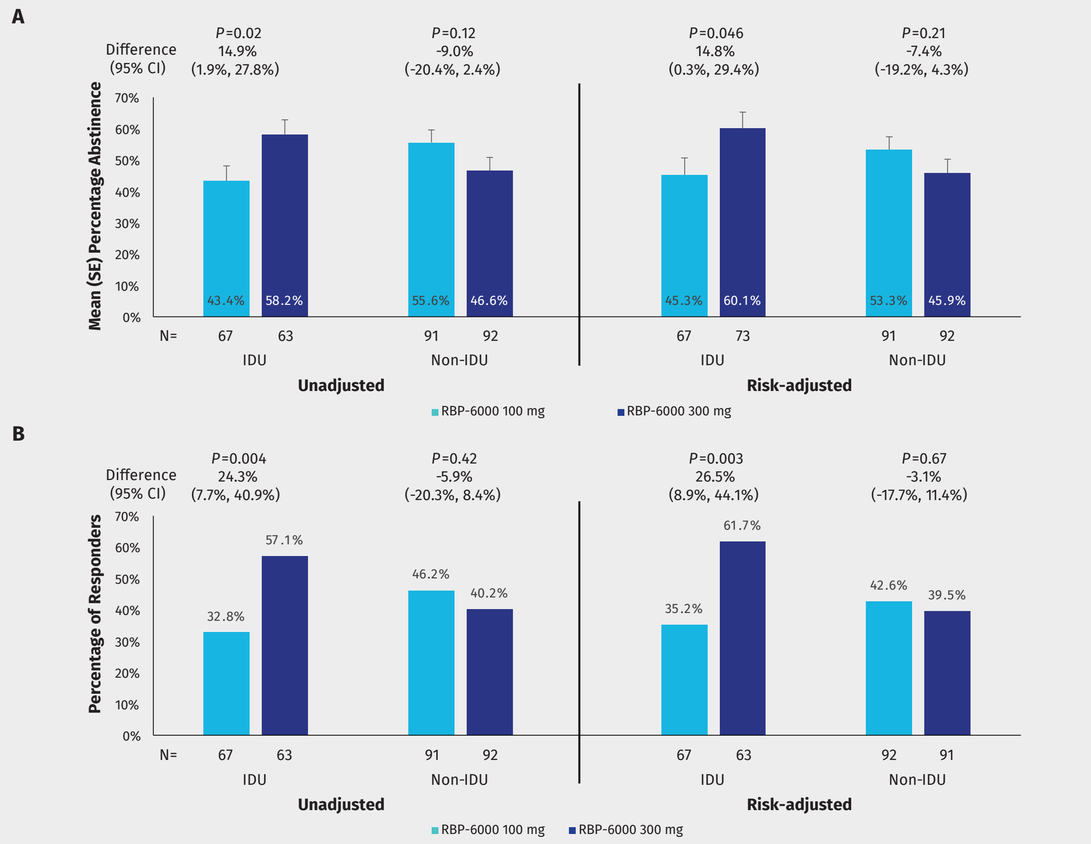
| | Before Inverse Probability Weighting | | After Inverse Probability Weighting[a] | |
|---|---|---|---|---|
| | 100 mg (n=91) | 300 mg (n=92) | 100 mg (n=91) | 300 mg (n=92) |
| Mean age (SD), years | 41.7 (10.4) | 40.1 (10.9) | 40.68 (10.18) | 40.67 (11.02) |
| Male gender, n (%) | 60 (65.9) | 57 (62.0) | 63.9 | 63.9 |
| Race, n (%) | | | | |
| Black | 31 (34.1) | 33 (35.9) | 33.9 | 33.7 |
| White/other | 60 (65.9) | 59 (64.1) | 66.1 | 66.3 |
| BMI, mean (SD), kg/m$^2$ | 25.99 (4.61) | 26.95 (4.81) | 26.42 (4.64) | 26.51 (4.76) |
| Opioid use, mean (SD), years | 11.82 (8.83) | 11.17 (9.22) | 11.35 (8.66) | 11.37 (9.01) |
| Alcohol user, n (%) | 71 (78.0) | 71 (77.2) | 77.8 | 77.6 |
| Tobacco user, n (%) | 83 (91.2) | 81 (88.0) | 90.6 | 90.0 |
| Cocaine user, n (%) | 40 (44.0) | 35 (38.0) | 41.7 | 40.8 |
| Cocaine use during Weeks 1–9, % (SD) | 81.16 (33.05) | 77.13 (37.05) | 78.29 (34.75) | 78.40 (35.53) |
| Last COWS, mean (SD)[b] | 1.51 (1.81) | 1.26 (1.90) | 1.36 (1.68) | 1.37 (2.04) |
| Last Opioid Craving VAS, mean (SD)[b] | 4.86 (12.63) | 2.97 (6.75) | 3.68 (10.54) | 3.31 (7.17) |
| Currently employed, n (%)[b] | 43 (47.3) | 49 (53.3) | 51.8 | 51.8 |
| Positive opioid assessment, n (%)[b] | 36 (39.6) | 44 (47.8) | 45.3 | 45.6 |
| Negative opioid assessment, n (%)[b] | 55 (60.4) | 48 (52.2) | 54.7 | 54.4 |

