CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 209-819
Drug Name:	Sublocade (buprenorphine controlled release injection)
Indication(s):	Treatment of moderate to severe opioid use disorder in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product
Applicant:	Indivior, Inc.
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1. EXECUTIVE SUMMARY

Indivior, Inc. submitted a New Drug Application (NDA) for RBP-6000 (buprenorphine subcutaneous monthly injection). This application seeks an indication for treatment of moderate to severe opioid use disorder (OUD) in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. RBP-6000 is proposed to be part of a complete treatment plan that includes counselling and psychosocial support.

A single confirmatory phase 3 efficacy study, study RB-US-13-0001, was conducted to demonstrate the efficacy of RBP-6000 in comparison to placebo. This was a randomized, double-blind, placebo-controlled, multicenter study designed to assess the efficacy, safety, and tolerability of multiple monthly subcutaneous injections of RBP-6000 (100 mg and 300 mg) in treatment-seeking subjects with a diagnosis of moderate or severe OUD. The primary efficacy endpoint was the cumulative distribution function (CDF) of percentage of negative drug use, which was defined as the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use collected from Week 5 through Week 24.

Based on my review, study RB-US-13-0001 demonstrated the superiority of RBP-6000 (100 mg and 300 mg regimens) over placebo for the proposed indication. However, it appears that efficacy of the two dose regimens of RBP-6000 were similar. There is no definitive evidence that one regimen is more efficacious than the other. This was supported by analyses of various secondary endpoints.

An advisory committee meeting was held on October 31, 2017 to discuss this NDA. The committee voted 18 to 1 for approval. Some committee members said they would like to see more data about which patients should be given the higher dose, though some said they would like to have the 300-mg dose despite the lack of data supporting any additional benefit.

The review team should consider overall benefit-risk profile of the two dose regimens and advices from the advisory committee while making approval decision.

2. INTRODUCTION

2.1 Overview

Buprenorphine is listed in American Society of Addiction Medicines guidelines as one of the medications to be used along with psychosocial support as part of a medication assisted treatment program for patients diagnosed with OUD. Buprenorphine sublingual products have been increasingly identified in the illicit drug market, and it is known that they are diverted, abused, and misused. Additionally, they have been implicated in several cases of accidental

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poisonings in children. The applicant conducted two studies to support efficacy, a phase 3 efficacy study (RB-US-13-0001) and an opioid blockade study (RB-US-13-0002).

RBP-6000 is a subcutaneously injected, extended-release sterile product of buprenorphine with an established delivery system (ATRIGEL). According to the applicant, RBP-6000 forms a depot when injected subcutaneously and releases buprenorphine for a minimum of 28 days. The applicant claims that RBP-6000 delivers sustained levels of buprenorphine plasma concentrations and achieves consistent and optimal occupancy of mu-opioid receptors in the brain. The applicant believes that RBP-6000 provides clinically significant control of opioid withdrawal symptoms, helps prevent illicit opioid use, and limits the possibility of misuse and diversion.

The clinical development program of RBP-6000 was discussed with the division under IND 107,607. At the pre-IND meeting held on April 27, 2010, the division stated that it may be possible to establish efficacy using a single efficacy study assuming the population is limited to patients who are stabilized on conventional formulation. If the product was envisioned for use as an initial treatment or treatment following a brief induction with sublingual buprenorphine, then another confirmatory study would be required. At a Type C meeting occurred on May 14, 2013, the division suggested the applicant conduct an opioid blockade study to identify a blocking dose to be used for the confirmatory efficacy study. At the End-of-phase 2 meeting held on September 30, 2014, the division informed the applicant that the proposed primary efficacy endpoint was conceptually acceptable and the treatment difference must be clinically meaningful. The division also agreed with the proposed statistical methods for efficacy analyses. In an advice letter dated March 19, 2015, the division expressed concerns on the design of Study RB-US-13-0001. The division suggested the applicant consider a double-dummy design comparing RBP-6000 to a transmucosal buprenorphine product or a dose -control trial. The division also recommended the applicant incorporate a blinded tapering period using active buprenorphine to prevent withdrawal symptoms in the placebo arm and prevent potential unblinding. The applicant amended the on-going study to incorporate the division's advice by adding a tapering period. Approximately one third of the subjects enrolled received tapering. At the pre-NDA meeting on December 14, 2016, the division informed the applicant that an Integrated Summary of Efficacy (ISE) is required for filing the NDA.

An advisory committee meeting was held on October 31, 2017 to discuss this NDA. The committee voted 18 to 1 for approval. Some committee members said they would like to see more data about which patients should be given the higher dose, though some said they would like to have it available despite the lack of data supporting any additional benefit.

My statistical review focuses on whether data from Study RB-US-13-0001 demonstrated the efficacy of RBP-6000 for the proposed indication.

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2.2 Data Sources

All data were supplied electronically by the applicant as SAS transport files and can be found at the following location in the CDER electronic document room: \\Cdsesub1\evsprod\NDA209819\0001\m5\datasets\rb-us-13-0001.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted the legacy datasets as well as the AdaM and SDTM datasets. The datasets and associated define files were of acceptable quality, and were sufficient for validating study results.

The applicant excluded 15 subjects from site 20 from efficacy analyses due to site compliance issues which resulted in site closure by the applicant. My sensitivity analyses including subjects from site 20 produced comparable results and the conclusion did not change, there was a statistically significant treatment effect noted for RBP-6000.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study RB-US-13-0001 was a randomized, double-blind, placebo-controlled, parallel group, multicenter study designed to assess the efficacy, safety and tolerability of multiple subcutaneous (SC) injections of RBP-6000 (100 mg and 300 mg) over 24 weeks in treatment-seeking subjects with -OUD. The study consisted of a screening phase up to 2 weeks, an open-label run-in phase up to 2 weeks, a randomized, double-blind treatment phase of 24 weeks, and a follow-up period. The study randomized subjects from 33 sites in the United States. Subjects who completed the study may be offered entry into a long-term safety study of RBP-6000 (Study RB-US-13-0003).