[a]With propensity score to balance risk factors that could potentially impact the treatment response post-Week 9. Only re-weighted percentages are provided.
[b]Last measurement at or before Week 9.
BMI=body mass index; COWS=Clinical Opiate Withdrawal Scale; SD=standard deviation; VAS=visual analogue scale.

### Efficacy

- Among IDU, the risk-adjusted percentage abstinence (Weeks 10–25) was significantly higher for RBP-6000 300 mg than for RBP-6000 100 mg ($P$=0.046) (**Figure 2A**).
  - Among non-IDU, the risk-adjusted percentage abstinence was not significantly different for RBP-6000 300 mg vs. RBP-6000 100 mg ($P$=0.21) (**Figure 2A**).
- After risk adjustment, the Responder rate was significantly higher for IDU receiving RBP-6000 300 mg than for those receiving RBP-6000 100 mg ($P$=0.003) (**Figure 2B**).
  - There was no significant difference in the Responder rates for RBP-600 300 mg and RBP 100 mg among non-IDUs ($P$=0.67) (**Figure 2B**).

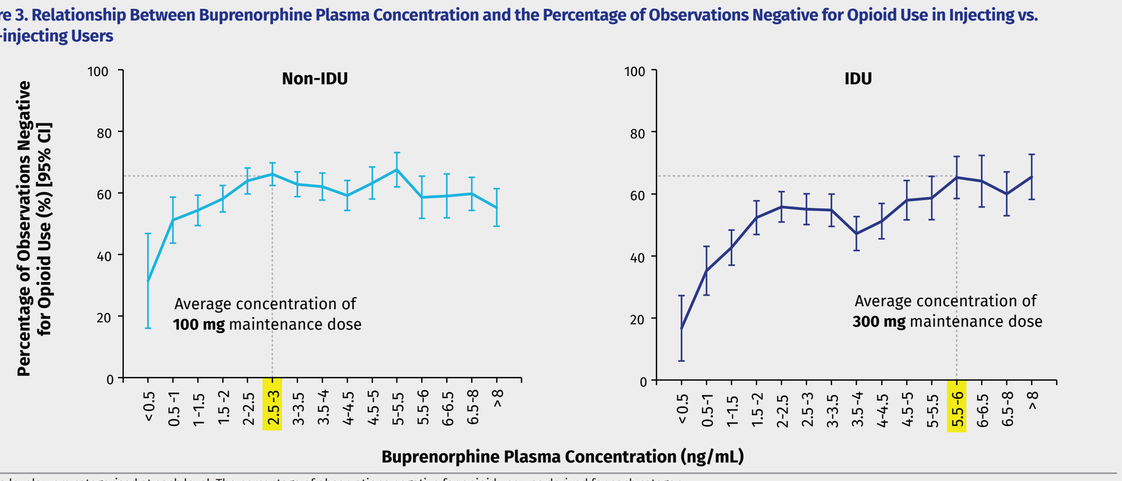
**Figure 2. A) Percentage Abstinence From Week 10–25[a]; B) Percentage of Responders From Week 21–25[b]**