All subjects who entered the open-label run-in induction phase were treated with SUBOXONE (buprenorphine/naloxone) sublingual film for 3 days followed by a dose-adjustment period of 4 to 11 days. Subjects who completed the open-label run-in phase and met randomization criteria were randomized on Day 1 of the double-blind treatment phase. Study drug was administered as a SC injection every 4 weeks for a total of 6 doses. Subjects also received individual manual-guided behavior drug counselling (IDC) at least once per week throughout the study. Eligible subjects reported no significant opioid craving (≤ 20 mm on the Opioid Craving Visual Analog Scale) or withdrawal (a score of ≤ 12 on the Clinical Opiate Withdrawal Scale) after at least 7 days of SUBOXONE sublingual film therapy were randomized in a 4:4:1:1 ratio to receive one of the following regimens:

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- RBP-6000 regimen 1 (300 mg): RBP-6000 300 mg SC every 4 weeks for 6 doses+ IDC
- RBP-6000 regimen 2 (100 mg): RBP-6000 300 mg SC every 4 weeks for 2 doses+ IDC followed by RBP-6000 100 mg SC every 4 weeks for 4 doses + IDC
- placebo regimen 1: volume-matched to RBP-6000 regimen 1 + IDC
- placebo regimen 2: volume-matched to RBP-6000 regimen 2 + IDC

After about 341 subjects had been randomized, the protocol was amended to include a 5-day SUBOXONE sublingual film taper. The purpose of taper was to mitigate any potential withdrawal signs and symptoms in placebo-treated subjects, which could contribute to early drop-out, and to facilitate preservation of the blind of the study. A total of 163 subjects received a 5-day SUBOXONE sublingual film taper following the first injection of study treatment. After injection of study treatment, subjects were not permitted supplemental SUBOXONE sublingual film except for the 5-day taper that began on Day 1. Subjects who required additional supplemental SUBOXONE sublingual film or other sublingual buprenorphine pharmacotherapy after Day 1 were to be withdrawn for lack of efficacy and referred for appropriate treatment.

Following randomization, subjects were to return to the clinic weekly for a urine drug screen (UDS), Timeline Follow Back (TLFB) interviews, assessments using Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), and Opioid Craving Visual Analog Scale (VAS). The TLFB interview asked subjects to retrospectively estimate their drug use since the last visit. Assessments using the Clinical Global Impression Improvement (CGI-I) and Clinical Global Impression-Severity (CGI-S) scales were performed after each injection. Periodic health economics and outcomes research (HEOR) assessments were also conducted. An additional blinded UDS could have been performed if abuse was suspected during the double-blind phase. Prior to any injection of study drug, if the investigator was concerned about possible benzodiazepine use, an in-office benzodiazepine urine test could be performed. If the test was positive, the investigator was to contact the appropriate personnel to discuss whether to administer study treatment.

The pre-defined primary efficacy endpoint was the cumulative distribution function (CDF) of the percentage of negative drug use, which was defined as the percentage of urine samples negative for opioids combined with self-reports of negative illicit opioid use (collected from Week 5 through Week 24). The purpose of analyzing efficacy starting from Week 5 instead of Week 1 was to allow subjects to stabilize in treatment. Percentage of negative drug use was computed for each subject as the number of weeks of negative drug use divided by 20. For example, if a subject had 10 weeks of negative urine samples and TLFB self-report negative for opioids, the percentage of negative drug use of this subject was 50%.

The key secondary endpoint was treatment success, defined as any subject with ≥80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use from Week 5 through Week 24. Other secondary endpoints included percentage of subjects who were abstinent, change from baseline in VAS, CGI-I, and CGI-S from Week 5 through Week 24.

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3.2.2 Statistical Methodologies

The primary efficacy endpoint was analyzed using the Wilcoxon rank-sum test. Efficacy analyses were conducted using the full analysis population (FAS), defined as all randomized subjects who received at least one dose of study treatment. The two randomized placebo groups were combined and analyzed as one placebo group. To account for multiplicity, each dose of RBP-6000 was tested against placebo at the 0.025 level. Missing UDS samples and self-reports were imputed as positive in the primary analysis.

The protocol stated that if at least one of the RBP-6000 dose regimens would be superior to placebo with respect to the primary efficacy endpoint the key secondary efficacy endpoint, treatment success, would be tested using the Hochberg step-up procedure.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 504 subjects were randomized, 100 to placebo, 203 to RBP-6000 100 mg group, and 201 to RBP-6000 300 mg group. Approximately 60% of the subjects in RBP-6000 groups completed the study compared with approximately 34% in the placebo group (Table 1). The dispositions of the two active treatment groups were similar. The most common reasons for discontinuation in both active treatment groups were "lost to follow-up" and "subject withdrew consent". The percentage of subjects that discontinued due to "lack of efficacy" or "subject withdrew consent" was higher in the placebo group than the active groups. Similar percentages of subjects in the three treatment groups discontinued due to "lost to follow-up".

Table 1: Subject Disposition

Population	RBP-6000 100 mg	RBP-6000 300 mg	Placebo
All randomized (ITT)	**N=203**	**N=201**	**N=100**
Completed, n (%)*	125 (62%)	129 (64%)	34 (34%)
Discontinued, n(%)*	78 (38%)	72 (36%)	66 (66%)
Reason for discontinuation			
Adverse event	6 (3%)	10 (5%)	2 (2%)
Withdrawal symptoms	1 (0.5%)	1 (0.5%)	3 (3%)
Lost to follow-up	26 (13%)	23 (11%)	12 (12%)
Noncompliance with study drug	2 (1%)	0	2 (2%)
Physician decision	0	1 (0.5%)	1 (1%)
Subject withdrew consent	20 (10%)	21 (10%)	18 (18%)
Subject withdrawn by investigator	1 (0.5%)	0	3 (3%)
Lack of efficacy	3 (1.5%)	5 (2.5%)	18 (18%)
Protocol deviation	2 (1%)	5 (2.5%)	0
Other	17 (8%)	6 (3%)	7 (7%)

Source: Reviewer and Clinical study report, Table 14.1.1.1
*: Percentages are based on the total number of randomized patients.

The demographic and baseline characteristics are shown in Table 2 and were comparable across treatment groups. The majority of subjects were male (66%) and white (71%). More than 40% of

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the subjects were injection drug users. Subjects from site 20 are excluded from the FAS population.

Table 2: Summary of Demographics and Baseline Characteristics

	RBP-6000 100 mg (N=203)	RBP-6000 300 mg (N=201)	Placebo (N=100)
Age (days)			
Mean (SD)	40 (11)	39 (11)	39 (11)
Median	38	38	38
Min, Max	19, 64	19, 64	20, 63
Sex, n (%)			
Male	136 (67%)	135 (67%)	65 (65%)
Female	67 (33%)	66 (33%)	35 (35%)
Race, n (%)			
White	140 (69%)	144 (72%)	78 (78%)
Black or African American	57 (28%)	55 (27%)	20 (20%)
American Indian or Alaska Native	4 (2%)	1 (0%)	1 (1%)
Asian	0	0	0
Multiple	2 (1%)	1 (0%)	1 (1%)
Weight at screening (kg)			
Mean (SD)	77 (16)	80 (17)	76 (16)
Median	75	78	73
Min, Max	46, 123	45, 128	48, 132
Baseline BMI (kg/m^2)			
Mean (SD)	25 (4)	26 (4)	25 (4)
Median	25	26	25
Min, Max	18, 35	18, 35	18, 35
Substance use at screening			
Opioid use –injectable route	90 (44%)	84 (42%)	50 (50%)
Tobacco	187 (92%)	186 (93%)	93 (93%)
Alcohol	160 (79%)	160 (80%)	81 (81%)
Drug use history			
Cannabinoids	113 (56%)	95 (47%)	53 (53%)
Cocaine	94 (46%)	80 (40%)	42 (42%)
Amphetamine/Methamphetamine	53 (26%)	29 (14%)	19 (19%)

Source: Reviewer and Clinical Study Report Table 14.1.2.3; SD: standard deviation;

3.2.4 Results and Conclusions

Figure 1 below illustrates the CDF of percentage of negative urine samples for Weeks 5 to 24 with missing samples and self-reported opioid use incorporated as positive. This figure differs from the typical plot of a CDF which displays the percent of subjects who had a given outcome or less. The graphs show the percentage of subjects who provided a given percentage of negative samples or better. For example, in this study, approximately 35% of the subjects in the active treatment groups had at least 70% of negative drug use. The difference from placebo in the distribution function was statistically significant with p-value<0.0001 for each dose regimen of the active treatment based on the Wilcoxon rank-sum test.

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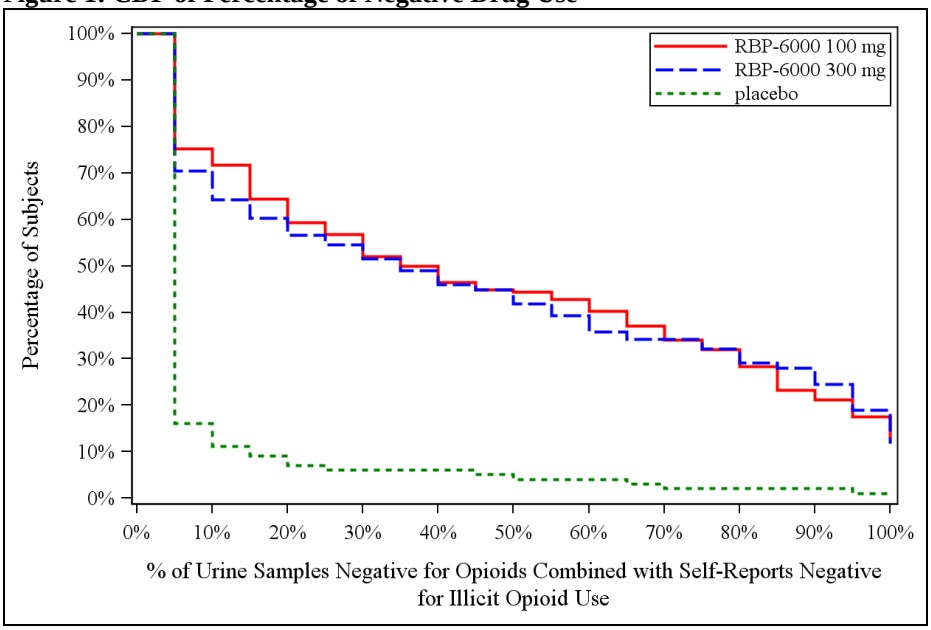
Figure 1: CDF of Percentage of Negative Drug Use



Source: Reviewer

Table 3 presents the CDF values of Figure 1 at different percentages of negative drug use in 10% increments. As can be seen in Figure 1 and Table 3, about 12% of subjects in each active treatment group had no positive or missing samples or self-report of illicit use over the 20-week efficacy ascertainment period. The pre-specified responder definition allowed 4 missing or positive samples out of the 20 collected. The proportion of subjects meeting that criterion as well as the proportion of subjects who had no indicators of illicit use were both higher in each of the active treatment groups than the placebo group with nominal statistical significance based on Fisher's Exact test.

Table 3: Cumulative Percentage of Negative Drug Use from Weeks 5 to 24

	Number (%) of Subjects		
Percentage of Negative Drug Use	**RBP-6000 100 mg (N=194)**	**RBP-6000 300 mg (N=196)**	**Placebo (N=99)**
≥ 0%	194 (100)	196 (100)	99 (100)
≥ 10%	139 (72)	126 (64)	11 (11)
≥ 20%	115 (59)	111 (57)	7 (7)
≥ 30%	101 (52)	101 (52)	6 (6)
≥ 40%	90 (46)	90 (46)	6 (6)
≥ 50%	86 (44)	82 (42)	4 (4)
≥ 60%	78 (40)	70 (36)	4 (4)
≥ 70%	66 (34)	67 (34)	2 (2)
≥ 80%	55 (28)	57 (29)	2 (2)
≥ 90%	41 (21)	48 (24)	2 (2)
100%	25 (13)	23 (12)	1 (1)

Source: Reviewer.

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The overall percent of negative drug use does not differentiate between, for example, a subject who is abstinent for half the study and then relapses to daily illicit drug use, a subject who continues to use illicit drugs daily for half the study and then stops completely, and a subject who uses intermittently, half the days throughout the study. These subjects might have 50% of their tests negative. To allow an appreciation of the temporal sequence of a subjects' test results, the results of drug use over the 24 weeks for each subject is shown in Figure 2. Each treatment arm is presented separately. Each line on the y-axis depicts the urine results for an individual subject. On the x-axis are the time points during which urine samples were collected. Blue dots represent opioid-negative urine samples, while red dots represent opioid-positive urine samples. The red "x" dots indicate where urine samples were negative or missing but subjects self-reported opioids use. This is indicated as TLFB positive on the graph. The data points that appear black in these presentations are "+" symbols and denote intermittent missing urine data.

Subjects who did not complete the study are shown at the top of each display and are sorted based on time in the study. Samples after the last dot in the row were missing and were imputed as positive for the purposes of analysis. Completers are shown at the bottom of each display, arranged by time to last positive urine sample.

Ideally, a subject achieving treatment success would have many more blue data points than red data points, particularly along the right-hand side of the x-axis which represents longer periods of time on treatment. Clearly, regardless of the dose regimen, there are more blue dots in the active treatment groups than the placebo group. In the placebo group, there were very few blue dots, regardless of whether subjects discontinued or remained in the study. The outcomes of the two active injections are visually similar. There is no clear indication that one is better than the other.