[a]Based on urine samples negative for illicit opioids and self-report.
[b]Responders defined as having at least 4 out of 5 (i.e., 80%) weeks of negative opioid use during Weeks 21–25 based on urine samples negative for illicit opioids and self-report.
CI=confidence interval; IDU=injection drug users; SE=standard error.

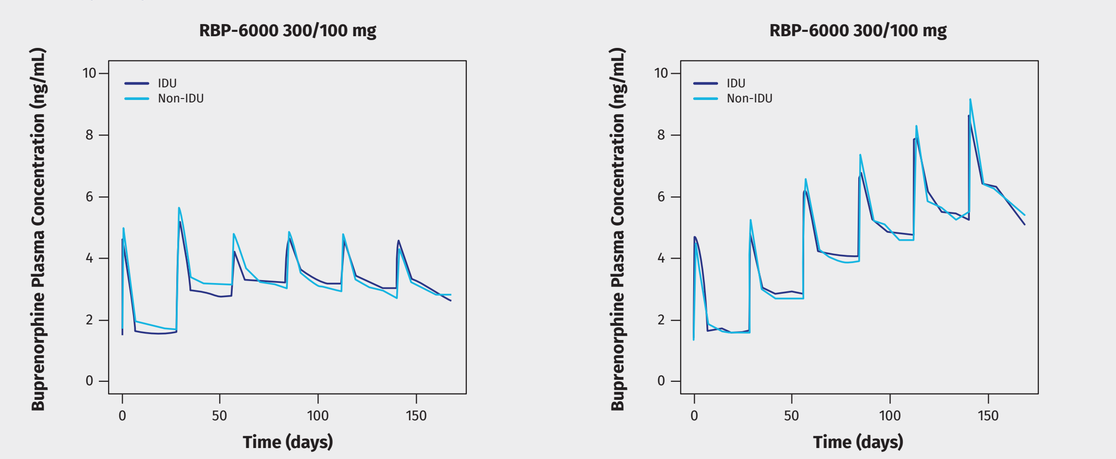
- The results of these post hoc analyses are consistent with exposure-response data (**Figure 3**).
  - Non-IDU achieved maximal response at buprenorphine concentrations of 2.5–3 ng/mL (corresponding to average plasma concentrations for RBP-6000 100 mg at steady state).
  - IDU achieved maximal response at higher buprenorphine plasma concentrations ~6 ng/mL, corresponding to average plasma concentrations for RBP-6000 300 mg at steady state (Injection 6).
- No differences in buprenorphine plasma concentration-time profiles were observed between IDU and non-IDU populations (**Figure 4**).

**Figure 3. Relationship Between Buprenorphine Plasma Concentration and the Percentage of Observations Negative for Opioid Use in Injecting vs. Non-injecting Users**




Plasma levels were categorised at each level. The percentage of observations negative for opioid use was derived for each category.
CI=confidence interval.

**Figure 4. Mean Buprenorphine Plasma Concentrations Over Time**




## Conclusions

- Post hoc analyses suggest IDU benefit from the higher buprenorphine plasma exposure achieved with the 300 mg maintenance dose of RBP-6000.
- These differences were more pronounced during the period when differences in plasma exposure were the greatest.
- Additional studies to evaluate which patients benefit from the higher maintenance dose of RBP-6000 are planned.

## References

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## Conflict of Interest Statement

MF, NLF, CML, SZ, FG, AA, SL, and CH are employees of Indivior, Inc.

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