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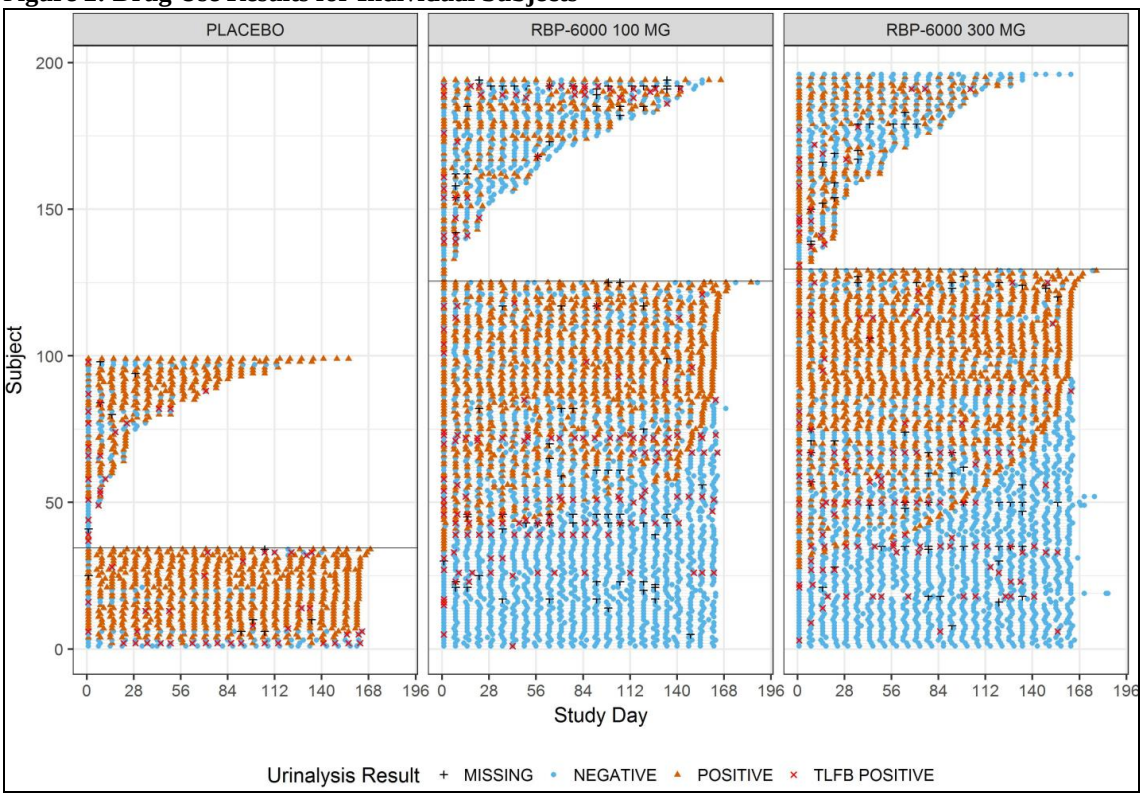
Figure 2: Drug Use Results for Individual Subjects



Source: Reviewer

Analyses of secondary endpoints were supportive of the primary analysis. The observed average scores of COWS, SOWS, and opioid craving VAS of the two active regimens were also similar and numerically better than those of placebo (Appendix Figures 8 to 10).

To investigate whether the study conclusion will change by comparing each dose regimen to its matching placebo, the CDF of percentage of negative drug use was produced for each matching placebo and compared with the corresponding dose regimen. Each dose regimen was also superior to its matching placebo with statistical significance. The CDFs (Appendix Figure 11) of the two matching placebos were very similar and I deemed it was appropriate to pool the two placebo groups in the primary analysis.

To explore the impact of missing data due to subject discontinuation on the primary analysis, I conducted several sensitivity analyses. In my first analysis, the percent of negative drug use of placebo dropouts were based on observed data prior to discontinuation and dropouts on the active arm were considered treatment failures. In my second sensitivity analysis, the percentage of negative drug use was calculated based on available data for all subjects except those discontinued due to lack of efficacy, for which the missing data were imputed positive. A third analysis imputed all missing data as opioid negative except for those due to lack of efficacy, which represents the most unlikely case in favor of placebo. The CDF plots from these

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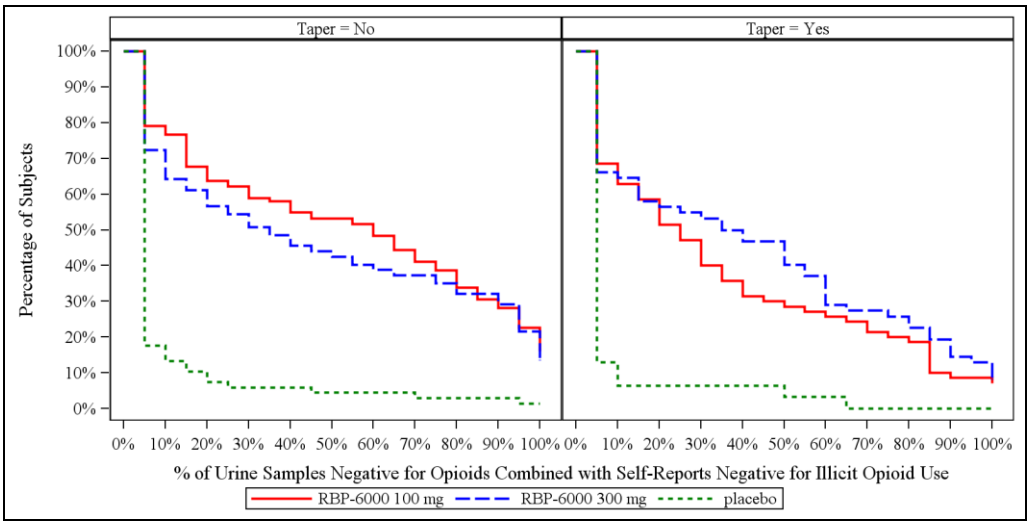
sensitivity analyses are provided in the Appendix (Figures 12 to 14). Regardless of the assumptions for missing data due to subject discontinuations, all analyses supported the conclusion from the primary analysis, there was a statistically significant treatment effect noted for both dose regimens of RB-6000.

As previously mentioned, the protocol was amended to incorporate a taper at the end of the sublingual film run-in to mitigate the potential effects of abrupt discontinuation on subjects blindly switched to placebo injections, which could increase the rate of discontinuations in the placebo arm. A total of 163 (32%) subjects received a 5-day SUBOXONE sublingual film taper following the first injection of study treatment. To examine the effect of tapering, the CDFs of percentage of negative drug use are depicted by tapering status in Figure 3. The figures illustrate that there was no obvious difference in retention or response in the placebo group based on presence or absence of tapering. Moreover, the difference between the two active injections was not statistically significant.

Figure 3: CDF of Percentage of Negative Drug Use by Tapering Status



Source: Reviewer

3.3 Evaluation of Safety

The evaluation of the safety data was conducted by the clinical reviewer, Dr. Emily Deng. There were no major safety findings. Please refer to Dr. Deng's review for detailed information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Sex, Age and Race

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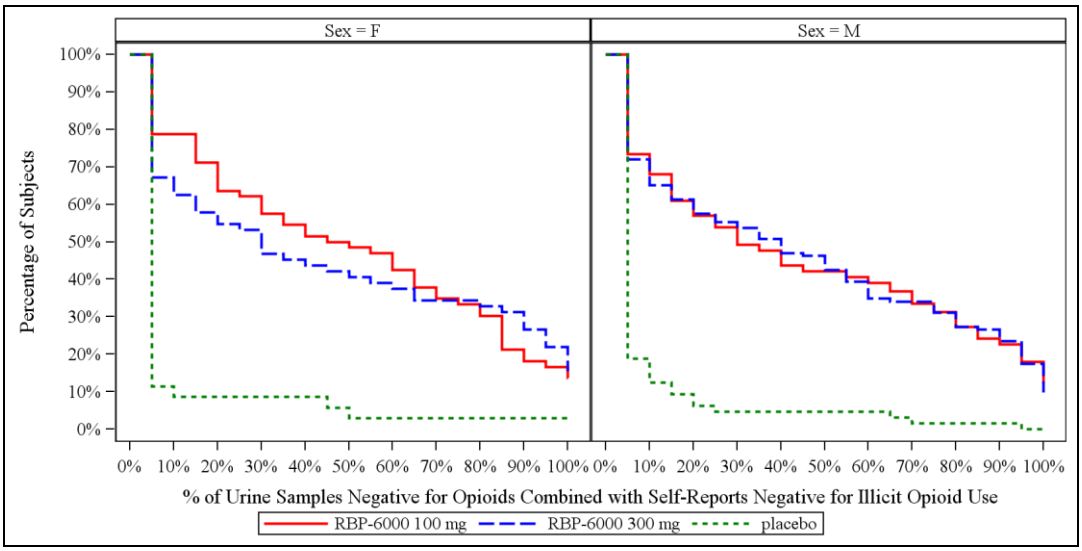
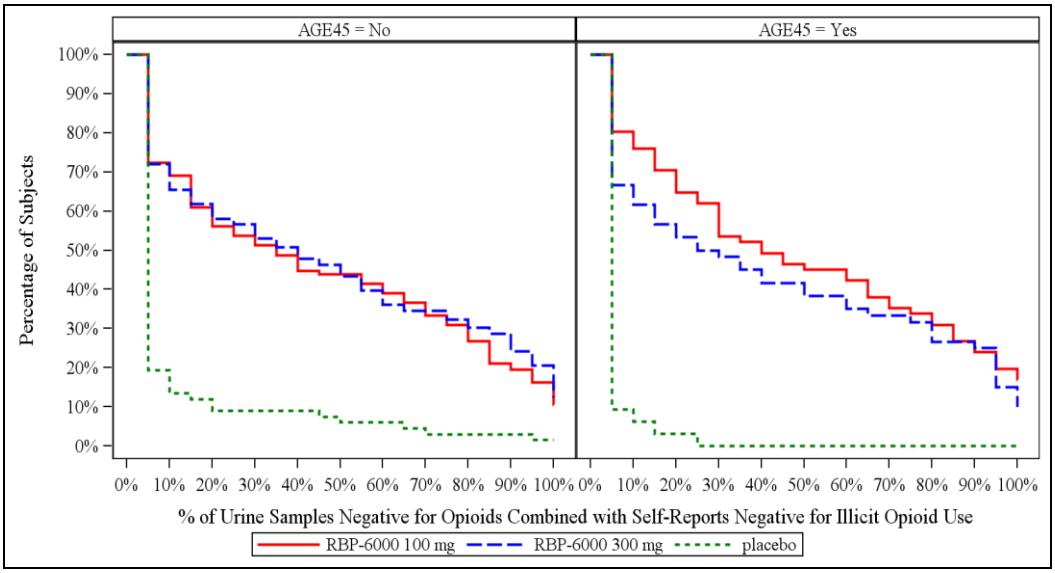
The CDF of percentage of negative drug use during weeks 5 to 24 is depicted for each treatment group by sex, age (older than 44 or not), and race (white vs non-white) in Figures 4 to 6. Findings from these subgroup analyses are consistent with those from the overall population.

Figure 4: CDF of Percentage of Negative Drug Use by Tapering Sex



Source: Reviewer

Figure 5: CDF of Percentage of Negative Drug Use by Age (older than 44 or not)



Source: Reviewer

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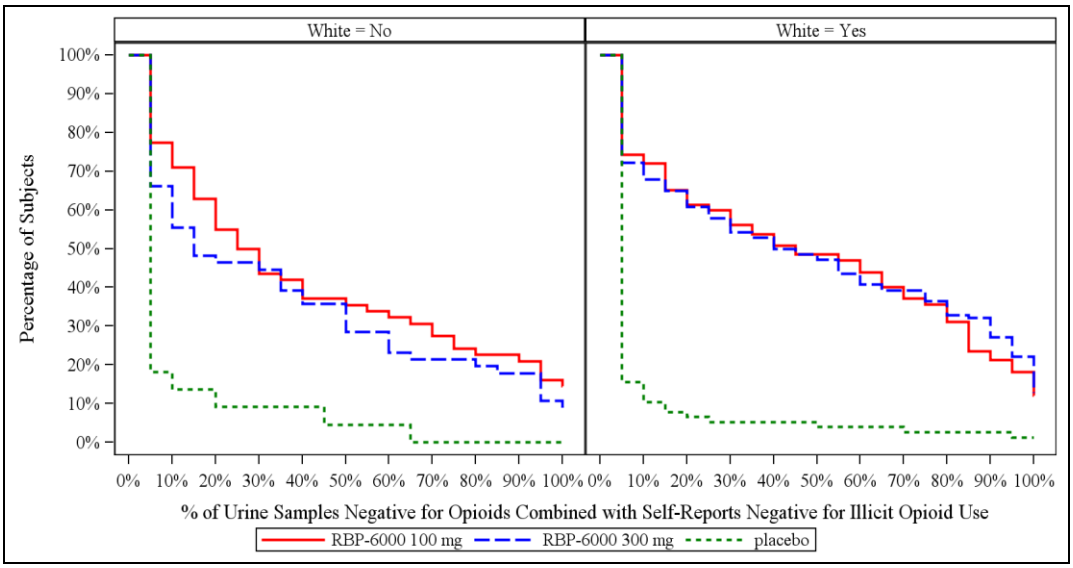
Figure 6: CDF of Percentage of Negative Drug Use by Race (White or Non-white)



Source: Reviewer

4.2 Other Special/Subgroup Populations

There was a clinical question about the efficacy among subjects who were injection drug users. Figure 7 presents results of the primary analysis based on history of injection drug use (yes or no). Both active injection regimens were superior to placebo, regardless of the history of injection drug use. The 300-mg dose regimen was numerically better among the injection drug users but worse among the non-injection drug users than the 100-mg dose regimen. The difference between the two dose regimens was not statistically significant in both subgroups.

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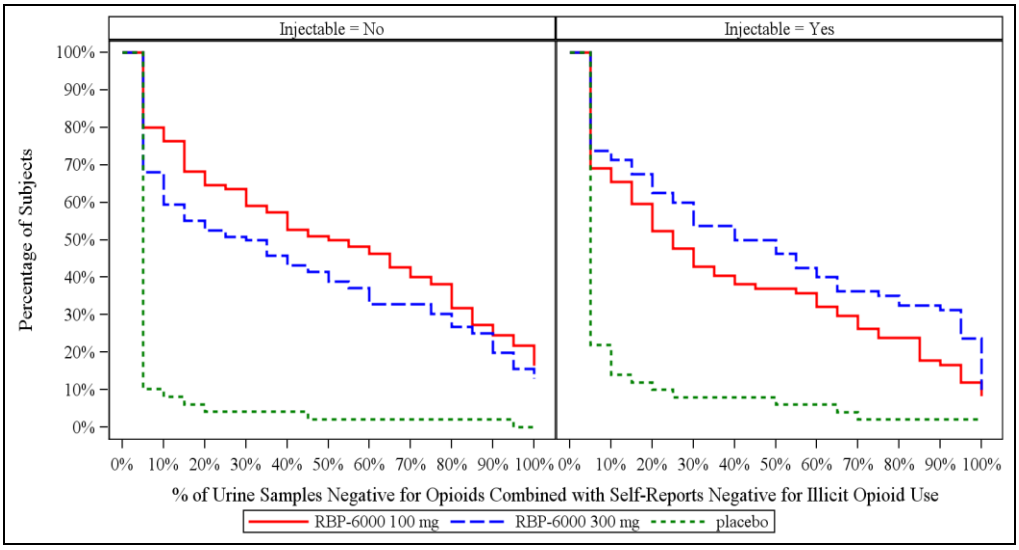
Figure 7: CDF of Percentage of Negative Drug Use by Injection Drug Use



Source: Reviewer

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Some minor statistical issues that did not affect the study conclusion are summarized below.

- Site 20 was excluded from the efficacy analyses because of compliance issues. However, the applicant did not present any sensitivity analysis to investigate the potential impact on the study conclusion. I conducted a sensitivity analysis including subjects from site 20. The inclusion of subjects from this site did not change the conclusion from the primary analysis, there was a statistically significant treatment effect noted for both doses of RBP-6000.

- During site inspection, the agency discovered that the investigator of site (b) (6) had an unreported conflict of interest. I conducted a sensitivity analysis excluding site (b) (6). The results were very similar.

- The datasets contain some extra urine drug screen results in addition to scheduled ones that were not considered in the applicant's efficacy analyses. I conducted a sensitivity analysis incorporating these extra urine results into the primary analysis. The results were consistent with the primary analysis.

5.2 Collective Evidence

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The primary analysis demonstrated the superiority of the two dose regimens of RBP-6000 over placebo. The conclusion was supported by various sensitivity analyses as well as results from analyses on secondary endpoints including COWS, SOWS and opioid craving VAS. Moreover, there was no evidence to conclude one dose regimen is more efficacious than the other.

5.3 Conclusions and Recommendations

The single phase 3 efficacy study demonstrated the superiority of the two dose regimens of RBP-6000 over placebo for the proposed indication. However, there was no evidence that the 300-mg dose regimen is more efficacious than the 100-mg dose regimen. The review team should consider overall benefit-risk profile of the two dose regimens while making approval decision.

5.4 Labeling Recommendations

The labeling is still under review while this review is finalized. The applicant described results from the opioid blockade study and efficacy study in Section 14 of the labeling. (b) (4)

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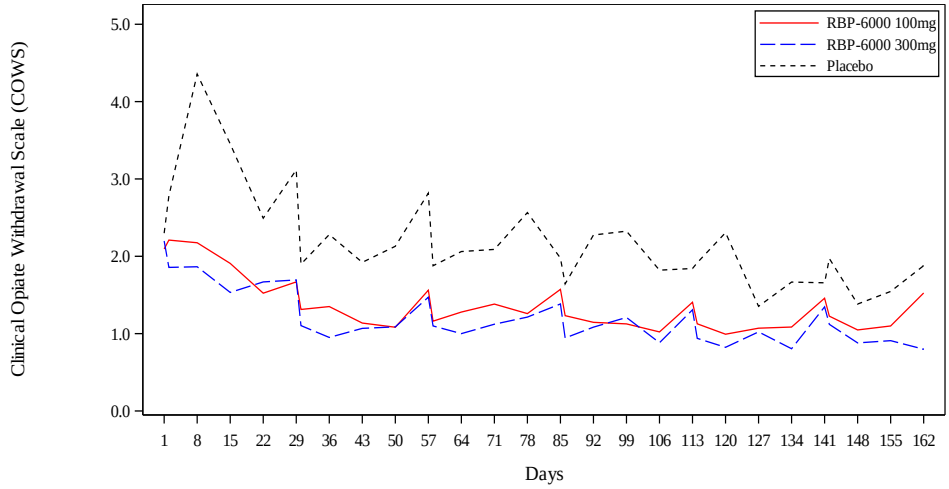
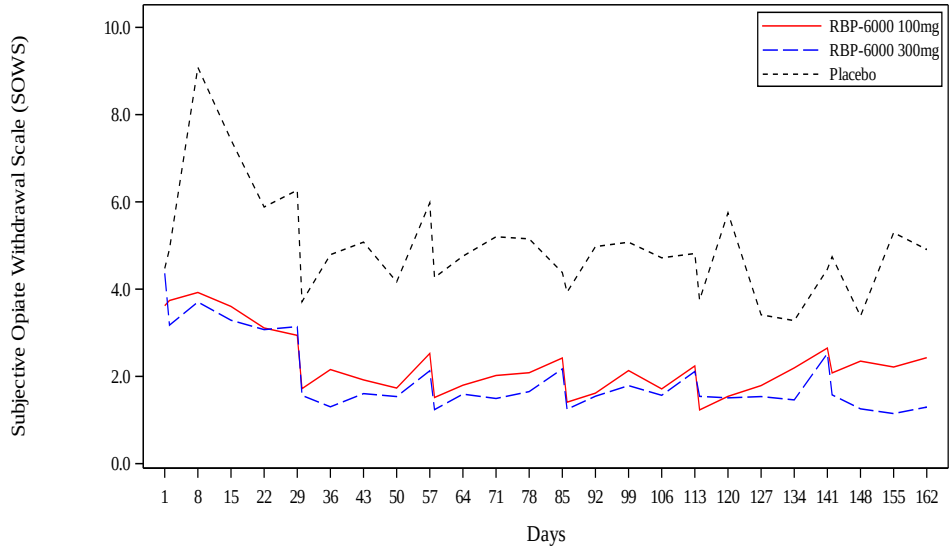
Appendix

Figure 8: Average COWS Over Time



Available Subjects (n)							
Placebo	97	60	49	42	38	35	33
RBP-6000 100	191	166	155	145	138	131	118
RBP-6000 300	192	170	155	146	133	130	124

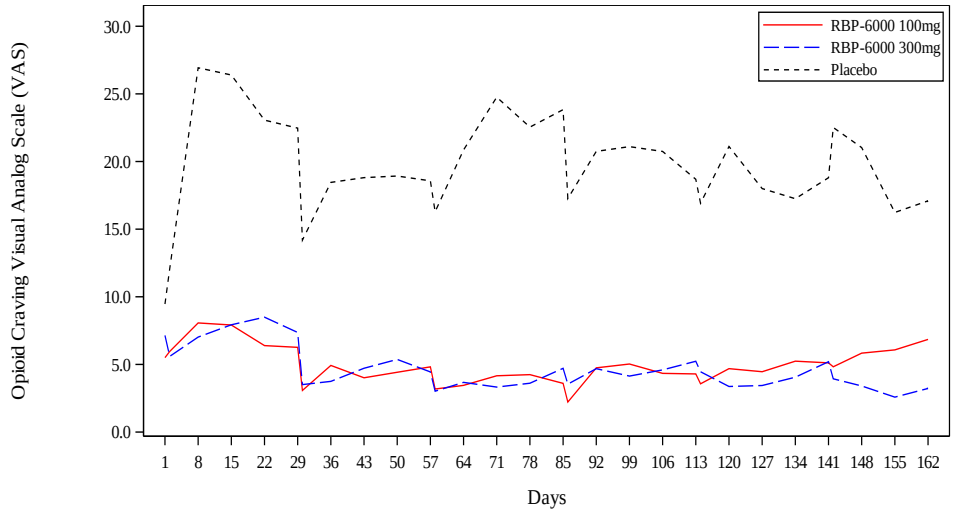
Figure 9: Average SOWS Over Time



Available Subjects (n)							
Placebo	97	60	49	42	38	35	33
RBP-6000 100	192	168	156	145	138	131	119
RBP-6000 300	193	171	155	146	133	130	125

Reference ID: 4177813

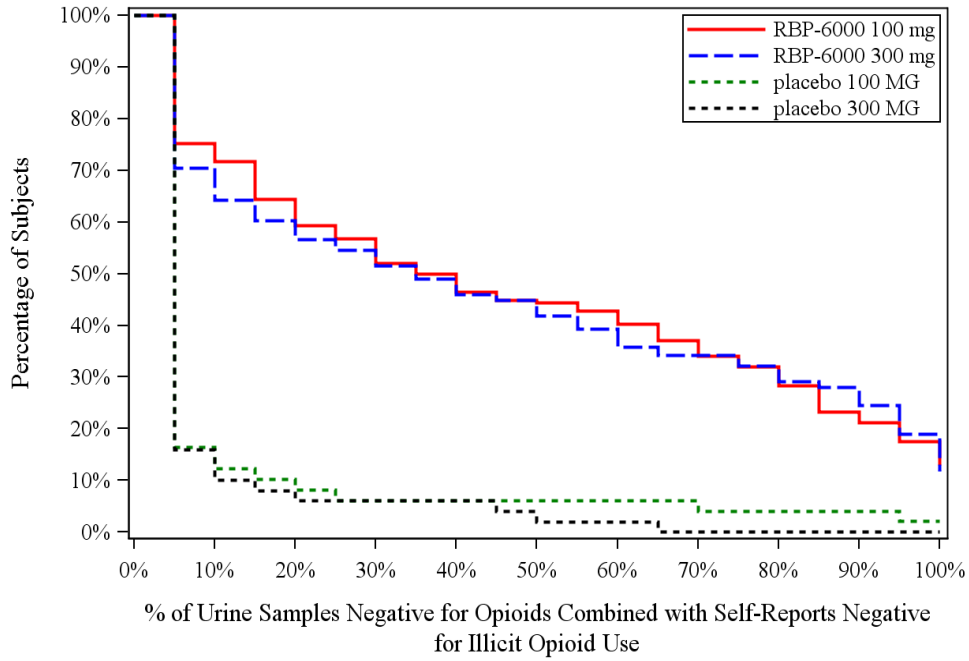
Figure 10: Average Craving VAS Over Time



Available Subjects (n)

Placebo	97	60	49	42	38	35	33
RBP-6000 100	192	168	156	145	138	131	119
RBP-6000 300	193	171	155	146	133	130	125

Figure 11: Comparison of CDF of Negative Drug Use based on Matching Placebo



Reference ID: 4177813

Figure 12: Sensitivity Analysis 1 (placebo based on observed data with no imputation)

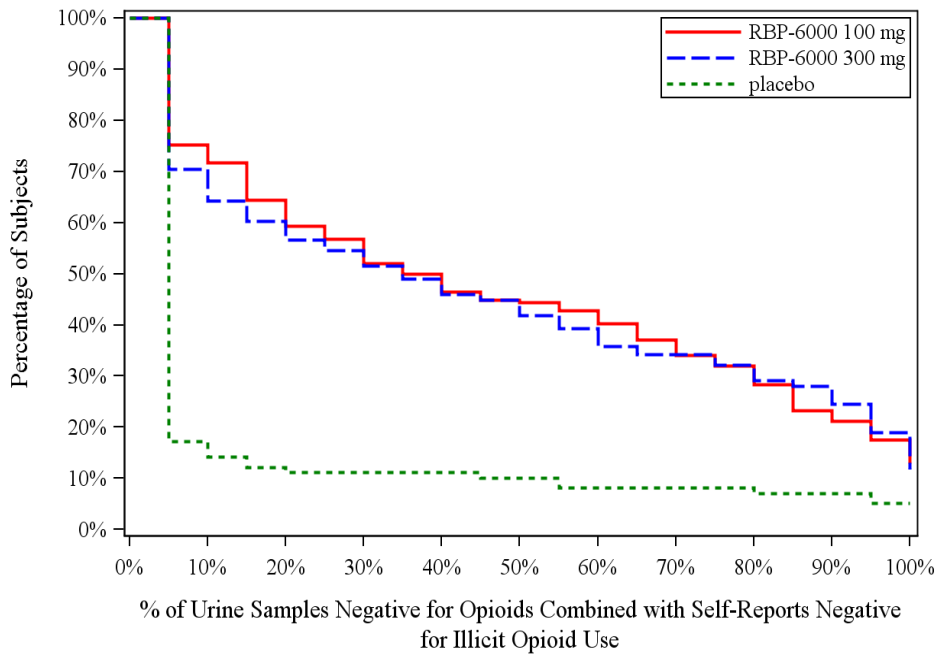
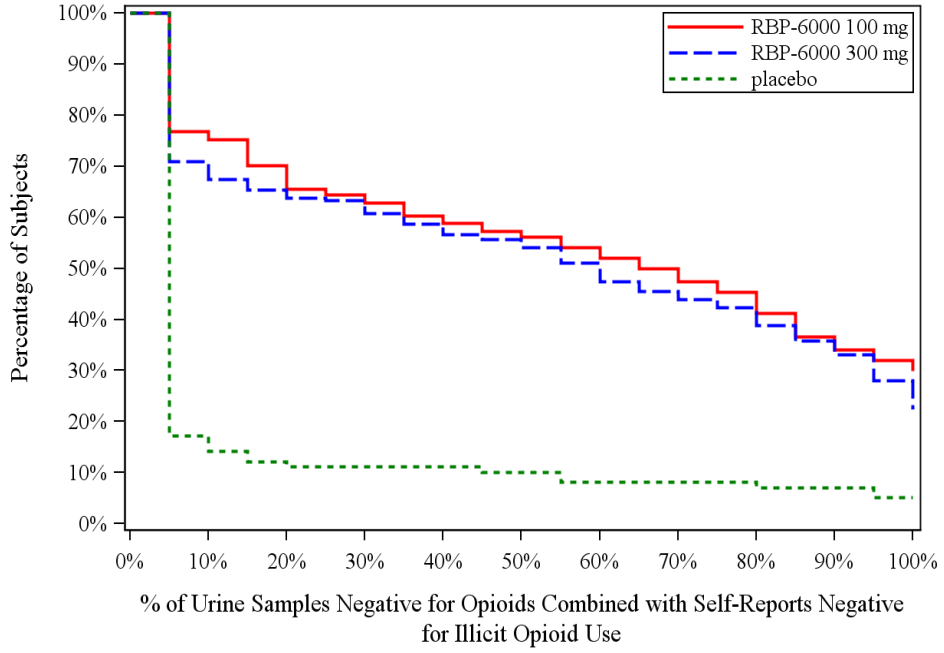
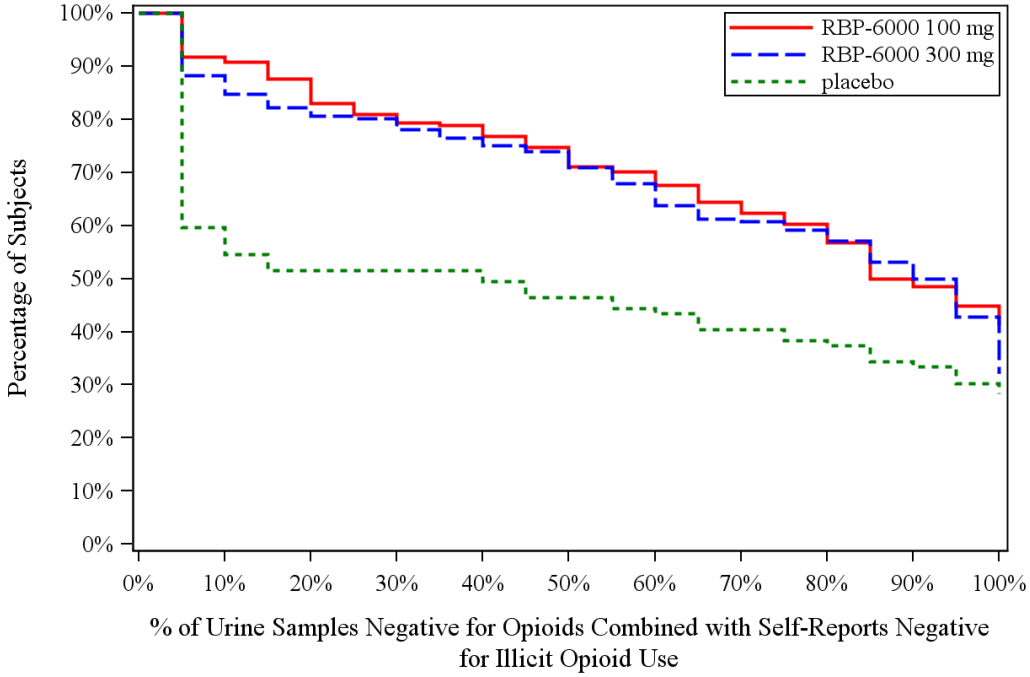


Figure 13: Sensitivity Analysis 2 (all based on observed data except for lack of efficacy)



Reference ID: 4177813

Figure 14: Sensitivity Analysis 3 (all imputed negative except for lack of efficacy)



Reference ID: 4177813

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/s/

FENG LI
11/06/2017

DAVID M PETULLO
11/06/2017
I concur.